Long-Acting Injectable Aripiprazole: How Might It Fit In Our Tool Box?

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Abstract

Schizophrenia is a severe mental illness with a lifetime prevalence of approximately one percent worldwide. Maintenance antipsychotic treatment has been effective in preventing relapses in long-term follow-up studies. Logically it can be proposed that long-acting injectable antipsychotics (LAI) might reduce both unintentional and intentional nonadherence. Long-acting injectable aripiprazole was approved for the treatment of schizophrenia by the U.S. FDA on 28th February 2013 and will be marketed under the name Abilify Maintena. Aripiprazole LAI (ALAI) is a lyophilized powder that needs to be reconstituted with sterile water to form an injectable suspension without affecting the original molecule. The monthly injection interval is very attractive since patients prefer fewer injections. From a tolerability perspective, ALAI appears to be both weight neutral and lacking metabolic side effects. This can confer an advantage over the other currently available second-generation antipsychotic LAIs. Simple constitution with sterile water and no requirement to refrigerate make storage and administration easier. Like all medications, there are always potential disadvantages to ALAI. There is a period of oral coverage, while not as long as for long-acting risperidone microspheres (RLAI), that is required. Care must be taken to review concomitant medications for the presence of metabolic inducers and inhibitors. One would also expect some patients to be sensitive to extrapyramidal symptoms, especially akathisia which is well documented in the oral preparation. All things considered, we welcome our new tool, ALAI, to our workplace and predict both clinical practice and post marketing analysis and studies will discover its true value.

Key Words: Long-Acting Injectable, Antipsychotics, Aripiprazole, LAI, Maintenance, Schizophrenia

Introduction

Schizophrenia is a severe mental illness with a lifetime prevalence of approximately one percent worldwide. Due to its often chronic disabling course, it bears a significant socioeconomic burden. The financial costs of schizophrenia include direct expenditures such as inpatient, outpatient, and long-term psychiatric and medical care, as well as indirect costs due to productivity loss suffered by individuals with schizophrenia, their family members, and caregivers. The yearly total cost of schizophrenia was estimated to be $62.7 billion in the U.S. in 2002 (1).

Antipsychotics are the main class of medications used to treat the symptoms of schizophrenia. Since the discovery of the first antipsychotic—chlorpromazine—in the 1950s, there has been significant progress in our understanding of the psychopathology of schizophrenia and the presumed mechanism of action of the variety of antipsychotics developed. An appreciation of the motor side effects of the early antipsychotics led to the development of the second-generation antipsychotics (SGAs), which as a group appear to have fewer neurologic side effects. However, the SGAs are not free of other side effects, most notably a greater preponderance of weight gain, hyperlipidemia and risk of diabetes. More recently approved antipsychotics have been specifically brought to market with the aim of reducing all these concerns.

In the chronic course of this illness, characterized by exacerbations, preventing relapses is critical. Each relapse imparts a greater risk of worsening disability, risk to self or others and potential treatment resistance (2, 3). Relapses have also shown to significantly increase the cost of care (4). Maintenance antipsychotic treatment has been effective in preventing relapses in long-term follow-up studies (5-9). Numerous studies have shown a relationship between relapse

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and suboptimal adherence to antipsychotics. Weiden et al. showed that even small gaps in medication possession led to large increases in rehospitalizations (10). Understanding the causes of adherence is complex. Patients and their providers grossly underestimate medication compliance (11). Other possible reasons include unintentional forgetting of dose or doses, misunderstanding the directions from the physician (12), or intentional declining (due to lack of efficacy, side effects or poor insight). Logically it can be proposed that long-acting injectable antipsychotics (LAIs) might reduce both unintentional and intentional nonadherence. It is important to appreciate that LAIs are only effective if the injection is given. The patient can still refuse to come for their two week or monthly injection. However, once a patient misses their interval injection, they have declared a potential nonadherent period. Interventions can be employed to help bring the patient back to treatment before they have a full exacerbation of symptoms.

The concept that LAIs can reduce relapse is not without controversy. The seminal Hogarty et al. study reported a superiority of long-acting fluphenazine over its oral counterpart (13). This superiority was apparent only after the first year and the numbers used to compare were relatively small. A more recent study in Finland, by Tiihonen et al., showed that use of LAIs prevented rehospitalization three times more than oral formulation of the same antipsychotic (14). However, Rosenheck et al., in a large study of U.S. veterans, did not show superiority of long-acting risperidone microspheres (RLAI) versus oral medications (15). One apparent difficulty in LAI studies is design constraints. A more naturalistic observational study like the Tiihonen et al. study tends to show superiority of LAIs while randomized trials like Rosenheck et al. do not. It has been proposed that the selection of agreeable/consentable persons in a randomized trial and relatively intense treatment in both oral and injectable arms attenuates differences in the delivery systems.

