

Request for permission for pharmaceutical industry oral testimony at Idaho Medicaid's P&T Committee meeting on 11-18-2016.

Submission # 5a

This request has not been approved for oral testimony (10/28/16).

Gennrich, Jane

From: US MedInfo <US.MedInfo@alkermes.com>
Sent: Wednesday, October 19, 2016 11:52 AM
To: Eide, Tamara J.
Cc: Karen Nishihara; Deborah Profant; Sejal Faldu
Subject: ARISTADA Testimony
Attachments: Moore TA et al J Clin Psychiatry 2007.pdf; Remenar_Mol. Pharmaceutics 2014.pdf; Turncliff_Schizophrenia Research 2014.pdf; Meltzer_J Clin Psychiatry 2015.pdf; ARISTADA PI and Med Guide 7-2016.pdf; Aristada Medicaid Testimony Cover Letter.pdf; Aristada Medicaid Testimony for Idaho.pdf; Lehman AF et al. Am J Psychiatry. 2004.pdf

Dear Idaho Medicaid Pharmacy & Therapeutics Committee,

Thank you for reviewing ARISTADA® at the November 18th, 2016 meeting. Dr. Karen Nishihara will be presenting on behalf of Alkermes.

Please see attached for the following documents:

1. ARISTADA Product Testimony Cover Letter
2. ARISTADA Product Testimony
3. ARISTADA Prescribing Information and Medication Guide (updated 7/2016)
4. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin. Psychiatry.2015;76(8):1085-1090.
5. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry.2004;161(2 Suppl):1-56.
6. Moore T, Buchanan R, Buckley P, Chiles J, Conley R, Crismon M, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia:2006 update. J Clin Psychiatry.2007;68:1751-1762.
7. Remenar, J. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics. Molecular Pharmaceutics.2014;11:1739-1749.
8. Turncliff R, et al. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly long-acting injectable atypical antipsychotic, following deltoid gluteal administration in adult subjects with schizophrenia. Schizophr Res.2014;159(2-3):404-410

Thank you.

Warm Regards,

Medical Information

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Dear Idaho P&T committee,

As requested, this letter outlines the clinical information and citation pages for the ARISTADA® testimony.

- ARISTADA, aripiprazole lauroxil, is an atypical antipsychotic indicated for the treatment of schizophrenia ARISTADA (package insert); pg 1 lines 19-20.
- The primary efficacy variable in the 12-week randomized placebo-controlled clinical study was the change from baseline to endpoint (day 85) in Positive and Negative Syndrome Scale (PANSS) total score. Meltzer HY, et al. J. Clin Psychiatry. 2015;76(8):1085-1090; pg 1087 right column, lines 1-4 Statistically significant separation from placebo on PANSS total score change was observed for each aripiprazole lauroxil dose group. Meltzer HY, et al. J Clin Psychiatry. 2015;76 (8):1085-1090; pg1088 Figure 2A
- The most common TEAEs were insomnia, akathisia, and headache. Meltzer HY, et al. J Clin Psychiatry. 2015;76(8):1085-1090; pg 1089 Table 2
- Depending on an individual patient's needs, treatment with ARISTADA can be initiated at a dose of 441mg, 662 mg, or 882 mg administered monthly or with the 882 mg dose every 6 weeks. ARISTADA (package insert); pg 2 lines 17-20. In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days. ARISTADA (package insert); pg 3 lines 6-7. Dose or dosing interval adjustments may be required for other factors including, but not limited to drug interactions and missed doses beyond 6-8 weeks. ARISTADA (package insert); pg 3 lines 33-35; pg 4 lines 1-22; pg 3 lines 12-26
- Aripiprazole lauroxil's unique formulation along with the LinkeRx® technology extends exposure to aripiprazole. Remenar J, et al. Molecular Pharmaceutics.2014;11:1739-1749; pg 1741 lines 14-18 Turncliff R, et al. Schizophr Res. 2014;159 (2-3):404-410; pg 406 left column, lines 20-23 and pg 408 left column, lines 11-17

Sincerely,

Alkermes Medical Affairs
852 Winter Street
Waltham, MA 02451-1420
usmedinfo@alkermes.com

References:

1. Alkermes, Inc. ARISTADA® (package insert). Waltham, MA; July 2016.
2. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin. Psychiatry.2015;76(8):1085-1090.
3. Remenar, J. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics.Molecular Pharmaceutics.2014;11:1739-1749.
4. Turncliff R, et al. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia.Schizophr Res.2014;159(2-3):404-410.

Medicaid Testimony for Aripiprazole Lauroxil (ARISTADA®)

My name is Dr. Karen Nishihara, Medical Science Director at Alkermes. Thank you for the opportunity to provide testimony on Aripiprazole Lauroxil (ARISTADA), a recently approved extended release injectable atypical antipsychotic for Intramuscular (or IM) use.

I will highlight a few key clinical points today.

INDICATIONS and MOA:

ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia, and a prodrug of aripiprazole. Following intramuscular injection, ARISTADA is likely converted to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole.

EFFICACY:

The efficacy of ARISTADA is, in part, based on the 12 week randomized, double blind, placebo-controlled registration trial published by Meltzer et al. in the Journal of Clinical Psychiatry, in 2015.²

The primary efficacy variable was the change from baseline to endpoint (day 85) in PANSS total score.

Statistically significant separation from placebo, on PANSS total score change, was observed for each aripiprazole lauroxil (ARISTADA) dose group

- the LS mean changes from baseline in PANSS total score for AL 441 mg, AL 882 mg, and placebo were -20.9, -21.8, and -9.8, respectively.

SAFETY/ADVERSE EVENTS:

The most common TEAEs were insomnia, akathisia and headache

- Akathisia was the most commonly observed adverse reaction with ARISTADA (incidence $\geq 5\%$)

Injection site reactions were reported by 4% of patients treated with 441 mg ARISTADA and 5% of patients treated with 882 mg ARISTADA compared to 2% of patients treated with placebo (most of these were injection site pain).

IMPORTANT SAFETY INFORMATION:

ARISTADA has a Black Boxed WARNING for INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

DOSING:

ARISTADA is only to be administered as an intramuscular injection by a healthcare professional.

For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability.

Depending on individual patient's needs, treatment with ARISTADA can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly, which corresponds to 300 mg, 450 mg and 600 mg of aripiprazole, respectively. Treatment may also be initiated with the 882 mg dose every 6 weeks.

Administer ARISTADA either in the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg or 882 mg)

In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days.

With the addition of oral aripiprazole supplementation for 21 days at the time of the first ARISTADA dose, aripiprazole concentrations reach therapeutic levels within 4 days. When making dose and dosing interval adjustments, the pharmacokinetics and prolonged-release characteristics of ARISTADA should be considered. In the event of early dosing, an ARISTADA injection should not be given earlier than 14 days after the previous injection.

Dose or dosing interval adjustments may be required for other factors including, but not limited to drug interactions (i.e., CYP2D6 poor metabolizers; patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than 2 weeks) and missed doses beyond 6-8 weeks depending on the amount of time lapsed and dose of ARISTADA administered.

Specifics for these types of dose & dosing interval adjustments in addition to oral daily equivalent dosing for aripiprazole and IM ARISTADA dose are outlined in the prescribing information.

GUIDELINES:

According to APA guidelines, patients with recurrent relapses related to not taking their oral medication are candidates for a long-acting injectable antipsychotic³, while the TMAP (Texas Medication Algorithm Project) recommends that the clinicians consider Long Acting Injectable Antipsychotics in patients who are inadequately adherent 'at any stage' of schizophrenia.⁴

HOW SUPPLIED:

ARISTADA is available in a pre-filled syringe containing ARISTADA sterile aqueous suspension and does not require refrigeration. ARISTADA should be stored at room temperature with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

CONTRAINDICATIONS:

Known hypersensitivity to aripiprazole.

ABSORPTION AND DISTRIBUTION:

Based on population pharmacokinetic analysis, the apparent volume of distribution of aripiprazole following intramuscular injection of ARISTADA was 268 L, indicating extensive extravascular distribution following absorption. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 mg/day to 30 mg/day oral aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

LinkeRx® PHARMACOKINETICS

Aripiprazole Lauroxil's unique formulation along with the LinkeRx® technology provides controlled and predictable pharmacokinetics of aripiprazole and extends exposure to the active molecule.^{5,6} Median simulated steady-state aripiprazole plasma concentrations following administration of ARISTADA (based on a population pharmacokinetic (PK) model that incorporated data from four Phase I studies and the pivotal Phase III efficacy study and included a total of 21,620 plasma concentration records from 616 patients)⁷ demonstrate that, at steady-state, all approved dosing regimens for ARISTADA result in aripiprazole concentrations within the therapeutic range of 102-435 ng/mL, which was established by Alkermes based on mean steady-state minimum concentrations (C_{min}) achieved following oral aripiprazole 10 mg/day and mean steady-state maximum concentrations (C_{max}) following oral aripiprazole 30 mg/day.⁸ Steady-state is achieved with ARISTADA following the fourth monthly injection.¹

Due to the prolonged release characteristics of ARISTADA, median simulated aripiprazole concentrations following a missed dose demonstrate that marginal decreases in median aripiprazole plasma concentrations were observed for each of the evaluated dosing regimens.⁷ If a 441 mg dose is administered within 6 weeks, no additional oral supplementation is required.¹ If a 662 mg or 882 mg dose is administered within 8 weeks, no additional oral supplementation is required.¹ When a dose is missed, administer the next dose of ARISTADA as soon as possible. Whether oral supplementation is required depends on the strength of the last dose administered and the amount of time that has lapsed and that information is contained in the full prescribing information.¹

SUMMARY:

ARISTADA is the first long-acting atypical antipsychotic with both once-monthly and six-week dosing options. Aripiprazole lauroxil (ARISTADA) is indicated for the treatment of schizophrenia based on a 12-week, randomized, double-blind, placebo controlled, fixed-dose study in adult patients with schizophrenia meeting DSM IV TR criteria. This study showed an improvement of psychotic symptoms that was statistically significant and clinically meaningful, based on: Symptom improvement, as measured by PANSS total scores; and both ARISTADA treatment groups demonstrated statistically significantly better CGI-I scores versus placebo. The most common adverse event was akathisia. These results support aripiprazole lauroxil (ARISTADA) as an important new treatment option for schizophrenia. Therefore, we respectfully request your consideration to minimize restrictions relative to ARISTADA.

For the complete boxed warning and additional information, I have available for you today the full Prescribing Information for Aripiprazole Lauroxil (ARISTADA).

References:

1. Alkermes, Inc. ARISTADA® (package insert). Waltham, MA; 2016.
2. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin. Psychiatry.* 2015;76(8):1085-1090.

3. Lehman A, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 Suppl):1-56.
4. Moore T, Buchanan, R, Buckley, P, Chiles, J., Conley, R., Crismon, M. et al. (2007) The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry* 68:1751–1762.
5. Remenar, J. *Molecular Pharmaceutics*. 2014;11:1739-1749.
6. Turncliff R, et al. *Schizophr Res*. 2014;159(2-3):404-410.
7. Hard, M, et al. Aripiprazole Lauroxil Pharmacokinetics: Application of Modeling and Simulation for Dosing Considerations of a Long-Acting Injectable Antipsychotic in Persons With Schizophrenia, ASCP, Scottsdale, AZ, 2016.
8. FDA Web Site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207533Orig1s000ClinPharmR.pdf. Accessed March 29, 2016.

The Texas Medication Algorithm Project Antipsychotic Algorithm for Schizophrenia: 2006 Update

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Background: A panel of academic psychiatrists and pharmacists, clinicians from the Texas public mental health system, advocates, and consumers met in June 2006 in Dallas, Tex., to review recent evidence in the pharmacologic treatment of schizophrenia. The goal of the consensus conference was to update and revise the Texas Medication Algorithm Project (TMAP) algorithm for schizophrenia used in the Texas Implementation of Medication Algorithms, a statewide quality assurance program for treatment of major psychiatric illness.

Method: Four questions were identified via premeeting teleconferences. (1) Should antipsychotic treatment of first-episode schizophrenia be different from that of multipisode schizophrenia? (2) In which algorithm stages should first-generation antipsychotics (FGAs) be an option? (3) How many antipsychotic trials should precede a clozapine trial? (4) What is the status of augmentation strategies for clozapine? Subgroups reviewed the evidence in each area and presented their findings at the conference.

Results: The algorithm was updated to incorporate the following recommendations. (1) Persons with first-episode schizophrenia typically require lower antipsychotic doses and are more sensitive to side effects such as weight gain and extrapyramidal symptoms (group consensus). Second-generation antipsychotics (SGAs) are preferred for treatment of first-episode schizophrenia (majority opinion). (2) FGAs should be included in algorithm stages after first episode that include SGAs other than clozapine as options (group consensus). (3) The recommended number of trials of other antipsychotics that should precede a clozapine trial is 2, but earlier use of clozapine should be considered in the presence of persistent problems such as suicidality, comorbid violence, and substance abuse (group consensus). (4) Augmentation is reasonable for persons with inadequate response to clozapine, but published results on augmenting agents have not identified replicable positive results (group consensus).

Conclusions: These recommendations are meant to provide a framework for clinical decision making, not to replace clinical judgment. As with any algorithm, treatment practices will evolve beyond the recommendations of this consensus conference as new evidence and additional medications become available.

(*J Clin Psychiatry* 2007;68:1751-1762)

Received April 30, 2007; accepted Aug. 28, 2007. From the Department of Psychiatry, The University of Texas Health Science Center at San Antonio (Drs. Moore and A. L. Miller); Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore (Drs. Buchanan and Conley); the Department of Psychiatry, Medical College of Georgia, Augusta (Dr. Buckley); the Department of Psychiatry, University of Washington School of Medicine, Seattle (Dr. Chiles); College of Pharmacy, The University of Texas at Austin (Dr. Crismon); the Department of Mental Health Services and Policy Research, New York State Psychiatric Institute, New York (Dr. Essock); New York Office of State Mental Health, N.Y. (Dr. Finnerty); West Los Angeles VA Health Care Center, Calif. (Dr. Marder); the Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City (Dr. D. D. Miller); the Department of Psychiatry and Behavioral Sciences, Duke University, Durham, N.C. (Dr. McEvoy); the Department of Psychiatry, The Zucker Hillside Hospital of the North Shore-Long Island Jewish Health System, Glen Oaks, N.Y., Feinstein Institute for Medical Research, Manhasset, N.Y., and the Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, N.Y. (Dr. Robinson); the Department of Psychiatry, Georgetown University School of Medicine, and VISNS MIRECC, Department of Veterans Affairs, Washington, D.C. (Dr. Schooler); the Texas Department of State Health Services, Austin (Dr. Shon); and the Department of Psychiatry, University of North Carolina at Chapel Hill (Dr. Stroup).

Funding for this conference was provided by the Texas Department of State Health Services, Austin. No funding for the conference was sought from or provided by pharmaceutical companies. The conference proceedings were closed and confidential. No industry representatives were present at the conference or included in decision making.

Acknowledgments appear at the end of this article.

Financial disclosure appears at the end of this article.

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This article summarizes the recommendations of a consensus process to update the Texas Medication Algorithm Project (TMAP) antipsychotic algorithm for schizophrenia. The update conference took place in June 2006 in Dallas, Tex.

First published in 1996, the schizophrenia algorithm of TMAP has been used in public mental health settings in at least 20 states, an estimate based on requests for training or technical assistance to 3 of the authors (M.L.C., A.L.M., and S.P.S.). The initiative to use TMAP algorithms in all public mental health facilities in Texas is the Texas Implementation of Medication Algorithms, a statewide quality assurance program for the treatment of major psychiatric illness. While it is difficult to evaluate exactly

what characteristics have contributed to this level of interest, 3 factors are typically cited by users and potential users of TMAP: (1) the algorithm and the user's manual were developed in a public mental health system, (2) the on-line availability of the user's manual with detailed recommendations and documentation forms, and (3) the currency of its recommendations.

If they are to continue to be useful for clinicians, the TMAP algorithms and user's manual must stay current, incorporating important new information in a timely fashion. "Important new information" means not only information about new drugs, but also newer information about drugs already in the algorithm, individually and as a group. There are no established rules to follow in deciding when and how to update guidelines and algorithms. Thus, it becomes a matter of expert consensus that an update is needed. The consensus view that an update is warranted is substantially influenced by accumulation of recent large randomized controlled trials (RCTs) that address clinically important questions. Prior updates of the TMAP schizophrenia algorithm have primarily been prompted by information about newer antipsychotics that need to be placed in the algorithm in light of what we know about them and their characteristics relative to other antipsychotics. Since the TMAP schizophrenia algorithm consensus conference in 2003, however, the most important new information regards effectiveness of drugs already in the algorithm. In particular, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)¹ and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CU-LASS)² trials have raised critical questions about the relative value of newer and older antipsychotics for treatment of chronic schizophrenia. Additionally, several large studies have addressed the issue of clozapine augmentation for persons with treatment-resistant schizophrenia.³⁻⁷

The TMAP initiative has been a collaboration among the Texas Department of State Health Services (formerly the Texas Department of Mental Health and Mental Retardation [TDMHMR]), the medical schools at The University of Texas Southwestern Medical Center at Dallas and The University of Texas Health Science Center at San Antonio, The University of Texas at Austin College of Pharmacy, public mental health providers, consumers, families, and mental health advocates in Texas.

The TMAP schizophrenia algorithm was originally developed in 1996. A consensus panel of academic experts, TDMHMR clinicians, administrators, consumers, family members, and mental health advocates convened to develop guidelines for the treatment of schizophrenia based on the Expert Consensus Guideline Series⁸ and the Patient Outcomes Research Team project.⁹ Using these previous efforts, TMAP investigators wanted to create a very specific and detailed treatment guideline that included quantitative outcome measures and clear directions on

medication management.¹⁰ To achieve this goal, clinical procedure manuals covering most aspects of antipsychotic medication management were also created for this project. The manuals have been updated along with the algorithms.

The TMAP medication algorithms are constructed in stages. Stage 1 is the medication or group of medications most highly recommended for the initial presentation of the illness with subsequent stages to be tried sequentially should response to the previous stage be unacceptable. Clinicians explicitly are given the option of skipping algorithm stages if clinical circumstances warrant.

In previous versions of the TMAP schizophrenia algorithm, stage 1 was labeled as "first episode or no prior treatment with second-generation antipsychotics (SGAs)." With the widespread use of SGAs, however, there are increasing numbers of persons who have never had a first-generation antipsychotic (FGA) trial, so, in this update of the guidelines, we define stage 1 strictly as first-episode cases.

The previous update was published in 2004 (Figure 1).¹¹ At that time, ziprasidone and aripiprazole were added as treatment options in stage 1 of the antipsychotic algorithm. The FGAs were included with SGAs in stage 2A of the algorithm as an alternative for persons with symptoms unresponsive to 2 SGAs before progressing to clozapine treatment, although clozapine was the recommended option after 2 failed trials with SGAs.

The process of deciding on topics for the 2006 conference is described in the Method. The evidence for decisions on these topics and the subsequent recommendations are reviewed in the Results.

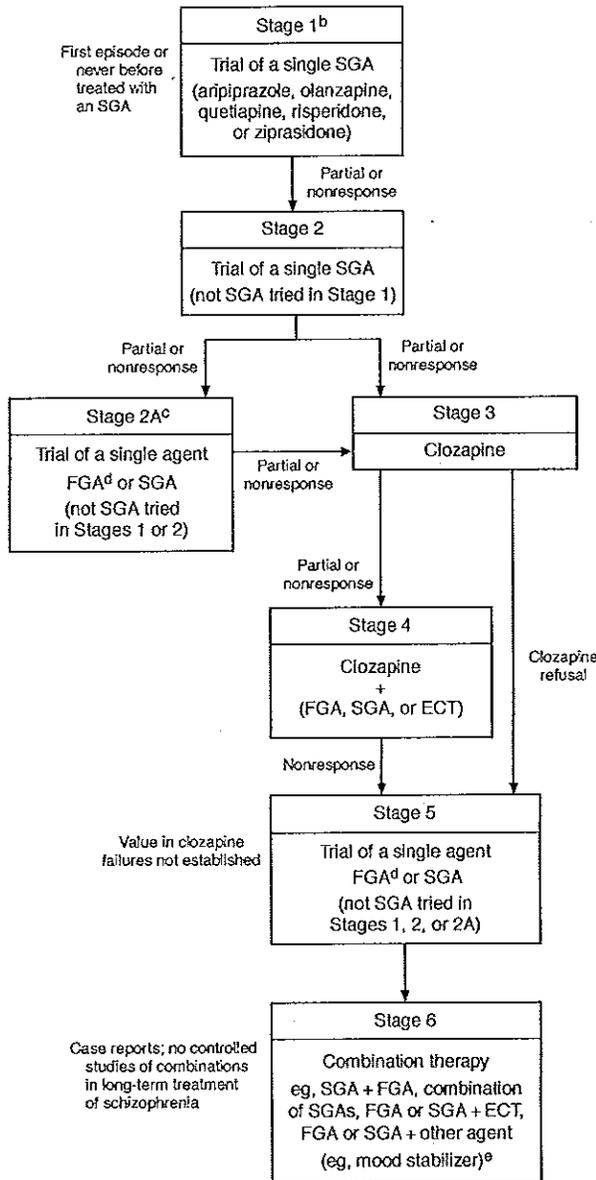
METHOD

In June 2006, the consensus panel, consisting of experts in the pharmacologic treatment of schizophrenia, experienced clinicians, consumers, and consumer advocates, convened in Dallas, Tex., to update the TMAP schizophrenia medication algorithm. In the months preceding the update conference, the expert panel had 3 teleconferences to review the old algorithm, discuss significant new evidence that could influence algorithm revisions, and select specific questions/topics for review at the conference. Four questions were identified. (1) Should antipsychotic treatment of persons with first-episode schizophrenia be different from that of persons with multiepisode schizophrenia? (2) In which algorithm stages should FGAs be an option? (3) How many antipsychotic trials should precede initiation of clozapine? (4) What is the status of augmentation strategies for clozapine? These topics were then assigned to work groups to review the literature prior to the conference, present their findings, and make preliminary recommendations to the full group at the meeting in Dallas. Whenever possible,

Figure 1. TMAP Antipsychotic Algorithm: 2003^a

Choice of antipsychotic should be guided by considering the clinical characteristic of the patient and the efficacy and side-effect profiles of the medication

Forward stage(s) can be skipped depending on the clinical picture or history of antipsychotic failures, and returning to an earlier stage may be justified by history of past response



^aReprinted with permission from the Texas Department of State Health Services.

