Switching antipsychotic medication to aripiprazole: position paper by a panel of Italian psychiatrists.

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Abstract

INTRODUCTION:
Patients with schizophrenia or bipolar disorder treated with antipsychotic medication can frequently experience lack of efficacy and persistent side-effects, so much so that switching from one antipsychotic to another with a different side-effect profile has become a recommended strategy for improving the tolerability and safety of long-term antipsychotic treatment. Aripiprazole is an atypical antipsychotic with proven efficacy in schizophrenia and bipolar I disorder, with a pharmacological profile distinct from other available antipsychotics and a side-effect profile that is different from other agents in the class; these characteristics make it a possible alternative in patients requiring a change in antipsychotic treatment due to lack of efficacy or persistent side-effects.
AREAS COVERED:
A panel of Italian experts in psychiatry met to discuss the appropriateness of current strategies for the switch to aripiprazole in patients with schizophrenia or bipolar disorder once a clinician has decided to adopt this choice and also to propose alternate strategies where required. The strategies for the switch to aripiprazole presented in this position paper consider various scenarios encountered in clinical practice, highlight the importance of tapering the prior antipsychotic based on its pharmacological characteristics and provide detailed guidance throughout the entire switching process. Literature searches were conducted using the PubMed database and the search strategy (aripiprazole and switching); additional references were added from the reference lists of the papers obtained and also from the authors' knowledge of the topic.
EXPERT OPINION:
Few studies have addressed the indications for antipsychotic switching and the best practical strategies to achieve the desired goal in the clinical practice setting. Studies on antipsychotic switching should clarify why, when and how a switch should be done. The results should standardize the reasons for switching an antipsychotic, assess the optimal time to switch and evaluate the best ways to switch. Both clinical and pharmacological factors should be considered when a patient needs to switch antipsychotics, and specific guidelines for antipsychotic switching that address all these factors are needed.
KEYWORDS:
antipsychotics; aripiprazole; bipolar I disorder; schizophrenia; switching

1. Introduction

Aripiprazole is an atypical antipsychotic with a pharmacological profile distinct from other available antipsychotics; its efficacy in the treatment of psychotic symptoms is thought to be mediated by the combination of partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A}receptors and antagonist activity at serotonin 5-HT_{2A} receptors [1]Otsuka Pharmaceutical Europe Ltd. Summary of product characteristics. Abilify (aripiprazole) 5 mg

tablets. 2014. In Europe, aripiprazole (marketed as Abilify® Viale G. Richard, 7 20143 Milano (MI), Italy) is licensed for the treatment of: schizophrenia in adults and in adolescents aged ≥ 15 years; moderate-to-severe manic episodes in bipolar I disorder and in the prevention of new manic episodes in adults; and moderate-to-severe manic episodes in adolescents aged ≥ 13 years (up to 12 weeks of treatment) [1]. The efficacy of aripiprazole on psychotic symptoms in schizophrenia and bipolar I disorder has been demonstrated in several short- and long-term studies [2-16] Clinical trials and real-world experience have shown that aripiprazole has a relatively favorable side-effect profile [2,11]; notably, it does not cause excessive sedation [17,18] and has a relatively low metabolic risk [10,12,18-20] a property that it shares with other antipsychotics such as ziprasidone, lurasidone, amisulpride or asenapine [21]. Also, aripiprazole is not associated with hyperprolactinaemia [17,22,23] The potential clinical benefits from the partial agonist activity at the dopaminergic D2 receptors have not yet been studied sufficiently to recommend this medication in particular populations such as patients with bipolar disorder or schizophrenia and pre-existing movement disorders such as Parkinson's disease, where many clinicians perceive the very low inhibition constant of aripiprazole as a detriment relative to other agents with D2 affinity, which bind more loosely.

