EXPERT REVIEWS

Aripiprazole treatment for patients with schizophrenia: from acute treatment to maintenance treatment

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The most current treatment guidelines for schizophrenia recommend more than 1 year of maintenance therapy after the first psychotic episode, and more than 5 years of maintenance therapy after multiple psychotic episodes. Approximately two-thirds of such patients are known to relapse within 1 year and almost 90% of such patients may recur within 2 years. To maintain adequate consistent treatment, balancing the efficacy and safety/tolerability should be one of the most important clinical issues. In this respect, aripiprazole appears to be a good treatment option owing to its comparable efficacy, favorable safety and tolerability profile, including low incidence of parkinsonian symptoms, lack of prolactin elevation, decreased adrenergic and anticholinergic side effects, less weight gain and low incidence of metabolic syndrome. Hence this article aims to summarize the currently available clinical trial data of aripiprazole published from a number of large-scale randomized controlled studies, including a newer formulation of intramuscular injection as well as a once-monthly intramuscular depot formulation, to update knowledge of treatment options in patients with schizophrenia.

KEYWORDS: acute treatment • aripiprazole • maintenance treatment • schizophrenia

Schizophrenia is a clinical syndrome with very disruptive psychopathology involving cognition, emotion, perception and other aspects of behavior. Positive symptoms, such as hallucination, delusion and disorganized behavior, negative symptoms, such as emotional blunting, and social withdrawal, and cognitive impairment may substantially and adversely affect the patient's whole domain of life. As a result, it prevents the patient from maintaining personal and social relationships and also engaging in productive work [1,2].

According to the findings of a number of studies, the prevalence rate of schizophrenia reaches 0.4–1.9% throughout the world [3].

Antipsychotics were found to reduce psychotic symptoms and relapse rate, and 70% of such patients treated with antipsychotics may experience remission [4]. The current schizophrenia treatment guideline recommends more than 1 year of maintenance therapy after the first psychotic episode, and more than 5 years of maintenance therapy after multiple psychotic episodes [4]. If no antipsychotic maintenance treatment is carried out, 60–70% of patients experience relapse within 1 year and almost 90% of such patients may recur within 2 years [5,6]. Therefore, maintenance therapy is essential for schizophrenia patients. For maintaining the treatment, balancing the efficacy and safety/tolerability should be one of the most important clinical issues. In this respect, it seems likely that the favorable safety and tolerability profile of aripiprazole, including its low incidence of parkinsonian symptoms, lack of prolactin elevation, decreased adrenergic and anticholinergic side effects, less weight gain and low incidence of metabolic syndrome, is also mediated by receptor binding profile, and may contribute to stable maintenance therapy.

Subsequent to its approval by the US FDA in 2002 for the treatment of schizophrenia, aripiprazole was also approved for the treatment of bipolar mania in 2004 (monotherapy for acute and maintenance treatment of manic and mixed episodes). It was eventually approved for adolescent schizophrenia (13–17 years) in 2007, and later for child and adolescent bipolar disorder (10–17 years). In

November 2007, aripiprazole was the first medication approved as an add-on therapy to antidepressants for patients with major depressive disorder in the USA [7]. In addition, aripiprazole has also been commercially available as an intramuscular (im.) formulation since 2006 with an indication for the treatment of adult schizophrenia and bipolar mania in patients experiencing acute agitation in the USA. Another formulation is the orally disintegrating tablet approved in 2006. A long-acting depot formulation intended to improve patient compliance and to offer an effective maintenance therapy, has been in developmental phase. The aripiprazole im. depot 52-week study evaluating the efficacy and safety of this investigational once-monthly im. depot formulation for maintenance treatment was terminated early based on interim efficacy analyses that met the prespecified termination rules of the protocol.

Hence, this article will summarize the currently available clinical trial data of aripiprazole published from a number of large-scale randomized controlled studies including a newer formulation of im. injection, as well as a once-monthly im. depot formulation, to update knowledge of treatment options in patients with schizophrenia.

Balancing benefit/risk of currently available antipsychotics

Typical antipsychotic treatment for schizophrenia patients started in 1952 with the introduction of chlorpromazine and mainly works via the antagonism of dopamine D2 receptor [8]. Even though their efficacy has been proven, extrapyramidal symptoms (EPSs) has been a principal obstacle to the easy use of typical antipsychotics [8]. Atypical antipsychotics (e.g., risperidone, olanzapine, ziprasidone, amisulpride, quetiapine, clozapine, aripiprazole and paliperidone) introduced since the 1980s reduced such EPSs through a new mechanism of action that works not only on the dopamine receptor but also on the serotonin receptor. Moreover, since their efficacy has been as good as typical antipsychotics, these medications have quickly replaced typical antipsychotics as the first-line therapy for the treatment of schizophrenia [9,10]. However, it has been reported that atypical antipsychotics, except aripiprazole and ziprasidone, also cause weight gain, which may have a propensity of developing obesity, metabolic disease and other metabolic risks [8,11–15]. Other side effects, such as sedation, cardiac conduction abnormalities, anticholinergic effect, prolactin elevation and sexual side effects, have also been reported [14,16]. These side effects play a critical role in the reduced compliance and may lead to increased risk of relapse [17]. Hence, most studies are inconclusive and their results are inconsistent concerning acceptability (benefit/risk ratio) owing to methodologically inherent limitations. More clinical data on medication compliance, subjective satisfaction with mediation, improvement in quality of life and socioeconomic cost would lead to a better choice of individualized treatment with each antipsychotic.

Pharmacodynamics

The effects of aripiprazole are mainly attributable to partial agonism of the dopamine D2 receptor and serotonin 5-HT1A receptor and antagonism of the serotonin 5-HT2A receptor [8,18,19]. In addition, aripiprazole acts as an antagonist with limited affinities for α-1 adrenergic, H1-histaminic and 5-HT6 receptor [20]. It is an inverse agonist of 5-HT2B receptor and a partial agonist of 5-HT2A, 5-HT2C, 5-HT7, D3 and D4 receptors [20]. It has a very low affinity to α-2 adrenergic receptor and M1 muscarinic cholinergic receptor [21].

Instead of blocking the D2 receptor completely, aripiprazole works as a partial agonist by reducing the dopamine activity when it is high and increasing it when it is low [22,23]. Mamo *et al.* reported in their PET study that the D2 occupancy level had a significant correlation with the plasma concentration of aripiprazole and D2 occupancy rate was 85% even at a low dose of 10 mg [24]. However, whether aripiprazole will work as a D2 partial agonist *in vivo* or as a functionally selective D2 ligand has not been identified.