^bIf patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.

^cCurrent expert opinion favors choice of clozapine.

^dAssuming no history of failure on FGA.

^eWhenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving psychotic symptoms, the patient is considered to be in Stage 6.

Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TMAP = Texas Medication Algorithm Project.

the consensus panel members based their decisions on empirical evidence, but when inadequate evidence was available, panelists could draw on expert opinion and clinical judgment with the goal of reaching consensus. "Group consensus" on a recommendation means that the full panel agreed on a recommendation, and the evidence underlying this consensus view is presented. In the single instance in which group consensus was not reached, the recommendation endorsed by the majority is presented, and the evidence for both the majority and minority views is presented.

RESULTS

Should Antipsychotic Treatment of Persons With First-Episode Schizophrenia Be Different From That of Persons With Multiepisode Schizophrenia?

Recommendation 1. Recommended treatment of first-episode schizophrenia differs from that of multiepisode illness in that effective antipsychotic dose ranges are lower, individuals are more sensitive to metabolic and extrapyramidal side effects (EPS), and there is greater likelihood of achieving a symptom-free response (group consensus). The SGAs are preferred for treatment of first-episode schizophrenia (majority opinion).

Previous recommendation. Group consensus stated that first-episode schizophrenia should be treated with an SGA, and no stage-specific recommendations about dosing or side effects were made.

Current evidence review. Overall, the evidence available regarding antipsychotic treatment specific to first-episode schizophrenia, in comparison with that for multi-episode schizophrenia, is limited.

However, the available data suggest that persons with first-episode schizophrenia respond differently than persons with multiepisode schizophrenia to antipsychotic treatment. A number of studies have found that the average efficacious antipsychotic dose for the treatment of first-episode schizophrenia is often about half the average dose needed to treat chronic schizophrenia.¹²⁻¹⁷ The single exception may be quetiapine.¹⁸⁻²⁰ It should be noted that dosing of aripiprazole and ziprasidone has not been systematically studied in first-episode schizophrenia. In addition, the short-term positive symptom response rates found in first-episode studies are high in comparison with those typically found in persons with multiepisode schizophrenia. The high response rates are notable given that first-episode studies often use more stringent response criteria than studies of multiepisode illness. However, first-episode persons also may be more sensitive to the adverse effects of antipsychotics. Persons with first-episode schizophrenia have been noted to be particularly sensitive to metabolic changes, weight gain, and EPS.¹⁵⁻¹⁸

Recent studies of FGAs and SGAs in persons with chronic schizophrenia, discussed in detail in the subse-

quent section, have failed to show overall advantages for SGAs compared with selected FGAs. Very few studies have compared multiple SGAs to FGAs. Moreover, all subjects in the CATIE study and most in CUtLASS were diagnosed with chronic schizophrenia, which precludes direct extrapolation of the results of these studies to the treatment of first-episode schizophrenia. Thus, the expert panel had limited empirical data on which to base any potential revision of this algorithm.

The expert panel was sharply divided on the extent of reliance on these studies in deciding whether FGAs should be a recommended option in stage 1 of the revised algorithm. A complicating factor is that the effects of the medications within each class, either FGA or SGA, vary. The limited number of antipsychotics studied in first-episode schizophrenia may not be representative of the range of effects of the medications within each class. The FGAs studied in first-episode schizophrenia have been mostly limited to high-potency agents (haloperidol and fluphenazine). The SGAs studied include clozapine, risperidone, olanzapine, and quetiapine. In persons with multi-episode schizophrenia, SGAs vary in the degree to which they produce metabolic side effects. The SGAs with lower metabolic side-effect risk in multi-episode schizophrenia (ziprasidone and aripiprazole) have not been studied yet in first-episode schizophrenia.

A majority of the panel favored recommending only SGAs, but a significant minority thought FGAs should be included. The arguments and data on either side of this question, arranged by clinical topic, are presented next.

Efficacy. Large sample size, randomized, controlled comparisons of SGAs with FGAs for first-episode schizophrenia have included trials of (1) clozapine versus chlorpromazine,¹² (2) olanzapine versus haloperidol,¹⁵ and (3) risperidone versus haloperidol.^{14,16} In these studies, rates of short-term response were higher than those typically found in chronic schizophrenia but did not differ significantly between SGAs and FGAs. Two studies directly comparing SGAs also found no differences in initial responses between agents.^{17,18} Medication doses in first-episode trials have often been lower than those used in trials with multi-episode schizophrenia. The dosing for quetiapine may differ from this pattern. In the first-episode study, Comparison of Atypicals in First Episode (CAFE),¹⁸ following double-blind dose adjustment, the mean modal daily dose for olanzapine (11.7 mg) and risperidone (2.4 mg) was low, but the dose used for quetiapine (506 mg) was quite similar to the quetiapine dose used in the CATIE study of chronic schizophrenia.¹

Two studies sponsored by pharmaceutical companies have found potential advantages for SGAs over FGAs for maintenance treatment, although they did not find short-term efficacy differences. In a study of time to relapse of first-episode persons initially responding to risperidone or haloperidol, Schooler et al.¹⁶ reported a longer mean time

to relapse with risperidone compared with haloperidol (466 days vs. 205 days). In a secondary analysis, Green et al.²¹ found a longer mean time to treatment discontinuation with olanzapine compared with haloperidol (322 days vs. 230 days). More information about FGAs and SGAs for first-episode schizophrenia will be available with the completion of a pragmatic trial of first-episode schizophrenia currently underway in Europe that compares olanzapine, amisulpride, ziprasidone, quetiapine, and low-dose haloperidol.²²

Tardive dyskinesia (TD). Data specific to first-episode schizophrenia confirm that persons with schizophrenia can develop TD during the first years of treatment. Some first-episode studies suggest that persons with first-episode schizophrenia are at similar risk as multi-episode persons for developing TD. Chakos et al.²³ found a 6.3% incidence of TD at 1 year and an 11.5% incidence at 2 years using high daily doses of fluphenazine and haloperidol for treatment of first-episode schizophrenia. Oosthuizen and colleagues²⁴ found the 12-month incidence of probable or persistent TD according to the Schooler and Kane criteria was 12.3% among 57 subjects treated with low-dose haloperidol (mean dose of 1.68 mg/day).

The panel was divided regarding 3 key questions about TD relevant to treatment of first-episode schizophrenia. These questions can be summarized as follows. (1) Are there differences in TD incidence between FGAs and SGAs? (2) With careful monitoring, can most cases of TD be detected while still very mild and their progression stopped or even reversed by switching from the causative agent? (3) How do the risks of TD and its effect on quality of life balance against other side effects that are associated with use of some SGAs, such as the metabolic syndrome and its sequelae?

Data comparing TD incidence between FGAs and SGAs with first-episode patients are sparse. Schooler and colleagues¹⁶ reported no differences in TD incidence between risperidone and low-dose haloperidol, but Green and colleagues²¹ reported higher scores on the Abnormal Involuntary Movement Scale for low-dose haloperidol than olanzapine at weeks 24, 52, and 104. Given the few first-episode studies, the panel considered data on TD incidence with multi-episode patients. A recent meta-analysis of studies with multi-episode patients concluded that the risk of TD with SGAs is about 1% per year with SGAs and 5% with FGAs.²⁵ Some panel members questioned whether the latter figure, however, may be influenced by use of high doses of high-potency FGAs and if the difference in TD incidence might be lower in a comparison between SGAs and moderate doses of midpotency FGAs, such as perphenazine. In spite of agreement that there may be considerable variations within the SGA and FGA groups of drugs, the panel remained divided. A majority, however, concluded that available data support the

conclusion that clinically important differences in rates of TD exist between SGAs and FGAs. More definitive data are needed to resolve the relative risk among the non-high-potency FGAs and SGAs.

The fact that TD can be reversible is unquestionable. Less clear from existing data (available with multiepisode patients) is whether careful monitoring detects most cases before they become irreversible, allowing for timely switching to an agent putatively less likely to cause TD.^{16,26-29} Many clinicians would be more sanguine about use of selected FGAs at low doses in first-episode schizophrenia if they were confident that early detection would be routine practice and that switching could reverse mild TD.

Tardive dyskinesia and metabolic side effects are sometimes juxtaposed as though clinician and consumer must choose between them in selecting an antipsychotic. In reality, risks differ across agents, and no agent inevitably causes TD or major metabolic side effects in all persons. Thus, the "lesser of 2 evils" argument in antipsychotic selection for first-episode schizophrenia does not take into account the very different side-effect profiles of each SGA or even the differences among the FGAs. However, there is a dearth of data on treatment of first-episode schizophrenia with ziprasidone or aripiprazole, the 2 SGAs least likely to cause metabolic side effects.

Acute EPS. Each of the first-episode SGA versus FGA studies cited in the efficacy section above found more EPS with the FGA comparator than with the SGA comparator. In the Schooler et al. study,¹⁶ this EPS difference occurred even when comparing low-dose haloperidol (mean modal dose of 2.9 mg/day) with risperidone (mean modal dose of 3.3 mg/day). Extrapyramidal side effects occur in first-episode schizophrenia, even with the SGAs, at a clinically meaningful frequency. Lieberman et al.¹⁵ reported a 26% rate of parkinsonism with olanzapine treatment, and Robinson and colleagues,¹⁷ using a different definition of parkinsonism, found a rate of 9% with olanzapine and 16% with risperidone. The panel was divided about whether the EPS advantages for SGAs over FGAs generalize to treatment with a midpotency FGA such as perphenazine in low-to-moderate doses. In the CATIE study, the perphenazine group had more EPS discontinuations, although EPS ratings of this group did not differ from the SGA comparators.¹ Extrapyramidal side effects are potentially disturbing, and even mild levels of EPS are associated with medication nonadherence by persons with first-episode schizophrenia.³⁰

Metabolic side effects. In 3 large first-episode FGA/SGA comparison studies that reported weight data, subjects gained less weight with FGAs. After 12 weeks of treatment, Lieberman and colleagues¹⁵ found that 61% of their olanzapine-treated subjects gained more than 7% of baseline weight as compared with 23% of the haloperidol-treated subjects. In contrast, the FGA/SGA weight

gain differences were considerably less in the clozapine versus chlorpromazine and risperidone versus haloperidol studies.^{12,16} First-episode studies comparing SGAs have also reported substantial weight gain with SGA treatment.^{17,18} Weight gain after 12 weeks of treatment in the CAFE trial by medication were olanzapine, 16 lb; quetiapine, 8 lb; and risperidone, 9 lb.¹⁸ As noted above, first-episode data for aripiprazole and ziprasidone are lacking.

Discussion. The expert panel did not reach consensus on whether to include FGAs as a recommended option for first-episode schizophrenia. As noted above, the comparative studies generally used haloperidol, a high-potency FGA (albeit at low doses) and not midpotency FGAs. The majority thought that the data on TD, sensitivity to EPS, and possible longer-term effectiveness advantages warranted a preference for SGAs over FGAs for first-episode schizophrenia at this time. It should be noted that there was considerable concern expressed by consumer and some clinician members of the panel that inclusion of FGAs might be used as a basis for a policy that would require initial use of an FGA before any SGA solely because of lower drug costs. The expert panel concurred that choice of antipsychotic is a decision to be individualized on clinical grounds and that a policy favoring any single agent would not be justified by the evidence.

Given concerns about the long-term effects of early weight gain, one might argue that the SGAs least likely to produce weight gain should be used in preference to those with greater weight-gain potential. Against this approach, however, is (1) the lack of comparative first-episode data with aripiprazole and ziprasidone and (2) the need to individualize treatment. Thus, while the panel agreed that weight-gain potential is a very important consideration in antipsychotic selection for first-episode treatment, there may be instances in which this is not the preeminent issue. The panel considered that careful monitoring of all side effects and making indicated changes in dose or medication in a timely fashion were preferable to a blanket recommendation of some SGAs over others.

In Which Algorithm Stages Should FGAs Be an Option?

Recommendation 2. First-generation antipsychotics are an option in stage 2 of the antipsychotic algorithm after a trial of 1 SGA and in all subsequent stages that include SGAs as a group (group consensus).

Previous recommendation. Monotherapy with first-generation antipsychotics was an option in stage 2A, after trials of 2 SGAs, and in stage 5.

Current evidence review. Since the 2003 TMAP algorithm update, a number of meta-analyses and reviews of antipsychotic effectiveness have been published. In addition, several major RCTs have been completed.

The meta-analyses incorporate studies done almost exclusively prior to the last update and arrive at a range of

sometimes conflicting conclusions with regard to FGA/SGA differences: (1) efficacy is superior for some or all SGAs,³¹⁻³⁶ (2) efficacy is not superior for any SGAs except clozapine,^{9,37-41} and (3) EPS occur less often with SGAs, but this depends somewhat on which FGAs were studied and at what doses.^{31,33,36-41} By definition, these meta-analyses and reviews are limited to published comparison trials, which are dominated by registration trials intended to achieve regulatory approval for individual SGAs. Moreover, most of the trials used haloperidol as a comparator, often in doses that were high by today's standards. Selection of haloperidol as a comparator and choices of doses used are understandable in terms of community practices at the time the studies were designed, but the question of the advantages of the SGAs compared with more modest doses of FGAs, especially midpotency FGAs, has not been well addressed. Thus, the more recent RCTs noted below strongly influenced the panel's deliberations.

The CATIE phase 1 study found an advantage for olanzapine on the primary outcome, discontinuation of treatment for any cause, compared with quetiapine and risperidone but not compared with perphenazine or ziprasidone.¹ Olanzapine had fewer discontinuations due to lack of efficacy compared with perphenazine, risperidone, and quetiapine. Perphenazine, a moderate-potency FGA, was not statistically different from quetiapine, risperidone, and ziprasidone in all-cause discontinuation, efficacy, or tolerability discontinuations. Perphenazine was not significantly different from olanzapine in tolerability discontinuations. There were no differences between any of the antipsychotics on EPS or akathisia rating scales. Olanzapine had more discontinuations due to metabolic/weight side effects. Perphenazine had more EPS-related discontinuations compared with the SGAs. There were no differences in neurocognitive functioning between the drugs at the primary endpoint of 6 months.⁴² Perphenazine was no less effective than any of the newer drugs on measures of quality of life.⁴³ Perphenazine was associated with lower costs than the newer drugs,¹ all of which were still under patent protection at the time of the study.

Phase 1 of CULASS, which was conducted in the United Kingdom, did not find SGAs as a group to be better than FGAs on quality of life (primary outcome) and other secondary scales.² Mean total costs were similar between the FGAs and SGAs, in spite of higher drug acquisition costs for the SGAs, because most of the costs in the study were associated with inpatient care. Forty-nine percent of the persons assigned to an FGA received sulpiride, an agent that is not available in the United States. As a result, the findings from this study are not fully applicable to psychiatric practice in the United States. It should also be noted that the CULASS study allowed clinician-determined antipsychotic switches, including between SGAs and FGAs, potentially blurring the comparison between classes.

A study conducted in the Veterans Administration that compared olanzapine and haloperidol (plus prophylactic benztropine) showed no difference in retention rates, symptom improvement, or quality of life between the 2 agents.⁴⁴ Persons taking olanzapine did have significantly less akathisia than those taking combined haloperidol and benztropine. Olanzapine did have a small advantage on some of the neuropsychiatric subscales used in the study.

A Finnish observational study by Tiihonen et al.⁴⁵ found that FGAs and SGAs varied in terms of effectiveness and adherence in community-based populations. Initial use of clozapine, olanzapine, and depot perphenazine was associated with lower rates of discontinuation for any reason versus oral haloperidol. Current use of clozapine, olanzapine, and depot perphenazine was associated with lower risk of rehospitalization.⁴⁵

Discussion. The CATIE and CULASS trials particularly bring into question the superiority of the SGAs over FGAs in tolerability, side effects, and reduction of negative symptoms in treating persons with chronic schizophrenia. Each of these studies has been criticized on methodological grounds,⁴⁶⁻⁵¹ and there is considerable debate in the field as to how much they should influence clinical practice. While recognizing the merit of some criticisms of these studies, the panel concluded that the criticisms do not invalidate the results. It is therefore appropriate to incorporate the findings of these studies into recommendations about clinical practice.

Relative risks of long-term outcomes such as TD, sequelae of the metabolic syndrome, and risk of premature death remain to be adequately defined with the SGAs and FGAs. Providers need more and better comparative data on these long-term risks, as well as better information on which to base matching of consumer characteristics with antipsychotic properties.

The consumers and advocates stressed strongly the need for collaborative decision making between consumer and prescriber, with a focus on differential risks of TD and on the disfigurement and social stigma that can result from having TD. The panel emphasized the importance of avoiding use of FGAs at high doses and in persons at high risk for TD (e.g., elderly, persons with a history of EPS, persons with traumatic brain injuries). Additionally, the panel expressed considerable clinical concern about "fail-first" policies in which trials of relatively inexpensive antipsychotics would be required before trials of more expensive agents.

The panel recognized that, given expectations of roughly comparable efficacy, the decision regarding which antipsychotic to select for an individual should be driven by differences in the side-effect profiles of the medications under consideration and by which antipsychotic is more or less tolerable for the person in question. The corollary of this approach to medication selection is the need for monitoring side effects after initiation of each

new medication, preferably using validated scales and measures.

How Many Antipsychotic Trials Should Precede Initiation of Clozapine?

Recommendation 3. Two clear antipsychotic trial failures warrant initiation of clozapine, and long delays in clozapine treatment should be avoided. Moreover, persistent symptoms of suicidality or violence or a comorbid substance abuse disorder should prompt earlier institution of clozapine treatment (group consensus).

Previous recommendation. Two to 3 antipsychotic trials should be tried before initiating clozapine.

Current evidence review. Data obtained in 1999 from Novartis (manufacturer of clozapine) estimated that 160,000 persons with schizophrenia spectrum disorders had received a trial of clozapine in the United States. If an estimated 20% to 30% of the 2.6 million persons with schizophrenia in the United States at that time were treatment resistant (25%, N = 650,000); then only 25% of the persons with treatment-resistant schizophrenia had ever received clozapine, which is indicated in treatment-resistant schizophrenia.⁵²

Since the 2003 schizophrenia update, there have been few new studies evaluating clozapine efficacy. The CATIE trial compared clozapine with other SGAs in phase 2. Persons experiencing efficacy failure while taking their initial study SGA had a longer median time to discontinuation of clozapine compared with quetiapine, risperidone, and olanzapine (10.5 months vs. 2.7–3.3 months).⁵³

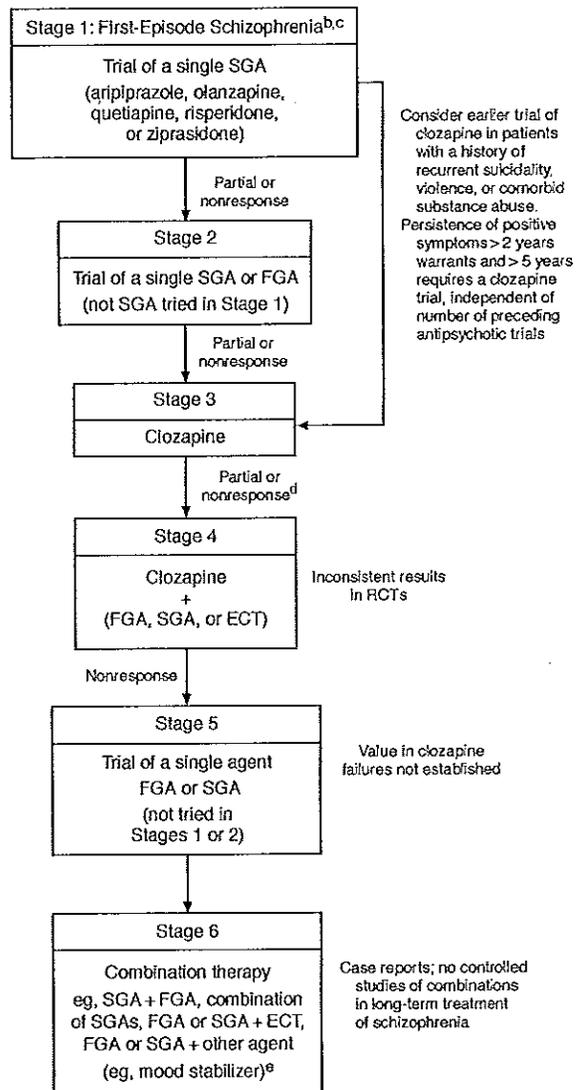
Clozapine has also shown benefits for persons with a history of suicidality,^{54,55} violence,^{56–58} or a comorbid substance abuse disorder.⁵⁹

Discussion. The panel noted that dissemination of the TMAP algorithm does not seem to have increased clozapine use, even though progression to clozapine is explicitly encouraged in the procedures manual. This apparent reluctance to use clozapine is in accord with phase 2 results of CATIE, in which many participants did not enter the efficacy pathway (phase 2E) in favor of entering the tolerability pathway (phase 2T), perhaps to avoid being randomly assigned to clozapine treatment (clozapine was an option in phase 2E but not in phase 2T). In light of the evidence from CATIE confirming clozapine's unique effectiveness,^{60–62} the panel agreed that the algorithm diagram should include a strong statement advocating clozapine use for individuals with treatment-refractory symptoms (Figure 2). The panel recognized that there are processes of coming to accept the diagnosis and the need for medication treatment that often must occur when a person is first diagnosed with schizophrenia and that these processes can take time and can interfere with undertaking consistent treatment. Apparent failure of medications during this period is often due to erratic adherence, and

Figure 2. TMAP Antipsychotic Algorithm: 2006^a

Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side-effect profiles of the medication

Forward stage(s) can be skipped depending on the clinical picture or history of antipsychotic failures, and returning to an earlier stage may be justified by history of past response



^aReprinted with permission from the Texas Department of State Health Services.