Brief Review of Current LAIs

In the U.S., there are several long-acting injectables (LAIs) available, including two first-generation antipsychotics—haloperidol and fluphenazine (more first-generation LAIs available worldwide)—and three second-generation antipsychotics—olanzapine, risperidone and paliperidone LAI.

Like their oral progenitors, haloperidol and fluphenazine LAI tend to have a higher incidence of extrapyramidal symptoms (EPS) than the second-generation LAIs. Both formulations use a long chain fatty acid such as decanoate or enanthate, and steady state with injections is not obtained for weeks or even months after initiation. This may require the patient to take oral antipsychotics for a period of time. Loading doses of these typical LAIs help to attain the steady level faster but increases the risk of emergent side effects (16). The injections also have to be given in a Z-tracking technique to avoid leakage after injection, which requires training the staff administering the injection.

Risperidone long-acting injection (RLAI) was the first available second-generation antipsychotic brought to market delivered in a biodegradable microsphere preparation. Due to the pharmacokinetics of this formulation, its release is delayed for 2–3 weeks and the peak release is not until 28 days after initiation. Thus, patients have to take oral risperidone for at least 3–4 weeks after starting on RLAI (17). Moderate weight gain and hyperprolactinemia are some of the concerning side effects from this medication similar to oral risperidone (18). Due to the characteristic of the microsphere preparation, there are no benefits of giving loading doses of RLAI. The need to keep this medication refrigerated before administration puts constraints on storage and ease of distribution of this medication.

Olanzapine long-acting injection (OLAI) formulation employs a pamoate moiety suspended in water and attains plasma levels in less than a week and does not require oral supplementation. Though there is a possibility of a 4-weekly dosing at maximum 405 mg—if one desires to have an oral equivalence of more than 15 mg a day—biweekly administration of 300 mg per injection is recommended (19, 20). Common side effects include sedation, weight gain, and concern for developing metabolic complications (similar to oral olanzapine) (21, 22).

While the efficacy of OLAI has been shown to be robust (21, 22), its usage has been limited by the discovery of a post-injection syndrome. Termed Post-Injection Delirium Sedation Syndrome (PDSS), this syndrome is characterized by a relatively sudden development of sedation, confusion, slurred speech, altered gait or unconsciousness in 1.4% of patients receiving the injection (23). Despite effective methods to treat this side effect, practitioner concern and the requirement to observe the patient for up to three hours after every injection has limited its use in many outpatient settings (19).

Paliperidone long-acting injection (PLAI) has been viewed as a significant advancement over its related predecessor RLAI. Since it is a crystalline-based preparation of the active metabolite of risperidone, it is released from the muscles as early as day 1 after the injections and peaking on the 13th day (24, 25). This makes it very appealing to inpatient facilities, which seek to shorten the length of stay and eliminates the need for oral supplementation. A loading protocol allows blood levels to be obtained earlier, as has historically been utilized with the first-generation LAIs. Also, the use of prefilled syringes with no need for refrigeration or special training for administration and the once every 4 weeks dosing of this medication makes it advantageous for outpatient

clinics as well. Doses higher than 156 mg/4 weeks, which have shown significant efficacy compared to placebo, tend to have higher incidence of weight gain and EPS (24).

An Argument for Additional LAIs

Before considering any new LAI, one must ask the question, does the field need another? The short answer is a resounding yes. In the U.S., the five available LAIs are beneficial but limited. They certainly do not mirror the much larger array of oral antipsychotics at the clinician's disposal. While numerous studies have shown that all antipsychotics are equally effective (save clozapine's superiority in treatment-resistant patients), preferential individual patient response is also well documented. Increasing the number of LAIs would allow the clinician to increase the chance of finding an effective treatment with the least side effects for their individual patient. The two first-generation LAIs are time tested, but have limited appeal secondary to their strong extrapyramidal side effects. Of the three second-generation LAIs, RLAI and PLAI are closely related entities, with PLAI a major improvement on RLAI given its more immediate distribution and monthly interval. Both RLAI and PLAI raise prolactin and, in some patients, can produce EPS in the treatment range. OLAI is an effective antipsychotic, but like its oral counterpart, there are weight and metabolic concerns and the PDSS has limited its acceptance. So introducing more LAIs would broaden the efficacy options for patients and ideally be medications designed to have low weight gain, EPS and prolactin elevation.

