Intramuscular aripiprazole for the treatment of agitation in schizophrenia and bipolar disorder: from clinical research to clinical practice

Aripiprazolo intramuscolare per il trattamento dell'agitazione nella schizofrenia e nel disturbo bipolare: dalla ricerca alla pratica clinica

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Summary

Objectives

To review the major findings of clinical research on the pharmacokinetics, therapeutic efficacy and tolerability of IM aripiprazole as a treatment option for agitation associated with schizophrenia and bipolar I disorder and to provide an expert comment based on the authors' clinical experience in real world psychiatric practice.

Methods

Articles on intramuscular aripiprazole published in English between 1997 and 2012 were identified through a MEDLINE search. Relevant clinical studies and review articles were found using the text- and keyword-search term aripiprazole alone and in combination with intramuscular, bipolar, schizophrenia, and agitation. The reference lists of identified articles, especially review articles, were checked for any additional studies that might have been missed in the original MEDLINE search.

Results

Acute agitation associated with schizophrenia and bipolar I disorder is a medical emergency that requires prompt pharmacological intervention to relieve patient distress and to prevent harm to self or others. Current guidelines for the management of acute agitation in schizophrenia and bipolar I disorder recommend intervention with antipsychotic agents and/or benzodiazepines, initiated as soon as possible after other conditions leading to agitation have been ruled out. Oral aripiprazole demonstrated efficacy in schizophrenia and bipolar 1 disorder (manic and mixed episodes and maintenance treatment), and resulted associated with a low risk for extrapyramidal symptoms, adverse cardiac effects, hyperprolactinemia and adverse metabolic effects. Intramuscular (IM) formulation of aripiprazole has been approved for treatment of agitation associated with schizophrenia or bipolar I disorder manic. The efficacy of IM aripiprazole in reducing agitation was assessed in two large, multinational, double-blind, placebo-controlled studies in patients with schizophrenia, schizoaffective or schizophreniform disorder 23 24, and in a similarly designed trial in patients with bipolar I disorder. IM aripiprazole was generally well tolerated in the three studies in schizophrenia and bipolar I disorder. The discontinuation rate due to adverse events was generally very low: 0.8% in the aripiprazole group versus 0.5% in the placebo group (pooled analysis). In our clinical practice, the most common reasons for choosing IM aripiprazole (apart from efficacy) are: (1) very low risk of cardiovascular events and heart conduction abnormalities; (2) relatively low risk of EPS; (3) very low risk of excessive sedation; (4) the ability to use concomitant benzodiazepines provided that careful monitoring for orthostatic hypotension is undertaken. Furthermore, based on our clinical experience, IM aripiprazole appears to act more rapidly and be more effective than oral aripiprazole in reducing acute agitation, possibly due to the higher Cmax associated with the IM formulation. However, to our knowledge, oral and IM aripiprazole have not been directly compared in a clinical trial.

Conclusions

IM aripiprazole is an effective treatment for agitation in patients with bipolar disorder or schizophrenia and is characterized by a relatively favorable tolerability profile.

Key words

Aripiprazole • Bipolar disorder • Schizophrenia

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Introduction

Patients with schizophrenia or bipolar I disorder experience states of severe agitation characterized by irritability, high responsiveness to internal and external stimuli, motor restlessness and disturbed, aggressive or self-injurious behaviour. Acute agitation is regarded as a medical emergency due to the substantial risk of behaviours that are dangerous to self or others. As psychotic disorders are usually chronic or recurrent [1], acute agitation may occur repeatedly, and its rapid treatment is a crucial aspect in the management of psychotic patients.

Current guidelines for the management of acute agitation in schizophrenia and bipolar I disorder recommend intervention with antipsychotic agents and/or benzodiazepines, initiated as soon as possible after other conditions leading to agitation have been ruled out [4 7].