^bFirst-episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side effects. Lack of consensus on inclusion of FGAs as option for first episode.

^cIf patient is inadequately adherent at any stage, the clinician should assess contributing factors and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.

^dA treatment-refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Cognitive-behavioral therapy and other psychosocial augmentations should be considered.

^eWhenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving psychotic symptoms, the patient is considered to be in Stage 6.

Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TMAP = Texas Medication Algorithm Project.

clinicians may want to consider use of a long-acting injectable antipsychotic. The panel noted that most persons are started on clozapine after many years of illness and concluded that clinicians should strongly consider clozapine use earlier in the course of illness. A consensus was reached on the recommendations that a person with persistent positive symptoms during 2 years of consistent medication treatment should be considered for clozapine therapy, and 5 years of inadequate response should mandate offering a trial of clozapine, independent of the number of previous antipsychotic trials.

The panel also noted that formation of clozapine clinics, while improving efficiency and logistics of clozapine treatment in the short run, may have had the unintended consequence of limiting the number of providers who are comfortable with and proficient at prescribing clozapine, thereby reducing training opportunities for residents. While noting that clozapine should not be reserved only for specialty practice or clinics (e.g., a referral for ECT), the panel also acknowledged that clinicians with limited exposure to clozapine do need to be provided with administrative and clinical support to gain expertise in clozapine therapy.

The choice of moving on to clozapine treatment is often complex. No universally accepted definition of treatment-resistant schizophrenia exists.⁶³ The classic clozapine study in treatment-resistant schizophrenia by Kane et al.⁶⁴ defined treatment resistance as failure with at least 2 FGAs from 2 different chemical classes, but this definition has not been systematically reassessed since the availability of multiple SGAs. For purposes of defining an adequate antipsychotic trial, at least 4 weeks of taking full therapeutic doses of the antipsychotic was recommended at the Mt. Sinai conference on use of antipsychotics in schizophrenia.⁶⁵

What Is the Status of Augmentation Strategies for Clozapine?

Recommendation 4. Clozapine augmentation should be with an SGA, an FGA, or ECT at stage 4 preceded by a "treatment-refractory" evaluation (group consensus).

Previous recommendation. Augmentation of clozapine with an SGA, an FGA, or ECT at stage 4.

Current evidence review. Since the 2003 update, there have been a number of RCTs with risperidone, lamotrigine, or sulpiride augmentation of clozapine.

Four randomized, double-blind, placebo-controlled trials of risperidone augmentation of clozapine have been published.³⁻⁶ In each of the 4 studies, all participants improved significantly over time, particularly during weeks 2 to 6 (regardless of treatment). Three of 4 trials found no advantage of risperidone versus placebo augmentation of clozapine in subjects with a history of partial or poor response to clozapine monotherapy. Thus, the evidence favoring risperidone augmentation is weak.

One published randomized, double-blind, placebo-controlled, 14-week, crossover trial of 34 inpatients examined lamotrigine augmentation of clozapine.⁷ Clozapine plasma concentrations did not change significantly with the addition of either lamotrigine or placebo. Lamotrigine added to clozapine was superior to placebo added to clozapine for positive and general symptoms in persons with schizophrenia inadequately responsive to clozapine alone, but the mean changes in symptoms were fairly small.

In 2 as yet unpublished studies of antipsychotic augmentation with lamotrigine performed by GlaxoSmithKline, a total of 419 persons with schizophrenia and persistent residual symptoms were enrolled. Results can be viewed on the company's Web site.^{66,67} Sixty-four subjects (15%) were taking clozapine in the 2 double-blind, placebo-controlled, 12-week trials. Participants were given 100 to 400 mg of lamotrigine gradually added to ongoing antipsychotic treatment. Changes from baseline in the Positive and Negative Symptom Scale (PANSS) total score were similar with added lamotrigine or placebo in both studies. No statistically significant improvement in positive, negative, or general subscales was observed for lamotrigine compared with placebo in either study for the entire study group.

A recent review of cognitive behavioral therapy (CBT) in schizophrenia by Turkington and colleagues⁶⁸ concludes that although more RCTs of CBT need to be performed in the area of schizophrenia, the evidence to date supports adjunctive use of CBT with antipsychotic medication for persistent psychotic symptoms. This is an available "augmenting" intervention for persons taking clozapine with persistent psychotic symptoms.

Use of adjunctive ECT with clozapine was reviewed at the last update.¹¹ Case series indicate positive effects, but no RCTs have been published.

Discussion. The evidence from randomized trials is mixed with regard to risperidone and lamotrigine augmentation of clozapine. On the other hand, there are no RCTs that have tested other agents for persons responding inadequately to clozapine, and a good deal of clinical experience suggests that persons not doing well on clozapine become worse when they discontinue the medication. Therefore, the panel elected to keep augmentation of clozapine as an option before trying another antipsychotic. Even though there are negative data for risperidone and lamotrigine as clozapine-augmenting agents, it could be quite incorrect to single them out as ineffective since results for agents other than sulpiride are not based on RCTs.

The panel did support the addition of a statement encouraging a "treatment-refractory evaluation" (including clozapine serum concentrations) before considering clozapine augmentation. "A treatment-refractory evaluation should be performed to re-examine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Cognitive-behavioral therapy and/or other psy-

chosocial interventions should be considered." The expert panel emphasized that not all psychosocial interventions are equal and that any therapeutic intervention should be carefully chosen on the basis of best available evidence.

In addition, the mixed results of clozapine augmentation strategies serve to emphasize the need to optimize clozapine treatment. Attention to side effects and vigorous treatment of them when troublesome to the consumer or when medically problematic is critically important. Several studies have found that clozapine serum concentrations can be useful to help guide dosing.⁶⁹⁻⁷²

A fifth panel recommendation preceded the consensus conference and was arrived at in a series of teleconferences of the academic panel members in late 2005. The recommendation was reviewed and ratified at the 2006 conference. Because this recommendation has not been previously published, it is included here.

Recommendation 5. Long-acting injectable risperidone should be added to haloperidol decanoate and fluphenazine decanoate as options for treatment of persons with medication adherence problems (group consensus).

Previous recommendation. Long-acting injectable risperidone was not available at the time of the 2003 update.

Current evidence review. Studies varying in length from 12 weeks to 12 months have shown that long-acting injectable risperidone significantly reduces symptomatology in doses from 25 to 75 mg given once every 2 weeks.⁷³⁻⁷⁵ Subgroup analyses examining open-label switching from oral risperidone to long-acting injectable and switching from FGA long-acting injectables to long-acting risperidone injectable showed further reduction in total PANSS scores.^{76,77}

A double-blind, randomized trial evaluated time to relapse comparing 25- and 50-mg doses of long-acting injectable risperidone. The projected time to relapse was 161.8 weeks for the 25-mg dose and 259.0 weeks for the 50-mg dose. The 1-year incidence of relapse was 21.6% (N = 35) and 14.9% (N = 24) for the 25- and 50-mg doses, respectively.⁷⁸

Discussion. Safety and efficacy data support long-acting injectable risperidone's addition to the algorithm, but a lack of studies comparing the drug with other oral antipsychotics and other long-acting injectables makes it difficult for providers to assess the utility of long-acting risperidone injectable relative to other options. The requirement for extended use of an oral antipsychotic while awaiting release of risperidone from microspheres presents challenges for brief inpatient stays and persons with problematic outpatient adherence to oral medications. Further studies of long-acting injectable risperidone are underway and should shed light on this preparation's role in the treatment armamentarium.

DISCUSSION

The revised TMAP recommendations represent the panel's assessment of the best available evidence on key clinical questions influencing antipsychotic prescribing for people with schizophrenia. Recent large-scale studies have added significantly to the evidence base, yet the number of recommendations that are based primarily on consensus rather than on randomized, blinded, placebo-controlled evidence is still distressingly high. In part, this is because many of the most critical questions in treatment of any chronic illness require studies that last for years. Such studies are expensive, very difficult to design and carry out, and provide few short-term rewards to sponsors or investigators and will only occur if there is a commitment to them on the basis of their national public importance.

Controlled trials of all the agents being used for first-episode schizophrenia are badly needed, as are longer-term studies of medication effects on long-term course of illness after onset. Further studies that build on CATIE and CUtLASS in addressing selection of antipsychotics on the basis of individual consumer characteristics and history could be extraordinarily helpful in identifying rational sequences of medications for individuals. The role of long-acting injectable antipsychotics in the current era needs much greater clarity. Clinicians still have no evidence-based choices for persons who do not respond adequately to clozapine. Moreover, given that clozapine showed no real advantages over chlorpromazine for first-episode psychosis,⁴⁵ greater understanding of when in the course of illness the unique characteristics of clozapine become essential for "treatment resistance" is badly needed.

On the basis of the limited data available and the lack of long-term data addressing FGAs versus SGAs, the group raised the following clinical questions that should be addressed by future research. Has the frequent use of relatively high doses of haloperidol as active comparator thrown us off the track in evaluating relative EPS/TD risks of newer antipsychotics? Is the FGA versus SGA distinction regarding EPS/TD less pronounced with low-to-moderate doses of midpotency FGAs? The group concurred that head-to-head trials incorporating FGAs other than haloperidol (using low-to-moderate dosing), trials examining consumer antipsychotic preferences and corresponding adherence differences, and more in-depth trials examining differences in negative symptoms would help clarify the utility of any FGA/SGA distinction.

The panel noted with dismay that clozapine use seems to be decreasing, even while the evidence base for it is growing. Since the most widely disseminated guidelines and algorithms, including TMAP, point clinicians to clozapine for treatment resistance, the explanation for this phenomenon is not that the field is in doubt about the

recommendation. Rather, the problem seems to lie with implementation at all levels—state, region, clinic, and practitioner. Research to identify and eliminate the barriers to clozapine use and to ameliorate clozapine's side effects, especially in the metabolic arena, should be a national health priority.

Lastly, the panel discussed some methodological issues that pertain to improving the evidence base that underlies treatment guidelines and algorithms. First, feasibility and ethical and ecological validity considerations each affect the degree to which important clinical treatment questions are amenable to being answered by results of RCTs. A greater effort is needed to achieve expert clinical consensus on defining the key questions and the alternate research strategies for addressing those questions not amenable to RCTs. Second, to the extent that results of studies have vital public policy implications, it becomes absolutely essential that the scientific justification for generalizing from the study population to the population with the disorder be as strong as possible. Historically, RCTs in schizophrenia have enrolled tightly defined populations using inclusion and exclusion criteria such as absence of substance abuse that clearly limit generalizability. Pragmatic studies such as CATIE have sought to enroll subjects who are representative of the entire treatment population, but persons who elect to participate in any studies may be different from those who do not and thus can result in some uncertainty about generalizability of results. Efforts to design and carry out large pragmatic trials that address key clinical questions are critically important and deserving of public support.

Clearly, this version of the algorithm is far from the last word on pharmacologic treatment for schizophrenia. Important questions currently under investigation include the role of augmenting strategies for treatment of negative symptoms, comparative studies of antipsychotic medications in first-episode schizophrenia, comparisons of risperidone microspheres to oral antipsychotic medications, and the role of ECT as an augmenting treatment for persons with schizophrenia refractory to clozapine treatment. Further, new antipsychotic medications are under development, some with novel mechanisms of action. Future updates will be developed as sufficient new data accumulate to warrant revisions.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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A Randomized, Double-Blind, Placebo-Controlled Trial of Aripiprazole Lauroxil in Acute Exacerbation of Schizophrenia

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ABSTRACT

Objective: This study evaluated the efficacy, safety, and tolerability of aripiprazole lauroxil, a novel long-acting injectable atypical antipsychotic, for the treatment of schizophrenia.

Method: An international multicenter, randomized, double-blind, placebo-controlled trial was conducted between December 2011 and March 2014. Patients (N=623) aged 18 to 70 years with schizophrenia (*DSM-IV-TR* criteria), experiencing an acute exacerbation, were randomized in a 1:1:1 ratio to receive gluteal intramuscular injection of aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or matching placebo once monthly for 12 weeks. The primary efficacy outcome was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to day 85. The Clinical Global Impressions-Improvement scale (CGI-I) score at day 85 was the secondary efficacy outcome. Safety and tolerability were assessed.

Results: The PANSS total score (mean \pm standard error [SE]) improved significantly from baseline to day 85 in the aripiprazole lauroxil 441 mg and 882 mg groups, with placebo-adjusted differences of -10.9 ± 1.8 ($P < .001$) and -11.9 ± 1.8 ($P < .001$), respectively. Significant ($P \leq .004$) improvements in both active treatment groups were demonstrated as early as day 8 and continued throughout the treatment period. The proportion of patients who were very much or much improved on the CGI-I was significantly greater with aripiprazole lauroxil 441 mg and 882 mg treatment versus placebo ($P < .001$). The most common treatment-emergent adverse events were insomnia, akathisia, headache, and anxiety. The incidence of injection site reactions was low, predominantly described as injection site pain, and was associated with the first injection.

Conclusions: Aripiprazole lauroxil demonstrated robust efficacy for treatment of patients experiencing acute exacerbation of schizophrenia. The improvement in psychotic symptoms was statistically significant and clinically meaningful. Symptom improvement occurred rapidly after initiation of aripiprazole lauroxil treatment and was maintained throughout the study. Both aripiprazole lauroxil 441 mg and 882 mg doses were well tolerated. These results support aripiprazole lauroxil as an important new treatment option for schizophrenia.

Trial Registration: ClinicalTrials.gov identifier: NCT01469039; Clinicaltrialsregister.eu identifier: 2012-003445-15

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Despite the availability of effective medications for the treatment of schizophrenia, approximately 80% of patients relapse within 5 years. Poor adherence has been associated with relapse and worsening of long-term functional and mental outcomes¹ and is the most common cause of relapse.²⁻⁵ Long-acting injectable (LAI) atypical antipsychotics are an important treatment option for schizophrenia, with demonstrated efficacy in reducing the severity of both positive and negative symptoms. Long-acting antipsychotic formulations were developed to promote greater treatment adherence and improved pharmacokinetics.⁶ Results from clinical trials have shown comparable or greater efficacy with LAIs than their oral equivalents, and medication adherence consistently improves when patients have switched from an oral to a LAI regimen.^{7,8} In addition, the sustained dosing and the ability of physicians and caregivers to monitor the regularity and frequency of LAI administration have demonstrated a beneficial impact on patient outcomes.⁸ Although LAI formulations of some atypical antipsychotics are available, new formulations offer the potential to provide flexibility for patients and providers in terms of dose and dosing interval, differentiated pharmacokinetic profile and tolerability, and ease of administration.

Aripiprazole lauroxil is a novel LAI atypical antipsychotic currently in development for the treatment of schizophrenia. The proprietary technology (LinkeRx) utilized to develop aripiprazole lauroxil allows for controlled release after injection and extends exposure to the active molecule.⁹ The technology, combined with aripiprazole lauroxil's unique formulation, allows for multiple dose strengths and dosing intervals, which provides flexibility to address patient heterogeneity and to allow for individualized patient care. Aripiprazole lauroxil doses studied in the clinical development program were designed to be consistent with the range of oral aripiprazole doses (10 to 30 mg) most often used to treat schizophrenia.

Following injection, the biotransformation of aripiprazole lauroxil involves enzyme-mediated hydrolysis to form N-hydroxymethyl-aripiprazole, which subsequently undergoes water-mediated hydrolysis to aripiprazole. Early clinical development of aripiprazole lauroxil demonstrated aripiprazole plasma concentrations reached maximal levels in 37 to 48 days and persisted for at least 88 days following a single injection. In a study of adults with schizophrenia, repeat dosing of intramuscular gluteal injections of aripiprazole lauroxil 441 mg (300-mg aripiprazole equivalent), 662 mg (450-mg aripiprazole equivalent), and 882 mg (600-mg aripiprazole equivalent) resulted in aripiprazole concentrations within the established therapeutic range and were well tolerated (data on file, Alkermes, Inc; Waltham, Massachusetts). In a subsequent study¹⁰ in patients

with schizophrenia, it was demonstrated that intramuscular injections of aripiprazole lauroxil 441 mg given in the deltoid and gluteal muscles resulted in comparable exposure to aripiprazole and were well tolerated. Therefore, this allows for both deltoid and gluteal intramuscular injection sites to be used interchangeably for administration of the aripiprazole lauroxil 441-mg dose.

The objective of this international, multicenter, randomized, double-blind, placebo-controlled trial was to evaluate the efficacy, safety, and tolerability of once-monthly aripiprazole lauroxil for the treatment of acute exacerbation in patients with schizophrenia.

METHOD

The study was conducted in 7 countries, including the United States, Ukraine, Russia, Bulgaria, Romania, Philippines, and Malaysia, between December 2011 and March 2014 in accordance with the Declaration of Helsinki, 1964, and Good Clinical Practice principles outlined in the International Conference on Harmonization, 1997. The protocol, amendments, and informed consent were approved by an institutional review board or local ethics committee for each site, and written informed consent of all patients was obtained prior to study participation after the nature of the procedures had been fully explained. This study was registered at ClinicalTrials.gov (identifier: NCT01469039) and clinicaltrialsregister.eu (identifier: 2012-003445-15).

Study Design

This was an international, multicenter, randomized, double-blind, placebo-controlled study of aripiprazole lauroxil conducted in adult patients with acute exacerbation of schizophrenia. Patients initially were evaluated at a screening visit up to 10 days prior to randomization. Patients meeting initial screening eligibility criteria were admitted to an inpatient study unit. Currently prescribed antipsychotics were discontinued after screening and prior to administration of study drug. Aripiprazole-naïve patients were given a test dose of oral aripiprazole 5 mg administered daily for 2 days prior to randomization to assess tolerability. Patients who had previously taken and tolerated aripiprazole were not required to undergo the tolerability assessment.

Patient Selection

Eligible patients were 18 to 70 years of age and diagnosed with schizophrenia as defined by *DSM-IV-TR* and confirmed by the Structured Clinical Interview for *DSM-IV* Disorders, Clinical Trials version.¹¹ All patients were currently experiencing an acute exacerbation or relapse with onset of <2 months prior to screening and <2 weeks' duration of hospitalization if inpatient at time of screening. Patients also were required to have experienced a clinically beneficial response to treatment with an antipsychotic medication, have never received clozapine, and have been an outpatient for >3 months during the year prior to enrollment. At screening and baseline, patients were required to have a Positive and

- Long-acting injectable (LAI) antipsychotics represent an important option for treating schizophrenia, with a significant body of evidence suggesting that LAIs improve adherence markedly, thereby resulting in better outcomes.
- Aripiprazole lauroxil demonstrated robust efficacy with clinically meaningful improvements in schizophrenia symptoms that were demonstrated early in treatment and persisted throughout the study.
- Aripiprazole lauroxil was well tolerated, with a safety profile similar to oral aripiprazole.