Aripiprazole LAI

Aripiprazole is an FDA-approved atypical antipsychotic with a unique receptor binding profile that allows both agonist and antagonist actions at the dopamine receptors. It has been postulated that, through dopamine and serotonin system stabilization, a partial D2 agonist would be able to act as an antagonist in pathways where an abundance of dopamine was producing psychosis (26, 27). However, it would act as an agonist in some dopaminergic pathways where low dopaminergic tone would produce side effects (nigrostriatal and hypothalmo-pituitary pathways) (28). Aripiprazole is not associated with significant weight gain (29), hyperprolcatinemia or QT prolongations (30-32). However, tremor and akathisia are common motor side effects noted with the use of aripiprazole (33).

Pharmacokinetics of LAI Aripiprazole

Aripiprazole LAI (ALAI) is a lyophilized powder that needs to be reconstituted with sterile water to form an injectable suspension without affecting the original molecule (33, 34). Fleischhacker et al. reported on a Phase 2, open-label, parallel-arm, multiple-dose, multicenter study evaluating the clinical stability, tolerability and pharmacokinetics of several doses of once-monthly ALAI. Forty-one patients with schizophrenia (ages 19–62) were studied and presented in abstract form at the 2011 Annual Meeting of the American Psychiatric Association (APA) (35). Following a 14-day titration/stabilization on oral aripiprazole (10 mg/day), 41 patients were randomized and administered ALAI either 400 mg (n=14), 300 mg (n=16) or 200 mg (n=11). On measures of efficacy and tolerability there was no worsening of symptoms from transition to the LAI and side effects were mild to moderate. Monthly administration of 300 mg and 400 mg ALAI (but not the 200 mg) was able to attain mean steady-state maximum aripiprazole plasma concentrations comparable with those achieved with multiple oral daily dosing of aripiprazole between 10–30 mg.

Therapeutic Efficacy of Aripiprazole LAI

Kane et al. conducted a 52-week, Phase 3, multicenter, randomized, double-blind study comparing ALAI to placebo to prevent relapse (34). The study included 710 patients with schizophrenia. All the subjects were either on oral aripiprazole or converted to oral aripiprazole monotherapy from other antipsychotics over the initial 4–6 weeks before they were stabilized in the oral stabilization phase lasting 4–12 weeks. Stabilization was defined with multiple objective criteria including PANSS (Positive and Negative Syndrome Scale), CGI-S (Clinical Global Impression-Severity of Illness), CGI-SS (Clinical Global Impression for Severity of Suicidality) scores and clinical status. After the oral stabilization phase, all subjects were assigned to single blind ALAI 400 mg in the IM-depot stabilization phase lasting for up to 36 weeks. Oral aripiprazole was discontinued after the first two weeks of initiating ALAI. After the IM depot stabilization phase, patients were randomly assigned to maintenance treatment with ALAI or placebo injections every four weeks for up to 52 weeks. Antidepressants, mood stabilizers or antipsychotics other than aripiprazole were prohibited throughout the study. Primary outcome measure was time to exacerbation of psychotic symptoms or impending relapse defined by CGI improvement score, event of hospitalization, and risk of suicide by CGI-SS score or violent behavior. PANSS total scores improved both in oral and ALAI stabilization phases. During the double-blind treatment phase, PANSS total scores increased significantly in the placebo arm compared to the ALAI arm as early as the second week of randomization. The study was terminated early as the Independent Data Monitoring Committee determined that the primary end point was reached with no safety issues. Time to impending relapse was significantly delayed and the risk of relapse was reduced with ALAI compared to placebo. The discontinuation rates were significantly less (24.9 versus 54.5%) in the ALAI arm compared to placebo.