A recent article proposed that aripiprazole may function mechanistically as a functionally selective ligand, inducing regionally specific differential signaling, rather than as a simple partial agonist (e.g., the Hill slopes of aripiprazole was significant >1.0 and the apparent D2 affinity of aripiprazole was not decreased significantly by GTP) [25]. The authors suggested that functional selectivity at D2 receptors, perhaps combined with actions at non-dopamine receptors, may contribute to the atypicality of aripiprazole [25]. Another study reported that the aripiprazole activity at the D2 receptor depended on the magnitude of receptor reserves and the available dopamine at the synapse, rather than functional selectivity [26].

Either way, the receptor binding profile of aripiprazole mediates favorable tolerability of aripiprazole, such as lower incidence of EPSs, no prolactin elevation, low adrenergic side effects and anticholinergic side effects, and low weight gain potential [21,27,28].

Pharmacokinetics

Aripiprazole is currently available in oral tablet, oral solution, orally disintegrating tablet, and im. injection forms [14], and a depot formulation is in the developmental phase [29]. The mean time of reaching the peak plasma concentration (C_{max}) after multiple-dose administration of 10 mg or 15 mg is 3 h [30]. The mean elimination half-life of aripiprazole is 75 h and the half life of dehydroaripiprazole, a major metabolite of aripiprazole, is 94 h [31]. A steady state level is reached approximately 14 days after starting the therapy [32]. Over 99% of aripiprazole binds with plasma proteins, especially with albumin [33]. Aripiprazole is mostly metabolized in the liver, especially through the CYP2D6 and CYP3A4 enzyme system. Aripiprazole does not inhibit nor induce cytochrome P450 isoenzymes [33]. Only limited data are available regarding the correlation between the dose and plasma concentration. A study found that the variability of the pharmacologic active sum of aripiprazole and dehydroaripiprazole was 25–30% lower than that of aripiprazole alone. It suggests that the pharmacokinetic variability of aripiprazole might be determined in part by the metabolism to dehydroaripiprazole [34]. The pharmacokinetics of the im. injection along with the im. depot once-monthly formulation will be described in the next section.

Efficacy of aripiprazole

A number of short-term studies [35–38] and long-term studies [39–46] on aripiprazole demonstrated its efficacy for the treatment of schizophreia. These short-term and long-term randomized controlled trials on the efficacy and safety of aripiprazole are summarized in Tables 1 & 2, respectively.

Short-term double-blind studies

Kane *et al.* conducted a 4-week, multicenter, randomized, double-blind study in which patients with schizophrenia or schizoaffective disorder were randomized to treatment with aripiprazole 15 mg/day (n = 102), aripiprazole 30 mg/day (n = 102), haloperidol 10 mg/day (n = 104) or placebo (n = 106). The Positive and Negative Syndrome Scale (PANSS) total score changes from baseline at week 4 were as follows: -15.5 for the aripiprazole 15 mg/day treatment group (p < 0.001); -11.4 for the aripiprazole 30 mg/day treatment group (p = 0.009); -13.8 for the haloperidol 10 mg/day treatment group (p = 0.001); and -2.9 for the placebo group. All treatment groups showed statistically significant reduction compared with the placebo group. The Clinical Global Impressions-Severity (CGI-S) score changes from baseline at week 4 were as follows: -0.6 for the aripiprazole 15 mg/day treatment group (p < 0.001); -0.4 for the aripiprazole 30 mg/day treatment group (p = 0.019); -0.5 for the haloperidol 10 mg/day treatment group (p = 0.002); and -0.1 for the placebo group. All treatment groups showed statistically significant reduction compared with the placebo group [36].

Potkin *et al.* performed a subsequent 4-week, multicenter, randomized, double-blind study in which schizophrenia or schizoaffective disorder patients who were hospitalized for acute relapse were randomized to treatment with aripiprazole 30 mg/day (n = 101), aripiprazole 20 mg/day (n = 101), risperidone 6 mg/day (n = 99) or placebo (n = 103). The PANSS total score changes from baseline at week 4 were as follows: -13.9 for the aripiprazole 30 mg/day treatment group (p = 0.003); -14.5 for the aripiprazole 20 mg/day treatment group (p = 0.001); -15.7 for the risperidone 6 mg/day treatment group (p < 0.001); and -5 for the placebo group. All treatment groups showed statistically significant reduction compared with the placebo group. The CGI-S score changes from baseline at week 4 were as follows: -0.5 for the aripiprazole 30 mg/day treatment group (p = 0.03); -0.6 for the aripiprazole 20 mg/day treatment group (p = 0.006); -0.6 for the risperidone 6 mg/day treatment group (p = 0.006); and -0.2 for the placebo group. All treatment groups showed statistically significant reduction compared with the placebo group [38].

Marder *et al.* pooled and analyzed the results from five 4–6-week, multicenter, randomized, double-blind, placebo-controlled studies (two Phase II studies and three Phase III studies). A total of 1549 schizophrenia or schizoaffective disorder patients in acute relapse were included in the analysis (aripiprazole 2–30 mg/day [n = 932]; haloperidol 5–20 mg/day [n = 201] or placebo [n = 416]). The rate of stopping active treatment owing to lack of efficacy was the lowest in the aripiprazole treatment group (aripiprazole 12%, haloperidol 14% and placebo 20%) [37].

Findling *et al.* conducted a 6-week, multicenter, randomized, double-blind, placebo-controlled trial in which 13–17-year-old schizophrenia patients were randomly assigned to treatment with aripiprazole 10 mg/day (n = 99), aripiprazole 30 mg/day (n = 97) or placebo (n = 98). At week 6, the PANSS total score changes

Table 1. Overview of short-term randomized controlled trials of the efficacy and safety of aripiprazole in schizophrenia.