There have been a number of clinical trials as well as several case reports and series investigating switching from existing antipsychotic therapy to aripiprazole [23-38]. Generally, these studies and reports find that switching patients with schizophrenia and bipolar disorder to aripiprazole has several favorable effects, including the maintenance or improvement of psychiatric symptoms [24,25,28,29,33,34]; a decrease in psychiatric hospitalization rates [32]; reduction in symptoms of tardive dyskinesia [30,34,35]; improvements in cognitive function [30,31]; weight loss [24,29,33]; reduction of cardiovascular risk factors, lipid levels and prolactin [23,24,26,27,30,33,36-38]; restoration of sexual function [37] and a lessening of alcohol craving in patients with a dependence [25] Therefore, aripiprazole appears to be a valid alternative for patients with schizophrenia or bipolar disorder who need to change their current antipsychotic medication due to lack of efficacy or persistent side-effects, the most common reasons for changing antipsychotic medication [39].

In recent years, awareness of the potential problems arising from the side-effects of long-term antipsychotic treatment has increased significantly. Side-effects severely affect patients' safety and well-being and are a frequent cause of treatment discontinuation [18]. Today, switching from one antipsychotic to another with a different side-effect profile has become a recommended strategy for improving the tolerability and safety of long-term antipsychotic treatment [18,39]. Considerable effort has been devoted to design optimal switching strategies [18,39-42]. However, several aspects of the switch between antipsychotics remain insufficiently defined, and clinical practice-oriented recommendations on how best to change antipsychotic medication are needed.

With this in mind, five Italian experts in psychiatry discussed current strategies for the switch to aripiprazole in patients with schizophrenia or bipolar disorder during meetings organized and sponsored by Otsuka Pharmaceuticals Italy S.r.l., (Viale G. Richard, 720143 Milano (MI), Italy) and agreed on a series of recommendations for switching patients being treated with other antipsychotics to aripiprazole, once a clinician has decided to adopt this choice. Consensus was reached by discussing various clinical practice scenarios based on personal experience, national and international guidelines, and review of the published literature. This position paper presents the consensus reached regarding the optimal strategy

for switching to aripiprazole in various clinical settings, with the objective of providing practical guidance to healthcare professionals who decide to adopt this strategy.

2. Key issues for optimizing the switch to aripiprazole

Several factors should be taken into account when considering switching antipsychotic medications, including characteristics related to the patient, illness, medication and environment [40]. Medications should be evaluated individually based on the prescribing information; the receptor activity of the previous medication and potential pharmacodynamic and pharmacokinetic interactions should be evaluated [39,40,43]. In general, current guidelines for switching strategies agree that the switch between antipsychotics should be performed gradually and that the abrupt discontinuation of the previous medication should be avoided to prevent rebound effects induced by withdrawal of the prior antipsychotic [39,40,43].

Currently, recommended strategies for the switch to aripiprazole involve an overlap between the prior oral antipsychotic and aripiprazole [39,43-45]. According to the 'overlap and taper' strategy proposed by a UK multidisciplinary panel, aripiprazole is initiated at the minimal clinically efficacious dose and titrated as needed after a minimum of 2 weeks, while leaving the dose of the previous antipsychotic unchanged [45]. The dose of aripiprazole is then adjusted as necessary to optimize symptom control. Once a steady-state plasma concentration is reached and treatment response is satisfactory, the prior antipsychotic is tapered down very gradually over several weeks. According to the UK panel, this strategy should enable aripiprazole to begin to exert its dopamine D_2 receptor partial agonist effect while reducing the possibility of rebound symptoms (caused by dopamine hypersensitivity or cholinergic activation) when the prior dopamine-blocking antipsychotic is withdrawn. If withdrawal of the prior antipsychotic is too rapid, rebound psychosis can occur, particularly if the previous medication resulted in heavy dopamine receptor blockade [45].