The primary aim of treatment is to prevent harm and control disturbed behaviours. However, rapid control of agitation is also essential for developing patient cooperation, determining and addressing the causes of the acute episode, and for planning adequate maintenance therapy. Medications commonly used in the management of acute psychotic agitation include first-generation antipsychotic agents (e.g. chlorpromazine and haloperidol) and second-generation atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone) [4 5]. First-generation antipsychotics are still widely used due to their specificity and efficacy in controlling or reducing psychotic symptoms and agitation. However, the high incidence of adverse events limits their overall usefulness; the most common of these include extrapyramidal symptoms (EPS), tardive dyskinesia, excessive sedation and cardiovascular disturbances [8 9]. Atypical antipsychotics are associated with a reduced risk of EPS, but some of these agents have been shown to induce other adverse events, including weight gain, metabolic alterations, hyperprolactinaemia and QT-interval prolongation [10]. Second-generation antipsychotics have distinct receptor-binding properties, and therefore their benefit-risk profiles vary from drug to drug and should be evaluated individually [8 10]. In addition, given the considerable interpatient variability in antipsychotic response and tolerability, the choice of the antipsychotic agent should take into account the clinical and psychiatric condition of the patient, the presence of comorbidities and substance abuse, and the occurrence of adverse events with previous treatments [9 11].

Although psychotic agitation can be effectively managed by oral antipsychotics [12], acutely agitated patients may be unable or unwilling to take an oral preparation. IM preparations are preferred in such circumstances as they have a rapid effect and can be administered to severely agitated patients [4 5 7]. The efficacy and safety of IM formulations have been extensively addressed in recent studies [13 14]; IM second-generation antipsychotics are emerging among the first-choice interventions based on their rapid effect on agitation and overall efficacy to control psychotic symptoms [14].

Here we review the major findings of clinical research on the pharmacokinetics, therapeutic efficacy and tolerability of IM aripiprazole as a treatment option for agitation associated with schizophrenia and bipolar I disorder.

Pharmacology and clinical research

Pharmacodynamic and pharmacokinetic properties

Aripiprazole is a member of a new class of atypical antipsychotics termed 'dopamine-serotonin system stabilizers' [15 16]. Unlike other antipsychotics, which act mainly as dopamine D_2 receptor antagonists, aripiprazole is a partial agonist of D_2 [15 17 18] and serotonin 5-HT_{1A} receptors, as well as a 5-HT_{2A} receptor antagonist [15 17]. Although the precise mechanism of action of aripiprazole in schizophrenia and bipolar I disorders remains to be established, the drug's lack of significant affinity for muscarinic and histaminergic receptors, and low affinity for α-adrenergic receptors, may account for its low propensity for several adverse effects that sometime limit the clinical use of other drugs [19]. The efficacy of oral aripiprazole on the positive and negative symptoms of schizophrenia and its tolerability have been extensively reviewed elsewhere [11 20].

As reported for oral aripiprazole [11], the pharmacokinetics of IM aripiprazole are linear at doses ranging from 1 to 45 mg. In healthy volunteers, IM aripiprazole was rapidly absorbed and a 5 mg injection had an absolute bioavailability of 100% [21]. The median times to peak plasma concentration were 1 and 3 hours (h), compared with 3 to 5 h for oral aripiprazole. After an IM dose, exposure to aripiprazole is greater than the same dose given orally, with a 19% increase in the geometric mean peak plasma concentration (C_{max}) for IM versus oral aripiprazole. The area under the plasma concentration-time curve (AUC) 2 h after IM injection was increased by 90% compared with oral administration, while the AUC over 24 h was generally similar for the two formulations.

A recent study comparing three aripiprazole formulations (oral, IM, intravenous) showed that the time to C_{max} had marked variability [22]. Consistent with the findings of previous pharmacokinetic studies, C_{max} was reached more rapidly with IM than with oral aripiprazole. (78% and 5% of C_{max} values at 0.5 h postdose, respectively). The AUC in the first 2 h was 90% higher after IM administration than after oral administration [22]. This could lead to

higher brain concentrations of aripiprazole following IM administration.