Study (year)	Duration/interventions	Efficacy	Safety	Ref.
Kane *et al.* (2002)	4 weeks; RCT; ARP 15 mg/day (n = 102); ARP 30 mg/day (n = 102); HPD 10 mg/day (n = 104); PBO (n = 106)	Changes from baseline PANSS total score: ARP 15 mg = -15.5 (p < 0.001 vs PBO); ARP 30 mg = -11.4 (p = 0.009 vs PBO); HPD = -13.8 (p = 0.001 vs PBO); PBO = -2.9	ARP < HPD on EPS, prolactin elevation, QTc interval and weight gain	[36]
Potkin *et al.* (2003)	4 weeks; RCT; ARP 30 mg/day (n = 101); ARP 20 mg/day (n = 101); RPD 6 mg/day (n = 99); PBO (n = 103)	Changes from baseline PANSS total score: ARP 30 mg = -13.9 (p = 0.003 vs PBO); ARP 20 mg = -14.5 (p = 0.001 vs PBO); RPD = -15.7 (p < 0.001); PBO = -5	Prolactin level: RPR > ARP, by five times	[38]
Marder *et al.* (2003)	Pooled analysis five 4–6-week RCTs (two Phase II and three Phase III) ARP 2–30 mg/day (n = 932); HPD 5–20 mg/day (n = 201); PBO (n = 416)	The ARP treatment group had a lower rate of stopping active treatment due to lack of efficacy: ARP 12%; HPD 14%; PBO 20%	ARP ≒ PBO	[37]
Findling *et al.* (2008)	6 weeks; RCT; ARP 10 mg/day (n = 99); ARP 30 mg/day (n = 97); PBO (n = 98)	Changes from baseline PANSS total score: ARP 10 mg = -26.7 (p = 0.05 for PBO); ARP 30 mg = -28.6 (p = 0.007 for PBO); PBO = -21.2	ARP > PBO on EPSs, somnolence and tremor Proportional increase in prolactin (ARP 10 mg = -11.9, ARP 30 mg = -15.1, PBO = -8.45)	[35]

AE: Adverse event; ARP: Aripiprazole; EPS: Extrapyramdal symptom; HPD: Haloperidol; PANSS: Positive and Negative Syndrome Scale; PBO: Placebo; QTc: Corrected QT; RCT: Randomized, placebo-controlled clinical trial; RPD: Risperidone.

Table 2. Overview of long-term randomized controlled trials of the efficacy and safety of aripiprazole in schizophrenia.

Study (year)	Duration/interventions	Efficacy	Safety	Ref.
Kasper *et al.* (2003)	52 weeks; RDB; ARP 30 mg/day (n = 861); HPD 10 mg/day (n = 433)	ARP equals or superior to HPD Especially, ARP > HPD on PANSS negative subscale and MADRS total score improvement. ARP < HPD on time to discontinuation due to an AE or lack of efficacy (HR = 0.692; p = 0.0001)	ARP < HPD on EPSs (p < 0.0001)	[39]
Pigott *et al.* (2003)	26 weeks; RCT; ARP 15 mg/day (n = 155); PBO (n = 155)	Time-to-relapse and relapse rate, changes in PANSS total, PANSS positive, PANSS-derived BPRS, CGI-I and CGI-S scores: ARP > PBO	ARP > PBO on EPS (20.3 vs 13.1%) ARP > PBO on tremor (18 vs 10%)	[40]
McQuade *et al.* (2004)	26 weeks; RDB; ARP 15–30 mg/day (n = 156); OZP 10–20 mg/day (n = 161)	ARP ≒ OZP on in PANSS total score and CGI-I improvement	ARP < OZP on weight gain and some of lipids	[44]
Chrzanowski *Et al.* (2006)	52 weeks; ARP 15–30 mg/day (n = 104); OZP 10–20 mg/day (n = 110)	ARP ≒ OZP on changes in PANSS total score and acute relapse rate	ARP >OZP on EPS (18 vs 10%) and ARP < OZP on TC increase and weight gain	[45]
Kane *et al.* (2007)	Pooled analysis; two 52-week RDBs; ARP 20–30 mg/day (n = 853); HPD 7–10 mg/day (n = 430)	ARP > HPD on remission rate (32 vs 22%; p < 0.001, LOCF) and time to remission	ARP > HPD on discontinuation rate and rescue medication due to AEs (8.0 vs 18.4%; p < 0.001; 23 vs 57%; p < 0.001)	[41]
Kerwin *et al.* (2007)	26 weeks; naturalistic study (ARP vs SOC); ARP 10–30 mg/day (n = 284) vs OZP 5–20 mg/day (n = 75), QTP 100–800 mg/day (n = 110) or RPD 2–16 mg /day (n = 81)	ARP > SOC on CGI-I and quality of life scores ARP ≒ SOC on time to discontinuation (HR = 1.17; p = 0.247)	ARP < SOC on EPSs and prolactin increase; ARP > SOC on weight gain	[42]
Fleischhacker *et al.* (2009)	52 weeks; RDB; ARP 15–30 mg/day (n = 355); OZP 10–20 mg/day (n = 348)	ARP < OZP on change in PANSS total score	ARP > OZP on weight gain and lipid changes ARP ≒ OZP on the rates of discontinuation due to EPS-related AEs	[43]
Kane *et al.* (2009)	16 weeks; RCT of adjunctive ARP treatment; QTP 400–800 mg/day (n = 146) and RPD 4–8 mg/day (n = 177) to either ARP 2–15 mg/day (n = 168) or PBO (n = 155)	ARP ≒ PBO on changes in PANSS total score ARP ≒ PBO on time to discontinuation (HR = 1.01; p = 0.948)	ARP > PBO on prolactin decrease ARP ≒ PBO on treatment-emergent AEs	[46]

AE: Adverse event; ARP: Aripiprazole; BPRS: Brief Psychiatric Rating Scale; CGI-I: Clinical Global Impressions – Improvement; CGI-S: Clinical Global Impressions – Severity; EPS: Extrapyramydal symptom; HPD: Haloperidol; HR: Hazard ratio; LCOF: Last observation carried forward; MADRS: Montgomery–Åsberg Depression Rating Scale; OZP: Olanzapine; PANSS: Positive and Negative Syndrome Scale; PBO: Placebo; QTP: Quetiapine; RCT: Randomized, placebo-controlled clinical trial; RDB: Randomized, double-blind study; RPD: Risperidone; SOC: Standard of care; TC: Total cholesterol.

from baseline were as follows: -26.7 for the aripiprazole 10 mg/day treatment group (p = 0.05); -28.6 for the aripiprazole 30 mg/day treatment group (p = 0.007); and -21.2 for the placebo group. Both of the aripiprazole treatment groups showed statistically significant reduction compared with the placebo group. At week 6, the CGI-S score changes from baseline were: -1.2 for the aripiprazole 10 mg/day treatment group (p = 0.008); -1.3 for the aripiprazole 30 mg/day treatment group (p = 0.002); and -0.9 for the placebo group. Both of the aripiprazole treatment groups showed statistically significant reduction compared with the placebo group [35].