During the Italian discussions, the need for more detailed and practice-oriented recommendations for the switch to aripiprazole was unanimously agreed upon. In particular, there was agreement that the overlap phase of aripiprazole with the prior antipsychotic should be prolonged (versus the UK expert panel strategy [45] to prevent rebound effects and to ensure that steady-state aripiprazole levels are achieved before the previous medication is gradually withdrawn. Full consensus was also reached regarding the need for clear indications with regard to: initial dose of aripiprazole, how to reach the target dose of aripiprazole and the duration of the overlap phase. The consensus was that switching strategies should involve three steps. Step I: aripiprazole introduction; Step II: overlap of prior antipsychotic and aripiprazole; Step III: tapering of prior antipsychotic (of note, in the strategy proposed here, withdrawal of the prior antipsychotic is initiated after steady-state levels of aripiprazole at the target dose have been reached). The overall duration of the switching process should be approximately 8 weeks (unless the prior antipsychotic needs to be discontinued rapidly because of significant tolerability problems).

There was also unanimous agreement that several aspects of the switching strategy strongly depend on clinical factors including patient clinical state, reason for switching, previous antipsychotic and treatment setting. Therefore, it was agreed that the development of a single switching strategy was not possible and that general guidelines would be of limited use. Several clinical scenarios and subgroups of patients were recognized, and recommendations for the switching strategy to aripiprazole in each scenario were developed.

3. Patients with stable disease

3.1 When to switch to aripiprazole

In patients with stable disease, the change of antipsychotic is generally due to tolerability problems with current medication. These patients are usually treated in an outpatient or day hospital setting. The clinical experience of the expert panel suggested the most common tolerability problems that result in the switch to aripiprazole are metabolic abnormalities, prolactin increase, sexual dysfunction, sedation, cognitive impairment, orthostatic hypotension and anticholinergic side-effects (constipation, dry mouth, urinary retention). In patients with stable disease, the switch to aripiprazole may also occur in the presence of psychiatric comorbidities (e.g., stable patient with obsessive symptoms). Notably, in the event of any treatment-related safety issue (e.g., prolongation of the QT interval or agranulocytosis), current medication should be promptly discontinued.

Many agents used for the treatment of schizophrenia and bipolar disorder are associated with an increased risk of diabetes, hyperlipidemia and weight gain [46]; thus, in many patients metabolic side-effects can be a significant concern. However, in some cases these metabolic side-effects are ignored in favor of achieving stable psychiatric disease, and physicians may resort to the off-label use of oral antidiabetic agents or weight loss medications, which have been shown to have only a modest effect on weight and lipid levels [47-49], to avoid switching antipsychotic medications. To determine the risk of metabolic abnormalities in patients with schizophrenia and bipolar disorder, we recommend that baseline assessments of patient history with respect to cardiovascular disease, hyperlipidemia, glucose intolerance and smoking assessments be performed along with measurements of weight, waist circumference, lipids, glucose and blood pressure. In patients who are gaining weight, diet-related counseling, exercise and a decrease in caloric intake are recommended. In patients who have gained > 5% of their body weight, switching to an alternative medication should be considered [46,50].

3.2 Switching strategy

The recommended strategy for the switch to aripiprazole in stable patients is shown in Figure 1. Aripiprazole introduction (Step I) should be performed according to the following scheme: starting dose of 10 mg/day for 5 days, followed by an increase to 15 mg/day for an additional 5 days. Other authors recommend a starting dose of 15 mg [51]; however, we believe that a lower starting dose (e.g., 10 mg) is better tolerated by stable patients that are already receiving other antipsychotics. If the initial 10 mg/day dose is not tolerated, the subsequent dose can be reduced to 5 mg/day for 5 days, followed by an increase to 10 mg/day for an additional 5 days and then to the final dose of 15 mg/day. The recommended starting dose for adults is 10 or 15 mg/day [1]Otsuka Pharmaceutical Europe Ltd. Summary of product characteristics. Abilify (aripiprazole) 5 mg tablets. 2014; the rationale for suggesting a lower starting dose in the strategy described earlier is based on the reason why the medication is being switched: a low dose of 5 mg/day may be preferred in a patient who is switching because of metabolic issues (weight gain, dyslipidemia or hyperprolactinemia) but whose psychiatric symptoms are well controlled [43]. This scheme can be used in patients with schizophrenia and bipolar disorder, regardless of the previous antipsychotic treatment received. The aripiprazole target dose of 15 mg/day in Step I should be well tolerated by most stable patients. However, a target dose of 10 mg/day is also

possible, for example, in older patients or if tolerability problems occur, based on the clinical judgment of the treating physician.