Studies with oral aripiprazole showed that the drug and its main metabolite dehydroaripiprazole were extensively (> 99%) bound to plasma proteins (albumin) and widely distributed in the body. Because of this and its relatively long half-life (mean 75 h), aripiprazole accumulates with multiple oral doses, reaching steady-state plasma concentrations after 14 days [26].

IM aripiprazole is presumably metabolized by the same pathways involved in the metabolism of the oral formulation. In in vitro studies, oral aripiprazole was metabolized mainly by dehydrogenation and hydroxylation by hepatic cytochrome P450 (CYP) 3A4 and CYP2D6 enzymes, and by N-dealkylation by CYP3A4 enzymes. The active metabolite dehydroaripiprazole accounted for 40% of the aripiprazole AUC value for plasma at steady state. After a single, oral, radiolabelled dose, 25% of the radioactivity was found in urine and 55% in faeces [26].

Since aripiprazole is metabolized by CYP3A4 and CYP2D6 enzymes, drugs that induce or inhibit these enzymes can affect aripiprazole clearance. The dosage should therefore be adjusted when co-administering ketoconazole, quinidine, fluoxetine or paroxetine. A study in patients with schizophrenia showed that co-administration of divalproex sodium or lithium had no clinically relevant effects on the pharmacokinetics of aripiprazole (30 mg/day) [27]. Finally, *in vivo* studies indicate that aripiprazole itself is unlikely to affect the pharmacokinetics of other drugs metabolized by CYP enzymes.

Therapeutic efficacy

The efficacy of IM aripiprazole in reducing psychotic agitation was assessed in two large, multinational, double-blind, placebo-controlled studies in patients with schizophrenia, schizoaffective or schizophreniform disorder [23 24], and in a similarly designed trial in patients with bipolar I disorder [25].

In the first of the double-blind, placebo-controlled studies investigating the efficacy of IM aripiprazole for acute agitation in patients with schizophrenia or schizoaffective disorder, 448 patients were randomized to IM aripiprazole 9.75 mg, IM haloperidol 6.5 mg, or IM placebo [23]. Patients could receive up to three injections over the first 24 h, if necessary. The primary efficacy measure was the mean change in Positive and Negative Syndrome Scale (PANSS) - Excited Component (PEC) score from baseline to 2 h after the first dose (higher scores correspond to more severe agitation). The PEC consists of five items from the PANSS total scale (hostility, lack of cooperation, excitement, poor impulse control and tension), and each item scored on a scale of 1 (absent) to 7 (extreme). Secondary endpoints included the mean change from baseline to 2 h for scores on various evaluation scales specific for agitation [Clinical Global Impressions (CGI)-Severity of Illness Scale (CGI-S), CGI-Improvement Scale (CGI-I), Agitation-Calmness Evaluation Scale (ACES; 1 = marked agitation, 9 = unarousable), and others]. Aripiprazole was significantly more effective than placebo in reducing agitation, with significantly greater improvement in PEC scores at 2 h (-7.27 *vs.* -4.78, $p < 0.001$), as was haloperidol (-7.75, $p < 0.001$) [23]. An analysis of covariance demonstrated non-inferiority of aripiprazole to haloperidol. Improvement in agitation with aripiprazole was rapid, with significant differences versus placebo for mean changes in PEC scores evident after 1 hour, while a significant difference was achieved at 45 minutes in the haloperidol group [23]. Aripiprazole and haloperidol were also significantly more effective than placebo according to all secondary efficacy measures. Finally, the mean number of injections/patient and the proportion of patients requiring adjunctive benzodiazepines was significantly lower for aripiprazole than for placebo ($p < 0.01$) [23].

In a post hoc analysis of this study focusing on patients with agitation associated with schizophrenia (n = 325), aripiprazole was again significantly better than placebo in reducing agitation [28]. The mean changes in PEC scores 2 h after the first aripiprazole, haloperidol or placebo injection were -8.0, -8.3 and -5.7, respectively (both $p < 0.01$ *vs.* placebo). The respective PEC baseline values of these patients were 18.9, 18.8 and 18.9. Interestingly, the results obtained with IM treatment were maintained after the patients were switched to the respective oral treatments. Assessment of secondary efficacy results (CGI-I, CGI-S. ACES and CABS) in this subgroup also supported the superiority of IM aripiprazole versus placebo and its similar efficacy to IM haloperidol [28].