The short-term, double-blind trials cited above showed that aripiprazole is more effective than placebo and its treatment effect is comparable to that of other antipsychotics (haloperidol and risperidone). This indicates that aripiprazole treatment is effective when a patient is in acute stage or acute relapse.

Long-term double-blind studies

Kane *et al.* performed a 16-week, multicenter, randomized, double-blind, placebo-controlled trial in which patients with schizophrenia or schizoaffective disorder who were inadequately treated with quetiapine (400–800 mg/day, n = 146) or risperidone (4–8 mg/day, n = 177) monotherapy (CGI-S score 4–6 points) were randomly assigned to treatment with adjunctive aripiprazole 2–15 mg/day (n = 168) or adjunctive placebo (n = 155).

Adjunctive aripiprazole and placebo groups were similar in the mean change from baseline to end point in the PANSS total score (aripiprazole: -8.8; placebo: -8.9; p = 942) in this study [46].

Pigott *et al.* conducted a 26-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, where patients were randomly assigned to aripiprazole 15 mg/day (n = 155) or placebo (n = 155). The aripiprazole group's time to relapse was longer than the placebo group's (p < 0.001) and the relapse rate was also significantly lower than placebo group (p < 0.001). The aripiprazole group showed significant changes from baseline in PANSS total, PANSS positive, PANSS-derived Brief Psychiatric Rating Scale, CGI-S (over p ≤ 0.01) and Clinical Global Impressions–Improvement (CGI-I; p ≤ 0.05) compared with the placebo group [40]. Similar results were also found in a subsequent 26-week multicenter, randomized, double-blind study published in 2004 [44]. Chranowski *et al.* performed another 26-week, multicenter, randomized, double-blind trial followed by a 52-week, randomized open-label extension phase, in which patients who completed the initial treatment or who met the protocol definition of relapse after ≥2 weeks of double-blind treatment were randomized to aripiprazole 15–30 mg/day (n = 104) or olanzapine 10–20 mg/day (n = 110). The PANSS total score changes from baseline were as follows: among the chronic stable patients, -7.9 for the aripiprazole treatment group and -7.4 for the olazapine treatment group and there was no significant difference between the two groups (p = 0.694); among the acute relapse patients, -31.2 for the aripiprazole group and 29.6 for the olanzapine treatment group and there was no significant difference between the two groups (p = 0.563) [45]. Kerwin *et al.* conducted a 26-week, multicenter, randomized, open-label naturalistic study (aripiprazole vs standard of care [SOC]) for patients who needed medication change because of intolerance or uncontrolled clinical symptom (switching to either SOC group or aripiprazole). The selection of SOC was based on the clinician's judgment for the individual patient. A total of 284 patients were assigned to aripiprazole 10–30 mg/day 75, to olanzapine 5–20 mg/day, 110 to quetiapine 100–800 mg/day and 81 to risperidone 2–16 mg/day. In the Investigator Assessment Questionnaire, the aripiprazole treatment group was significantly more effective than the SOC treatment group from week 4 to week 26 (p < 0.001, last observation carried forward [LOCF]). At week 26, the aripiprazole treatment group was significantly more effective than the SOC group in CGI-I (p < 0.001) and quality of life scale (p < 0.001). A significantly higher proportion of patients receiving aripiprazole rated their study medication as 'much better' on the Preference of Medication Questionnaire scale than their prestudy medication compared with SOC patients (p < 0.001; week 26) [42]. There was no difference in the time to discontinuation between patients treated with aripiprazole and patients treated with SOC (hazard ratio [HR] = 1.17; p = 0.247).

We have several long-term studies of aripiprazole for schizophrenia. Kasper *et al.* performed a 52-week, multicenter, randomized, double-blind study in which schizophrenia patients in acute relapse were randomly treated with aripiprazole 30 mg/day (n = 861) or haloperidol 10 mg/day (n = 433). The aripiprazole group showed comparable or better long-term efficacy than the haloperidol group. A total of 52% of the aripiprazole group and 44% of the haloperidol group responded to the treatment (p < 0.003). In all symptom measures (PANSS total, PANSS positive, PANSS negative scale, CGI-S, CGI-I, Montgomety–Asberg Depression Rating Scale [MADRS] and Brief Psychiatric Rating Scale), the aripiprazole group showed greater improvement than the haloperidol group. Especially in the PANSS negative subscale and MARDS total score, the improvements were statistically significant (p < 0.05) [39]. The risk of discontinuation due to lack of response or adverse events (AEs) was 31% lower with aripiprazole than haloperidol (HR = 0.692; p = 0.0001)

Kane *et al.* pooled and analyzed two 52-week, multicenter, randomized, double-blind studies, where the aripiprazole group's remission rate was significantly higher than that of the haloperidol group, with a magnitude of difference of 10% favoring aripiprazole treatment (p <0.001, LOCF). Among the remitters, the aripiprazole group's time-to-remission was shorter than the haloperidol group's (log rank p = 0.0024) [41]. There was no difference in the time to discontinuation between patients treated with adjunctive aripiprazole and patients treated with placebo (HR = 1.01; p = 0.948).

Fleischhacker *et al.* conducted a 52-week, multicenter, randomized, double-blind study where the efficacy of aripiprazole as a maintenance treatment for schizophrenia was replicated. Patients in acute relapse were randomized to treatment with aripiprazole 15–30 mg/day (n = 355) or olanzapine 10–20 mg/day (n = 348). A total of 47% of the olanzapine group and 39% of the aripiprazole group completed the 52-week treatment. The olanzapine group's mean change in PANSS total score was significantly higher than that of the aripiprazole group from week 4 to week 52 (p < 0.05, LOCF) [43].

As seen in this section, aripiprazole is more effective than placebo and its treatment effect is also comparable to that of other antipsychotics (haloperidol or olanzapine). These data indicate that aripiprazole may be a reliable treatment option as a maintenance treatment for schizophrenia.

