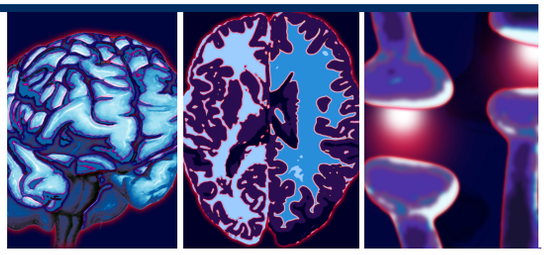
REVIEW



Extended-release intramuscular aripiprazole for maintenance pharmacotherapy in schizophrenia and related disorders

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Practice points

- Aripiprazole is a novel third-generation antipsychotic medication.
- Aripiprazole is available in oral and injectable intramuscular (im.) formulations (fast-acting variant); the long-acting im. variant is awaiting approval from regulatory authorities.
- Long-acting im. antipsychotics are the cornerstone of treatment both in schizophrenia patients with a preference for them, and for patients who are nonadherent to oral medication.
- Preliminary results suggest that long-acting im. aripiprazole can be administered once a month at doses of 200, 300 or 400 mg.
- Titration/switching from the oral to the depot formulation of aripiprazole appears to be straightforward.
- Preliminary data regarding aripiprazole depot demonstrate that this formulation is an effective antipsychotic associated with minimal extrapyramidal symptoms and metabolic side effects.
- If the initial data regarding efficacy and side-effect profile is replicated, aripiprazole depot might become an appealing alternative to currently available long-acting im. antipsychotics; all of which are associated with either extrapyramidal symptoms (first-generation antipsychotics) or metabolic syndrome (second-generation antipsychotics).

SUMMARY Aripiprazole is a third-generation antipsychotic. It is prepared in many different formulations including oral, intravenous and intramuscular. The intramuscular option is currently available in fast-acting form while the long-acting (extended-release, depot) formulation was just approved by the US FDA. The purpose of this article is to review the current literature regarding the long-acting formulation of aripiprazole. Medical literature published in English on 'aripiprazole' or 'Abilify®' (Otsuka America Pharmaceutical Inc., MD, USA) was found using Pubmed, Medline and EMBASE. Publications containing the words 'depot', 'long-acting' or 'intramuscular' in their title or abstract were utilized. In total, two publications were reviewed for the purposes of this article. There is a scarcity

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of publications on the effectiveness of long-acting aripiprazole in the treatment of schizophrenia and schizoaffective disorder. However, the available literature suggests that aripiprazole depot is a well tolerated, maintenance treatment option for schizophrenia.

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Chronic illnesses often require long-term pharmacological management. Adherence to medication in this population is always a challenging feat for both patients and clinicians. This is especially true for patients diagnosed with psychotic disorders such as schizophrenia or schizoaffective disorder, and for the psychiatrists caring for them. Antipsychotics are the mainstay treatment of psychotic disorders. Long-acting, extended-release antipsychotic formulations have been developed to address some issues related to suboptimal adherence to treatment in patients with psychotic disorders.

In recent years, long-acting, extended-release antipsychotics have become the cornerstone of treatment for poorly compliant patients with psychotic disorders such as schizophrenia and schizoaffective disorder. Long-acting, intramuscular (im.) antipsychotics are shown to significantly reduce the need for the rehospitalization of patients suffering from schizophrenia [1]. Compared with patients receiving oral antipsychotics, Tiihonen and colleagues demonstrated that the risk of rehospitalization among those on depot injections is reduced by one third [1]. Their study showed that only 50% of patients continued to take their oral antipsychotic medication beyond 30 days and that 60% of patients were rehospitalized within 2 years due to a relapse of their schizophrenia symptoms. Therefore, not only are depot antipsychotics associated with patient recovery, but also with a reduction in healthcare costs [2].