The important issue of switching patients from IM antipsychotic formulations (acute treatment) to the respective oral formulations (maintenance treatment) was also investigated in this study population [29]. Of the 448 patients who received 24-hour IM therapy, 380 (85%) completed treatment and were transitioned to oral formulations of aripiprazole 10-15 mg/day or haloperidol for 4 days: 76 from placebo, 153 from aripiprazole and 151 from haloperidol [29]. Patients initially randomized to placebo were switched to open-label oral aripiprazole and were not included in the analysis. The primary efficacy measure was the mean change in PEC score from the start of the oral phase (day 1) to day 5. Both oral aripiprazole and haloperidol were not only effective in maintaining PEC responses achieved with IM therapy, but further improvements were seen (non-significant mean change in PEC score: -1.37 for aripiprazole and -1.40 for haloperidol) [29].

The superiority of IM aripiprazole over placebo was confirmed in a 24-hour dose-ranging study by Tran-Johnson and colleagues [24]. Patients (n = 357) with acute agita-

tion and a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder were randomized to IM aripiprazole (1, 5.25, 9.75, or 15 mg), IM haloperidol 7.5 mg or placebo. The primary efficacy measure was the mean change in PEC score from baseline to 2 h after initial administration [24]. Aripiprazole, at doses > 1 mg, and haloperidol were significantly more effective than placebo in improving PEC score from baseline at 2 h ($p < 0.01$) [24], with significant improvements versus placebo seen as early as 45 minutes with aripiprazole 9.75 mg ($p \leq 0.05$) and a trend towards significance at 30 minutes ($p = 0.051$). With haloperidol, a significant reduction in PEC score was first apparent at 105 minutes ($p \leq 0.05$) [24]. In addition, the response rate (defined as the proportion of patients with a reduction in PEC score ≥40%) with aripiprazole 9.75 mg was significantly greater than placebo at 30 minutes (27% *vs.* 13%, $p = 0.05$). The significantly greater improvement in ACES score from baseline to 2 h ($p = 0.003$) showed that the greater efficacy seen with aripiprazole 9.75 mg *vs.* placebo was not associated with over-sedation [24].

The efficacy of IM aripiprazole for the treatment of agitation in patients with bipolar I disorder was evaluated in a trial involving 301 patients [24]. Patients experiencing acute agitation were randomized to receive IM aripiprazole 9.75 mg or 15 mg, IM lorazepam 2 mg or IM placebo. The primary efficacy endpoint was mean change in PEC score from baseline to 2 h. Consistent with the findings in patients with schizophrenia and its related disorders [22], aripiprazole was effective for treating agitation in patients with bipolar I disorder: mean improvements in PEC scores at 2 h were significantly greater with aripiprazole (9.75 mg, -8.7; 15 mg, -8.7) and lorazepam (-9.6) than with placebo (-5.8, $p \leq 0.001$), and were evident as early as 45 min after administration ($p < 0.05$) [22]. The frequency of over-sedation (as shown by an ACES score 8-9) with aripiprazole 9.75 mg (6.7%) was similar to that observed with placebo (6.8%) and lower than observed with aripiprazole 15 mg (17.3%) and lorazepam (19.1%), suggesting a net clinical benefit for aripiprazole 9.75 mg [25].

The data from the three efficacy studies [23-25] were pooled and three secondary efficacy analyses were performed focusing on: (1) 'non-sedated patients' (ACES score < 8-9); (2) patients with bipolar and schizophrenia, each divided into 'higher' agitation (PEC > 18) and 'lower' agitation (PEC < 18) groups; and (3) patients who received a second IM injection within the 24 hour study period [30]. Re-evaluation of the mean change from baseline in PEC scores showed that non-sedated patients with bipolar I disorder or schizophrenia (analysis 1) achieved significant improvement in mean PEC score with aripiprazole ($p < 0.005$). Analysis 2 showed that in patients with bipolar I disorder, aripiprazole significantly reduced agitation only in those with lower baseline agitation levels, whereas in patients with schizophrenia, aripiprazole was significantly more effective than placebo regardless of baseline agitation ($p < 0.01$) [30]. Patients with bipolar I disorder who had higher baseline agitation showed similar PEC decreases with aripiprazole (-9.9) and placebo (-7.9) [30]. Analysis 3 found that a second injection of aripiprazole significantly reduced agitation in all patients ($p < 0.05$) [30].