Safety & tolerability
Extrapyramidal symptoms
In many studies, the aripiprazole treatment group showed no difference in EPS rating scale scores and EPS occurrence rate compared with the placebo group [37,38,40]. Moreover, several studie reported that the group treated with aripiprazole showed significantly lower EPS rating scale scores and EPS occurrence rate compared to the group treated with haloperidol [36,39,41].

On the other hand, Pigott *et al.* reported that 20.3% of patients treated with aripiprazole showed EPSs while 13.1% of the placebo group showed EPSs [40]. In the Findling *et al.* trial, targeting 13–17-year-old patients, the aripiprazole group's EPSs occurrence rate was twice or more higher than the placebo group's [35]. In the Chzanowski *et al.* study, 18% of patients treated with aripiprazole showed EPSs while 10% of patients treated with olanzapine showed EPSs [45]. Tremor is one of the frequently observed side effects related to the use of aripiprazole.

Pigott *et al.* found that 8.5% of patients treated with aripiprazole developed tremor while only 1.3% of patients treated with placebo developed tremor [40].

Based on the above discussions, it is possible to conclude that aripiprazole is more tolerable than haloperidol regarding the incidences of EPSs, but the findings of several studies indicate that aripiprazole is not free from EPSs, such as tremor and akathisia. Therefore, the clinician's observation of EPSs is needed when aripiprazole is used.

EPS occurs when antipsychotic D2 receptor occupancy in the basal ganglia is over 80% [47]. It is thought that EPSs do not occur frequently in relation to aripiprazole treatment because aripiprazole acts as a partial agonism of D2 receptor in the basal ganglia and it does not block dopamine to the extent that it could cause EPSs [48].

Corrected QT prolongation

Many studies showed that aripiprazole is not related to corrected QT (QTc) prolongation [36,37,40].

Prolactin elevation

Drugs, such as risperdone and haloperidol, significantly increase the prolactin level. But aripiprazole is not related to prolactin increase. In many studies, prolactin level even decreased from baseline after aripiprazole treatment [35–38,43]. When patients receiving risperidone monotherapy were randomized to the adjunctive aripiprazole group or adjunctive placebo group for 16 weeks, the adjunctive aripiprazole group showed a significant reduction in prolactin level compared with the adjunctive placebo group [46]. It seems that aripiprazole is not significantly related to the increase of serum prolactin owing to partial D2 receptor agonism of the pituitary [49].

Weight change & metabolic side effect

The weight gain was significantly lower in the aripiprazole treatment group than the olanzapine treatment group [43–45]. On the other hand, in a 52-week study by Kasper *et al.*, it was found that there was no significant difference in mean weight change from the baseline between the aripiprazole treatment group (1.05 kg) and haloperidol treatment group (0.39kg; LOCF). However, when the baseline BMI was below 23 kg/m^2, there was a significant mean weight change from the baseline between the aripiprazole treatment group (1.05 kg) and the haloperidol treatment group (0.39 kg; p < 0.05). When the baseline BMI was over 27 kg/m^2, both the aripiprazole treatment group (-1.23 kg) and the haloperidol group (-0.78 kg) showed mean body weight loss from the baseline [39]. In a 26-week study by Pigott *et al.*, both the aripiprazole treatment group (-1.26 kg) and the placebo group (-0.87 kg) showed mean body weight loss. Even when the patients were divided into three groups of BMI of under 23 kg/m^2, BMI between 23 and 27 kg/m^2 and BMI of over 27 kg/m^2, all three groups showed weight loss [40]. In the aforementioned studies, the percentage of patients who demonstrated significant weight gain (over 7% gain from the baseline) from baseline in the aripiprazole treatment group were 6 [40], 14 [44] and 15% [45], respectively. It

seems that mean body weight loss after aripiprazole treatment in some studies is probably because the antipsychotics used before the study had a higher weight gain potential than aripiprazole.

Aripiprazole has low affinity to H1 histaminergic, α1 adrenergic and muscarinic receptors, which is thought to cause less weight gain [30,49].

In addition, olanzapine worsened the lipid profile while aripiprazole improved the lipid profile as it is related to the reduction of total cholesterol. Low density lipoprotein cholesterol and triglyceride, and increase of high density lipoprotein cholesterol [43–45].

Pregnancy-related safety

Aripiprazole has been classified as a pregnancy category C drug. There are several case reports showing successful outcomes from the use of aripiprazole during pregnancy [50,51]. However, there is no adequate and well-controlled study.

Safety for children & adolescents

In the studies targeting adult subjects, sedation due to aripiprazole was not higher than that due to placebo [37]. But in a study targeting 13–17-year-olds, the ratio of somnolence was 16.5% in the aripiprazole treatment group and 6% in the placebo treatment group [35]. Moreover, the same study showed that EPSs and tremor occurred over twice more in the aripiprazole group than in the placebo group [35]. Thus, aripiprazole's safety profile might be different between adults and adolescents, but there is not enough research on this.

Safety for elderly

In 2005, the FDA announced a black-box warning, which said that all atypical antipsychotics could increase the death rate of elderly patients with dementia [52]. In three 10-week, placebo-controlled trials using aripiprazole for elderly Alzheimer's dementia patients with psychotic symptoms (n = 938, age range: 56–99 years), AEs, such as lethargy, somnolence, incontinence, hyper-salivation and lightheadedness, occurred at least twice more frequently in the aripiprazole group than in the placebo group [14,53–55]. Systematic research data on the tolerability targeting elderly schizophrenia patients is insufficient at the moment, but the aging process itself changes drug metabolism, absorption and distribution [14]. Therefore, when treating an elderly patient, the doctor should be aware of unexpected side effects and have countermeasures to deal with them.

Acute short-acting intramuscular aripiprazole

A short-acting im. injection of aripiprazole was approved by the EU for the treatment of agitation and disturbed behavior in patients with schizophrenia or bipolar I disorder when the oral therapy is inappropriate, and by the FDA for the treatment of agitation in patients with schizophrenia or bipolar I disorder [16]. The fast management of agitation in psychotic disorder patients is very important. Oral treatment could be effective, but in many cases, it is impossible to administer oral medication to a patient who is severely agitated or shows violent behavior in a clinical setting. In these cases, im. medication can be very useful

because it can be administered easily and produces effects fast [48]. The im. antipsychotics reduce psychotic symptoms and agitation, but the effects are not related to sedation nor tranquilizing effect and antipsychotic effects appear in several minutes [47,56]. Benzodiazepine family drugs are also used to reduce agitation, but whether their antipsychotic effects are not related to the sedative effect is not clear [56]. For the treatment of agitation, in addition to aripiprazole, typical antipsychotics, such as haloperidol and zuclopenthixol, and atypical antipsychotics, such as olanzapine and ziprasidone, are used. Each of these drugs has a different duration of action and side-effect profile [56].