Table 1 highlights the barriers and benefits of adhering to the optimal management of schizophrenia both in patients and their attending physicians. Long-acting, injectable, im. antipsychotics relieve patients of the need to take daily medication and allow clinicians to monitor nonadherence when patients do not attend an injection visit [3]. Long-acting, injectable medications also represent a valid and reliable treatment option for those patients who prefer this method of medication delivery. They are especially suitable for patients who find daily oral medications inconvenient as well as a constant reminder of their illness. Moreover, many psychotic patients find it difficult to remember to take their medications on a daily basis. The option of taking a medication 12- to 13-times per year instead of 365-times is preferable for some patients. Long-acting, injectable medications can be especially useful for patients with limited understanding of their psychotic illness but who, nevertheless, agree to some form of treatment.

Typical antipsychotics were the first class of drugs for which long-acting, extended-release formulations were developed. This family includes haloperidol, zuclopenthixol, flupenthixol and fluphenazine among others. However, typical antipsychotics, both oral and depot formulations, are associated with the development of extrapyramidal symptoms (EPS) such as Parkinsonism, dystonia and tardive dyskinesia [4].

Given these troublesome and significant side effects, a new (second generation or atypical) class of antipsychotics was developed and is associated with a reduction in the development of EPS compared with conventional antipsychotics [5,6]. Moreover, compared with typical antipsychotics, the atypical class seems to have a greater impact on negative and cognitive symptoms [6], and reduces suicidality [7] and substance misuse [8]. While atypical antipsychotics are associated with fewer EPS when compared with typical antipsychotics, they are associated with significant metabolic side effects including weight gain, diabetes and hyperlipidemia [9]. While there are some advantages (as mentioned above) to using atypical over typical antipsychotics, large studies (e.g., CATIE) demonstrate that both classes of antipsychotics are equally efficacious with respect to discontinuation rates and associated with their respective side-effect burdens [10]. The CATIE study did not include aripiprazole. It compared perphenazine with quetiapine, olanzapine, risperidone and ziprasidone, and found that olanzapine was the most efficacious in terms of rates of discontinuation compared with the other drugs in this trial but was associated with the most metabolic side effects.

There are many depot formulations of antipsychotics available on the market. Of the newer antipsychotics, risperidone, paliperidone and olanzapine are available as long-acting formulations.

Table 1. Barriers and benefits to long-acting intramuscular pharmacotherapy of schizophrenia.

Barriers	Benefits
Patient-related factors	
Forgetting doses due to cognitive deficits Forgetting to buy medication due to executive dysfunction Skipping doses due irregular sleep patterns Poor insight into illness Substance misuse Disfiguring side effects secondary to EPS and associated stigma Reluctance to consider long-acting formulations: ▪ Viewed as constraining and coercive ▪ Fear of pain at site of injection ▪ Discomfort and shame related to site of injection (gluteal muscles)	No need to take medication daily Increased choice in medication delivery options Increased interaction and support from treating team Decreased rates of hospitalization Decreased relapse rates associated with depot treatment translates into less frequent acute exacerbations and the need for chemical restraints
Psychiatrist-related factors	
Overestimation of oral medication compliance Reluctance to use long-acting antipsychotic medication: ▪ Viewed as last resort ▪ Fear of extended side effects ▪ Viewed as a coercive treatment method ▪ Issues related to administration method and required precautions ▪ Long medication half-life (many weeks of treatment required before observing clinical benefit) ▪ Medication storage ▪ Accessibility and cost ▪ Fear of weakening therapeutic alliance ▪ Pessimism in regards to long-term outcomes	Close monitoring of adherence Stable serum levels Decreased rates of patient hospitalization Decreased healthcare utilization

Data taken from [9,42,43].
EPS: Extrapyramidal.

Aripiprazole is the most recent antipsychotic produced in a long-acting formulation; it was just approved by the US FDA on 28 February 2013 [101]. It is important to note, however, that at the time of writing the FDA had not yet approved the use of aripripazole depot. While the efficacy of the oral and short-acting formulations of aripiprazole has been reviewed extensively [11–14], there is a gap in both the literature and available reviews discussing the efficacy and use of aripiprazole depot in the treatment of patients with psychotic disorders. This review aims to palliate that gap and provide the most up-to-date literature review on long-acting, aripiprazole depot.