During Step II, aripiprazole and the previous antipsychotic therapy should continue to overlap. The dose of the previous medication should remain unchanged, while the target dose of aripiprazole at this stage should be 15 – 20 mg/day. The overlap between aripiprazole and the previous antipsychotic should be maintained for 15 days (steady-state plasma level of aripiprazole is reached in 14 days). The dose of aripiprazole may be increased to 20 mg/day in Step II, depending on physician judgment.
Once Step III is reached, aripiprazole should be continued at the target dose of 15 – 20 mg/day, with the possibility of an increase to the maximum recommended dose of 30 mg/day, if needed, while the previous antipsychotic is gradually tapered. The scheme for tapering the previous antipsychotic depends on the pharmacological characteristics of the antipsychotic (Table 1). The duration of the overlap period may be adjusted based on tolerability and response of patients. For instance, if a patient switches from a medication with relatively strong antihistaminergic or anticholinergic properties (e.g., clozapine, olanzapine or quetiapine), the possibility that upregulated and/or sensitized receptors promote the transmission of histaminergic or cholinergic activity should be considered. In such a case, a slower down-titration may reduce the risk of rebound agitation, insomnia, anxiety, restlessness, extrapyramidal symptoms (EPS) and akathisia. Similarly, switching from a strong anti-dopaminergic medication, such as risperidone, haloperidol or paliperidone, to a partial D2 agonist may result in psychosis or agitation, possibly due to hypersensitized and/or upregulated D2 receptors. In those cases, the possibility of a relatively slower down-titration should be considered. Ideally, the overlap and tapering strategy should be personalized and adjusted based on the individual patient response and clinical history (duration of treatment with the previous antipsychotic, doses used, etc.) [52]Dulcan MK. editor. Dulcan’s textbook of child and adolescent psychiatry. American Psychiatric Pub, Arlington, VA, USA; 2010 .

3.3 Withdrawal of previous antipsychotics

Proposed recommendations for the tapering of commonly used antipsychotics during the switch to aripiprazole are presented in Table 1. Switching medications can be expected to have some benefits for the patient, which include improvements in weight, lipid profile, blood pressure, prolactin levels, sedation and EPS (Table1) [18]. Switching from one antipsychotic to another is destabilizing for the patient and can lead to rebound effects and withdrawal symptoms. The withdrawal of receptor blockade when switching can lead to a range of side-effects, depending on what receptor is being affected; different antipsychotic agents have different affinities for the various receptors affected by this drug class (Table 1) [40]. Table 2 summarizes the potential effects associated with withdrawal of some of the most common antipsychotics used in patients with schizophrenia and bipolar disorder. Potential consequences of withdrawal of dopamine blockade include agitation, akathisia, withdrawal dyskinesia, psychosis and mania, while withdrawal of histaminic receptor blockade may result in anxiety, agitation, restlessness, EPS/akathisia and insomnia [40]. Removal of central muscarinic blockade may cause agitation, confusion, psychosis, insomnia, anxiety, EPS/akathisia and sialorrhea, while removal of serotonin receptor blockade may result in anxiety, EPS/akathisia and possibly psychosis and decreased appetite [40].

