Ther Adv Psychopharmacol
2018, Vol. 8(10) 271–285
DOI: 10.1177/2045125318772712
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TARC: Turkish aripiprazole consensus report- Aripiprazole use and switching from other antipsychotics to aripiprazole-consensus recommendations by a Turkish multidisciplinary panel

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Abstract: In this review, we have attempted to share our 10 years' clinical experience with aripiprazole use and switching from other antipsychotics to aripiprazole. There are various reasons for switching, including a partial or complete lack of efficacy, adverse side effects, and partial or noncompliance with medication. Aripiprazole has some unique receptor-binding qualities that provides some advantages over other antipsychotics in certain clinical situations. We have covered potential clinical scenarios for aripiprazole use as a single agent and switching from other agents in inpatient and outpatient settings. Patients switched from other antipsychotics to aripiprazole have been shown to benefit from significant improvements in clinical response and tolerability. This review examines the strategies for switching patients from antipsychotic drugs to aripiprazole.

Keywords: aripiprazole, depression, first episode, obsessive–compulsive disorder, schizophrenia, switching

Received: 1 September 2017; revised manuscript accepted: 5 February 2018.

Introduction

Aripiprazole is an atypical antipsychotic drug with a high affinity for dopamine D2 and D3 receptors, and serotonin 5-HT1A, 5-HT2 and 5-HT2B receptors.[1] Due to aripiprazole's partial agonist activity at D2 receptors, it has lower propensity for extrapyramidal symptoms.[2] Having a unique mechanism, aripiprazole has not only a lower liability for inducing hyperprolactinemia, but also has the ability to normalize elevated prolactin levels induced by previous antipsychotics. Aripiprazole, acting as a partial agonist at D2 and 5-HT1A receptors, is reported to be effective on anxiety, depressive symptoms, cognitive symptoms and negative symptoms. 5-HT2 receptors antagonism has positive effects on negative and cognitive symptoms. Aripiprazole has not only favorable impact on cognition due to increase in dopamine release in the prefrontal cortex and hippocampus but also unlikely to cause cognitive dysfunction due to its low affinity on acetylcholine muscarinic receptors.[3] Aripiprazole does not cause a high level of sedation, which is attributed to its mild antagonist effect on the histamine H_1 receptors.[4]

The acute and long-term efficacy of aripiprazole for treatment of schizophrenia and schizoaffective disorder has been demonstrated with long-term studies.[5–13] On the other hand, a Cochrane review that benchmarked aripiprazole with other atypical antipsychotics has shown that aripiprazole has similar efficacy, compared with clozapine, quetiapine, risperidone, ziprasidone and olanzapine; aripiprazole leads to improved quality of life, compared with clozapine and quetiapine; aripiprazole is associated with lower incidence of extrapyramidal symptoms (EPS); aripiprazole-associated weight gain is lower, compared with olanzapine, but higher than ziprasidone; and aripiprazole is associated with a higher incidence of early discontinuation of treatment, compared with olanzapine.[14]

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The efficacy of aripiprazole for treatment of bipolar disorder has been documented in different studies.[15–22] Treatment guidelines have indicated that the efficacy of aripiprazole for continuation treatment of acute mania and bipolar disorders is of 'high level', and aripiprazole has a 'good' risk-benefit ratio. In addition, treatment algorithms have suggested 'aripiprazole as a single agent' or 'aripiprazole combined with lithium or divalproex' as a first choice of treatment.[23,24] In a recent review, 'aripiprazole as a single agent' or 'augmentation with aripiprazole' has been suggested as the first choice for treatment of acute mania, and maintenance treatment of manic or mixed episodes.[25] The same review has also reported that aripiprazole is associated with lower medical costs compared with olanzapine, quetiapine, risperidone, and ziprasidone.[25]

Aripiprazole has been reported to be an effective augmenter where there is poor response to antidepressants in depressive disorders.[26–30] In a study which compares aripiprazole with other second-generation antipsychotics in depression, patients who used aripiprazole had a better 'health-related quality of life'.[31] Another study has compared 'supplemental treatment for aripiprazole', 'antidepressant combination' and 'changing antidepressant' strategies in patients with major depressive disorder who were nonresponsive to antidepressant; supplemental treatment for aripiprazole has been reported as more effective compared with the other strategies.[32]