Tolerability

IM aripiprazole was generally well tolerated in the three studies in schizophrenia and bipolar I disorder. The discontinuation rate due to adverse events was generally very low: 0.8% in the aripiprazole group versus 0.5% in the placebo group (pooled analysis) [13]. Discontinuation rates for the comparators haloperidol and lorazepam were also low (< 1%) [23-25]. Most treatment-emergent adverse events were of mild-to-moderate severity [30]. Pooled descriptive data from the three clinical trials showed that headache (incidence 12%), nausea (11%), dizziness (8%) and somnolence (7%) were the most frequently occurring adverse events during the 1-hour period after injection of aripiprazole 5.25 or 15 mg [13 30]. In comparison, in the placebo group, headache was reported by 7% of patients, followed by dizziness (5%), somnolence and sedation (4%), and nausea (3%) [13 30].

In the two trials of IM aripiprazole in patients with schizophrenia and related disorders, the most frequently occurring adverse events for haloperidol were insomnia (12%), headache (8%), somnolence (12%), akathisia (11%), dystonia (7%) and dizziness (7%) [23 24]. In the trial in patients with bipolar I disorder, the most common adverse events associated with lorazepam were sedation (12%), dizziness (10%) and somnolence (7%) [25].

Overall, IM aripiprazole had a favourable EPS profile across the three studies, with few patients experiencing EPS-related events [23-25]. In the study by Tran-Johnson and colleagues [23], EPS-related adverse events were reported in 2% of aripiprazole, 13% of haloperidol and 2% of placebo recipients. In the dose-ranging trial, at recommended doses, dystonia occurred in 0-2% of aripiprazole recipients, 7% of haloperidol recipients and 0% of placebo recipients, while akathisia was reported in 3-5%, 11% and 0% of patients, respectively [24]. In patients with bipolar I disorder, eight patients (5%) treated with aripiprazole, none receiving lorazepam and one (1%) receiving placebo experienced EPS-related adverse events [25]. It should be noted that objective measures of EPS (Simpson-Angus Scale, and Barnes Akathisia Rating Scale) yielded inconsistent findings in the three trials [13]. The data regarding EPS-related events should therefore be interpreted with caution.

Monitoring of vital signs and electrocardiograms (ECGs) revealed no clinically relevant hypotension or heart rate,

rhythm, or conduction abnormalities in any of the three trials, and differences between treatment and placebo groups were not clinically significant [6 28 30].

Data on the tolerability and safety of repeated IM injections of aripiprazole, the safety of doses > 30 mg, or IM administration at frequencies greater than every 2 h, are limited [13]. In one trial, 183 patients (41%) received a second injection of either aripiprazole or haloperidol within 24 h of the first injection [23]. Of these, 58 (32%) experienced an adverse event after the second injection, most frequently insomnia, agitation and nausea in the aripiprazole group, and insomnia, agitation and headache in the haloperidol group.

One study investigated safety outcomes in patients transitioning from IM to oral aripiprazole [29], based on study [23]. During the IM phase, 37%, 45% and 28% of patients reported treatment-emergent adverse events in the aripiprazole, haloperidol and placebo groups, respectively. During the 4-day oral phase of the study, the most common adverse events in the aripiprazole and haloperidol groups were agitation (16% and 17%, respectively), insomnia (13% and 11%), headache (both 10%) and anxiety (5% and 6.0%) [26]. Akathisia and EPS were reported in 2% and 1%, respectively, of patients switched to oral aripiprazole, and in 4% and 8% of those switched to oral haloperidol [29].