3.4 Use of adjunctive medications

Patients who experience side-effects and other unwanted symptoms during antipsychotic medication switching may benefit from the use of adjunctive medications aimed at relieving these symptoms, such as benzodiazepines, β blockers, antihistamines and anticholinergics [43]. Recommendations for the management of side-effects and rebound effects during switching and the adjunctive drugs that can be used are outlined in Table 2. We acknowledge that few patients are treated with antipsychotic monotherapy. Reviewing each of the possible combinations goes beyond the aims of the present paper. Although aripiprazole has demonstrated efficacy as an adjunct to mood stabilizers in bipolar disorder [53-57], we remind clinicians to always consider the potential pharmacokinetic and pharmacodynamic interactions whenever a switch to aripiprazole is made. For instance, if aripiprazole is prescribed with an inducer of the CYP3A4 enzyme (such as carbamazepine), a higher dose may be needed.

3.5 Switching to aripiprazole in patients receiving clozapine

Previous Italian consensus guidelines on the use of aripiprazole in patients with schizophrenia suggested a cautious approach to switching patients receiving clozapine to aripiprazole, because the use of clozapine is restricted to those patients resistant to other antipsychotics [58]. In these new switching guidelines, it was agreed that in cases where clozapine is ineffective for positive symptoms (e.g., delusions, hallucinations) or in cases where an abrupt discontinuation of clozapine is needed (e.g., agranulocytosis, acute pancreatitis), a direct switch to aripiprazole is generally not recommended. In our clinical practice, it is very rare that we discontinue clozapine in the absence of severe or life-threatening problems. When that occurs, we usually avoid a direct switch to aripiprazole but rather switch to an antipsychotic such as olanzapine or amisulpride. In our experience, those medications are more likely to reduce clozapine withdrawal symptoms, possibly due to pharmacodynamic reasons (e.g., shared antihistamine and anticholinergic properties between clozapine and olanzapine).

Once the switch from clozapine to an alternative medication is completed, a slow switch to aripiprazole may be considered, if clinically indicated (e.g., where there is olanzapine-related weight gain or amisulpride-related hyperprolactinemia).

4. Patients in the acute phase

4.1 Switch to aripiprazole in the acute phase

The switch to aripiprazole in patients who experience an acute episode of psychosis in schizophrenia and of mania in bipolar disorder despite existing antipsychotic treatment is complex, as symptoms, reasons for changing the antipsychotic and treatment setting are very heterogeneous. Two main groups of patients were recognized: patients with an acute episode that can be managed in the outpatient setting and patients with a severe acute episode that requires hospitalization.

4.1.1 Treatment in the outpatient setting

Switching antipsychotic treatment in outpatients occurs for a number of reasons, including suboptimal adherence, lack of efficacy and tolerability issues. Like the switching strategy outlined earlier, the switch to aripiprazole in patients who experience an acute episode manageable in the outpatient setting also involves three steps (Figure 2). In Step I, the

previous antipsychotic should be maintained at its current dose and aripiprazole initiated at a dose of 15 mg/day. The dose of aripiprazole should then be adjusted within 48 h as follows: increased to 30 mg/day in patients with a severe episode; maintained at 15 mg/day in patients with moderately disturbed behavior; decreased to 10 mg/day if side-effects (e.g., akathisia) occur. Usually, in Step II, the previous antipsychotic and aripiprazole should overlap for 5 – 15 days. The duration of this phase could be shorter or longer in the presence of side-effects or withdrawal symptoms. In Step III, the previous antipsychotic should be gradually withdrawn, according to the schemes described in Table 1.

4.1.2 Acute phase requiring hospitalization

Patients who experience a severe episode despite antipsychotic treatment are switched to aripiprazole because of lack of efficacy of their current antipsychotic medication. Patients with a severe episode need prompt inpatient treatment. These patients may receive aripiprazole solution for injection (one vial, intramuscular injection; injection can be repeated after 2 h up to a maximum of three vials/day) [59]. If agitation persists between injections, benzodiazepines may be given. The treatment with aripiprazole solution for injection should be discontinued as soon as clinically appropriate, and patients should be switched to aripiprazole 15 – 30 mg/day p.o. (depending on tolerability) as shown in the scheme of Figure 3A. In these patients, the previous antipsychotic may be discontinued immediately, unless an overlap between prior medication and aripiprazole is required for tolerability/safety reasons. The overlap duration should not exceed 72 h, regardless of the previous antipsychotic.