Discussion

■ Pharmacodynamics

Aripiprazole is a quinolinone derivative and a unique molecule. Aripiprazole should be categorized and labeled as a third-generation antipsychotic as its mechanism of action is quite different from other atypical, second-generation antipsychotics. Molecules such as asenapine, clozapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone and ziprasidone are labeled as second-generation antipsychotics given their antagonistic properties at the level of postsynaptic dopamine$_2$ (D_2) receptors and serotonin $5HT_{2A}$ receptors. Aripiprazole, on the other hand, is a D_2 partial agonist, acting on both postsynaptic D_2 receptors and presynaptic autoreceptors. In addition, aripiprazole is a partial agonist of the serotonin$_{1A}$ receptor and an antagonist of the serotonin$_{2A}$ receptor. Compared with the second-generation antipsychotics, aripiprazole has the highest D_2-binding affinity with a K_i value between 0.1 and 1 nM [15], while its serotonin$_{2A}$ (K_i between 1 and 10 nM) binding affinity is similar to that of

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risperidone, quetiapine and olanzapine, and, finally, its serotonin $_{1A}$ binding affinity is within the same range as ziprasidone (K_i between 0.1 and10 nM) but higher than risperidone, quetiapine and olanzapine (average K_i between 100 and 1000 nM).

Aripiprazole, unlike other atypical antipsychotics, is a partial agonist at D_2 receptors. Therefore, it acts as an antagonist (decreases dopamine neurotransmission) in hyperdopaminergic states/conditions and as an agonist (increases dopamine neurotransmission) in hypodopaminergic states/conditions [16,17]. Aripiprazole's partial agonistic-binding properties allow it to act as a dopamine neurotransmission stabilizer, thus reducing dopamine receptor upregulation, prolactin elevation and the development of EPS. Aripiprazole's partial agonist property hay help to explain its benefits for negative and and affective symptoms associated with schizophrenia and schizoaffective disorders (to be discussed later in this article).

Aripiprazole's serotonin-binding profile decreases dopamine blockade via its antagonistic properties at the level of the serotonin$_{2A}$ receptor, thereby decreasing the propensity toward EPS at the level of the nigrostriatal dopamine pathway and leading to the potential improvement of negative symptoms at the level of the mesocortical pathway [18–20]. Aripiprazole's serotonin$_{1A}$ receptor agonism confers this molecule with antianxiolytic activity and is thought to also decrease the risk of EPS [21].

Pharmacokinetics

Aripiprazole is absorbed quickly following oral administration and reaches peak concentration within 3 h; the half-life of aripiprazole is 75 h while that of its metabolite dehydroaripiprazole is 94 h [22]. The pharmacokinetics of aripiprazole are dose proportional (linear) over a range of 5–30 mg/day and reach a steady state within 14 days. The bioavailability of this drug is 87% [23].

The pharamacokinetics of im. (not extended-release depot formulation) aripiprazole is also linear. A more rapid absorption is observed following im. injection compared with oral administration [24]. Aripiprazole binds extensively to albumin (99%). Aripiprazole is metabolized primarily via the cytochrome P450 enzymes 3A4 and 2D6 via dehydrogenation, hydroxylation and *N*-dealkylation. In steady state, 40% of aripiprazole is in the form of its major metabolite dehydroaripiprazole [23]. Excretion occurs via the kidney and liver.

Drug interactions

Based on the metabolism of aripiprazole, medication interactions have been documented. For example, carbamazepine reduces aripiprazole serum concentrations by inducing cytochrome 3A4, while ketoconazole and quinide increase aripiprazole serum concentrations by inhibiting 3A4 and 2D6, respectively. Aripiprazole does not interact with valproic acid, lithium, warfarin or omeprazole, and does not require a dose adjustment when used concomitantly with any of those medications [23].

Special populations

As per most published reviews on aripiprazole, there are no dosage adjustments for patient age, gender, race, smoking status and hepatic or renal function [11]. It would appear that aripiprazole is secreted in the breast milk of lactating rats and the recommendation is that nursing mothers do not breastfeed if they are receiving aripiprazole [23].

Efficacy

The efficacy of the oral and short-acting formulations of aripiprazole has been studied extensively [11–14]. The efficacy of oral aripiprazole has been measured in 4- and 6-week, placebo-controlled trials of hospitalized patients suffering acute relapses of schizophrenia or schizoaffective disorder [25–28]. Oral aripiprazole has also been evaluated in a 26-week, placebo-controlled trial in stabilized adult patients with schizophrenia or schizoaffective disorder [29].