Clinical Points

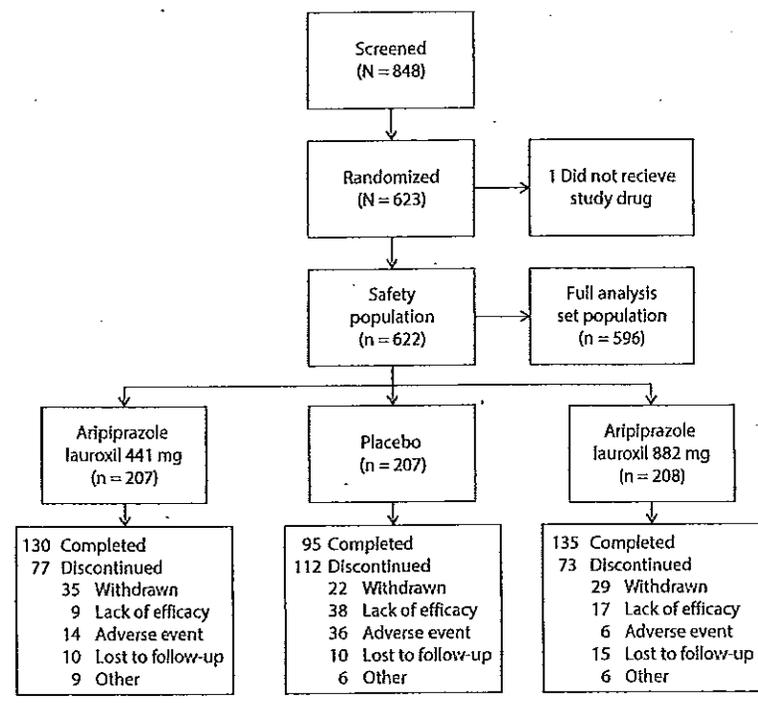
Negative Syndrome Scale (PANSS)¹² total score of 70 to 120 and a score of ≥ 4 for ≥ 2 of the selected positive scale items (item 1: delusions; item 2: conceptual disorganization; item 3: hallucinatory behavior; item 6: suspiciousness/persecution). Patients were also required to have a Clinical Global Impressions-Severity of Illness scale (CGI-S)¹³ score of ≥ 4 (range, 1 = normal [not at all ill] to 7 = among the most extremely ill patients).

Key exclusion criteria included comorbid schizoaffective disorder, bipolar disorder, major depressive disorder, dementia, delirium, amnesic or any other cognitive disorder currently or within the past 2 years, any clinically significant medical illness or laboratory abnormality, prior inadequate response to oral aripiprazole (unless poor adherence was a contributing factor), LAI antipsychotic treatment within 60 days of screening, diagnosis of substance dependence within 6 months or substance abuse within 3 months of screening, or women who were pregnant, lactating, or breastfeeding.

Study Treatments

Eligible patients were randomized 1:1:1 in a double-blind fashion to aripiprazole lauroxil 441 mg (300-mg aripiprazole equivalent), aripiprazole lauroxil 882 mg (600-mg aripiprazole equivalent), or placebo (fat emulsion for human use; Intralipid) injected into the gluteal muscle once every 4 weeks (days 1, 29, and 57). The gluteal muscle was selected as the injection site to maintain blinding to study drug since only the aripiprazole lauroxil 441-mg dose can be administered in the deltoid muscle. Because of the different volumes of the aripiprazole lauroxil 441-mg and 882-mg doses, patients randomized to placebo were further randomized 1:1 in a double-blind fashion to low- or high-volume placebo. Thus, the overall randomization ratio to aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, placebo low volume, and placebo high volume was 2:2:1:1. In addition to intramuscular study drug, patients received oral study drug daily administered in a double-blind fashion for the first 3 weeks after randomization to achieve early therapeutic exposure to aripiprazole from the combined release of aripiprazole lauroxil and oral aripiprazole in the context of a placebo-controlled acute schizophrenia study. Patients randomized to an aripiprazole lauroxil treatment group received oral aripiprazole (15 mg), and patients randomized to placebo received matching oral placebo for 3

Figure 1. Patient Disposition



weeks after randomization. Patients remained in the inpatient study unit for at least 2 weeks after administration of the first dose of intramuscular study drug and were discharged after the study investigator determined that they were clinically stable. Efficacy, safety, and tolerability were assessed throughout the treatment period. After discharge from the inpatient study unit, outpatient visits occurred at days 22, 29, 43, 57, 71, and 85. Follow-up visits for safety assessments were scheduled to occur at days 113 and 141.

Study Assessments

The PANSS and CGI-S scales were administered at screening and on days 1, 8, 15, 22, 29, 57, and 85. The Clinical Global Impressions-Improvement scale (CGI-I)¹³ was administered at days 8, 15, 22, 29, 57, and 85.

Safety was evaluated based on the incidence of treatment-emergent adverse events (TEAEs), the incidence of adverse events (AEs) leading to discontinuation, vital sign measurements, physical examination findings, laboratory test results, electrocardiogram findings, and concomitant medications.

Injection site reaction evaluation (pain, erythema, hematoma, discoloration, and induration) was performed following every injection and on days 8 and 15 and every 2 weeks following the second injection and monthly during the follow-up period.

Statistical Methods

Efficacy analyses were performed using data from the full analysis set (FAS; $n = 596$), defined as all randomized patients who received at least 1 dose of intramuscular study drug and had at least 1 primary efficacy assessment after administration

of intramuscular study drug. The primary efficacy end point was the change from baseline to day 85 in PANSS total score and was analyzed using an analysis of covariance (ANCOVA) with a last observation carried forward (LOCF) approach in the FAS population. The ANCOVA model included study region and treatment group as factors and baseline PANSS total score as a covariate. The primary efficacy end point was also analyzed using a mixed model for repeated measures (MMRM) in the FAS population as a sensitivity analysis to assess the robustness of the primary efficacy results. The MMRM model included study region, treatment group, visit, and treatment group-by-visit interaction as factors and baseline PANSS total score as a covariate, and an unstructured covariance matrix was used to model within-subject variability. The secondary efficacy end point was the CGI-I score at day 85, which was analyzed using a nonparametric Wilcoxon rank sum test using the LOCF approach. The proportion of patients achieving a CGI-I score of 1 (very much improved) or 2 (much improved) at each assessment was compared with a logistic

regression model adjusting for study region as sensitivity analysis. For primary and secondary analyses, each of the aripiprazole lauroxil groups was compared with the placebo group. The Hommel method was used to adjust for multiple comparisons.¹⁴ Post hoc analyses were conducted using MMRM to evaluate the effect of aripiprazole lauroxil in patients with greater severity of illness at baseline using the median PANSS score at baseline as the cutoff.

Safety and tolerability analyses were performed using data from the safety population, defined as all patients who received at least 1 dose of intramuscular study drug.

Assuming a common standard deviation of 20, and a dropout rate of approximately 40% and 60% for the treatment and placebo groups, respectively, an estimated sample size of approximately 180 efficacy evaluable patients per treatment group was estimated to provide at least 90% power to detect a 8-point difference in the primary efficacy end point at 2-sided significance level overall of .05, adjusted for 2 comparisons with placebo using the Hommel procedure.¹⁴

RESULTS

Patients

Patient disposition is reported in Figure 1. A total of 848 patients were screened, and 623 were randomized. One patient was randomized but did not receive the study drug due to inclusion/exclusion violation; therefore, 622 patients were included in the safety population. Of these, 596 were included in the FAS population. Overall, the majority of subjects were male (67.9%) with a median age of 39.0 years (Table 1). Subjects were predominantly white (46.7%) or black/African American (39.8%). Most subjects were

Table 1. Baseline Patient Characteristics, Safety Population

| Characteristic | Aripiprazole Lauroxil | | Placebo (n=208) |
|---|-----------------------|-------------------|--------------------|
| | 441 mg (n=207) | 882 mg (n=208) | |
| Men, n (%) | 141 (68.1) | 143 (68.8) | 139 (66.8) |
| Age, mean (SD), y | 39.9 (10.1) | 39.7 (11.1) | 39.5 (11.9) |
| BMI (kg/m ²), mean (SD) | 27.7 (5.3) | 27.3 (5.7) | 27.0 (5.1) |
| Race, n (%) | | | |
| White | 99 (47.8) | 98 (47.1) | 94 (45.2) |
| Black/African American | 83 (40.1) | 81 (38.9) | 84 (40.4) |
| Asian | 24 (11.6) | 28 (13.5) | 29 (13.9) |
| Other | 1 (0.5) | 1 (0.5) | 1 (0.5) |
| Region, n (%) | | | |
| North America | 103 (49.8) | 102 (49.0) | 102 (49.0) |
| Europe | 81 (39.1) | 78 (37.5) | 80 (38.5) |
| Asia | 23 (11.1) | 28 (13.5) | 26 (12.5) |
| PANSS total score, mean (SD) ^a | 92.6 (10.2) | 92.0 (10.8) | 93.9 (11.3) |
| >92 ^b | 101.3 (6.0) | 101.0 (6.4) | 102.7 (7.9) |
| CGI-S score, mean (SD) ^a | 4.9 (0.59) | 4.9 (0.61) | 4.9 (0.61) |

^aFull analysis set population: for aripiprazole lauroxil 441 mg, n=196; for aripiprazole 882 mg, n=204; and for placebo group, n=196.

^bFull analysis set subpopulation with baseline PANSS total score >92: for aripiprazole lauroxil 441 mg, n=95; for aripiprazole 882 mg, n=100; and for placebo group, n=99.

Abbreviations: BMI=body mass index, CGI-S=Clinical Global Impressions-Severity of Illness scale, PANSS=Positive and Negative Syndrome Scale.

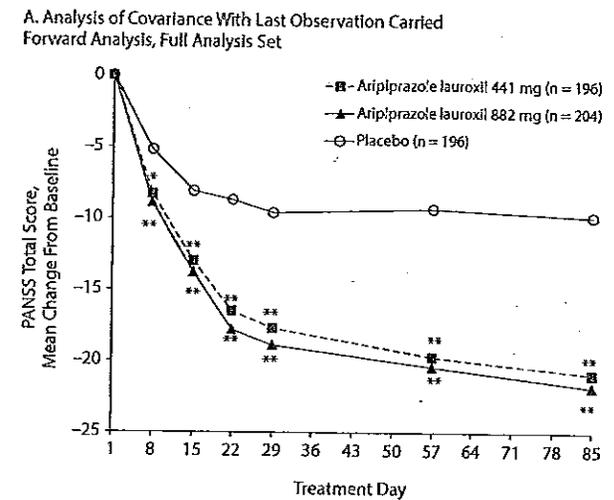
enrolled in North America (49.3%) or Europe (38.4%). The age, gender, primary race, ethnicity, and region/countries were evenly distributed among the 3 groups. Patients were markedly to severely ill, with PANSS total scores (mean [SD]) of 92.6 (10.2), 92.0 (10.8), and 93.9 (11.3) for the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively. The proportion of patients receiving all 3 intramuscular injections was 65.2% and 67.8% for the aripiprazole lauroxil 441-mg and 882-mg dose groups, which was statistically significant and higher than 48.3% for placebo ($\chi^2=12.06$ [$P=.0005$] and $\chi^2=16.17$ [$P<.0001$] for 441 mg and 882 mg, respectively).

Efficacy

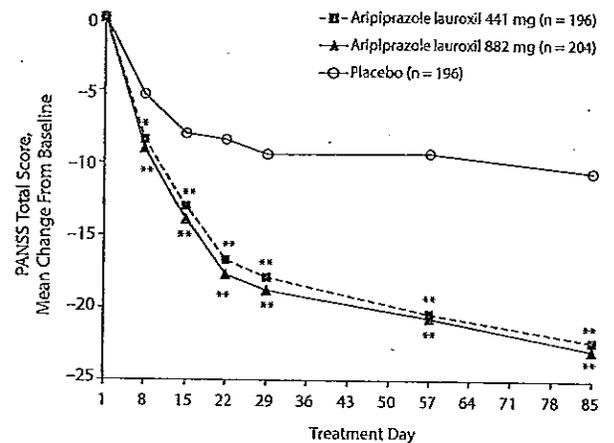
A clinically meaningful and statistically significant improvement from baseline to day 85 in PANSS total score was demonstrated for the aripiprazole lauroxil 441-mg and 882-mg groups, with placebo-adjusted least squares mean differences of -10.9 (1.8) ($P<.001$) and -11.9 (1.8) ($P<.001$), respectively (see Supplementary eTable 1 at PSYCHIATRIST.COM). Significant improvements in PANSS total score for both active treatment groups were observed as early as day 8 and continued through the end of the double-blind treatment period in both ANCOVA with LOCF and MMRM approaches (Figure 2). In a post hoc MMRM analysis in a subpopulation of patients with more severe symptoms (baseline median PANSS score of >92 as cutoff), the observed placebo-adjusted mean change in PANSS total score at day 85 was -14.7 (3.5) for the aripiprazole lauroxil 441-mg dose group ($P<.0001$) and -16.6 (3.4) for the 882-mg dose group ($P<.0001$) (Supplementary eTable 1).

Both aripiprazole lauroxil treatment groups had significantly better CGI-I scores at day 85 compared to placebo ($P<.001$) using Wilcoxon rank sum test. The

Figure 2. Mean Change From Baseline to Each Assessment for the Positive and Negative Syndrome Scale (PANSS) Total Score Over 85 Days^a



B. Mixed Model for Repeated Measures Analysis, Full Analysis Set



^aP values are for aripiprazole lauroxil 441-mg and aripiprazole lauroxil 882-mg dose group versus placebo.

* $P=.004$.

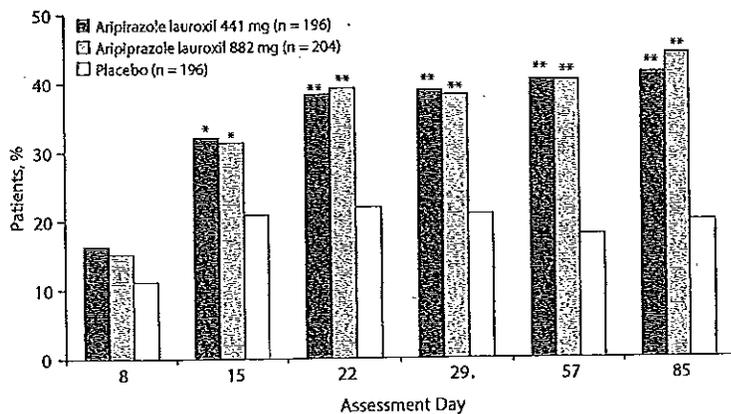
** $P<.001$.

proportion of patients who were very much or much improved was also significantly greater in the aripiprazole lauroxil 441-mg and 882-mg groups compared to placebo at all assessments after day 8 ($P<.05$ to $P<.001$; Figure 3).

Safety and Tolerability

Overall, the incidence of most AEs was similar among groups, and AEs were mild or moderate in intensity. Serious adverse events (SAEs) were reported in 11 patients during the treatment period: 3 (1.4%), 4 (1.9%), and 4 (1.9%) in the aripiprazole lauroxil 441-mg, 882-mg, and placebo groups, respectively, including 1 death (victim of homicide) in the placebo group. Only 1 SAE, which was reported in a patient with akathisia in the aripiprazole lauroxil 882-mg dose group, was considered related to the study drug. No individual SAE was reported by more than 1 patient. Severe TEAEs were similar across the 3 groups and were reported in 9 (4.3%),

Figure 3. Proportion of Patients Reporting Ratings of Very Much or Much Improved on the Clinical Global Impressions-Improvement Scale^a



^aProportion of patients with very much improved or much improved in full analysis set at each assessment time points. *P* values are for the aripiprazole lauroxil 441-mg and 882-mg dose groups versus placebo. Logistic regression model adjusting for study region. Missing values were imputed with no improvement.

**P* < .05.

***P* < .001.

Table 2. Treatment-Emergent Adverse Events (TEAEs) Occurring in $\geq 2\%$ of Aripiprazole Lauroxil-Treated Patients, Safety Population

| Preferred Term (%) | Aripiprazole Lauroxil | | Placebo (n=207) |
|---------------------|-----------------------|----------------|-----------------|
| | 441 mg (n=207) | 882 mg (n=208) | |
| Any TEAE | 58.9 | 57.2 | 62.3 |
| Insomnia | 9.7 | 12.0 | 11.6 |
| Akathisia | 11.6 | 11.5 | 4.3 |
| Headache | 8.2 | 8.7 | 8.2 |
| Anxiety | 2.9 | 5.3 | 6.8 |
| Injection site pain | 3.4 | 4.8 | 1.9 |
| Toothache | 2.4 | 3.8 | 0.5 |
| Nausea | 2.9 | 3.4 | 1.9 |
| Constipation | 2.9 | 2.4 | 3.9 |
| Diarrhea | 2.4 | 2.4 | 3.4 |
| Weight increase | 2.9 | 2.4 | 0.5 |
| Neck pain | 1.0 | 2.4 | 1.4 |
| Sedation | 1.9 | 2.4 | 1.4 |
| Schizophrenia | 5.8 | 2.4 | 10.6 |
| Restlessness | 2.9 | 1.9 | 1.9 |
| Blood CPK increase | 4.3 | 1.4 | 0.5 |

Abbreviation: CPK=creatinine phosphokinase.

9 (4.3%), and 12 (5.8%) of patients in the aripiprazole lauroxil 441-mg, 882-mg, and placebo groups, respectively. More patients in the placebo group discontinued due to AEs (17.9%) than patients in either aripiprazole lauroxil group (6.8% for 441 mg and 2.9% for 882 mg), which was attributed to exacerbation of the underlying illness.

Treatment-emergent adverse events occurring in $\geq 2\%$ of patients in the aripiprazole lauroxil treatment groups are reported in Table 2. The most common TEAEs occurring in $> 5\%$ of patients in the aripiprazole lauroxil groups were insomnia, akathisia, headache, and anxiety. Akathisia was the only TEAE with an incidence of $\geq 5\%$ in each aripiprazole lauroxil group that was at least twice the rate of placebo (11.6%, 11.5%, and 4.3%). The majority ($> 75\%$) of all akathisia episodes occurred before the second injection,

generally within the first 3 weeks, when the patients in the aripiprazole lauroxil groups were also receiving oral aripiprazole. There were 3 cases of akathisia that occurred after the second injection in the aripiprazole lauroxil 441-mg group and 1 case in the placebo group. No cases of akathisia occurred in the aripiprazole lauroxil 882-mg group beyond 1 month after the first injection.

The incidence of injection site reactions was low overall, occurring in 8 (3.9%), 12 (5.8%), and 4 (1.9%) patients in the aripiprazole lauroxil 441-mg, 882-mg, and placebo groups, respectively. Pain was the most common description used for injection site reactions, 7 (3.4%), 10 (4.8%), and 4 (1.9%) for the aripiprazole lauroxil 441-mg, 882-mg, and placebo groups, respectively, with very few reports of swelling, redness or induration, or other reaction. Most reports of injection site pain were associated with the first injection (Supplementary eFigure 1).

DISCUSSION

This randomized, double-blind, placebo-controlled trial demonstrated the robust efficacy of aripiprazole lauroxil, a novel, LAI atypical antipsychotic for treatment of schizophrenia. Significant improvement in schizophrenia symptoms was evident as early as day 8 and was maintained throughout the 12-week treatment period. Both aripiprazole lauroxil 441-mg and 882-mg doses were well tolerated.

The placebo-adjusted improvement in PANSS total score from baseline to the end of the study was clinically meaningful and statistically significant for both aripiprazole lauroxil dose groups tested, and indeed, the somewhat larger effects demonstrated in the more severely ill patient population (> 92 PANSS total score at baseline) further demonstrate the robust efficacy of both doses of aripiprazole lauroxil. The severity of illness as measured by the PANSS total score was also significantly improved at the end of the treatment period for the aripiprazole lauroxil groups compared to placebo. In addition, early and durable improvement in the CGI-I categories of very much improved or much improved occurred more frequently in the aripiprazole lauroxil patients compared to placebo. Consistent positive findings in sensitivity analysis for the PANSS primary outcome and the CGI-I secondary outcome measures further support the robust efficacy of aripiprazole lauroxil treatment. In addition, given that fewer patients in the placebo group received all 3 injections compared to the aripiprazole lauroxil groups, the treatment effect of aripiprazole lauroxil may have been underestimated as a result of the greater number of dropouts in the placebo group due to lack of efficacy.

The results of the present study are similar to reports of other randomized controlled trials examining the

efficacy of LAI atypical antipsychotics in patients with chronic stable schizophrenia and those experiencing acute exacerbations.¹⁵⁻¹⁷ The greater improvement observed in the PANSS total score associated with aripiprazole lauroxil 882 mg compared to aripiprazole lauroxil 441 mg in the subpopulation of more severe patients (mean [SD] PANSS score > 92 at baseline, 101.3 [6.0] for aripiprazole lauroxil 441 mg and 101.0 [6.4] for aripiprazole lauroxil 882 mg) suggests there may potentially be an additional benefit of the higher dose in patients experiencing more severe symptoms.

Both aripiprazole lauroxil 441-mg and 882-mg doses were well tolerated, with a side effect profile consistent with oral aripiprazole. The overall incidence of TEAEs was low and did not appear to be dose dependent. Akathisia was the only common TEAE occurring in at least 5% of treated patients with an incidence greater than twice that of placebo. However, akathisia tended to occur during the initial phase of the study when patients were treated with both oral aripiprazole and aripiprazole lauroxil. This combined exposure may have been a contributing factor, as akathisia is a known side effect of aripiprazole. The incidence

of injection site reactions was low, mainly injection site pain, which resolved after the first treatment.