If aripiprazole solution for injection is not available, patients with a severe acute episode should be treated with oral aripiprazole and benzodiazepines (e.g., lorazepam). The strategy for switching to oral aripiprazole is shown in Figure 3B. In Step I, the prior antipsychotic can be maintained at its current dose (unless there are significant side-effects, before or after starting aripiprazole) and aripiprazole initiated at 15 mg/day, to be increased to 30 mg/day within 48 h, if well tolerated. The overlap between the previous antipsychotic (unchanged dose) and aripiprazole (target dose 30 mg/day) may last 1 – 3 weeks (Step II). In Step III, the previous antipsychotic should be gradually discontinued as indicated in Table 1.

5. Conclusion

Several factors should be taken into account when switching antipsychotic medication, including the clinical status of the patient and the pharmacological characteristics of current and new antipsychotics. Specific guidelines for antipsychotic switching that address all these factors are urgently needed. The strategies for the switch to aripiprazole presented in this position paper consider various scenarios encountered in clinical practice, highlight the importance of tapering the prior antipsychotic based on its pharmacological characteristics and provide detailed guidance throughout the entire switching process. In stable patients, who generally change medication because of tolerability and safety issues, the switch to aripiprazole should be slow and the prior antipsychotic should be gradually withdrawn only after steady-state levels of aripiprazole have been reached.

6. Expert opinion

The need to switch from one antipsychotic drug to another is a frequent challenge in the long-term management of patients with bipolar disorder and schizophrenia, and there is an increasing amount of clinical trial data in patients with schizophrenia or bipolar disorder outlining the merits of switching from one atypical antipsychotic to another when the first is suboptimal, both when switching to aripiprazole or when switching from aripiprazole to agents such as iloperidone or lurasidone

However, this paper is not intended to advocate the switch from or to aripiprazole in a particular group of patients or clinical situation. Our goal is to provide an expert opinion on how a switch to aripiprazole can be made once a clinician and a patient have agreed to such a choice.

Few studies have addressed the indications for antipsychotic switching and the best practical strategies to achieve the desired goal in the clinical practice setting. Studies on antipsychotic switching should clarify why, when and how a switch should be done. The results should standardize the reasons for switching an antipsychotic, assess the optimum time to switch and evaluate the best ways to switch. Ideally, those studies should provide real-world practical indications.

The strategies for the switch to aripiprazole presented in this position paper consider various scenarios encountered in clinical practice, highlight the importance of tapering the prior antipsychotic based on its pharmacological characteristics and provide detailed guidance throughout the entire switching process.

More studies are needed to clarify the indications for switching antipsychotic drugs in patients with schizophrenia or bipolar disorder. Also, more studies are necessary to explore in depth the risks of switching and the strategies to avoid adverse events such as relapse or destabilization, withdrawal conditions such as cholinergic rebound (with symptoms such as nausea, vomiting, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paraesthesia, gastrointestinal distress, headaches and nightmares), withdrawal dyskinesia, rebound akathisia, rebound dystonia and worsening of tardive dyskinesia. Future research should elucidate and standardize the best strategies to personalize the switching based on pharmacokinetic and pharmacodynamic evaluations, matched with specific and agreed-on target objectives, judicious selection of post-switch antipsychotics and titration strategies based on current and past symptoms, and careful follow-up and evaluation of progress.

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Notes

*Schemes for previous antipsychotic tapering are reported in Table 1; in the presence of side-effects, the previous drug may be tapered more rapidly or aripiprazole may be titrated up more slowly.
ARI: Aripiprazole.
*Schemes for previous antipsychotic tapering are reported in Table 1; in the presence of side-effects, the previous drug can be tapered more rapidly.
*Schemes for previous antipsychotic tapering are reported in Table 1; in the presence of side-effects, the previous drug can be tapered more rapidly.
BZD: Benzodiazepine; IM: Intramuscular.

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