Table 1 Percentage of Incidences of Significant Weight Gain and Increase in Metabolic Parameters from Normal or Baseline (34)

	Phase 3 (Stabilization)	Phase 4 (Double-blind maintenance treatment)	
Parameter	**Aripiprazole IM-depot**	**Aripiprazole IM-depot**	**Placebo**
Weight (>7% increase from baseline)	5.4	6.4	5.2
Glucose	3.3	4.5	2.5
Total Cholesterol	2.9	2.6	3.2
HDL-cholesterol	16.2	12.9	10.8
LDL-cholesterol	1.9	0	0
Triglycerides	4.8	7.7	9.0

Safety of Aripiprazole LAI

From the limited data available at this point, ALAI appears to be well tolerated with no significant adverse events (AEs) requiring additional monitoring. In the Fleischhacker et al. open-label study described above, patients were assigned to 400 mg (n=14), 300 mg (n=16) or 200 mg (n=11). The percentage of patients with more than one AEs was 64.3% (n=9 out of 14), 73.3% (n=11 out of 15) and 60% (n=6 out of 10) in 400-mg, 300-mg and 200-mg groups, respectively (35). The most frequent AEs were injection site pain (28.6%) and tremor (21.4%) among patients receiving 400 mg; vomiting, somnolence, QTc interval change (13.3% each) among patients receiving 300 mg, and headache (20%) among patients receiving 200 mg. Most AEs were mild to moderate in severity.

In the Kane et al. (34) study, the most common AEs related to ALAI (>5% of ALAI subjects and greater than placebo) were insomnia, headache and tremor. Serious AEs were observed in 1.4 and 4.3% of patients in the oral and IM-depot stabilization, respectively. The overall discontinuation rates due to adverse events were low in both oral (3%) and IM depot (4.9%) stabilization phases. The discontinuation rates due to AEs were about 7.1% for aripiprazole LAI compared to 13.4% in patients receiving placebo in the double-blind phase.

In the double-blind treatment phase, a total of 14.9% of patients on ALAI experienced EPS AEs compared to 9.7% of the placebo patients. The most frequent EPS AEs with ALAI compared to placebo were akathisia (5.6 vs. 6.0%), dyskinesia (0.7 vs. 1.5%), dystonia (1.9 vs. 1.5%) and parkinsonism (8.2 vs. 3%). Akathisia has been noted to be a common adverse event with oral aripiprazole, occurring early in the treatment and leading to more frequent discontinuation from treatment compared to placebo and other antipsychotics (36). Though the injections of ALAI were well tolerated with comparable injection pain scores, incidence of injection-site induration was higher among ALAI subjects compared to placebo. The incidence of significant weight gain (>7% baseline weight) and treatment-emergent metabolic abnormalities was similar between ALAI and placebo (see Table 1). The incidence of clinically relevant serum prolactin level elevations was lower than placebo in the double-blind phase (1.9 vs. 7.1%). There were no differences between placebo and ALAI with regards to incidence of orthostatic hypotension, change in EKG parameters, and mean change in QTc intervals or vital sign readings.

Abilify Maintena™

Long-acting injectable aripiprazole was approved by the U.S. FDA on 28th February 2013 and will be marketed under the name Abilify Maintena. Like its oral predecessor it carries the same warnings including the black box warning of increased mortality in elderly patients with dementia-related psychosis (13). The medication is available as a lyophilized powder which needs to be reconstituted with the specific amount of sterile water included in the kit to form an opaque milky-white suspension. After reconstitution, the suspension can be stored in the vial but cannot be stored in the syringe. While not as convenient as LAIs distributed in pre-constituted vials, the ability to use a single vial to constitute a number of dose options is an advantage. To reconstitute, a specific volume of the sterile water must be injected into the vial to achieve either the 400-mg or 300-mg suspension dose. A 300-mg vial can be used to inject 300-mg, 200-mg or 160-mg doses, whereas a 400-mg vial can be used to inject all of the above and the 400-mg dose (see Table 2). This implies that, assuming the cost of 400-mg vial being higher than 300-mg vial, the 400-mg vial should be used only for doses of 400 mg to be cost effective. The reconstitution and administration, though complicated, provides flexibility for prescribers to modify the dose in smaller increments compared to preset fixed dosages in other available second-generation LAIs.

Fourteen consecutive days of concurrent use of oral aripiprazole or other antipsychotic is recommended to maintain therapeutic concentration, although the median maximum plasma concentration is attained in 5–7 days.