Aripiprazole lauroxil is a novel LAI atypical antipsychotic with multiple safe and effective doses and the ability to be administered in either the deltoid (441-mg dose only) or gluteal muscles as demonstrated in a phase 1 study.¹⁰ These characteristics may allow for individualized treatment to meet patient needs.

This study evaluated efficacy and safety of 2 fixed-dose regimens of aripiprazole lauroxil with no opportunity for dose adjustments over the course of the study. It is possible, therefore, that some patients might have benefited more from dose adjustment and flexible dosing. This should be further evaluated in future studies.

In summary, this study demonstrated robust efficacy of multiple doses of aripiprazole lauroxil with a safety and tolerability profile similar to oral aripiprazole. The clinical profile of aripiprazole lauroxil combined with the flexibility afforded by the novel technology and ability to administer in the deltoid and gluteal muscles may represent a new treatment option for both clinicians and their patients with schizophrenia.

Drug names: aripiprazole (Abilify and others), clozapine (Clozaril, FazaClo, and others).

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Supplementary material: Available at PSYCHIATRIST.COM.

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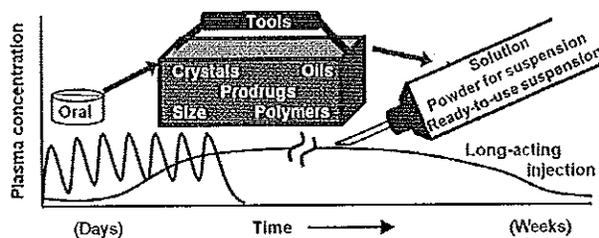
Making the Leap from Daily Oral Dosing to Long-Acting Injectables: Lessons from the Antipsychotics

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ABSTRACT: There are now long-acting versions of six antipsychotic drugs on the U.S. market, and with them, five unique combinations of molecular form and delivery strategy long-acting-injectable-antipsychotics (LAIAs) show evidence of reduced relapses of schizophrenia, but their introduction has been slow, taking at least nine years after the approval of each oral drug. Oily solutions of lipophilic prodrugs were the first to enter the LAIA market, but they relied on esterification of a hydroxyl handle that was lost with the emergence of the atypical antipsychotics. A review of the literature and patents shows that companies tested many different approaches before reaching the currently marketed versions, including aqueous suspensions of poorly soluble salts, polymeric microspheres, and new approaches to making prodrugs. Yet, very little has been published to support faster development of safe long-acting injectables (LAIs). This review introduces some of the critical considerations in creating an LAI; then it analyzes the existing products and discusses areas where further research is needed. The available literature suggests that lipophilic prodrugs may be inherently safer than poorly soluble salts as LAIs. Other areas needing additional study include (1) the range of physical properties acceptable for LAIs and the effect of prodrug tail length in achieving them, and (2) the role of physiological responses at the injection site in the release of drug from a depot.

KEYWORDS: long-acting injectable, prodrug, aqueous suspension, safety, lag phase, burst, physical properties



A. INTRODUCTION

Long-acting injectable (LAI) medicines have been used to treat several diseases, including schizophrenia, bacterial infections, prostate cancer, and diabetes, with recent papers highlighting efforts to apply LAI technology to the treatment of HIV.^{1,2} The hallmark application of LAI formulations in the 20th century was the treatment of schizophrenia, a devastating psychiatric condition associated with frequent relapse, loss of function, and low compliance to oral therapy. A recent review detailed the impact of LAI therapy on clinical, functional, and economic outcomes of schizophrenic patients, including the emerging understanding of benefits from introducing LAIs early in the treatment of disease.³ Despite evidence of improvement in patient outcomes, there have also been issues with some LAIs, including cases of "Post-Injection Delirium Sedation Syndrome" (PDSS) caused by the sudden release of olanzapine from Zyprexa Relprevv. An LAI for treating bacterial infections, penicillin benzathine, carries a label warning of deaths from inadvertent intravenous injection and of severe neurological damage from injections too close to nerves. Such incidents should not distract from the positive patient outcomes, but they do highlight the need for improved understanding of the technologies employed to ensure safe and effective release of drug.

The history of delivery technologies used in marketed LAIA's in the U.S. is shown in Figure 1, where it appears as an evolution from solutions in oil to aqueous suspensions.⁴ The LAIAs were introduced beginning in the 1960s as solutions of

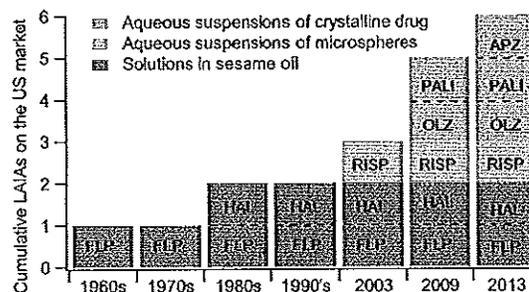


Figure 1. Number of LAIA Drugs on the U.S. Market Based on Delivery Strategy.

simple ester prodrugs in sesame oil, and these remained the only option for more than three decades. A second generation of safer oral antipsychotics with lower incidence of side effects emerged in the 1990s, and their LAI versions slowly entered the U.S. market as listed in Table 1. The first of the atypical antipsychotics to be approved as an LAI was risperidone (RISP) in polymeric microspheres, where the polymer controls the rate of drug release after injection in aqueous suspension. Since 2009, all newly approved LAIAs have been formulated for

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Table 1. FDA Approval Dates for Antipsychotic Drugs with LAI Versions in the U.S.

| active drug (abbrev ^a) | type ^b | FDA approval | form of drug in product (abbrev ^a) | formulation |
|------------------------------------|-------------------|--------------|--|------------------------------------|
| Fluphenazine (FLP) | oral | 1959 | HCl salt (FLP-HCl) | tablet |
| | LAI | 1967 | enanthate prodrug (FLP-C7) | solution in sesame oil |
| | LAI | 1972 | decanoate prodrug (FLP-C10) | solution in sesame oil |
| Haloperidol (HAL) | oral | 1967 | free base (HAL) | tablet |
| | LAI | 1986 | decanoate prodrug (HAL-C10) | solution in sesame oil |
| Risperidone (RISP) | oral | 1993 | free base (RISP) | tablet |
| | LAI | 2003 | free base (RISP) | polymeric microspheres |
| Olanzapine (OLZ) | oral | 1996 | free base (OLZ) | tablet |
| | LAI | 2009 | pamoate salt (OLZ-pamoate) | powder for aqueous suspension |
| Paliperidone (PALI) | oral | 2006 | free base (PALI) | tablet |
| | LAI | 2009 | palmitate prodrug (PALI-C16) | nanocrystals in aqueous suspension |
| Aripiprazole (APZ) | oral | 2002 | free base (APZ) | tablet |
| | LAI | 2013 | monohydrate (APZ-H ₂ O) | powder for aqueous suspension |
| | LAI | phase 3 | lauroxil ester prodrug (APZ-CH ₂ O-C12) | ready-to-use aqueous suspension |

^aAbbrev denotes the abbreviations that will be used for each compound within the text. ^bType refers to the type of product, either oral or LAI.

injection as aqueous suspensions of crystalline drug forms, where the low solubility and slow dissolution rate of the crystalline solid controls the rate of absorption. Nine years passed between the approval of oral risperidone and the LAI Risperdal Consta. Making the transition for olanzapine and aripiprazole took 10 and 13 years, respectively. Considering the clear benefits of LAIA therapy, the long delay between oral and LAI may seem surprising. However, closer examination reveals the difficulty in delivering these molecules as LAIs and that the technology evolved in response to the changing physicochemical properties of the new drug molecules.

This review grew from efforts to select an optimum prodrug and delivery strategy for aripiprazole (APZ) after discovering a series of prodrugs where esters are reversibly linked to the lactam of APZ through a hydrolytically labile hydroxymethyl group. The approach yielded a large number of prodrug candidates with different physical properties, but little guidance could be found for selecting one to take forward into development as an LAI. Here, data from journal articles and patents are gathered and interpreted in order to explain the last half-century of LAI development, particularly antipsychotics. Additionally, the data have been analyzed to identify areas that are poorly understood and in need of additional research.

The goal is to enable researchers to quickly transition important oral therapies to safe and effective LAIs by helping them to understand the interplay between molecular properties and existing delivery strategies. The remaining sections are structured as follows: section B introduces subjects that are applicable to multiple delivery strategies, such as prodrugs and particle size control; section C is primarily a review of the literature and patents associated with currently marketed LAIAs, but organized by delivery technology and including examples of failures as well as successes; finally, section D provides an analysis of areas in need of further research, including prodrugs for aqueous suspension, the "lag phase" after injection of aqueous suspensions and the safety of poorly soluble salts relative to lipophilic prodrugs.

B. GENERAL CONSIDERATIONS FOR TRANSITIONING FROM ORAL TO LAI

The pharmaceutical industry is geared toward making relatively small molecules that will dissolve and permeate through membranes to allow for good oral absorption and daily dosing. LAI technology aims to maintain safe and effective levels of

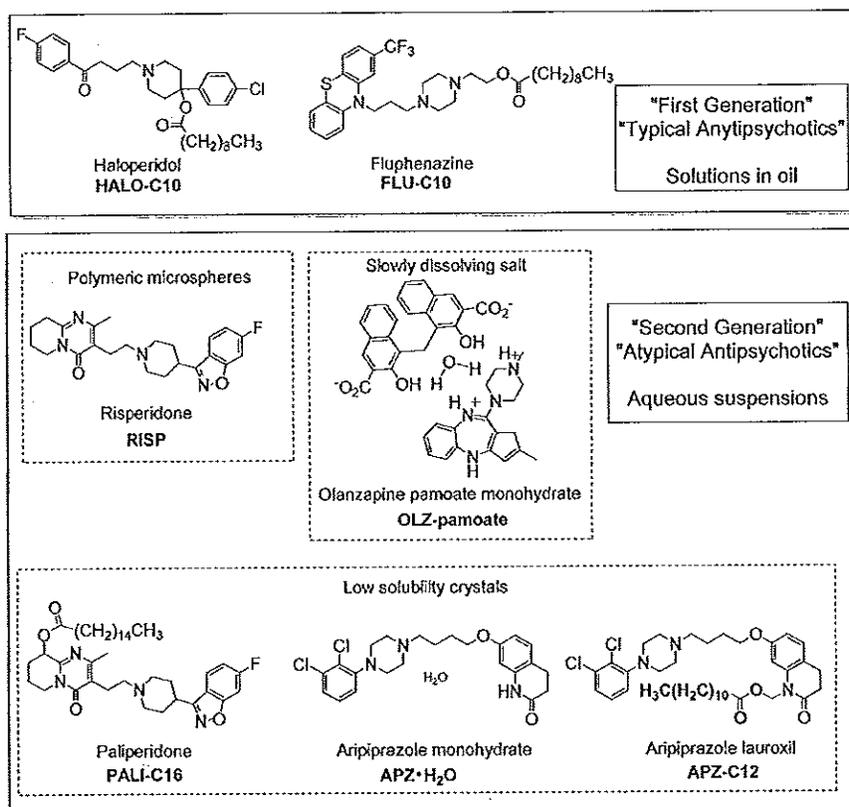
those active drugs, typically for at least 2 weeks following the injection; this requires dosing a large amount of drug. A quick scan of package inserts for the oral antipsychotics show that most of these products have serious side effects, such as sedation or coma, at higher blood concentrations. Sudden release of too much drug is often referred to as "dose dumping" and causes a "spike" in the plasma concentrations. Evaluating the possibility and consequences of dose dumping is a critical activity in the selection of delivery technology for a given molecule.

B1. Local Effects on the Release of Antipsychotics.

The intramuscular injection site is approximated by buffered saline at pH 7.4–7.6 in the laboratory, but events such as the "Post-injection Delirium/Sedation Syndrome (PDSS)" that occurs in 0.07% of patients receiving OLZ-pamoate serve as reminders that there are differences that must be considered.⁵ In a small number of injections, it is believed that either (1) a small amount of drug is injected directly into a vein and/or (2) a vein is punctured by the needle, causing blood to leak into the injection site. The solubility of OLZ-pamoate is on the order of 15-fold higher in plasma than in pH 7.6 buffer, allowing for a rapid solubilization of drug when blood leaks into the site. However, an increased solubility in plasma should not necessarily be used as an exclusion test when assessing a candidate, since some compounds with extremely low aqueous solubility (<10 ng/mL) may rely on components native to serum such as albumin and lipoproteins for solubilization. The key is to determine the extent of the solubilization during an event such as accidental infiltration of blood to the injection site, and the consequences of a high plasma level if this is a possibility.

The pH of tissue can drop as low as pH 6.5 for several hours⁶ in response to trauma, such as a cut, and this can affect the solubility of some antipsychotics. All of the known antipsychotic molecules in LAI formulations contain a piperidine or piperazine ring with an acid dissociation constant, or pK_a , between 7 and 9. The higher the pK_a , the larger the thermodynamic drive to ionize if the pH drops. Since ionization typically increases aqueous solubility, this is especially important to understand for suspensions of crystalline drug where the formulation provides no physical barriers to ionization. The solubility of RISP ($pK_a = 8.2$), for example, is relatively low at 0.028 mg/mL in deionized water at room temperature (native pH = 8.9), but it increases 10-fold to 0.29

Scheme I. Structures of Antipsychotic Drug Molecules Used in LAI Products



mg/mL in pH 7.6 buffer, and >100-fold to 4.4 mg/mL at pH 6.6.⁷ APZ has a lower pK_a value of 7.4 and estimates of solubility in water are around 10 $\mu\text{g/mL}$ ⁸ while its solubility remains low in buffer at pH 6.8.⁹ The solubility of OLZ-pamoate is known to be about four times lower at pH 6.8 than at pH 7.4 while crystalline OLZ free base is likely to increase in this range. It is also important to remember that ionization could change the relationship between the drug and excipients within oil depots or polymeric microspheres.

B2. Prodrugs. Prodrugs have been widely used to address drug delivery problems,^{10,11} and they have been a central strategy in the transition from oral drugs to LAIs. Esterification of alcohols with fatty acids can drastically reduce the aqueous solubility and increase solubility in oils for injection. Since the fatty acids are endogenous and most commonly occur with even-numbered tails of four to 28 carbons,¹² there exists the ability to tune the physical properties of the molecule, including melting point, solubility, and partition coefficient. Most esters are efficiently cleaved to the active by esterases, which exist throughout the body. Furthermore, simple ester prodrugs are typically considered to be safe and are no longer considered to be new chemical entities (NCEs) by the FDA for purposes of regulatory exclusivity.¹³

Despite the wide acceptance of ester prodrugs, risk reduction strategies dictate selection of prodrugs that cleave rapidly after release from the injection site whenever possible. With this philosophy, the prodrug is used primarily to regulate the rate of dissolution for a crystalline entity, or the rate of diffusion or partitioning out of a controlled-release depot. Alternative degradation/elimination pathways could also begin to play a role if the ester was slow to hydrolyze, thereby reducing

potency and increasing the risk of failure in toxicity studies. However, there are certainly cases where a slow hydrolysis rate has been beneficial: HALO-C10 is a case where the ester cleavage is unusually slow in blood and plasma; Nambu, et al, have suggested that the slow conversion in blood increases the safety of the prodrug by giving it time to redistribute into tissue rather than causing a spike in active HAL concentration.¹⁴

Easy access to handles for prodrugs ended with the emergence of the atypical antipsychotics RISP, OLZ, and APZ which lack -OH groups.

Scheme I shows the structures of the antipsychotics that are available as LAIs in the U.S., showing active parent moiety and highlighting molecular level modifications used in the extended release versions (blue for esters, red for nonester covalent linkers). The first-generation antipsychotics HALO and FLU, along with others outside of the U.S., contained -OH groups that were easily esterified to provide prodrugs with conveniently high solubility and partitioning into sesame oil. RISP, OLZ, and APZ have all been developed using other delivery strategies. High loads of RISP were successfully incorporated into poly(lactic-co-glycolic) acid (PLGA) microspheres that slowly release the drug to allow biweekly dosing. OLZ was recrystallized as a salt of pamoic acid having lower aqueous solubility and is injected as an aqueous suspension. Micronized APZ·H₂O was suspended in aqueous media and lyophilized to await reconstitution immediately prior to dosing.

Despite having marketed LAI versions of the second generation antipsychotics, prodrug versions of each have been created, all for different purposes. PALI, the active metabolite of RISP, was developed as PALI-C16 and is marketed as Invega Sustenna. The prodrug allows monthly dosing as a ready-to-

inject, room temperature stable suspension. The microsphere version of RISP (Riperdal Consta) remains highly effective, but requires refrigeration, reconstitution, and biweekly dosing. However, PALI is an active metabolite of RISP, so there can be differences in activity that make one more appropriate for a given patient. APZ-C12 is in phase 3 trials and has a unique chemistry using a hydroxy-methyl linker to allow reversible attachment of an ester to the lactam. Attaching the acyl chain directly onto the lactam $-NH$ would yield a relatively stable molecule rather than a prodrug, but the hydroxymethyl group is a hydrolytically reversible moiety that remains stable as long as it is esterified. The resulting prodrug is sufficiently stable to be stored as a ready-to-use suspension. Finally, a recent paper reported on carbamate linked esters of OLZ,¹⁵ intended as a strategy to reduce the differences in solubility between buffer and plasma, and thereby potentially reduce or eliminate incidents of PDSS resulting from rapid release of drug. More detail on the selection of prodrugs for use in different delivery strategies will be included in later sections.

B3. Particle Size. Particle size must be controlled in order to make sure the solid particles fit through the supplied needle without clogging and that the drug releases at the proper rate. The solubility and intrinsic dissolution rate are inherent properties of a crystalline molecule, but the actual rate of dissolution is expected to increase at smaller particle sizes (higher surface area). In oral drug delivery, the physical form of a compound is often changed to improve dissolution rate, but this can lead to instability in an LAI. For example, APZ has many polymorphs, solvates and salts, but will recrystallize to the thermodynamic APZ·H₂O^{8,16} form in the aqueous environment of tissue for days, weeks or months after injection. Without a polymer-based formulation or a prodrug to control the release, the only means to fine-tune the dissolution rate is through particle size. For PALI and APZ prodrugs, different tail lengths could be expected to provide different solubility and dissolution rates, but the particle size remains an essential parameter for optimizing the release and ensuring reproducibility. Fortunately, the technologies and understanding needed for precise milling and stabilizing small crystals after milling have grown tremendously through research into improving the oral bioavailability of poorly soluble drug molecules.

The late 1990s through the early 2000s saw the emergence of the first “nanomilled” drug products, where particles are wet milled in the presence of polymers or surfactants to provide submicrometer particles, and these have been reviewed previously.^{17,18} Suspensions of crystalline drugs in aqueous vehicles containing dissolved stabilizing excipients are milled by stirring at high energy with solid milling media (typically polystyrene or ceramic beads). The resulting colloidal dispersions can be stable, or the particles can grow through flocculation to give agglomerates, or through “Ostwald ripening” where the larger crystals grow as smaller ones dissolve. Molecules with higher aqueous solubility, or suspensions stabilized by excipients that can solubilize the drug, are likely to see higher growth rates. Since tablets are the most sought-after dosage form for oral delivery, there has also been a large body of research into drying the milled solids while ensuring that critical attributes remain upon reconstitution when the tablet disintegrates. These same principles can be applied to aqueous suspensions for injection. If the milled crystals are physically or chemically too unstable for storage in the aqueous medium, then the water can be lyophilized to leave a cake for reconstitution in the clinic. There are two added

difficulties when milling for intramuscular (IM) use: the first is the need for sterility and the second is the limited set of stabilizers that are approved for the IM route. If an excipient that is novel to IM administration is required to maintain the desired particle size during storage in aqueous suspension, then the team must either deliver particles for resuspension or accept the challenges and risks associated with gaining approval for the new excipient.

B4. Excipients. The number of acceptable excipients currently approved for IM dosing is extremely limited compared to oral dosing.¹⁹ Introducing a new route of administration to an existing excipient brings additional costs and uncertainty to a program.²⁰ The excipients used in LAIs that are delivered as aqueous suspensions are shown in Table 2.

Table 2. Excipients in LAIs for Aqueous Suspension

| | viscosity modifier | surfactant | other |
|----------------------|--------------------|------------|----------------------|
| RISP | Na-CMC | PS20 | PLGA ^a |
| OLZ-PAM | Na-CMC | PS20 | |
| PALI-C16 | -- | PS20 | PEG4000 ^b |
| APZ·H ₂ O | Na-CMC | | |

^aPLGA is a polymer that controls the release of RISP from the depot.
^bPEG4000 will increase viscosity very little compared to Na-CMC, but it can be present as a steric stabilizer for the nanomilled PALI-C16 crystals.

Sodium carboxymethyl cellulose (Na-CMC) and polysorbate 20 (PS20) are each present in three of the atypical antipsychotic products, and PEG4000 is present in the formulation of PALI-C16. Buffers and tonicity agents used in intravenous (IV) injections are also typically acceptable. These vehicles will wet and suspend most hydrophobic solids, but they do not always prevent formation of dense, difficult-to-resuspend sediments or to stabilize crystals toward growth after milling to a fine particle size.