A multidisciplinary panel entitled 'Switching from other antipsychotics to aripiprazole and aripiprazole use' was convened in Turkey to provide practical guidance for prescribing aripiprazole. This report describes the consensus recommendations agreed during the meeting and reflects the 10-year experience of aripiprazole use in Turkey. A comprehensive literature search was conducted to support these recommendations. There are similar initiatives in other countries, and some of these documents were reviewed during preparation of this report.[33,34]

Switching to aripiprazole from other antipsychotic drugs

Switching between antipsychotics in the treatment of schizophrenia and bipolar disorder is a common practice among psychiatrists. Most common reasons for considering an alternative are insufficient efficacy and persistent side effects.[35] Naturalistic observation studies have suggested that compliance to treatment is poor with antipsychotics in general,[36] which is mainly due to treatment-related adverse events and treatment dissatisfaction among patients.[37] The widespread use of second-generation (atypical) antipsychotics led to a decrease in EPS; however, various side effects including metabolic issues (mainly weight gain), hyperprolactinemia and prolonged QTc have been consistently reported.[30,38–41]

In general, metabolic syndrome represents the major disadvantage of the second-generation antipsychotics. Aripiprazole has the most favorable profile among this category with respect to metabolic side effects.[42,43] In a meta-analysis based on the data collected from 784 patients with schizophrenia or schizoaffective disorder from different countries and ethnicities, significant weight loss has been reported following the transition to aripiprazole from another antipsychotic.[44] Aripiprazole does not cause hyperprolactinemia; in fact, addition of aripiprazole to other antipsychotics leads to a decrease in elevated prolactin levels.[4] Aripiprazole is considered a safe antipsychotic from a cardiovascular standpoint, having the lowest risk of prolonged QTc and coronary heart disease.[5,45–47] Among all antipsychotics, aripiprazole is associated with lower frequency of sexual side effects.[48,49] Given its positive effects on cognitive symptoms and negative symptoms, aripiprazole can be preferred for patients who experience such side effects.[50–53] Aripiprazole has been reported to cause less sedation and somnolence, compared with other antipsychotics.[54,55] Due to lower level of anticholinergic effects, it is expected that side effects such as xerostomia and constipation are seen at a lower frequency.[56] The advantages of aripiprazole include effectiveness in depressive symptoms in schizophrenia, positive effects on quality of life, and preference by patients.[6,52] Aripiprazole has been reported as effective for treatment of depressive disorders, alcohol-use disorder associated with bipolar disorder and schizoaffective disorder; in another study, aripiprazole treatment has been reported to reduce the severity in alcohol-use disorder.[57–59] It has also been reported that aripiprazole treatment leads to a significant reduction of obsessive–compulsive symptoms in schizophrenia, and in obsessive–compulsive disorder (OCD) when added to selective serotonin reuptake inhibitor (SSRI) treatment.[60,61]

Table 1. Side effects that can lead to antipsychotic switching; antipsychotics that can cause side effects and alternative antipsychotics.

Reasons for switching	Possible causes	Alternative antipsychotics
Metabolic side effects (weight gain/dyslipidemia/ altered glucose tolerance)	Olanzapine, quetiapine	Aripiprazole, amisulpride, ziprasidone, haloperidol
Hyperprolactinemia	Amisulpride, risperidone, paliperidone	Aripiprazole, quetiapine
EPS	Haloperidol, risperidone, amisulpride	Aripiprazole, olanzapine, quetiapine
Tardive dyskinesia	Haloperidol, risperidone	Clozapine, aripiprazole, olanzapine, quetiapine
Insufficient efficacy/ dissatisfaction	Quetiapine, haloperidol	Aripiprazole
Postural hypotension	Chlorpromazine, quetiapine	Aripiprazole, amisulpride, haloperidol
Prolonged QTc	Ziprasidone, sulpiride	Aripiprazole
Sedation	Quetiapine, olanzapine, first-generation antipsychotics	Aripiprazole, paliperidone
Sexual side effects	Amisulpride, risperidone, paliperidone	Aripiprazole, quetiapine
Negative/depressive symptoms	First-generation antipsychotics, risperidone	Aripiprazole, amisulpride, paliperidone
Cognitive function	First-generation antipsychotics, olanzapine, quetiapine	Aripiprazole, paliperidone, amisulpride
Comorbid obsessive–compulsive symptoms	Olanzapine, risperidone	Aripiprazole, amisulpride, haloperidol

The main side effects of switching and proposed alternatives are shown in Table 1. As shown in Table 1, aripiprazole is recommended as the next choice for the switch when several side effects are seen.