Aripiprazole has also been studied in active-comparator trials that have compared it to risperidone, olanzapine, haloperidol and ziprasidone. Generally, aripiprazole has an efficacy similar to risperidone and ziprasidone, but it is less effective in controlling the symptoms of schizophrenia and schizoaffective disorder over a 4–6-week treatment period when compared with olanzapine [30–32]. Longer-term efficacy studies have shown that treatment with aripiprazole is as efficacious as olanzapine and haloperidol [33–35].

It should be noted that the im. formulations (rapid onset and extended release) of aripiprazole have not been studied as extensively as the oral formulation. While there are no active-comparator, double-blind studies comparing the efficacy of extended-release aripiprazole

to other long-acting im. antipsychotics, there is one double-blind, placebo-controlled study comparing the efficacy and safety of im. aripiprazole to im. haloperidol for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder. This study's conclusions indicate that treatment with im. aripiprazole is as effective and well-tolerated as im. haloperidol for the management of acute agitation in psychotic patients [36,37]. Citrome published a review with the purpose of calculating the effect sizes for both efficacy and tolerability of im. ziprasidone, olanzapine and aripiprazole for agitation compared with placebo or active comparators using the number needed to treat and the number needed to harm [14]. Results demonstrated that the lowest number needed to treat was observed for the studies of ziprasidone and olanzapine compared with aripiprazole (the number needed to treat were 3, 3 and 5 patients, respectively).

■ Approved use

At the time of writing, the FDA had approved the use of oral aripiprazole in the treatment of acute schizophrenia. Aripiprazole had also been approved for the treatment of type I bipolar disorder, as either a monotherapy or as an adjunct to lithium or valproic acid. The FDA has recently approved aripiprazole as an adjunct in the treatment of major depressive disorder. In pediatric populations, aripiprazole has been approved for the treatment of irritability associated with autistic disorder. Rapid-acting im. aripiprazole has been approved for the management of acute agitation associated with schizophrenia or bipolar I disorder.

At the time of this article, the FDA had yet to approve the extended-release depot formulation of aripiprazole. As per the drug company's website, approval should occur in 2013 following issues with the solvent used to dissolve the medication [102].

■ Aripiprazole: long-acting, extended-release im. depot studies

Aripiprazole depot is a sterilized lyophilized cake that is reconstituted in sterile water and injected once a month into the gluteal muscle. In the depot formulation, aripiprazole is encapsulated in microspheres made of a polymer that degrades over time conferring the long-acting property to the depot formulation [38].

At the time of this review, only two studies on extended-release aripiprazole were available. The first set of data was published by Fleischhacker and colleagues in the form of a poster at the 164th annual meeting of the American Psychiatric Association (Honolulu, HI, USA) in 2011 and reviewed by Park *et al.* [39]. The first study was a Phase III, parallel-arm, multidose, multicenter study. The second publication presents results of the Phase III trial of the depot formulation of aripiprazole, first presented at the 165th annual meeting of the American Psychiatric Association (San Francisco, CA, USA) in 2012 and subsequently published as a peer-reviewed article in the *Journal of Clinical Psychiatry* [40]. This second study was a 52-week, multicenter, randomized, double-blind, placebo-controlled study. Both studies stemmed from the same group of investigators.