B5. Intellectual Property and Market Considerations. While the main focus of this review is scientific, the product will never be developed if it is destined to lose money. The concept must at the very least have “freedom to operate,” but patent protection is almost essential in order to recoup development costs. The boilerplate language of many patents on new drugs will include claims to “prodrugs thereof,” which could block any competitor from using any prodrug until that patent expires. However, such broad claims do not make all prodrugs of the compound obvious, and a novel prodrug can be patented and developed to enter the market upon expiration of the blocking patent. In some cases, patent law has established that a simple straight chain ester of a molecule that contains an alcohol or carboxylic acid could be considered obvious to one of ordinary skill in the relevant art and therefore, not patentable. Unique or less common prodrugs, or those that have unpredictable benefits, can still be considered novel.

There are typically hundreds if not thousands of patents relating to any drug that is approved and profitable, especially if it is marketed in the U.S.. A SciFinder search conducted in October 2013 found 306 patents including PALI, 538 for APZ, 993 for RISP, and 1022 for OLZ. While the majority of these patents do not relate directly to LAIs, there is clearly a large volume of material to navigate. Transitioning an orally administered molecule to an LAI is an expensive process involving toxicity studies and clinical trials, and the costs must be recovered before exclusivity expires and generic competitors

are allowed to compete. If there is another LAI version of the drug on the market, or the possibility that one could be introduced, then the analysis must also consider what competitive advantages the new concept could provide over the other product(s). It is difficult to overstate the importance of consulting experts in patent law, regulatory exclusivity, and market research from the point of conception through the full development of an LAI.

C. DELIVERY TECHNOLOGIES

The following sections will take a deeper look at four different delivery strategies: solutions in oil, polymeric microspheres, crystalline solids for aqueous suspension, and ready-to-use aqueous suspensions. The latter three are all aqueous-suspension technologies, but they have significant difference in ease of use. Polymeric microspheres are based on PLGA, which has a low glass transition temperature, especially with drugs encapsulated. To remain stable on storage, they must be refrigerated until mixed with diluent immediately prior to injection. Solids for aqueous suspension require mixing immediately prior to injection because of poor chemical stability of the drug, poor control of particle growth or aggregation when in suspension. Each has its own directions-for-use for addition of diluent, wetting of particles and achieving a uniform suspension that ensures accurate delivery of the solids. Premade suspensions, especially when preloaded into a syringe, are the simplest for use in small practices without a separate lab room for mixing, though even these will typically require a protocol of tapping or shaking to ensure successful injection.

C1. Solutions in Oil. The majority of marketed antipsychotics have a maximum dosing volume of no more than 3 mL per injection site.^{9,21} In determining whether a solution in oil is appropriate, one must first know the solubility of the drug within the oil and the highest dose that patients will need. Clearly, an antipsychotic like APZ with a solubility of <1 mg/mL in oils and a daily dose of >5 mg would not work. HALO-C10, FLU-C10 and the other first-generation antipsychotics are all soluble to >100 mg/mL in sesame oil. Suspensions of crystalline prodrugs in oil do occasionally appear in patents; for example PALI-C10 and PALI-C16 suspended in sesame oil were both evaluated alongside the now-marketed nanocrystal aqueous suspension of PALI-C16, with the oil suspensions providing lower exposure.²² A RISP-pamoate salt was also dosed as a suspension in sesame oil and found to be active for up to 3 weeks,²³ but the authors observed burst effects when using this strategy. To date, no LAIA suspensions in oil have made it to market.²²

Many vegetable and synthetic oils have been tested as depots for antipsychotics as well as steroids, but sesame oil has become the oil of choice for LAIAs. Sesame oil (SO) has a high viscosity and is generally well-tolerated. High viscosity provides a longer half-life for clearance from both muscle and the subcutaneous (s.c.) space. In a study of radiolabeled oils in rabbit, it was found that 300 μ L injections of peanut oil (viscosity = 39 cps), have $t_{1/2}$ of 22–26 days following subcutaneous and IM injections.²⁴ The lower viscosity oil ethyl oleate (EO, viscosity = 3.9 cps) is cleared much faster, with $t_{1/2}$ of only 9–11 days. The effect of viscosity on release rate vanished at low injection volumes (50 μ L) when the release of small molecules was only monitored for 6 h.²⁵

Lymphatic uptake is considered important in the absorption of FLU-C10 and HAL-C10 from oil depots,^{26–29} though this is

at odds with the literature on clearance of oils from tissue. Neat oils are not readily taken up lymphatically when injected as pure substances.³⁰ Howard and Hadgraft looked for radioactivity in lymph after dosing radio-labeled EO and Arachis oil (peanut oil) and found that no more than 5% of oil was absorbed lymphatically.²⁴ It is believed that lymphatic uptake requires spreading of the oil along the fascial planes of the muscle toward lymphatic vessels; high viscosity retards spreading and flow while small droplets flow more easily.³¹ If correct, reducing viscosity, emulsifying the oil or adding a component that would reduce interfacial tension between the oil and aqueous environments could all lead to faster uptake with a larger lymphatic component. An example from a patent on APZ prodrugs demonstrates the increase in area under the plasma concentration versus time curve, AUC, available from emulsifying the oil phase.³² Here, the prodrug APZ-C10 dissolved in EO was injected into rat either neat or pre-emulsified in water with glycerol and the surfactant dipalmitoylphosphatidylcholine (DPPC). The 0–14 day AUC increased from 67 to 1490 ng*ml/day when emulsified. FLU-C10 and HALO-C10 both have pK_a 's of 8.1–8.2, and therefore, some degree of ionization is to be expected in tissue with a pH of 7.4. The charged species are amphiphilic, having long fatty tails, and could reasonably be expected to have an influence on the properties of the sesame oil and its interaction with water, though no data have been published. Regardless of the mechanism of release from the oil, Oh-E, et al. demonstrated that HAL-C10 is primarily absorbed into the lymphatic system and that the ester is most likely cleaved by esterases within lymphocytes.³³

C1a. Modifying Molecules for Oil Depots. The three primary drug characteristics to consider for developing a solution in oil are solubility, partition coefficient and chemical stability. Ester prodrugs offer a means to tailor the solubility and logP of a drug by changing the length of the tail. The ester bond is known to be stable in oils and is unlikely to add any new stability liabilities to a parent drug. Beyond the need to have suitable solubility in oil, the partition coefficient appears to be a critical parameter for achieving sustained release, though it can be difficult to measure for highly lipophilic compounds. A molecule with high aqueous solubility and hydrophilicity will partition out of oil and be released too quickly; a molecule with high affinity for the oil phase may release too slowly. Based on evaluation of successful LAIs, the decanoate tail (C10) appears to have the best release rate for many molecules.

The effect of ester tail length on the release of fluphenazine from oil depots has been reported by Florence and Vezin.³⁴ The shorter tail FLU-enanthate(C7) was the first LAIA to reach the market. It was a solution in sesame oil that required dosing every 2 weeks. FLU-C10 replaced FLU-C7 due to its slower release from oil, which reduced the dosing frequency to once per 3 weeks. Release from oils was slower for longer chain esters. In a functional assay where fluphenazine is used to suppress apomorphine-induced retching in dogs, FLU-C10 showed activity for 30 days with a 50% reduction in retching versus the control group. FLU-C16 showed a peak reduction of approximately 35% with activity observed up to 20 days, while FLU-C18 showed activity for a relatively narrow window of only 10 days. An aqueous suspension of FLU-C18 gave improved activity comparable to the solution of FLU-C16 in oil, showing that the lower activity of the FLU-C18 oil depot stems from slower release of prodrug from the depot rather than from failure to cleave the prodrug after release. Since the

pure oils can have half-lives exceeding 30 days, release from the depot relies on the partitioning of drug out of the oil. While the partition coefficient of FLU-C16 and FLU-C18 could not be measured (presumably due to the limitation of low aqueous solubility), there is a 30-fold increase in partition coefficient just from increasing the tail length by three carbon atoms from C7 to C10.

A further comparison of "drug/prodrug in oil strategies" comes from the patent describing aqueous suspensions of PALI-C16.²² Here, pharmacokinetic studies compared PALI-C10 and PALI-C16 in sesame oil or Miglyol to aqueous suspensions of PALI-C16. From the data provided, PALI-C10 released faster from sesame oil than PALI-C16 and provided higher exposure to drug even at the four-week time point. Dosing the PALI-C16 from Miglyol, a mixture of medium chain triglycerides with lower viscosity than sesame oil, provided higher exposure and faster release, but low levels at the four-week time point. The authors stated that the Miglyol formulations "exhibited considerably less systemic and local tolerance than the sesame oil based formulations", but those formulations provided higher initial exposure to the prodrugs, so without further information, it is not clear whether the excipient or high drug levels were to blame. Just as for FLU-C18, the aqueous suspension of crystalline PALI-C16 also provided higher exposure to drug than the sesame oil formulation. A note of caution on this experiment is that the full details of the oil-based formulations were not disclosed in the examples, and the language in the examples suggests that the PALI-C10, and possibly others, may have been suspensions of crystals in oil, not solutions.

C2. Polymeric Microspheres. Polylactic acid (PLA) and PLGA polymers have been considered the most desirable of the synthetic and naturally occurring polymers that have been tested for controlled-release delivery systems.³⁵ PLGA is used in surgical sutures and is known to be biocompatible. The degradation rate of the polymer can be controlled with the lactide/glycolide ratio and molecular weight. Higher molecular weight (mw) polymers will typically have a slightly higher glass transition temperature (T_g) and a longer period of slow release after initial dosing. PLGA has been used to make various types of drug-eluting systems, including microspheres, implants, and *in situ* formed gels. The manufacturing of these delivery systems has been previously reviewed by Petersen.³⁶ Okada and Tagouchi provided evidence for organization of free carboxylate terminals toward pockets of charged drug molecules with the hydrophobic polymer chains left to form a more rigid matrix between pockets of drugs as one possible mechanism for retaining higher drug loads.³⁵

The ability of PLGA to meter the release of small molecules allowed RISP to become the first LAI of an atypical antipsychotic, Risperdal Consta, which remains the only antipsychotic delivered as a polymeric microsphere for aqueous suspension and injection. RISP has relatively low solubility in its nonionized state, but with a pK_a of 8.2, the solubility increases rapidly with decreasing pH.⁷ As previously stated, the pH at injection sites can drop in response to trauma, including potentially the deposition of a large mass of foreign solids. A polymeric barrier that slows the rate of diffusion can protect against rapid release during brief periods of pH change at an injection site.

Risperdal Consta is manufactured using an oil/water (o/w) emulsion process. PLGA and RISP are dissolved in ethyl acetate and benzyl alcohol to form the oil phase and then

emulsified with water containing polyvinyl alcohol. The emulsion is diluted into water to extract the majority of the organic solvent and the microspheres are collected.³⁷ The microspheres are then suspended using water with added ethanol to further extract the solvents from the microsphere. The T_g of PLGA in the microspheres can be below room temperature until the solvent content gets low. Therefore, the temperature is maintained below 10 °C during the first steps of the extraction and wash process. A benefit of the water/ethanol wash process is the removal of any water-soluble drug from the surface of microspheres, which greatly reduces the burst effect and prevents a spike in plasma concentrations of drug in the hours after injection. The most complete reduction in initial burst is obtained by drying the microspheres to <0.2% moisture content prior to a final resuspension step.³⁸ The final microspheres contain >30% RISP by weight.

The mw of the PLGA is a major factor in the rate of drug release, but the mw decreases during the manufacturing process and during release. Tertiary amines, including FLU and RISP are among the drugs that are known to catalyze the degradation of PLGA.³⁹ Microspheres of PLGA 50:50 were prepared either as placebos or with drug loaded up to 16.6% FLU-HCl in an oil/water emulsion process.⁴⁰ The PLGA in the resulting microspheres decreased from approximately 43 kDa in the placebo, to 30, 27, and 23 kDa with drug loads of 4.2%, 8.2% and 16.6%. Figure 2 shows an overlay of data from the work of

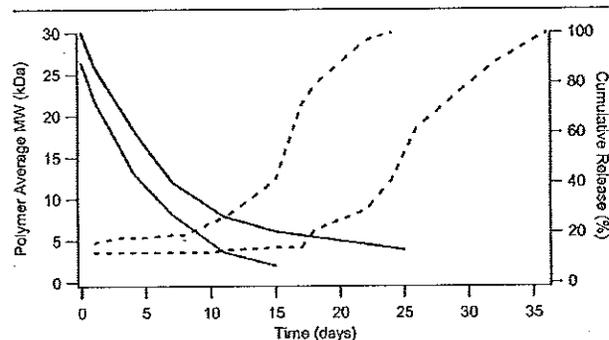


Figure 2. Overlay showing the degradation of PLGA (solid lines) and the cumulative *in vitro* release of FLU (dotted lines) as a function of time from microspheres having 4.2% (blue) or 8.2% (red) FLU in 50/50 PLGA.

Dunne et al.⁴⁰ Here, the decrease in polymer molecular weight and the cumulative release of drug are plotted as a function of time during a dissolution study of the microspheres containing 4.2% and 8.2% FLU-HCl. Both samples show an initial release of drug in the first day followed by a lag period where little drug release is observed. The polymer continues to degrade throughout the lag phase, with drug release accelerating as the polymer mw falls further below ~10 kDa. A similar correlation between PLGA mw and release was observed for dexamethasone/PLGA microspheres as reported by Zolnik and Burgess.⁴¹ There is also a lag phase in the release of RISP from Risperdal Consta, and a separately published report on the RISP catalyzed hydrolysis of PLGA.³⁹

Nahata and Saini published a detailed account of studies aimed at optimizing OLZ-PLGA microspheres, and they were able to provide 14-day release.⁴² Their work included several variables, including solvent evaporation method, choice and concentration of surfactant during the o/w emulsion step, volume and content of the external aqueous phase during the

Table 3. Data from a Dog Study Comparing IM Injections of 2.5 mg/kg of PALI as a PALI-C16 Aqueous Suspension, a PALI-C16 Suspension in Sesame Oil, or a PALI-C10 Suspension in Sesame Oil

| compd | formulation | C_{max} (ng/mL) | needle | T_{max} (d) | AUC _{0-24h} (ng·h/mL) | C_{12h} (ng/mL) |
|------------------------|---------------|-------------------|--------|---------------|--------------------------------|-------------------|
| PALI-C16 ²² | 15.6% aq susp | 54.6 ± 7.3 | 21G | 11.5 | 18 210 | 8.8 |
| PALI-C16 ²² | sesame oil | 21.9 ± 9.4 | 19G | 8.8 | 7054 | 4.2 |
| PALI-C10 ²² | sesame oil | 33.1 ± 18.2 | 19G | 5.5 | 13 875 | 12.0 |

solvent extraction and drying methodology. Importantly, they monitored encapsulation efficiency and initial burst as a function of target drug load. The term “initial burst” refers to the percentage of the total drug load that dissolves and is released from the formulation in the first hours after dosing. While it was possible to get high encapsulation and relatively low initial burst at low drug loading, the burst was not brought below 20% at more realistic drug loads of 25–30% in the microspheres. They also explored PLGA with monomer ratios of 50:50, 75:25 and 85:15, but the burst remained above 20%. Unfortunately, high plasma concentrations of OLZ bring unacceptable side effects (PDSS) that would not be solved by the microspheres in this study.

Despite the success of Risperdal Consta, there are disadvantages to developing microsphere-based products. The relatively low Tg of PLGA and the susceptibility of the polymer toward hydrolytic degradation necessitates refrigerated storage to ensure the physical stability of, and proper release from, the microspheres. The process requires specialized expertise, especially for scaling-up and production of sterile microspheres. Though no study on the subject has been published, high costs of manufacturing and production were cited as a reason for Genentech's withdrawal of Nutropin Depot in PLGA microspheres from the market.⁴³ Likewise, the expense of making PLGA microspheres was listed in one of the patents protecting Abilify Maintena as a reason for injecting suspensions of crystalline APZ.⁴⁴ In contrast, the experience and equipment to develop products involving synthesis of prodrugs, dissolution into oils, crystallization and/or milling are well established within most pharmaceutical companies.

C3. Crystals for Aqueous Suspension. A ready-to-use aqueous suspension would be the most convenient formulation for a physician by which to inject a crystalline compound. However, the compound must be stable against chemical degradation in water, the particle size must remain in a usable range until injected, and the particles must not form a dense sediment that is too difficult to resuspend after shipping or storage.⁴⁵ If these criteria cannot be met, then the crystals must be supplied as a powder for suspension. This may be the fastest way to get a new compound into development with a switch to ready-to-use suspension later in development or postmarket approval.

Zyprexa Relprevv (OLZ-pamoate) and Abilify Maintena (APZ·H₂O) are currently marketed as powders for reconstitution, where the product contains a sterile vial of powder and a sterile diluent along with appropriate syringes and needles. Both of these compounds have solubilities in the range of 0.1–10 µg/mL, while the compounds formulated as ready-to-use suspensions, APZ-C12 and PALI-C16, have solubilities below 0.1 µg/mL. (APZ-C12 and PAL-C16 have been synthesized at Alkermes and the solubility in 50 mM phosphate buffered saline (studied over the pH range of 6.0–8.0) was below the limit of detection in HPLC-UV methods that could detect the compounds down to ~0.1 µg/mL.) This higher solubility may actually be one of the limiting factors; chemical

degradation typically occurs much faster for dissolved compounds than for molecules that are locked into a stable crystal lattice. Therefore, the rate of degradation that is so often measured in solution stability studies during development is really only applicable to the dissolved fraction.

One patent protecting the Abilify Maintena product claims a freeze-dried cake containing APZ with a particle size in the range of 1–10 µm and all of the excipients so that only sterile water is required to reconstitute the formulation for injection.⁴⁶ The patent provides two examples for preparing crystals of the proper particle size. The first example employs a DYNO-MILL with high density zirconium oxide beads to reduce the particle size of crystalline APZ·H₂O in suspension with all of the excipients at about 10% solids load. The resulting suspension is ready for lyophilization. The second example uses the impinging jet method where a fine stream of APZ/ethanol solution is impinged with a fine stream of water. The resulting crystals are filtered, dried, and resuspended into an aqueous vehicle with all of the excipients and then freeze-dried in vials to give the final product. Both examples produced very similar particle-size distributions with a mean particle size of 2.5 µm. The available literature does not disclose the reason for lyophilizing rather than packaging as a ready-to-use suspension. However, an injectable aqueous solution of APZ is marketed for immediate release to treat acute agitation, which suggests that the molecule is chemically stable in water and that the bigger difficulty may be related to the physical behavior of the suspended crystals on storage or shipping.

C4. Ready-to-Use Aqueous Suspension. The only ready-to-use LAIA on the market as of 2013 was PALI-C16, and the trial of patents shows this product to be the culmination of over a decade of work to go from oral risperidone to a once-monthly injection. It was described as an improvement upon injections of a RISP-pamoate salt in the patent where it was first disclosed, since suspensions of RISP-pamoate provided extended release, but with high initial plasma concentrations, i.e., a burst effect.²² The innovator provided results from pharmacokinetic (PK) studies in dogs that compared PALI-C10 as a suspension in oil to PALI-C16 suspensions in oil and in water as shown in Table 3. The description of the study suggests that the decanoate was a solid that was not completely soluble in oil, but it does not state whether the solid was crystalline. It is clear that the PALI-C16 aqueous suspension gives higher plasma exposure and C_{max} than either of the suspensions in sesame oil. The lower viscosity of the aqueous suspension also allows for injection through a narrower 21-gauge needle.

The patents for paliperidone palmitate demonstrate the quick evaluation of delivery technologies with a convergence on nanomilling to reach submicrometer particles.^{22,47} The use of wet-media milling was of growing interest in the late 1990s, with the company NanoSystems (later Elan Drug Technologies and now part of Alkermes plc) leading the technology development, and Janssen Pharmaceutica applied the technique to esters of paliperidone.¹⁸

Table 4 shows PK data from dogs dosed with suspensions containing 7% Pali-C16 milled to give specific surface area

Table 4. Particle Size Dependence on PK in Dog after IM Injection of PALI-C16 in Aqueous Suspension^a

| particle size ^b (μm) | specific surface area (m^2/g) | C_{max} (ng/mL) | T_{max} (days) | $\text{AUC}_{0-\infty}$ (ng·h/mL) |
|---|--|--------------------------|-------------------------|-----------------------------------|
| 6.03 | 1.3 | 41.2 (± 22.1) | 12 (± 5) | 19487 (± 7697) |
| 1.38 | 6.5 | 86.4 (± 30.5) | 7 (± 3) | 25769 (± 9782) |
| 0.74 | 13.5 | 139 (± 33) | 1.8 (± 1.5) | 28603 (± 4305) |
| 0.52 | >15 | 132 (± 60) | 6.3 (± 1.5) | 34852 (± 14055) |

^a7.02% PALI-C16 in aqueous suspension dosed IM to dog in the left hind paw at 2.5 mg/kg using a 21 G 1.5" BD microlance needle. ^b50% of particles in the sample are smaller than the value in this column, based on data reported from a Mastersizer X light scattering particle size analyzer.

ranging from 1.3 to >15 m^2/g , as included in a patent from 1999.⁴⁷ There is a clear trend of C_{max} and AUC increases as well as T_{max} decreases with growing surface area and shrinking particle size, though the smallest particle size broke from the trend in C_{max} and T_{max} . Interestingly, the body of the patent states the drug is cleared particularly fast in dog compared to human and that the PK data in humans accordingly showed a much larger effect on particle size than had been predicted, though no data are provided.