Evaluation before switching to aripiprazole

Before switching to aripiprazole, patients with schizophrenia, schizoaffective disorder or bipolar disorder should be evaluated in detail, as would be done in the case of switching to any other antipsychotic. Past psychiatric history, medical history and psychotropic-use history, most recent psychiatric functioning and psychiatric review of symptoms (positive, negative, depressive and cognitive symptoms, social and occupational functionality, quality of life) should be considered; the reason for switching to aripiprazole and expectations should be outlined. It is recommended that the decision for switching be made in a collaborative effort by the patient and the clinician (if needed, together with the carer).[62] Weight, waist circumference, fasting blood glucose level, glycated hemoglobin level, lipid profile, and prolactin level should be measured prior to switch. Assessment of extrapyramidal symptoms, nutritional status, diet, and physical activity is necessary. Electrocardiogram is indicated for patients with a history of hypertension or cardiovascular disease, or patients receiving inpatient treatment.[62]

It is important to inform patients about common issues associated with transition, including withdrawal symptoms, drug–drug interactions, and possible relapse in psychiatric symptoms should be discussed. During the switching period, it is important to monitor patients closely, with frequent outpatient visits.

Table 2. Patients who are likely to benefit from switching to aripiprazole.

Newly diagnosed patients or patients who have not received antipsychotic treatment before
Patients who are unable to tolerate the antipsychotic medication they use
Patients who experience problems (e.g. metabolic) with current antipsychotic
Patients whose symptoms cannot be maintained with current antipsychotic
Patients who discontinue antipsychotic treatment (due to insufficient symptom control or tolerability problems)
Patients who switched from another second-generation antipsychotic to aripiprazole

Starting aripiprazole treatment and patients likely to benefit from switching to aripiprazole

According to a multidisciplinary panel on use of aripiprazole for treatment of schizophrenia, patients: who are newly diagnosed or have not received any treatment; who are unable to tolerate the current antipsychotic; who developed metabolic side effects; whose symptoms did not remit; who experienced acute exacerbation while on the current antipsychotic or who discontinued current antipsychotic due to poor efficacy or tolerance, are likely to benefit from aripiprazole treatment.[33] There have been other reports of successful transition to aripiprazole in patients with shorter disease duration and antipsychotic use, patients with less symptom severity, and patients who do not have a history of recurrent relapse[63–65] (Table 2).

Method of switching to aripiprazole

Some studies have suggested that a rapid switch to aripiprazole is acceptable[66–69]; yet, at least one study has reported that a rapid switch can be hazardous.[70] There are also other reports that propose switching to aripiprazole should be gradual.[33,34]

Switching to aripiprazole in patients with stable schizophrenia in outpatient setting

Switching to aripiprazole for treatment of patients with stable schizophrenia is summarized in Figure 1. These patients generally experience side effects from existing treatment, or respond poorly to the existing treatment. In addition to the existing treatment, it is appropriate to initiate aripiprazole treatment with 2.5–5 mg/day, increase the dose to 5–10 mg/day at the end of first week, and then to 10–15 mg/day at the end of second week. Once the target dose of 10–15 mg/day is reached, aripiprazole and previous antipsychotics should be used together for at least 2 weeks. Afterwards, previous antipsychotic treatment should be discontinued by reducing the dose by 25% with minimum 2-week intervals (e.g. for a given dose of 20 mg/day, 15►10►5; for a given dose of 4 mg/day, 3►2►1 and stop). In some cases, it may be necessary to titrate the aripiprazole dose up to 30 mg. In such cases, the dose should be first increased to 15–20 mg, and should be maintained for at least 2 weeks. If necessary, the dose can be increased to 30 mg. In view of the current literature, aripiprazole treatment can vary within 10–30 mg/day dose range for maintenance treatment of schizophrenia.[71–73]

Switching to aripiprazole in patients with history of recurrent psychotic relapse in the outpatient setting