The first study by Fleischhacker *et al.* investigated the pharmacokinetics of once-monthly im. aripiprazole depot in 41 patients with a diagnosis of schizophrenia [32]. These patients were randomly administered either 400-, 300- or 200-mg doses of aripiprazole depot after a 14-day titration/stabilization with oral aripiprazole (10 mg/day). There were 14 patients randomized to the 400-mg group, 16 to the 300-mg group and 11 to the 200-mg group. At steady state, the mean maximum/minimum serum concentration of aripiprazole was 316/212 ng/ml for the 40- mg im. group, 269/156 ng/ml for the 300-mg im. group and 100/95 ng/ml for the 200-mg im. group. According to this study, most pharmacokinetic parameters were equivalent for the 300- and 400-mg doses of im. aripiprazole but not for the 200-mg im. dose. The median time to peak plasma concentration of aripiprazole's main metabolite was 6.6 and 12.5 days, with doses of 400 and 300 mg, respectively. The mean elimination half-life for aripiprazole was 47 and 30 days, with doses of 400 and 300 mg, respectively. Park and colleagues suggest that aripiprazole depot at doses of 300 and 400 mg achieved mean steady state maximum plasma concentrations comparable to those shown in oral doses of aripiprazole between 10 and 30 mg [39]. This same study reported that 71.4, 50 and 36.4% of patients administered 400-, 300- and 200-mg im. aripiprazole, respectively completed the study. The main reason for discontinuation in the group given the 200-mg dose was withdrawal of consent. A total of 25% of patients discontinued the 300-mg depot formulation secondary to side effects. None of the patients on 400 mg discontinued treatment. Rates of

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adverse effects were 64.3 and 73.3% for 400- and 300-mg im. depot groups, respectively. For the 200-mg group the most common side effect was headache. For the 300-mg group the most common side effects were vomiting, somnolence and QTc interval change. Finally, for the 400-mg group the most common side effect was injection-site pain. This study did not report on the efficacy of the medication.

The study above was designed to investigate the pharmacokinetic and tolerability profile of three different doses of im. aripiprazole and was used as a stepping-stone to the group's second study described below. This study has many limitations, the most significant ones being the small number of subjects, high percentage of adverse effects and lack of efficacy data. Finally, there is a lack of information regarding the clinical profile of the patients chosen for this study and their clinical outcomes upon study completion.

The group's follow-up publication was a long-term study investigating the efficacy, safety and tolerability of im. aripiprazole in patients with schizophrenia. This study was conducted from July 2008 to February 2011. It was stopped several months before its targeted end date when interim analysis satisfied the group's termination criteria on the protocol.

Seven hundred and ten patients were initially enrolled in Kane *et al.*'s study [40]. Subjects requiring long-term treatment with antipsychotic medication entered a 4–12-week oral stabilization phase and were administered between 10 and 30 mg of aripiprazole. Subjects meeting stability criteria for 4 weeks (out-patient status, Positive and Negative Syndrome Scale score of less than or equal to 80, lack of specific symptoms in Positive and Negative Syndrome Scale subscales of conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content, Clinical Global Impression Scale score of less than or equal to four and Clinical Global Impression Suicidality Scale [severity of suicidality] score of less than or equal to two on part one, and less than or equal to five on part five) entered the stabilization phase of the study which involved the administration of 400-mg aripiprazole depot every 4 weeks. Subjects meeting stabilization criteria (same as initial criteria noted above) after 12 weeks were then randomly assigned to aripiprazole depot or placebo during a 52-week, double-blind maintenance phase. The primary outcome of this study was time to exacerbation of psychotic symptoms, as well as monitoring the safety and tolerability of aripiprazole.

Of the 710 subjects enrolled, 403 were randomly assigned to the double-blind treatment phase; 269 received im. depot medication while 134 received placebo. Given that this study was placebo controlled, an interim analysis was conducted after 50% of the targeted events of impending relapse were accrued. The primary reason for discontinuation in the last phase of the study was based on the results of the preplanned interim analysis. The study was terminated early to avoid continued exposure to placebo. The time to impending relapse into symptoms of schizophrenia was significantly delayed with aripiprazole im. depot compared with placebo. Relapse rates were also significantly lower in the treatment group as compared with the placebo group. Twenty-seven subjects (out of 269) in the treatment group relapsed versus 53 (out of 134) in the placebo group. The reasons for relapse, in order of importance, were: clinical deterioration as per Clinical Global Impression Scale/Positive and Negative Syndrome Scale scores, hospitalization, suicide risk and violent behavior. Discontinuation rates were higher in the placebo versus treatment group (54.5 vs 24.9%, respectively).