D. EMERGING WORK AND AREAS FOR FURTHER RESEARCH

The literature and patents describe the currently marketed LAIAs, but they offer little guidance for selecting prodrugs or delivery options when assessing a new molecule. Two of the current LAIAs could potentially be improved through the use of prodrug-based delivery; the market desire for ready-to-use aqueous suspensions provides opportunities for both APZ and OLZ. Any strategy to improve OLZ should also seek to eliminate the possibility of PDSS. HALO and FLU have been on the market for decades, but one might question whether there is any benefit of switching to aqueous suspensions of a new crystal form. Prodrug strategies for OLZ and APZ have recently been disclosed along with physical data for fatty tails ranging in length from 2 to 18 carbons.^{15,48} The data show that a large variability in properties such as melting point can be expected within a series and that the trends are largely unpredictable without actually synthesizing and characterizing all molecules within the target series.

D1. Selecting Prodrugs for Aqueous Suspension. Florence and Vezin published the first study comparing the activities of two long chain fatty acids of a single prodrug as aqueous suspensions in 1982.³⁴ The study showed that FLU-C16 is more active than FLU-C18, that the activity is particle-size dependent, and that aqueous suspensions of long-chain analogues can outperform their respective solutions in oil. In this early paper, the aqueous suspensions are described as "solidified emulsions" that are available because the prodrugs melt around 50 °C. (We prepared and confirmed these compounds are crystalline with the melting points reported.) One of the patents for PALI-C16 states that other esters were prepared and tested in oils and aqueous suspensions.²² The text concluded that PALI-C16 aqueous suspensions were most favorable, but no data have been published, so the criteria remain unclear. The melting point of PALI-C16 is reported to

be 118 °C,⁴⁹ which is clearly high enough to make stable aqueous suspensions. Perhaps FLU-C18 with its lower melting point (mp) would also have shelf-stable suspensions, but one might expect a melting point depression in water that is uncomfortably close to body temperature. Unfortunately, there are too few studies published to help researchers decide on a minimally acceptable mp for crystalline prodrugs in aqueous suspension.

A recently published study on carbamate linked esters of OLZ (CLEOs) demonstrated a trend in mp change with tail length. This prodrug series was shown to have a single crystal packing motif with layers of parent separated by layers of lipid tail. The trends of tail length versus mp have also been recently disclosed for hydroxymethyl linked esters of APZ and pioglitazone (not an antipsychotic).⁴⁸ An overlay of these data is shown in Figure 3. The data for the APZ esters stand out

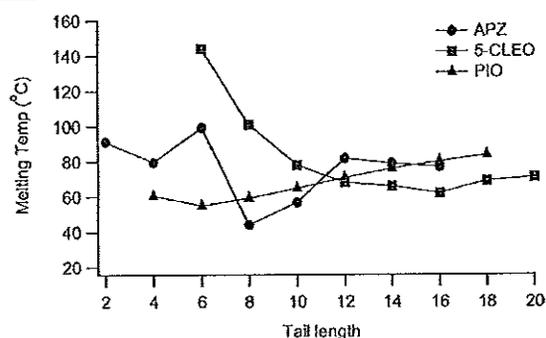


Figure 3. Overlay of melting point vs tail length (total carbon atoms) for APZ, 5-CLEO, and pioglitazone (PIO) linked esters.

in that there are two maxima in the mp trend at APZ-C6 and APZ-C12 with a minimum in between. In the abstract, the authors relate the behavior to changes in crystal packing. With melting points near 100 and 80 °C, both of these molecules were tested in human phase 1 clinical trials as aqueous suspensions, and APZ-C12 continued into a phase 3 pivotal trial that was recently completed with positive results.

D2. Understanding the Lag Phase in LAI Aqueous Suspension. There is a lag period where little drug is absorbed after injections of LAI depots of RISP, PALI-C16, and APZ·H₂O, which necessitates continuing oral therapy after the initial injection. After the second or third dose, drug still being released from earlier injections provides coverage during the subsequent lag periods, and oral augmentation is withdrawn. The lag, as seen in Figure 2 for Risperdal Consta, has been explained as a need for polymer to degrade sufficiently to allow for faster diffusion of the drug.³⁹ A 1–3 week lag period for crystalline drugs cannot be so easily explained, since the crystal does not become more soluble by virtue of sitting longer in the injection site. The body responds to all foreign materials shortly after they are injected, and the impact of this response as it evolves in the weeks following injection is just beginning to receive attention. A poster presented at the Controlled Release Society meeting in 2013 addressed this issue and described the immune response at the injection site, but did not make a conclusive link between the response and the lag period for an undisclosed lipophilic prodrug injected as an aqueous suspension.⁵⁰ Paquette et al. recently reported on the local tissue response to suspensions of APZ·H₂O and OLZ-pamoate.⁵¹ These crystalline drugs were both shown to induce

foreign body responses where the drug became encapsulated following injection, but the paper did not provide PK data. Further work is needed to explain not only the lag phase but also the physiological components responsible for dissolution and mobilization of molecules with nanogram per milliliter level aqueous solubility from depots.

D3. Potential Safety Advantage of Lipophilic Prodrugs over Poorly Soluble Salts. Most of the parent antipsychotics are capable of inducing sedation at sufficiently high plasma concentrations, but only OLZ-pamoate carries a boxed warning of PDSS, which results from unexpected solubilization of the molecule. Outside of antipsychotics, a similarly rare toxicity is observed for LAI penicillin benzathine, where slow release is also controlled through use of a poorly soluble salt form. In contrast, a literature review for PALI-C16 found no incidences of sedation postinjection.^{45,52} It is easy to rationalize these differences in terms of the lower solubility of the lipophilic prodrug and slow enzymatic reversion of long chain fatty esters back to the parent drug. In the event of accidental solubilization, the conversion of prodrug to parent occurs as a function of the half-life of ester activity, which may be less than 5 min for short chain esters or several hours for some with longer tails.

The lipophilicity/hydrophobicity of prodrugs may be the single largest safety advantage over salts or formulation-based strategies to retard release, trumping both solubility and slow esterase-mediated conversion. This factor drives the tendency to bind nonspecifically to surfaces and partition out of water into whatever organic phase is present. The most direct published demonstration of this phenomenon in the antipsychotic arena compared intravenous administration of FLU-C10 dissolved in ethanol to an aqueous solution of FLU-2HCl, with the results for one of four dogs shown in Figure 4.²⁹ The

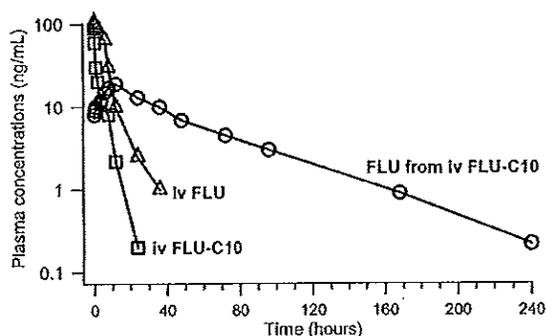


Figure 4. Comparison of plasma levels of FLU and FLU-D (FLU-C10) in dog after intravenous administration of aqueous FLU-2HCl or ethanolic FLU-C10.

plots for all four dogs were shown in the original manuscript, and the results are all consistent: immediately after injection of either compound, the concentration of the injected molecule is near 100 ng/mL; the prodrug leaves the plasma faster than the more water-soluble parent; the maximum concentration of active FLU delivered from the prodrug is 5-fold lower than the amount of prodrug injected; and FLU-C10 has formed a reservoir somewhere outside of the plasma from which it continues to slowly convert to active for more than 7 days. This experiment demonstrates that it is possible for some lipophilic prodrugs to prevent side effects resulting from mis-injection into a vein. Poorly soluble salts cannot compete, as the

counterion cannot be expected to remain associated or paired with the dissolved drug in the sea of other ions that is present in the body; once a salt dissolves, it will behave as the parent drug, and this is a fundamental difference from lipophilic prodrugs. Whether or not a prodrug approach could improve the safety of OLZ remains to be seen.

E. CONCLUSIONS

The LAIs that are administered as aqueous suspensions each use a unique combination of drug and delivery technologies, and very little data have been published that would help guide a team to the best strategy for their molecule. PLGA polymeric delivery systems may be the only viable option for small molecules that are water-soluble, especially if small changes in physiological pH can significantly increase the solubility. Poorly soluble salt forms of small molecules may be more prone to “bursts” than other strategies, especially when compared with lipophilic prodrugs. Even when no -OH group is present on the parent molecule, creative strategies have been used to reversibly place fatty acid tails on RISP, APZ, and OLZ. However, it is clear that no tail length is universally preferable for prodrugs that will become aqueous suspensions: PALI entered the market as the C16 prodrug; the C6 and C12 linked esters of APZ have both been tested in phase I human clinical trials; and FLU-C16 and -C18 esters were both found to be long-acting in rat models. Further publication of studies comparing the physical properties and behavior of different prodrugs of a given molecule could help to accelerate the transition of oral drugs to safe and reliable LAIs.

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Notes

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Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia

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ABSTRACT

Aripiprazole lauroxil is a linker lipid ester of aripiprazole for extended-release intramuscular (IM) injection. This multicenter, randomized, open-label study evaluated the pharmacokinetics (PK), relative bioavailability, and tolerability of a single IM deltoid or gluteal injection of aripiprazole lauroxil in adult subjects with chronic stable schizophrenia or schizoaffective disorder. Forty-six subjects were randomized 1:1 to aripiprazole lauroxil 441 mg IM in the deltoid or gluteal muscle. Samples were collected through 89 days post-dose to measure levels of aripiprazole lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole. Forty-three (93.5%) subjects completed all study assessments; most were CYP2D6 extensive or immediate metabolizers (96%); two (4%) were poor metabolizers. The PK of aripiprazole following aripiprazole lauroxil was characterized by a steady rise in plasma concentrations (T_{max} 44–50 days), a broad peak, and prolonged exposure attributable to the dissolution of aripiprazole lauroxil and formation rate-limited elimination of aripiprazole ($t_{1/2} = 15.4$ – 19.2 days). Deltoid vs. gluteal administration resulted in slightly higher C_{max} aripiprazole concentrations {1.31 (1.02, 1.67); GMR 90% CI}; total exposure (AUC_{inf}) was similar between sites of administration [0.84 (0.57, 1.24)]. *N*-hydroxymethyl-aripiprazole and dehydro-aripiprazole exposures were 10% and 33–36%, respectively, of aripiprazole exposure following aripiprazole lauroxil. The most common adverse events were injection site pain in 20 subjects (43.5%) and headache in 6 subjects (13.0%) of mild intensity occurring at a similar rate with deltoid and gluteal administration. Exposure ranges with deltoid and gluteal administration overlapped, suggesting that these sites may be used interchangeably. Despite a higher incidence of adverse events, deltoid muscle provides a more accessible injection site and could facilitate patient acceptance.

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1. Introduction

Schizophrenia is a chronic, disabling and progressive disease with a lifetime prevalence of 0.8% to 1% of the general population (Messias et al., 2007; McGrath et al., 2008). Nonadherence is a major risk factor for relapse in schizophrenia where even brief periods of nonadherence can increase the risk of hospitalization (Masand et al., 2009; Weiden et al., 2004; Leucht and Heres, 2006). It is estimated that approximately 50% of patients omit taking 30% or more of their medications for schizophrenia (Velligan et al., 2006; Kamali et al., 2006; Goff et al., 2010). Side effects of antipsychotics including extrapyramidal symptoms, weight gain and cognitive impairment contribute to nonadherence (Ascher-Svanum et al., 2006, 2009; DiBonaventura et al., 2012).

Long-acting intramuscular (IM) depot antipsychotics have the potential to improve long-term outcomes, at least in part, by improving adherence (Weiss et al., 2002; Lang et al., 2010). Comparative data

suggest that depot formulations may exhibit improved effects over oral antipsychotics for relapse prevention and lower risk of re-hospitalization (Peuskens et al., 2010; Leucht et al., 2011; Tiihonen et al., 2011; Grimaldi Bensourda et al., 2012).

Aripiprazole lauroxil is a covalently bonded modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. Conversion of aripiprazole lauroxil to aripiprazole in vivo is governed by slow dissolution of the aripiprazole lauroxil particles followed by hydrolysis, resulting in extended systemic exposure of aripiprazole. Conversion is driven by dissolution of aripiprazole lauroxil and subsequent enzyme-mediated cleavage, generating lauric acid and the *N*-hydroxymethyl aripiprazole intermediate. The covalently bonded hydroxymethyl group is then converted to aripiprazole following water-mediated hydrolysis. Development of aripiprazole lauroxil was undertaken to improve upon the clinical profile of a depot antipsychotic injection while benefiting from the clinical and safety profile of the parent compound, aripiprazole.

In an earlier clinical study, single doses of aripiprazole lauroxil 221 mg, 441 mg, and 588 mg administered to 40 subjects with schizophrenia revealed no clinically significant tolerability concerns (Turncliff et al., 2012). In a second study of aripiprazole lauroxil at doses of

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441 mg, 662 mg, and 882 mg in subjects with chronic stable schizophrenia who continued their on-going atypical antipsychotic treatment, clinical effect was maintained over 4 months with no unexpected tolerability concerns (data on file, Alkermes, Inc., Waltham, MA). This phase 1 clinical study was undertaken to determine the pharmacokinetics (PK), relative bioavailability and tolerability of aripiprazole lauroxil administered as a single 441 mg IM injection in the deltoid or gluteal muscle to adult subjects with chronic stable schizophrenia or schizoaffective disorder.

2. Methods

This was a phase 1 randomized, open-label, single-dose study conducted at four sites in the U.S. The study was done in accordance with the Declaration of Helsinki, 1964 and Good Clinical Practice principles outlined in the International Conference on Harmonization, 1997. The protocol, amendments, and informed consent were approved by an Institutional Review Board for each site, and written informed consent of all participants was obtained after the nature of the procedures had been fully explained and prior to study participation.

2.1. Study design

The study duration for each completing subject was approximately 117 days, including a 4-week screening period, an 8-day inpatient period, and an 82-day follow-up period. Initially, two sentinel subjects received aripiprazole lauroxil 221 mg in the deltoid muscle. Following review of safety data on aripiprazole lauroxil 221 mg, the remaining subjects were randomly assigned to receive aripiprazole lauroxil 441 mg administered as an IM injection in the deltoid or gluteal muscle.

2.2. Subject selection

Men and women age 18 to 55 years with chronic stable schizophrenia or schizoaffective disorder based on DSM-IV-TR criteria (APA, 2000) were eligible if they had a body mass index (BMI) of 18 to 40 kg/m², were on stable medication (other than aripiprazole) for ≥ 2 months, and had a documented history of previous aripiprazole use that was well tolerated. Subjects were required to be clinically stable with no hospitalization for acute psychiatric exacerbation within 3 months and a Clinical Global Impressions – Severity (CGI-S; Guy, 1976) score ≤ 3 at screening. Subjects were permitted to continue taking concomitant medications, including antipsychotics other than aripiprazole, during the study, provided that these medications were not prohibited by the exclusion criteria.

Subjects were excluded for use of aripiprazole within 60 days of screening, the presence of suicidal ideation (score of 4 or 5 on the Columbia Suicide Severity Rating Scale [C-SSRS, Posner et al., 2007]) within the past 2 months or any suicidal behavior occurring in the past year. Subjects also were excluded for a history of any unstable medical illness that could interfere with the conduct of the study, a corrected QT interval (Bazett formula) >450 ms for men or >470 ms for women, any clinically significant laboratory abnormality, receipt of medication by deltoid or gluteal administration prior to Day 1, use of medications that were inducers or inhibitors of cytochrome P450 (CYP) 3A4 or inhibitors of CYP2D6 within 30 days prior to Day 1, and alcohol or substance dependence within 12 months or substance abuse within 3 months before screening or positive test for drugs of abuse at screening. Women who were pregnant or breastfeeding were excluded.

2.3. Study assessments

Safety evaluations included monitoring for adverse events and injection site reactions, clinical laboratory testing (hematology, chemistry, urinalysis), physical examination, vital signs (heart rate, blood pressure, body temperature, respiratory rate), and 12-lead electrocardiogram

(ECG). A serum pregnancy test was performed at screening and a urine pregnancy test was performed at baseline.

The C-SSRS was administered at screening, baseline, and at study Days 1 and 7 through 23 to prospectively evaluate patients for suicidal ideation. The Extrapyramidal Symptom Rating Scale (ESRS, Chouinard and Margolese, 2005) was administered at baseline and Days 7, 15, 19 and 23 to evaluate patients for extrapyramidal symptoms.

Blood samples were collected at the pre-specified time points to determine plasma concentrations of aripiprazole lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole after IM dosing using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with a quantitation range of 1.00 to 500 ng/mL for all analytes. Samples were analyzed at Tandem Laboratories (Salt Lake City, Utah). PK sampling was performed on Day 1 predose, and at 1, 4, 8, and 12 h post dose. On Days 2 through 7, PK samples were collected within 1 h of the Day 1 dosing time. On Days 9, 11, 13, 15, 17, 19, 21, 23, 25, 28, 31, 38, 45, 52, 59, 70 and 80, samples were collected at any time during the day. On Day 89 or end-of-treatment, a single sample was collected at any time during the day. A blood sample was obtained on Day 1 for determination of CYP2D6 genotype.

2.4. Pharmacokinetic analysis

Individual plasma concentrations for aripiprazole lauroxil, *N*-hydroxymethyl-aripiprazole, aripiprazole and dehydro-aripiprazole, were summarized over time using descriptive statistics. PK parameters determined for aripiprazole, dehydro-aripiprazole and *N*-hydroxymethyl aripiprazole included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration time curve from time zero to the last quantifiable plasma concentration (AUC_{0-last}), area under the plasma concentration time curve from time zero to infinity (AUC_{0-inf}), and terminal elimination half-life ($t_{1/2}$). The relative bioavailability of aripiprazole and dehydro-aripiprazole was determined for deltoid versus gluteal IM administration of aripiprazole lauroxil.

2.5. Statistical analysis

The safety population was defined as all subjects who received at least one dose of aripiprazole lauroxil. The PK population was defined as all subjects who received at least one dose of study drug and had sufficient plasma concentration data to calculate at least one of the PK parameters for at least one of the analytes.

Plasma concentration data were summarized according to nominal (protocol-specified) sampling times. Non-compartmental PK analysis was performed using WinNonlin v5.3 utilizing actual elapsed times from dose. Values of C_{max} and T_{max} were determined from direct observation of the raw concentration data. AUC was calculated using the linear-up and log-down trapezoidal rule. AUC was extrapolated to infinity (AUC_{0-inf}) by adding the portion C_{last}/λ_z where C_{last} was the observed concentration at the last measurable sample and λ_z was the elimination rate constant of the terminal linear phase of the plasma concentration-time curve. If applicable, the terminal elimination half-life ($t_{1/2}$) was calculated as $\ln 2 / \lambda_z$. In the case where an extrapolated portion of $AUC_{0-inf} > 20\%$ ($AUC_{0-inf}/AUC_{0-last} > 1.2$), λ_z and associated parameters ($t_{1/2}$ and AUC_{0-inf}) were excluded from further analysis.

The relative bioavailability comparing deltoid IM administration to gluteal IM administration of aripiprazole lauroxil was summarized based on aripiprazole exposure ($F_{rel} = AUC_{deltoid} / AUC_{gluteal}$) for AUC_{0-last} and AUC_{0-inf} . In addition, 1-way analysis of variance (ANOVA) was performed on log-transformed PK parameters (AUC) as the dependent variables and treatment group (aripiprazole lauroxil 441 mg deltoid or gluteal) as the independent variable. Geometric means with 95% CI for each treatment group and geometric mean ratios along with 90% CI were presented. The technique of nonparametric superposition was employed to predict steady state concentrations of

aripiprazole following aripiprazole lauroxil administration in the deltoid or gluteal site.

3. Results

Overall, 51 subjects were screened, 46 were randomized to study medication, and 43 completed the study. Two subjects were lost to follow-up and one subject was discontinued for missed visits. Subject demographics across treatment groups were comparable at the time of randomization (Table 1). Assessment of CYP 2D6 genotype results revealed that most subjects were CYP2D6 extensive metabolizers (63%) or intermediate metabolizers (33%); only two subjects (4%) were poor metabolizers. More subjects were CYP2D6 extensive metabolizers in the aripiprazole lauroxil gluteal group than in the aripiprazole lauroxil deltoid group (72.7% vs. 54.5%).