Pharmacokinetic property of short-acting intramuscular aripiprazole

Similar to the pharmacokinetics of oral aripiprazole, that of short-acting im. aripiprazole is linear at a dose of 1–45 mg [31]. The median time of reaching peak plasma concentration is 3–5 h after the administration of oral aripiprazole, whereas it is 1–3 h after the administration of im. aripiprazole [31]. Short-acting im. aripiprazole goes through the same pathway as the oral administration [31].

Therapeutic efficacy & safety of short-acting intramuscular aripiprazole

In 2006, Andrezina *et al.* conducted a randomized, double-blind, placebo-controlled study targeting voluntarily hospitalized schizophrenia patients who were over 18 years old, whose PANSS excited component (PEC) scores were between 15 and 32 or whose PEC item scores were ≥4 (moderate) on ≥2 PEC items [57]. Before protocol-required procedure, all participants provided informed consent. A total of 125 of these patients were randomized to 9.75 mg of short-acting im. aripiprazole, 135 to 6.5 mg of im. haloperidol and 62 to im. placebo. Up to three injections could be given to a patient over 24 h if necessary and no additional injection was allowed within 2 h of prior injection. The mean improvement in PEC score after the first dose was -8.0 in the short-acting im. aripiprazole group, which was similar to the improvement in the im. haloperidol group (-8.3), but significantly greater than the improvement in the im. placebo group (-5.7; p ≤ 0.01). The mean improvement in Agitation–Calmness Evaluation Scale (ACES) score 2 h after the first dose was -1.8 (p = 0.041 vs im. placebo) in the im. aripiprazole group, and 2.0 in the im. haloperidol group (p = 0.004 vs im. placebo). These groups made significantly greater improvements compared with the im. placebo group (1.2). The mean improvement in Corrigan Agitated Behavior Scale 2 h after the first dose was -8.8 in the im. aripiprazole group (p < 0.001 vs im. placebo) and -9.0 in the im. haloperidol group (p < 0.001 vs im. placebo). Furthermore, these groups made significantly greater improvements compared with the im. placebo group (-5.5). As for safety, 16.5% of the im. haloperidol group and 1.6% of im. placebo group reported EPS-related AEs, whereas none of the short-acting im. aripiprazole group reported AEs. The occurrence of im. injection-site reaction (burning, pain or swelling) was low and there was no significant difference between the three groups. In an extension study by the

same authors in 2006, 175 were randomized to 9.75 mg of short-acting im. aripiprazole, 185 to 6.5 mg of im. haloperidol and 88 to im. placebo [58]. As in the previous study, this study also found that short-acting im. aripiprazole was comparable in efficacy to im. haloperidol and it was more tolerable than im. haloperidol in respect to safety.

Short-acting im. aripiprazole was also studied in patients with acute agitation associated with schizophrenia, schizoaffective disorder or schizophreniform disorder. Only the patients whose PEC score was between 15 and 32 and who obtained over four points in more than two of the five PEC items, discontinued all antipsychotics during the study period except the medication used in the study. Only those who signed the informed consent were included in the study. In this study, 57 patients were randomized to 1 mg of short-acting im. aripiprazole, 63 to 5.25 mg of short-acting im. aripiprazole, 57 to 9.75 mg of short-acting im. aripiprazole, 58 to 15 mg of short-acting im. aripiprazole, 58 to 7.5 mg of im. haloperidol and 62 to im. placebo [59]. After 2 h from the first dose, all short-acting im. aripiprazole groups except the 1-mg group and im. haloperidol group showed significant decrease in the PEC score compared with the im. placebo group (p < 0.01). From 45 min after the injection, the 9.5 mg short-acting im. aripiprazole group showed significant decrease in the PEC score compared with the im. placebo group. However, the im. haloperidol group showed significant decrease in PEC score compared with the im. placebo group from 105 min after the injection. The occurrence ratio of akathisia in the im. haloperidol group was 11%, but the average occurrence ratio of akathisa was 2% in the short-acting im. aripiprazole groups.

The aforementioned studies showed that short-acting im. aripiprazole is significantly more effective in the control of acute agitation associated with schizophrenia than placebo and it has comparable effect to haloperidol and it is tolerable in respect to safety. It was reported that oral antipsychotics increase the mortality rate of elderly agitated dementia patients [31]. There are not many studies on the effects of short-acting im. aripiprazole on elderly dementia patients. But in a study, 129 Alzheimer's disease or vascular dementia patients with acute agitation were administered with 5, 10 or 15 mg of short-acting im. aripiprazole or im. placebo. They were observed for 4 h. Except somnolence, no AE occurred more frequently in the short-acting im. aripiprazole groups than the placebo group and no EPS-related AE was observed [60]. A patient injected with 10 mg of short-acting im. aripiprazole died 24 days after the injection, but it was decided that there was no reasonable link between the death and the injection of study medication.

A recent study that pooled the pivotal studies on the treatment of acute agitation associated with schizophrenia or bipolar I disorder [61] has calculated the effect size and tolerability [58,59,62–66]: short-acting im. aripiprazole appeared to be less effective therapeutically than im. olanzapine or im. ziprasidone in regard to the number needed to treat. However, it is not conclusive that short-acting im. aripiprazole is less effective therapeutically than im. olanzapine or im. ziprasidone since these studies were not direct head-to-head controlled studies and there is a possibility

that lower doses of short-acting im. aripiprazole were used in these studies. Details are presented in the Table 3.