Switching to aripiprazole for treatment of outpatients with recurrent psychotic exacerbation is summarized in Figure 2. For this patient group, it is appropriate to start aripiprazole treatment at a dose of 10 mg/day. If possible problems are predicted, it is possible to start treatment with a dose of 5 mg/day. It is recommended to increase the dose by 5–10 mg with 1-week intervals and reach 20–30 mg/day. Once a 20 mg/day dose is reached, it is appropriate to wait for 2 weeks before increasing the dose to 30 mg/day. At 2 weeks after reaching the desired aripiprazole dose, the previous antipsychotic treatment can be discontinued by reducing the dose by 25% every 2 weeks. If the reason for stopping previous antipsychotic treatment is inefficacy, tapering it down by weekly dose reduction is recommended.

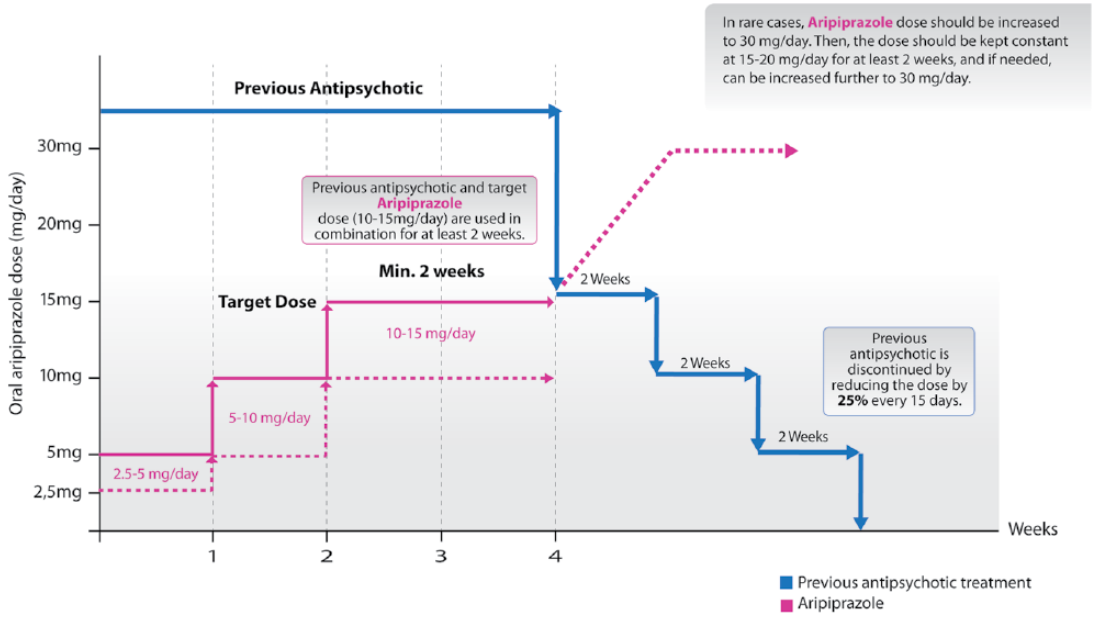

Figure 1. Switching to aripiprazole in case of outpatients with stable schizophrenia.