In order of importance, the most frequent adverse events secondary to treatment during the im. stabilization phase with aripiprazole were: insomnia, weight increase, tremor, insomnia and headache. During the double-blind phase, the most common side effects (more than or equal to 5%) reported by the treatment group were insomnia (27 vs 12%; im. aripiprazole vs placebo), tremor (16 vs 2%; im. aripiprazole vs placebo) and headache (16 vs 7%: im. aripiprazole vs placebo). It is interesting to note that a statistical analysis was not included in the section reporting adverse events; the only data provided were percentages of each adverse event in each treatment group.

The incidence of potentially clinically-relevant prolactin elevations during the double-blind phases was lower in the treatment group than in the placebo group. Changes in vital signs, ECG parameters (including QTc changes), and orthostatic hypotension were similar in both groups.

During the double-blind phase of this study, the difference in the emergence of *de novo* EPS (akathisia, dystonia, Parkinsonism and tardive dyskinesia) was similar in both groups. The

mean changes in the Abnormal Involuntary Movement Scale movement score was -0.02 (treatment) versus -0.02 (placebo) (p = 0.957 last observation carried forward [LOCF] analysis), Simpson Angus Scale total score was -0.02 (treatment) versus -0.06 (placebo) (p = 0.689 LOCF analysis) and Barnes Akathisia Rating Scale global score was 0.02 (treatment) versus -0.02 (placebo) (p = 0.303 LOCF analysis).

In the double-blind phase of this study, the difference in weight gain and metabolic anomalies was also similar in both groups (treatment and placebo groups). The reported mean change in body weight from double-blind baseline to the last visit was -0.2 kg (n = 267) for aripiprazole-im. depot and -0.4 kg (n = 134) for placebo (p = 0.812, LOCF analysis). Moreover, the incidence of clinically significant weight gain, defined as an increase in weight greater than or equal to 7% from baseline, was 6.4% for the treatment group compared with 5.2% for the placebo group. It is interesting to note that a statistical analysis was not included in the section reporting the measured metabolic parameters (glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides); the only data provided were the percentages of subjects above the normal range for each parameter in each group (treatment vs placebo). It is relevant to note that the subjects in both groups of the double-blind phase of this study were overweight (BMI over 25 kg/m^2) at baseline. The investigators did not provide any data that could potentially have helped elucidate if a given weight (low, normal or overweight) at baseline was a specific risk factor for weight gain while treated with aripiprazole. *Post-hoc* analyses derived from this study also show that mean change from baseline in Personal and Social Performance Scale scores showed improved stability of social performance with aripiprazole compared with placebo (treatment vs placebo: -1.7 vs -6.2; p = 0.0002). The mean change from baseline in the Investigator's Assessment Questionnaire total scores remained steady among patients who received aripiprazole im. (mean change of +1.3 vs +3.8 for placebo; p < 0.0001) [40].

In summary, the authors of this study conclude that im. aripiprazole is a safe treatment option for patients requiring long-acting antipsychotic medication. Based on their findings that adverse effects (aside from headache, insomnia and tremor) were similar in the treatment versus placebo group, they believe that im. aripiprazole is a safe and well-tolerated treatment for patients requiring long-acting antipsychotics.

There are several shortcomings to this study, rendering it difficult to generalize its results to the patient population with chronic schizophrenia. The study population was weaned off all other medications, including mood stabilizers and antidepressants, prior to commencing the study. It remains to be seen if the depot formulation is well tolerated in the presence of other drugs often prescribed to patients who also require long-acting antipsychotics. Furthermore, the authors highlight the potential biases associated with selecting a double-blind patient population that responded to oral and aripiprazole depot that could potentially affect study results. This group of 'responders' may have characteristics that are not generalizable to the patient population in a standard clinical practice.

Apart from these two studies, the authors of the current article were unable to find published data on the efficacy, tolerability and safety of aripiprazole depot. Clearly, more studies are required to fully elucidate if this medication is both safe and efficacious for long-term use in patients with psychotic and/or bipolar disorders requiring long-acting antipsychotic medication. Moreover, head-to-head studies comparing the efficacy, safety and tolerability of existing, long-acting, im. antipsychotics (risperidone, paliperidone, haloperidol and clopixol) and aripiprazole depot will be required to demonstrate if aripiprazole depot is as efficacious, safe and tolerable as the currently used long-acting im. medications.