Pharmacokinetic properties of once-monthly intramuscular depot aripiprazole

Aripiprazole im. depot is a sterile lyophilized cake that when reconstituted with sterile water for injection forms an injectable suspension. In a recent, Phase III, parallel-arm, multiple-dose, multicenter study, the pharmacokinetics of the once-monthly im. depot formulation was evaluated in patients with schizophrenia (19–62 years, n = 41) and published as an abstract form in the 2011 Annual Meeting of the American Psychiatric Association (APA) [67]. The 41 patients were randomly administered im. depot either 400 mg (n = 14), 300 mg (n = 16) or 200 mg (n = 11) after 14-day titration/stabilization on oral aripiprazole (10 mg/day). According to the results, the mean maximum concentration of drug in plasma at steady state ($C_{ss,max}$) was 316 ng/ml (im. depot 400 mg), 269 ng/ml (im. depot 300 mg) and 100 ng/ml (im. depot 200 mg), respectively, the mean minimum concentration of drug in plasma at steady state ($C_{ss,min}$) was 212 ng/m, 156 ng/ml and 95 ng/ml, respectively, while the mean integral of area under the curve (AUT_T) was 163, 140 and 54.5 µgh/ml, respectively. It was shown that the most pharmacokinetic parameters were proportional in doses of im. depot 300 and 400 mg, while those for im. depot 200 mg were not. The median time to peak plasma concentration for dehydroaripiprazole was 6.6–12.5 days with doses of 400 and 300 mg. The mean elimination half-life for aripiprazole was 47 and 30 days with doses of 400 and 300 mg, respectively. Details are also shown in Table 4. The mean plasma concentrations of aripiprazole and dehydroaripiprazole after im. depot injections are presented in Figures 1 & 2. Based on such findings, we may think that aripiprazole im. depot of both doses of 300 and 400 mg achieved mean steady-state maximum aripiprazole plasma concentrations comparable with those shown in oral doses of aripiprazole between 10–30 mg [32], by which im. depot 300 and 400 mg should be the most suitable doses having proper pharmacokinetic profiles for schizophrenia patients.

Therapeutic efficacy & safety of once-monthly intramuscular depot aripiprazole

Depot antipsychotics were found to significantly reduce the risk for rehospitalization for schizophrenia compared with oral formulations in a large Finnish study [68]. In the study, the risk for rehospitalization and drug therapy discontinuation were assessed in a nationwide cohort of 2588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland. The mean age of the patients was 37.8 years, and 62% were men. Approximately 60% (n = 1507 out of 2588) of subjects used an antipsychotic drug during the first 30 days after hospital discharge; however, only 45.7% were on their initial treatment for 30 days or longer. During the 2-year follow-up, 1496 patients (57.8%) were rehospitalized due to a

Table 3. Overview of randomized controlled trials of the efficacy and safety of intramuscular aripiprazole in schizophrenia.

Study (year)	Methods/interventions	Informed consent	Efficacy	Safety	Ref.
Andrezina *et al.* (2006)	24 h; RCT; im. ARP 9.75 mg (n = 125); im. HPD 6.5 mg (n = 135); im. PBO (n = 65)	Voluntarily admitted	ARP ≒ HPD (-8.0 vs -8.3) and ARP > PBO on in PEC score (-8.0 vs -5.7) ARP ≒ HPD > PBO (1.8 vs 2.0 vs 1.2) on ACES score ARP ≒ HPD > PBO (-8.8 vs-9.0 vs -5.5) on CABS score	ARP ≒ PBO > HPD on the incidence of EPS-related AEs ARP ≒ HPD ≒ PBO on the incidence of im. injection site reaction	[57]
Andrezina *et al.* (2006)	24 h; RCT; im. ARP 9.75 mg (n = 175); im. HPD 6.5 mg (n = 185); im. PBO (n = 88)	Voluntarily admitted	ARP ≒ HPD > PBO (-7.2 vs -7.8 vs -4.5) on PEC score ARP ≒ HPD > PBO (1.4 vs 1.6 vs 0.8) on ACES score ARP ≒ HPD > PBO (-8.0 vs -8.3 vs -4.5) on CABS score	ARP ≒ HPD ≒ PBO on sedation and injection site reaction	[58]
Tran-Johnson *et al.* (2007)	24 h; RCT; im. ARP 1 mg (n = 57); im. ARP 5.25 mg (n = 63); im. ARP 9.75 mg (n = 57); im. ARP 15 mg (n = 58); im. HPD 7.5 mg (n = 60); im. PBO (n = 62)	Voluntarily admitted	After 2 h, ARP all group > PBO on the PEC score After 45 min ARP 9.5 mg > PBO on the PEC score After 2 h ARP 9.75 mg > PBO on ACES score After 2 h, ARP 5.25, 9.75 and 15 mg > PBO on CABS score	ARP ≒ PBO> on akathisia (2 vs 0 vs 11%) ARP > PBO on headache (13 vs 1.6%)	[59]

ACES: Agitation–Calmness Evaluation Scale; AE: Adverse event; ARP: Aripiprazole; CABS: Corrigan Agitated Behavior Scale; EPS: Extrapyramydal symptom; HPD: Haloperidol; im.: Intramuscular; LCOF: Last observation carried forward; PANSS: Positive and Negative Syndrome Scale; PBO: Placebo; PEC: PANSS excited component; RCT: Randomized controlled trial.

relapse of schizophrenia symptoms. Compared with nonuse of antipsychotics, use of any antipsychotic significantly reduced the rehospitalization risk (HR = 0.38; 95% CI: 0.34–0.43). In a pair-wise comparison between depot injections and their equivalent oral formulations, the risk for rehospitalization for patients receiving depot medications was approximately a third of that for patients receiving oral medications (adjusted HR = 0.36; 95% CI: 0.17–0.75).

According to the data presented at the Annual Meeting of the APA 2011, im. depot of either 400 mg (n = 14), 300 mg (n = 16) or 200 mg (n = 11) was tested with 41 schizophrenia patients after 14-day titration/stabilization on oral aripiprazole (10 mg/day) [67]. In this study, 71.4, 50 and 36.4% of such patients on im. depot 400, 300 and 200 mg, respectively, completed the study. The main reason for discontinuation in the im. depot 200 mg (45.5%) was withdrawal of the consent, while in the im. depot 300 mg (25%) it was AEs ; the im. depot 400 mg had no discontinuation due to AEs. The AE rates were 64.3% (n = 9 out of 14), 73.3% (n = 11 out of 15) and 60% (n = 6 out of 10) in im. depot 400, 300 and 200 mg, respectively. The most frequent AEs were injection site pain, vomiting/somnolence/QTc interval change and headache in the im. depot 400, 300 and 200 mg, respectively. Most AEs were mild to moderate in severity. The efficacy data was not presented in the abstract. However, according to the manufacturer, a Phase III, 52-week, clinical study of the im. depot arpiprazole investigating the efficacy, safety and tolerability in patients with schizophrenia, was early terminated since the interim analysis already satisfied the termination criteria on the protocol. Hence, the 52-week im. depot study was stopped in June, 7 months ahead of the established schedule [101].