Table 2 Recommended Volume to Inject after Reconstitution of Abilify Maintena (13)

400-mg vial		300-mg vial	
Dose intended	Volume to inject	Dose	Volume to inject
400 mg	2 mL	—	—
300 mg	1.5 mL	300 mg	1.5 mL
200 mg	1 mL	200 mg	1 mL
160 mg	0.8 mL	160 mg	0.8 mL

Dose modifications have been emphasized in the package insert among patients who are poor CYP2D6 metabolizers or on concomitant CYP2D6 or CYP3A4 inhibitors for more than 14 days. It also advises to avoid using ALAI in the presence of a CYP3A4 inducer for more than 14 days, as the aripiprazole serum concentration drops to sub-therapeutic levels due to faster metabolism. This may pose constraints for prescribers using this long-acting antipsychotic over others. At the time of writing this review, pricing information is not available so any advantages or disadvantages from a cost perspective cannot be evaluated.

Table 3 Comparison Among Available LAIs in the United States

	Fluphenazine decanoate	Haloperidol decanoate	Risperidone microspheres	Paliperidone palmitate	Olanzapine pamoate	Aripiprazole monohydrate
Available dosage strengths	25 mg/mL (variable dose)	50 mg/mL, 100 mg/mL (variable dose)	12.5 mg, 25 mg, 37.5 mg, 50 mg	39 mg, 78 mg, 117 mg, 156 mg, 234 mg	210 mg, 300 mg, 405 mg	300 mg, 400 mg
Dose range	12.5 to 100 mg	20 to 450 mg	12.5 to 50 mg	39 to 234 mg	150 to 405 mg	160 to 400 mg
Maximum recommended dose	100 mg every 2 weeks	450 mg every 4 weeks	50 mg every 2 weeks	234 mg every 4 weeks	300 mg every 2 weeks or 405 mg every 4 weeks	400 mg
Injection site	Deltoid or gluteal	Deltoid or gluteal	Deltoid or gluteal	Deltoid or gluteal	Gluteal only	Gluteal only
Injection technique	Z-Track	Z-Track	Standard	Standard	Standard	Standard
Solubilization and vehicle	Ester in sesame seed oil	Ester in sesame seed oil	Microsphere matrix in aqueous suspension	Nanoparticles in aqueous suspension	Nanoparticles in aqueous suspension	Lyophilized powder reconstituted with sterile water to form an injectable suspension
Initiation or loading	Loading possible	Loading possible	None	Initiation required	Initiation required	None
Time to peak	8–24 hours	3–9 days	4–5 weeks	13 days	<1 week	5–7 days
Overlap with oral	1 week	4 weeks (none if loading)	3 weeks	None	None	2 weeks
Time to steady state	2–3 months	2–3 months	6–8 weeks	36 days	3 months	3–4 months

This oral coverage differs somewhat from the 3–4 weeks of oral coverage needed for RLAI, where there is no appreciable blood level until the microspheres are saturated and breakdown to release active risperidone. This, however, is a disadvantage compared to PLAI or OLAI, which require no additional oral dosing after the first dose of the initiation. The injections are recommended only in the gluteal region at this time. This may be related to the common practice of using this route during initial clinical trials for LAIs before approval. More post-marketing studies may be expected testing the intramuscular injections in the deltoid regions in the future.

Conclusions

So should ALAI be in our metaphorical "tool box?" There is a compelling argument that it should. First it expands the options for achieving efficacy in any individual patient. Not all patients will respond to any one medication and a broad sample of long-acting medications offers the clinician the best "shot" at success (see Table 3). The monthly injection interval is very attractive since patients prefer fewer injections, and the number of times that the patient has to come to the office (or be convinced to come) is reduced.

From a tolerability perspective, ALAI appears to be both weight neutral and lacking metabolic side effects. This can

confer an advantage over the other currently available SGA LAIs. Simple constitution with sterile water and no requirement to refrigerate make storage and administration easier. Like all medications, there are always potential disadvantages to ALAI. First, not all patients respond to aripiprazole and a previous history of nonresponse (excluding first questions of noncompliance) would rule this medication out. There is a period of oral coverage, while not as long as for RLAI, that is required. Care must be taken to review concomitant medications for the presence of metabolic inducers and inhibitors. One would also expect some patients to be sensitive to EPS, especially akathisia which is well documented in the oral preparation. If the experience with RLAI and PLAI are any indication, EPS should be lower due to the more governed maximum blood level per day. All things considered, we welcome our new tool—ALAI—to our workplace and predict both clinical practice and post-marketing analysis and studies will discover its true value.