3.1. Pharmacokinetics

Concentrations of aripiprazole lauroxil were not detectable in any subject. Plasma profiles of aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl-aripiprazole after a single 441 mg IM injection demonstrated the slow dissolution properties of aripiprazole lauroxil, with no evidence of early aripiprazole release, regardless of the administration site (Table 2). Following deltoid or gluteal administration of aripiprazole lauroxil 441 mg, mean aripiprazole plasma concentrations increased steadily through approximately Days 44 to 50, followed by slow decline through Day 89 (Fig. 1). Mean aripiprazole concentrations were higher following deltoid administration over the sampling interval, but largely overlapped with aripiprazole concentrations following gluteal administration due to variability.

Following deltoid or gluteal administration, the PK profile of metabolites behaved similarly to the parent aripiprazole. Dehydro-aripiprazole concentrations increased through Days 51 to 52. Similar to aripiprazole concentrations, mean dehydro-aripiprazole concentrations were slightly higher following deltoid administration and paralleled those of aripiprazole. Following peak levels, a linear decline in dehydro-aripiprazole concentrations was observed to Day 89. Total dehydro-aripiprazole exposure (AUC_{0-1ast}) was approximately 33% to 36% of aripiprazole exposure. Low, but measurable, *N*-hydroxymethyl-aripiprazole concentrations paralleled those of aripiprazole. Total exposure of *N*-hydroxymethyl aripiprazole (AUC_{0-1ast}) was approximately 10% of aripiprazole exposure; C_{max} [Mean (SD)] of the intermediate was 6.68 (2.63) and 5.84 (3.72) following deltoid and gluteal administration of aripiprazole lauroxil, respectively.

No clear relationship was observed between CYP2D6 genotype and aripiprazole exposure following IM administration of aripiprazole lauroxil to either the deltoid or gluteal muscle (Fig. 2).

3.2. Relative bioavailability of deltoid vs. gluteal administration

Examination of geometric mean ratio and 90% CI indicate that aripiprazole and dehydro-aripiprazole exposure was greater following deltoid administration than gluteal administration for C_{max} and AUC_{last} , while AUC_{0-1inf} values were comparable (Table 2). Deltoid administration resulted in approximately 23% to 34% greater C_{max} and AUC_{last} estimates for aripiprazole and 24% to 48% greater estimates for dehydro-aripiprazole. The observed range of aripiprazole and dehydro-aripiprazole exposures based on AUC_{0-1ast} overlapped between the two sites of administration (Table 3, Fig. 2). The AUC_{inf} geometric mean ratio (90% CI) for aripiprazole was 0.84 (0.57, 1.24).

When aripiprazole PK parameters were summarized by CYP2D6 genotype, there was no clear impact of metabolic status on aripiprazole or dehydro-aripiprazole exposure.

3.3. Predicted steady-state aripiprazole concentrations following deltoid vs. gluteal administration of aripiprazole lauroxil

The results of nonparametric superposition of aripiprazole concentrations following aripiprazole lauroxil administration are shown in Fig. 3. Utilizing the observed variability following a single dose, the steady-state mean and 95% confidence intervals are presented for aripiprazole following deltoid or gluteal administration of aripiprazole lauroxil 441 mg.

3.4. Tolerability

Overall, 38 (82.6%) subjects experienced at least one treatment-emergent AE (Table 4); all AEs were mild or moderate in intensity. While the number of subjects who experienced an AE was similar between groups, the number of individual AEs was higher in the deltoid administration group. The most common AE was injection site pain in 20 (43.5%) subjects; the incidence was higher in subjects receiving deltoid administration of aripiprazole lauroxil, however all were mild in nature. The most common systemic AEs were headache (13.0%), insomnia (10.9%), and toothache (10.9%). Twenty-four (52.2%) subjects experienced at least one treatment-related AE. Dyskinesia and dystonia each occurred in 3 subjects (13.6%) in the deltoid group, but these were not observed in the gluteal group. Other common AEs occurred at a similar

Table 1
Demographic and baseline characteristics by treatment group.

| | Aripiprazole lauroxil treatment group | | | Total (n = 46) |
|-------------------------------------|---------------------------------------|-------------------------|-------------------------|----------------|
| | 221 mg deltoid (n = 2) | 441 mg deltoid (n = 22) | 441 mg gluteal (n = 22) | |
| Age, years ^a | 46.5 (0.7) | 43.0 (8.8) | 41.6 (9.4) | 42.5 (8.9) |
| Age, range | 46–47 | 24–54 | 22–55 | 22–55 |
| Female, n (%) | 0 | 6 (27.3) | 8 (36.4) | 14 (30.4) |
| Race, n (%) | | | | |
| White | 0 | 6 (27.3) | 4 (18.2) | 10 (21.7) |
| Black or African American | 2 (100) | 15 (68.2) | 18 (81.8) | 35 (76.1) |
| Asian | 0 | 1 (4.5) | 0 | 1 (2.2) |
| BMI, kg/m ² ^a | 31.3 (9.4) | 28.6 (5.3) | 28.6 (5.0) | 28.7 (5.2) |
| CGI-S, n (%) | | | | |
| Normal, not at all ill | 0 | 0 | 1 (4.5) | 1 (2.2) |
| Borderline mentally ill | 2 (100) | 1 (4.5) | 3 (13.6) | 6 (13.0) |
| Mildly ill | 0 | 21 (95.5) | 18 (81.8) | 39 (84.8) |
| 2D6 Predicted phenotype, n (%) | | | | |
| Extensive metabolizer | 1 (50.0) | 12 (54.5) | 16 (72.7) | 29 (63.0) |
| Intermediate metabolizer | 1 (50.0) | 9 (40.9) | 5 (22.7) | 15 (32.6) |
| Poor metabolizer | 0 | 1 (4.5) | 1 (4.5) | 2 (4.3) |

^a Mean (standard deviation).

Table 2

Summary of aripiprazole and dehydro-aripiprazole pharmacokinetic parameters following deltoid or gluteal administration of aripiprazole lauroxil 441 mg [mean (SD)].

| Parameter | Aripiprazole lauroxil 441 mg Deltoid (n = 22) | | Aripiprazole lauroxil 441 mg gluteal (n = 22) | |
|----------------------------|---|----------------------|---|----------------------|
| | Aripiprazole | Dehydro-aripiprazole | Aripiprazole | Dehydro-aripiprazole |
| C_{max} (ng/mL) | 57.4 (21.6) | 19.8 (7.0) | 46.8 (23.6) | 16.8 (10.8) |
| %CV | 37.6 | 35.5 | 50.5 | 64.1 |
| Geometric mean | 53.4 | 18.3 | 40.9 | 13.7 |
| Median T_{max} (days) | 44.1 | 50.7 | 50.0 | 52.1 |
| Range | 29, 87 | 36, 87 | 27, 59 | 36, 87 |
| AUC_{last} (ng*days/mL) | 2744 (1150) | 904 (365) | 2275 (1077) | 815 (539) |
| %CV | 41.9 | 40.4 | 47.3 | 66.1 |
| Geometric mean | 2495 | 821 | 2022 | 663 |
| AUC_{0-inf} (ng*days/mL) | 3351 (1558) n = 10 | 1104 (432) n = 6 | 3598 (746) n = 7 | 1600 (812) n = 5 |
| %CV | 46.5 | 39.1 | 20.7 | 50.7 |
| Geometric mean | 2966 | 1033 | 3527 | 1438 |

frequency across the two groups. There were no severe AEs and no discontinuations due to AEs were observed.

There were no clinically significant effects of aripiprazole lauroxil on vital signs, physical examination or ECG recordings. No clinically meaningful differences in mean change from baseline for any vital sign or ECG parameters were observed between the treatment groups. Changes from baseline clinical laboratory tests were relatively small; no patterns of change with time or differences between the treatment groups were observed. Mean changes from baseline for ESRS total and subcategory scores were small at all time points. No clinically meaningful differences were observed for the mean change from baseline for ESRS total and subcategory scores between treatment groups. No post-baseline responses were noted on the C-SSRS that indicated suicidal risk or behavior for any subject.

4. Discussion

In this study, the pharmacokinetic profile of aripiprazole and dehydro-aripiprazole following a single IM dose of aripiprazole lauroxil demonstrated slow dissolution properties with no evidence of early aripiprazole release, regardless of administration via the deltoid or gluteal muscle. The slow dissolution rate of aripiprazole lauroxil governs the conversion to aripiprazole absorption to such an extent that the absorption rate becomes slower than the rate of elimination for aripiprazole (72 h; Mallikaarjun et al., 2008) and a "flip-flop" pharmacokinetic model results (Silber et al., 1987; Dunbar et al., 2006).

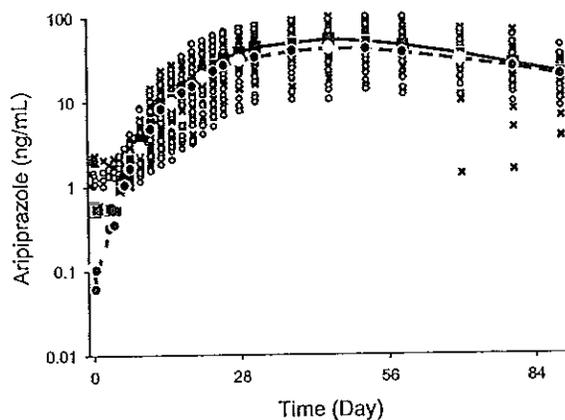


Fig. 1. Concentrations [mean (line) and individual data (symbols)] of aripiprazole following deltoid (circles) or gluteal (crosses and square) administration of aripiprazole lauroxil 441 mg.

Conversion of aripiprazole lauroxil to the *N*-hydroxymethyl aripiprazole intermediate occurs rapidly as no measurable concentrations of the novel prodrug were detected (LLOQ 1 ng/mL). The *N*-hydroxymethyl aripiprazole intermediate of aripiprazole lauroxil was detected at low levels, with overall exposure (AUC_{last}) relative to aripiprazole of approximately 10%. The extent of aripiprazole exposure showed extensive overlap whether administered into the deltoid or gluteal muscle. The variability (CV%) for both injection sites was in the range of 40% to 55% for C_{max} and AUC. In this study, the ratio of dehydro-aripiprazole to aripiprazole for AUC was 33% and 36% for deltoid and gluteal administration, respectively, which compares with 29%–33% for another aripiprazole LAI (Mallikaarjun et al., 2013) and to 33–39% following oral aripiprazole in healthy volunteers (Mallikaarjun et al., 2008).

Total aripiprazole exposure (AUC_{0-inf}) was similar across injection sites in the subset of subjects in which it could be calculated. While plasma samples were collected over a period of three months, the slow dissolution of aripiprazole lauroxil following IM administration resulted in absorption of aripiprazole over a significantly longer period of time. Across all subjects, mean exposure (AUC_{last}) was slightly higher following administration in the deltoid site than the gluteal site, although the range of exposures overlapped significantly across patients and is likely attributable to the plasma sample collection interval. This is consistent with previous studies of LAI formulations of risperidone

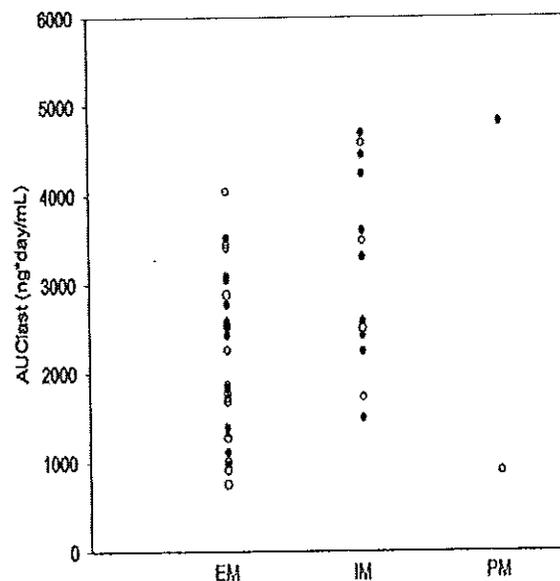


Fig. 2. Aripiprazole exposure (AUC_{0-inf}) following deltoid or gluteal administration of aripiprazole lauroxil 441 mg presented by CYP2D6 genotype. Solid circles reflect deltoid administration, and open circles reflect gluteal administration.

Table 3
Relative bioavailability assessment of aripiprazole following deltoid and gluteal administration of aripiprazole lauroxil 441 mg.

| | Aripiprazole lauroxil 441 mg deltoid | | | Aripiprazole lauroxil 441 mg gluteal | | | Deltoid/gluteal ratio | |
|------------------------------|--------------------------------------|------|------------|--------------------------------------|------|------------|-----------------------|------------|
| | N | GM | 95% CI | N | GM | 95% CI | GMR | 90% CI |
| C_{max} (ng/mL) | 22 | 53.4 | 43.4, 65.7 | 22 | 40.9 | 33.2, 50.3 | 1.31 | 1.02, 1.67 |
| AUC_{last} (days * ng/mL) | 22 | 2495 | 2019, 3083 | 22 | 2022 | 1636, 2498 | 1.23 | 0.96, 1.58 |
| AUC_{0-inf} (days * ng/mL) | 10 | 2966 | 2185, 4027 | 7 | 3527 | 2447, 5083 | 0.84 | 0.57, 1.24 |

GM = geometric mean; GMR = geometric mean ratio; CI = confidence interval.

and paliperidone wherein no significant differences in the PK profile or bioavailability for deltoid vs. gluteal IM administration was observed (Hough et al., 2009; Elliott et al., 2010; Thyssen et al., 2010; Quiroz et al., 2011).

Aripiprazole lauroxil is intended for once-monthly administration. As such, the results of the current study suggest that accumulation of aripiprazole would result upon repeat administration of aripiprazole lauroxil every 28 days. Due to the gradual rise in plasma concentrations of aripiprazole following aripiprazole lauroxil administration, supplementation with oral aripiprazole for 3 weeks is anticipated to be required upon initiation of therapy to maintain therapeutically relevant concentrations. Based on nonparametric superposition, predicted steady state aripiprazole concentrations following aripiprazole lauroxil administration are therapeutically relevant (Gründer et al., 2008) and are anticipated to show little difference by injection site. The predicted peak-to-trough ratio of 1.0 indicates a very flat profile, suggesting that higher doses of aripiprazole lauroxil may maintain therapeutically relevant concentrations over a longer dosing interval.

Single IM doses of aripiprazole lauroxil 221 mg in the deltoid muscle or 441 mg in the deltoid or gluteal muscle were well tolerated in subjects with chronic stable schizophrenia, although the incidence of injection site pain and certain other adverse events was higher with deltoid administration. The observation of increased incidence of injection site pain with deltoid administration was consistent with previous reports of LAIs, as evidenced by a rate of 41% vs. 26% (deltoid vs. gluteal) reported for paliperidone palmitate (Hough et al., 2009). The incidence of injection site pain declined markedly with repeat administration: in a 4 month study of aripiprazole lauroxil (441 mg) administered in the deltoid in 40 subjects, injection site pain was reported in 10 subjects (25%) (Alkermes, data on file). In a phase 3 study of aripiprazole lauroxil, <5% of patients reported injection site pain with 3 monthly gluteal administrations (Stankovic et al., 2014). Importantly, all subjects in this study remained on their current antipsychotic for the duration of the study, the most common of which were quetiapine, risperidone, olanzapine, paliperidone and ziprasidone. As such, the safety profile of

aripiprazole lauroxil in this study reflects the combined effects of the study drug and its metabolites as well as the subjects' concurrent treatment regimen for managing schizophrenia.

Aripiprazole exhibits partial agonist activity at dopamine D_2 receptors, partial agonist activity at serotonin $5-HT_{1A}$ receptors and antagonist activity at $5-HT_{2A}$ receptors (Burriss et al., 2002; Jordan et al., 2002; Shapiro et al., 2003; Stark et al., 2007). Compared with other antipsychotics, oral aripiprazole has demonstrated a low potential for metabolic disturbances and a low risk for hyperprolactinemia, which are important in the setting of a high incidence of medical co-morbidity and mortality in subjects with schizophrenia (Pigott et al., 2003; Goff et al., 2005; Fleischhacker et al., 2009). The efficacy, safety and tolerability profile of oral aripiprazole has been demonstrated over years of patient exposure. Thus, a long-acting injectable formulation of aripiprazole offers an attractive option for the long-term treatment of schizophrenia.

The gluteal site is most commonly used for IM injection because of the presence of adequate adipose tissue and the ability to inject larger volumes (Gray et al., 2009). The deltoid site is used less often because it may be associated with more injection site discomfort. Only small volumes, e.g., less than 2 mL, are recommended for deltoid injection because of the smaller muscle size and risk of injury to the radial nerve and brachial artery. A survey of healthcare professionals concerning administration of LAI antipsychotics found that the majority viewed the availability of both deltoid and gluteal routes of administration as beneficial (Geerts et al., 2013). Furthermore, the majority of respondents felt that deltoid administration was associated with less social embarrassment and was more respectful to the patient than gluteal administration. Subjects perceived deltoid injection favorably, although some expressed concern with increased injection site pain with deltoid injection (Heres et al., 2012).

Despite the long 12-week sampling period, plasma aripiprazole concentrations remained high and constant over the dosage interval as evidenced by T_{max} values in many subjects that occurred close to the end of the sampling window. Although a longer study duration may have

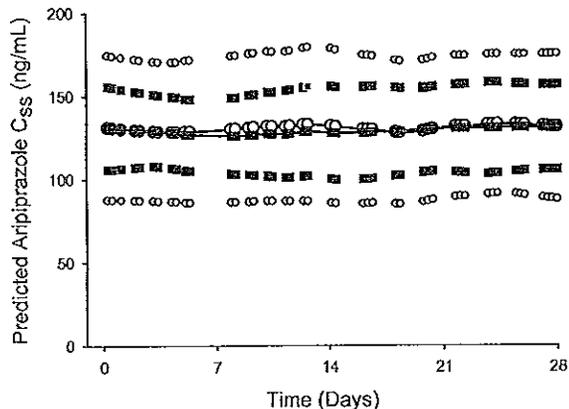


Fig. 3. Predicted aripiprazole steady-state concentration (C_{ss}) following repeated deltoid or gluteal administration of aripiprazole lauroxil 441 mg. Open circles reflect deltoid administration, and squares reflect gluteal administration [Mean (solid line) and 95% confidence interval].

Table 4
Incidence of treatment-emergent adverse events in >5% of subjects overall.

| | Aripiprazole lauroxil | | |
|---------------------------|----------------------------|----------------------------|------------------------|
| | 441 mg deltoid (n = 22) | 441 mg gluteal (n = 22) | Total (n = 46) |
| Subjects with ≥ 1 AE | 20 (90.9) | 17 (77.3) | 38 (82.6) ^a |
| Injection site pain | 14 (63.6) | 6 (27.3) | 20 (43.5) |
| Headache | 5 (22.7) | 1 (4.5) | 6 (13.0) |
| Insomnia | 3 (13.6) | 2 (9.1) | 5 (10.9) |
| Toothache | 2 (9.1) | 2 (9.1) | 5 (10.9) ^a |
| Abdominal discomfort | 3 (13.6) | 1 (4.5) | 4 (8.7) |
| Constipation | 3 (13.6) | 1 (4.5) | 4 (8.7) |
| Diarrhea | 3 (13.6) | 1 (4.5) | 4 (8.7) |
| Akathisia | 2 (9.1) | 1 (4.5) | 3 (6.5) |
| Back pain | 2 (9.1) | 1 (4.5) | 3 (6.5) |
| Dyskinesia | 3 (13.6) | 0 | 3 (6.5) |
| Dystonia | 3 (13.6) | 0 | 3 (6.5) |
| Nasopharyngitis | 1 (4.5) | 2 (9.1) | 3 (6.5) |

^a Includes 1 subject who received aripiprazole lauroxil 221 mg.

been feasible, subject discontinuation might have become problematic. The fact that concentrations persisted suggests that the half-life of aripiprazole is long following aripiprazole lauroxil administration. This is a desirable feature for a long acting injectable antipsychotic as it affords the patient some flexibility in scheduling the next dose. Another limitation of the study was sample size. Though the sample size was considered adequate and appropriate for the assessment of relative bio-availability of deltoid and gluteal sites, the number of subjects randomized did not allow for a robust assessment of the impact of CYP2D6 genotype on total exposure.

In summary, the results of this study indicated that single IM doses of aripiprazole lauroxil 441 mg administered into the deltoid or gluteal muscle were well tolerated in subjects with chronic stable schizophrenia, although a higher incidence of injection site reactions occurred with deltoid administration. Injection into the deltoid muscle resulted in higher mean exposure to aripiprazole and its two metabolites, although the range of exposures observed between the two administration sites overlapped. These results suggest that deltoid and gluteal injection sites may be used interchangeably for administration of aripiprazole lauroxil 441 mg.

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Contributors

R.T. and M.H. were involved in the concept, design, data analysis and interpretation, manuscript development and revisions and approved the manuscript for submission. R.R. Y.D. and E.E. were involved in concept, design, data interpretation, and manuscript revisions and approved the manuscript for submission.

Conflict of interest

Drs. Turncliff, Hard, Du, Risinger and Ehrich are employees of Alkermes Inc., the sole developer of aripiprazole lauroxil, a novel prodrug of aripiprazole.

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