Compliance

The average nonadherence rate of antipsychotic medication among patients with schizophrenia in the community is 40–60% [69], and there is a report that patients receiving antipsychotic therapy actually take less than 60% of the prescribed amount [70]. Schizohpreina symptoms themselves impede adherence to drug therapy and nonadherence contributes to approximately 40% of all relapses [71]. In a study reviewing seven studies targeting schizophrenia patients, the relapse risk of compliant patients between 6 months and 2 years after starting treatment was 3.7-times lower than that of noncompliant patients [72]. Side effects of a drug are directly related to compliance and atypical antipsychotics are not exceptions [43]. It is expected that aripiprazole will improve the adherence rate as it does not cause side effects, such as sedation, lipid profile disturbance, weight gain, EPS, QTc interval prolongation and hyperprolactinemia.

Expert commentary & five-year view

The prescription of antipsychotics is made in consideration of the preferences of patient and clinician, efficacy and safety, and local pharmacoeconomic circumstance. The most frequently prescribed atypical antipsychotics are aripiprazole, risperidone, olanzapine, amisulpiride, quetiapine, ziprasidone, paliperidone and clozapine. Several of these are available in other formulation

Table 4. Pharmacokinetics of once-monthly intramuscular depot aripiprazole.

Parameters	im. depot 400 mg	im. depot 300 mg	im. depot 200 mg
Aripiprazole			
$C_{ss\ max}$ (ng/ml)	316	269	100
T_{max} (day)	7.1	6.5	5.0
AUT_T (µgh/ml)	163	140	54.5
$T_{1/2}$ (day)	46.5	29.9	ND
$C_{ss\ min}$ (ng/ml)	212	156	95.0
Dehydroaripiprazole			
$C_{ss\ max}$ (ng/ml)	89.4	74.7	30.3
T_{max} (day)	6.6	12.5	5.5
AUT_T (µgh/ml)	47.8	38.9	14.7
$C_{ss\ min}$ (ng/ml)	64.1	54.1	26.2

AUT_T: Integral of area under the curve; $C_{ss\ max}$: Maximum concentration of drug in plasma at steady state; $C_{ss\ min}$: Minimum concentration of drug in plasma at steady state; im.: Intramuscular; ND: Not determined; $T_{1/2}$: Half-life.
Adapted with permission from the abstract of the Annual Meeting of the American Psychiatric Association [67].

forms. And each of these antipsychotics has a different cost, level of compliance, and AEs profile. Typical antipsychotics are also available and they have the advantage of lower cost and comparable efficacy, but they fall behind in safety and tolerability compared with atypical antipsychotics.

Given that side effects of a drug are as important as its efficacy, aripiprazole became popular because it involves low weight gain and metabolic concerns. Metabolic syndrome is increasingly gaining attention and quality of life is becoming as important as control of symptoms for schizophrenia patients. It is expected that such a trend will more strongly continue and the use of aripiprazole will increase in line with the trend as proven data.
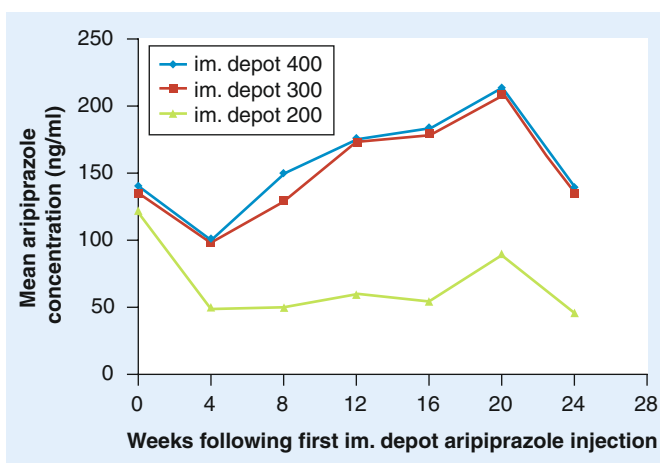
Figure 1. The trend of mean plasma concentration of aripiprazole (ng/ml) by weeks.
im.: Intramuscular.
Adapted with permission from the abstract of the Annual Meeting of the American Psychiatric Association [67].
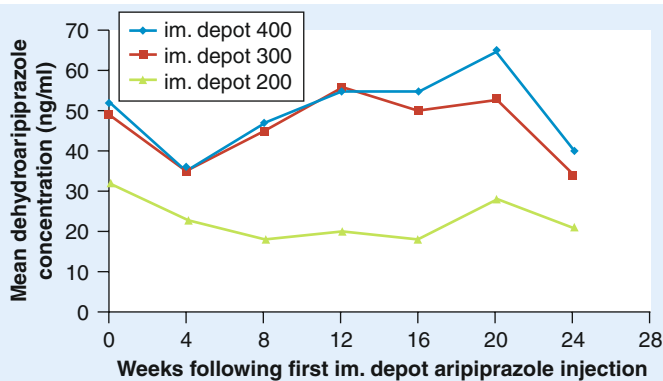
Figure 2. The trend of mean plasma concentration of dehydroaripiprazole (ng/ml) by weeks.
im.: Intramuscular.
Adapted with permission from the abstract of the Annual Meeting of the American Psychiatric Association [67].

Intramuscular injection of aripiprazole controls acutely agitated symptoms effectively. When the depot form of aripiprizole is eventually available in the market, it can be used for the patients who do not comply with continuous and maintenance treatment well, which will make for a further increase in treatment compliance.

However, current data on im. aripiprazole and im. depot aripiprazole are not sufficient in our clinical practice. Therefore, adequately powered and well designed further research based on clinical experiences is needed.

Key issues

- Schizophrenia is a highly prevalent disease and has a variety of symptoms, including disruptive psychopathology, such as cognition, emotion, perception and other aspects of behavior.
- Ariprazole has shown efficacy and safety in the treatment of schizophrenia.
- Maintenance treatment should always be kept in treatment of schizophrenia since the disorder is chronic and recurrent in its natural course.
- Many newer formulations of antipsychotics are available to enhance the treatment efficacy and efficiency, among which intramuscular depot aripiprazole will provide another treatment option to both clinicians and patients owing to its proven efficacy and safety.

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