References

1. McEvoy JP. The costs of schizophrenia. J Clin Psychiatry 2007;68(Suppl 14): 4-7.
2. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. Schizophr Bull 1998;24(1):75-85.
3. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull 1991;17(2):325-351.
4. Almond S, Knapp M, Francois C, Toumi M, Brugha T. Relapse in schizophrenia: costs, clinical outcomes and quality of life. Br J Psychiatry 2004;184:346-351.
5. Almerie MQ, Alkhateeb H, Essali A, Matar HE, Rezk E. Cessation of medication for people with schizophrenia already stable on chlorpromazine. Cochrane Database Syst Rev 2007(1):CD006329.
6. Gaebel W, Janner M, Frommann N, Pietzcker A, Kopcke W, Linden M, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. Schizophr Res 2002;53(1-2):145-159.
7. Gaebel W, Riesbeck M, Wolwer W, Klimke A, Eickhoff M, von Wilmsdorff M, et al. Relapse prevention in first-episode schizophrenia--maintenance vs intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia. J Clin Psychiatry 2011;72(2):205-218.
8. Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. Arch Gen Psychiatry 1995;52(3):173-188.
9. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2012;5:CD008016.
10. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004;55(8):886-891.
11. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. Psychiatr Clin North Am 2007;30(3):437-452.
12. Haddad PM, Lambert T, Lauriello J, editors. Antipsychotic long-acting injections. New York: Oxford University Press; 2011.
13. Abilify Maintena [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd.; 2013. Available from: http://www.otsuka-us.com/Products/Documents/Abilify.M.PI.pdf.
14. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011;168(6):603-609.
15. Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. NEJM 2011;364(9):842-851.
16. Jann MW, Ereshefsky L, Saklad SR. Clinical pharmacokinetics of the depot antipsychotics. Clin Pharmacokinet 1985;10(4):315-333.
17. Risperidal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals Ltd.; 2011. Available from: http://www.janssencns.com/shared/pi/risperdal/risperdalconsta.pdf.
18. Moller HJ. Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. Drugs 2007;67(11):1541-1566.
19. Zyprexa Relprevv [package insert]. Indianapolis, IN: Eli Lilly and Company; 2011. Available from: http://pi.lilly.com/us/zyprexa_relprevv.pdf.
20. Detke HC, Zhao F, Garhyan P, Carlson J, McDonnell D. Dose correspondence between olanzapine long-acting injection and oral olanzapine: recommendations for switching. Int Clin Psychopharmacol 2011;26(1):35-42.
21. Lauriello J, Lambert T, Andersen S, Lin D, Taylor CC, McDonnell D. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. J Clin Psychiatry 2008;69(5):790-799.
22. Kane JM, Detke HC, Naber D, Sethuraman G, Lin DY, Bergstrom RF, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry 2010;167(2):181-189.
23. Detke HC, McDonnell DP, Brunner E, Zhao F, Sorsaburu S, Stefaniak VJ, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. BMC Psychiatry 2010;10:43.
24. Citrome L. Paliperidone palmitate—review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. Int J Clin Pract 2010;64(2):216-239.
25. Invega Sustenna [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2012. Available from: http://www.janssencns.com/sustenna-prescribing-information.
26. Wood M, Reavill C. Aripiprazole acts as a selective dopamine D2 receptor partial agonist. Expert Opin Investig Drugs 2007;16(6):771-775.
27. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. J Clin Psychiatry 2001;62(12):923-924.
28. Rivas-Vazquez RA. Aripiprazole: a novel antipsychotic with dopamine stabilizing properties. Professional Psychology: Research and Practice 2003;34(1):108-111.
29. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373(9657):31-41.
30. Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63(9):763-771.
31. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003;61(2-3):123-136.
32. Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock EG, Ingenito GG; Aripiprazole Study Group. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. J Clin Psychiatry 2003;64(9):1048-1056.
33. Park MH, Han C, Pae CU, Lee SJ, Patkar AA, Masand PS, et al. Aripiprazole treatment for patients with schizophrenia: from acute treatment to maintenance treatment. Expert Rev Neurother 2011;11(11):1541-1552.
34. Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2012;73(5):617-624.
35. Fleischhacker WW, Sanchez R, McQuade R, Carson W, Forbes RA, Walling D, et al. Pharmacokinetic study of once-monthly aripiprazole extended-release injectable suspension in adult patients with schizophrenia. 164th Annual Meeting of the American Psychiatric Association 14–18 May 2011; Honolulu, Hawaii.
36. Kane JM, Barnes TR, Correll CU, Sachs G, Buckley P, Eudicone J, et al. Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials. J Psychopharmacol 2010;24(7):1019-1029.