IM aripiprazole led to infrequent injection site reactions [22 23]. Across trials, reactions such as pain, stinging and burning were reported in fewer than 5% of patients in all treatment groups [13].

Dosage and administration

IM aripiprazole is indicated in the EU for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or with manic episodes in bipolar I disorder. The recommended starting dose of IM aripiprazole is 9.75 mg [13]. In cases where additional IM doses are needed, the total daily dose should not exceed 30 mg (including all formulations of aripiprazole), nor should administration be more frequent than every 2 h [13]. No more than three injections should be administered in any 24-hour period. Patients who require continued treatment with aripiprazole should be switched to an oral formulation as soon as possible. Usually, a dosage adjustment based on patient age, gender, race, smoking status, kidney or hepatic function is not necessary. However, low doses should be considered in elderly patients (> 65 years old) or patients whose ability to metabolize the drug is severely compromised.

Aripiprazole is a substrate for CYP3A4 and CYP2D6 metabolism and it is recommended that the dose of aripiprazole be reduced by 50% when used with CYP3A4 or CYP2D6 inhibitors such as ketoconazole and fluoxetine [21]. CYP3A4 inducers, such as carbamazepine, may increase aripiprazole clearance, leading to lower blood levels [13]. In this case, the manufacturer recommends that the usual dose of aripiprazole be doubled [21].

Although co-administration of aripiprazole with lorazepam does not have any pharmacokinetic effects, this combination has been associated with over-sedation and orthostatic hypotension [13] and as such it is not possible to exclude a pharmacodynamic interaction. Therefore, careful monitoring is necessary when co-administering aripiprazole with lorazepam [13].

Data on the effects of aripiprazole during pregnancy are very limited. Aripiprazole is rated C (risk cannot be ruled out) in the FDA pregnancy rating system for the assessment of risk to the foetus. It is not known whether aripiprazole is excreted in human milk and therefore women taking aripiprazole should not breast feed [21].

Choice of IM aripiprazole

According to international guidelines for the treatment of acute psychotic agitation in patients with schizophrenia and bipolar disorder [4 5 7], selection of a specific antipsychotic agent should always be based on a careful benefit-risk evaluation. In our clinical practice, the most common reasons for choosing IM aripiprazole over other antipsychotics (apart from efficacy) are: (1) very low risk of cardiovascular events and heart conduction abnormalities; (2) relatively low risk of EPS; (3) very low risk of excessive sedation; (4) the ability to use concomitant benzodiazepines provided that careful monitoring for orthostatic hypotension is undertaken. Furthermore, based on our clinical experience, IM aripiprazole appears to act more rapidly and be more effective than oral aripiprazole in reducing acute agitation, possibly due to the higher C_{max} associated with the IM formulation. However, to our knowledge, oral and IM aripiprazole have not been directly compared in a clinical trial. Although benzodiazepines are associated with a low risk of cardiovascular events and heart conduction abnormalities, they have been investigated in patients with arrhythmias and so would be preferred over other drugs that have not been studied in such patients.

Adjunctive benzodiazepines are not usually added until at least 1 hour after aripiprazole injection. Patients can receive a second injection of aripiprazole if needed, but not until at least 2 h after the first. In cases of extreme and potentially dangerous agitation, adjunctive benzodiazepines are added earlier.

Combination with other drugs

Benzodiazepines have been used as concomitant medications with IM aripiprazole in clinical trials [23 25] and may be used as adjunctive short-term treatment [4 5]. In a

24-hour, double-blind study of patients presenting with acute agitation with a diagnosis of bipolar I disorder (manic or mixed), patients were randomized to placebo, IM aripiprazole 9.75 or 15 mg, or lorazepam 2 mg [25]. The use of oral non-benzodiazepine sleep agents such as zolpidem and zaleplon (not to exceed 10 mg/day) may have been given at least 1 hour after the second study injection and, if needed, at least 1 hour after the third study dose [25].