Conclusion

It is widely thought that long-acting, im. antipsychotics are underutilized despite clear evidence showing that their use is associated with a significant decrease in healthcare utilization in poorly adherent patients with schizophrenia or schizoaffective disorder [41]. In the past, first-generation antipsychotics were the only antipsychotics available in a long-acting formulation. However, this class of drugs is associated with significant EPS. Moreover, it is pertinent to note that these formulations are fabricated using either sesame seed (fluphenazine, haloperidol and pipotiazine) or coconut oil (flupentixol) making their use difficult, if not impossible, (in a bid to avoid an anaphylactic reaction) in patients who are either allergic or hypersensitive to sesame seed or coconut.

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Currently, the most commonly used second-generation, long-acting, injectable antipsychotics are risperidone, paliperidone and olanzapine. These medications are associated with weight gain, metabolic disturbances, orthostatic hypotension and ECG changes. It is also important to note that, compared with first-generation, long-acting antipsychotics, this class of medication is far more expensive. The average price of a long-acting second-generation antipsychotic is three- to six-times higher than first-generation, long-acting antipsychotics. Although most first-generation, long-acting antipsychotics can be stored at room temperature, precautions should be taken to ensure that long-acting risperidone is always kept refrigerated. While most im., long-acting antipsychotics are well tolerated, it is important to appreciate the risk of post-injection delirium–sedation syndrome associated with long-acting, im. olanzapine. This phenomenon is thought to be due to either an inadvertent partial intravascular injection or blood vessel injury during the injection that leads to seepage of the medication into the vascular system and causes higher than intended levels of olanzapine serum concentrations that, in turn, lead to over-sedation and potentially delirium.

In summary, when comparing first- versus second-generation, long-acting, im. antipsychotics, each of these classes have significant and appreciable benefits and drawbacks. Large head-to-head studies comparing both these classes are necessary in order to elucidate which of these formulations are the most efficacious, tolerated, accepted by patients and cost-effective.

The preliminary findings of the long-acting, im. aripiprazole study hold some promise as the study was terminated early. If replicated in other studies, the findings that aripiprazole depot was not associated with any significant movement disorders and metabolic disturbances will make this medication the drug of choice compared with other atypical antipsychotics that are riddled with significant metabolic side effects. If replicated, these findings will be beneficial for the treatment of schizophrenia and related disorders, as ongoing and uninterrupted pharmacotherapy is the best method to ensure relapse prevention for these illnesses. Increasing the number of available second- and third-generation, long-acting, im. antipsychotics provides psychiatrists with a wider array of treatment choices to help patients achieve optimal functioning. Only head-to-head studies will demonstrate if long-acting, im. aripiprazole is equivalent or truly superior to long-acting risperidone, paliperidone palmitate or long-acting olanzapine in terms of safety, tolerability and relapse prevention.

Finally, it is important to bear in mind that at the time of writing, regulatory bodies, such as the FDA or Health Canada, had not yet approved the use of long-acting, im. aripiprazole. Finally, it is important to bear in mind that Abilify Maintena™ has just been approved by the FDA for public use. Longer head-to-head studies will now be possible. Such studies will be necessary to establish if, in fact, im. aripiprazole proves to be superior to other second-generation, long-acting, im. antipsychotics.

Future perspective

The advent of long-acting, extended-release, typical antipsychotics (first generation) provided a unique opportunity to ensure medication compliance and to decrease rates of hospitalization in patients with psychotic disorders. However, this class of medication was associated with high rates of EPS leading to poor patient tolerability. This led to the development of atypical antipsychotics (second generation) which, while associated with fewer EPS, were later found to be associated with significant metabolic side effects. The advent of aripiprazole, a third-generation antipsychotic, appears to bear great promise in early studies that suggest that aripiprazole depot is associated with minimal and tolerable side effects from both an EPS and metabolic stand point. While initial data regarding im. aripiprazole appear quite promising, more studies are required to validate whether or not this drug causes EPS and metabolic syndrome. As clinicians begin to prescribe this medication to patients who require long-acting depot medications they will begin to see its full range of efficacy, effectiveness and tolerability.

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- ▪▪ of considerable interest

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