Duration of treatment

According to American Psychiatric Association guidelines, patients receiving IM antipsychotics should be switched to the oral formulation as soon as possible [4 5]. The main IM aripiprazole clinical trials followed patients for 24 h. In our clinical practice and experience, the duration of aripiprazole IM treatment is often longer than 24 h, ranging from 1 to 5 days. When we treat a patient with IM aripiprazole, we usually attempt a switch to the oral formulation. If agitation re-emerges after switching to oral treatment, we often switch back to the IM formulation and attempt a new switch to the oral treatment once agitation is controlled.

Discussion

Clinical trials have demonstrated the therapeutic efficacy and tolerability of IM aripiprazole for the treatment of agitation in patients with schizophrenia and bipolar I disorder. However, as observed with other medications and in the treatment of other conditions, the results obtained in highly selected populations in clinical trials are often difficult to reproduce in routine clinical practice. This is particularly true for psychotic patients, often characterized by poor adherence and cooperation, and by a number of comorbidities and conditions interfering with the administration of adequate treatment.

The clinical experience with aripiprazole is still relatively limited; however descriptive data from everyday practice is encouraging. Yet, more studies are required, especially to investigate long-term efficacy and safety outcomes and to directly compare aripiprazole with other antipsychotics.

An important factor to consider when selecting an antipsychotic is in fact its safety profile. Atypical antipsychotic are less likely to cause tardive dyskinesia and EPS than typical antipsychotics [6]. However, individual members of this class have distinct safety profiles and the incidence of adverse events varies accordingly. Due to its low propensity to cause weight gain, hyperglycaemia and dyslipidaemia, and low risk for hyperprolactinaemia [13], IM aripiprazole may be more appropriate than other atypical antipsychotics for patients at high risk for metabolic diseases [31], cardiovascular disease or hyperprolactinaemia. However, no thorough clinical trials have been performed to test IM aripiprazole in these specific patients so treatment choice should be made only after carefully reviewing the patient's individual requirements. For instance, benzodiazepines have been extensively investigated in patients with arrhythmias and should, therefore, be preferred for patients with heart rhythm abnormalities. Adjunctive medications may be of value during the manic episode in the treatment of agitation, as well as for anxiety or insomnia. The concomitant use of IM aripiprazole and benzodiazepines is frequently used in our practice and has proven to be safe and well tolerated. In our practice, treatment with IM aripiprazole, often administered concomitantly with other medications (benzodiazepines, lithium, valproate), is usually safe and well tolerated even in the presence of relevant comorbidities and cardiovascular risk factors. However, we reiterate that patients with severe cardiovascular conditions should be preferably treated with medications such as benzodiazepines.

In our practice, most patients treated with IM aripiprazole respond to treatment. In general, there are a few core principles that can lead to a successful treatment outcome, but the treatment strategy (e.g. choice of IM versus oral formulation, number of injections, target dose, concomitant/adjunctive treatments dose adjustment) should be tailored to each individual patient's profile, based on a careful clinical assessment and follow-up, to ensure the best personalized treatment aimed at a good tolerability and a successful outcome. It is our impression that the IM formulation is more effective and predictable than the oral formulation, for the treatment of agitation. However, in most cases, patients treated with IM aripiprazole can be successfully switched to oral aripiprazole once symptoms are controlled. The switch may be accomplished by means of various protocols depending on the clinical situation. For instance, some patients may be switched to the oral formulation after just 1 day of treatment while other patients may need longer. There are cases when patients develop new symptoms of mania and agitation upon switching to the oral formulation. In these cases, we usually consider a switch back to the IM formulation and a new attempt to re-instate treatment with oral aripiprazole once the symptoms are controlled. Of course, in case of particularly severe patients or in case of a new failure, we switch to an alternative medication.

Though more clinical research is necessary to better define the place of IM aripiprazole in the management of agitation in schizophrenia and bipolar I disorder, as well as to optimize treatment protocols (e.g. switching strategies and duration of treatment), we believe that IM aripiprazole has lived up to its promise and that the transition from clinical research to clinical practice has been successful.

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