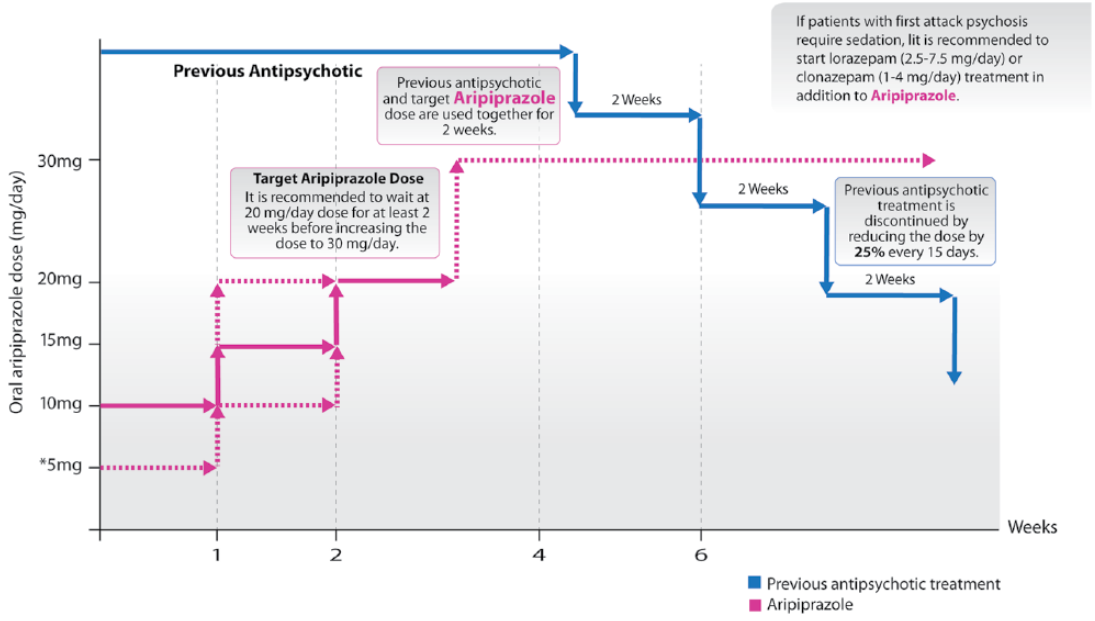

Figure 2. Switching to aripiprazole for treatment of outpatients with recurrent psychotic exacerbation.

Switching to aripiprazole in the inpatient setting

The switching to aripiprazole for inpatients with schizophrenia is summarized in Figure 3. In this patient group, the treatment should be started with a dose of 10 mg/day. Afterwards, the dose can be increased to 20–30 mg/day, with 5–10 mg increases every 3–4 days. In the inpatient setting, it is recommended to stay at 20 mg for at least 2 weeks. Clinicians should also consider augmentation with lorazepam (2.5–7.5 mg/day) or clonazepam (1–2 mg/day) during the switch to aripiprazole. Once the desired aripiprazole dose is reached, previous antipsychotic can be tapered off by reducing the dose by 25% no faster than every 2 weeks, unless the reason for the switch is solely due to the

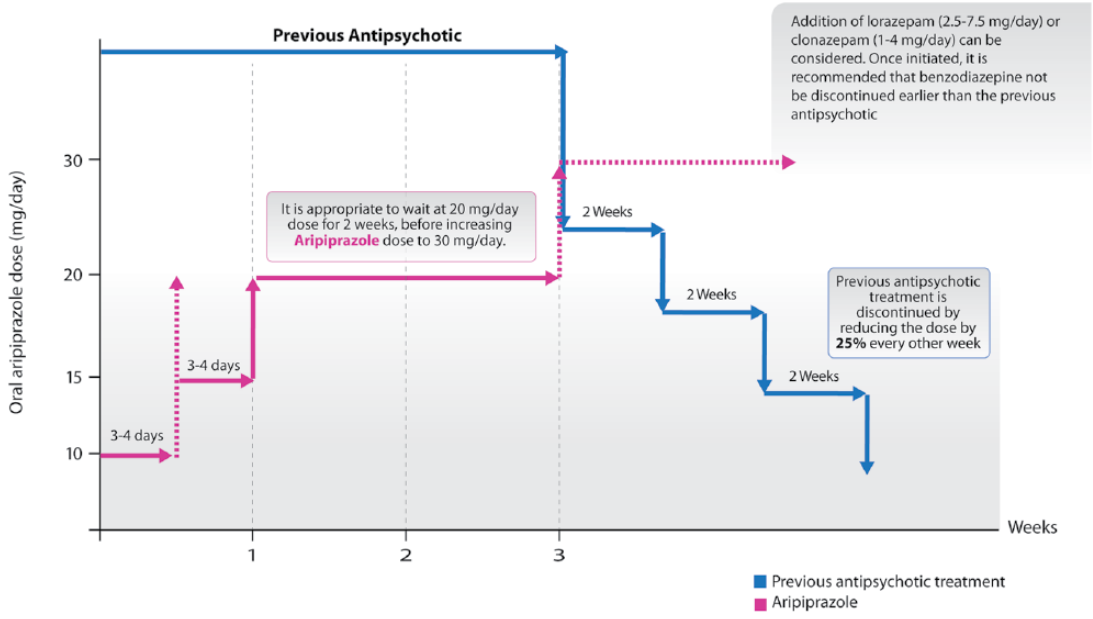

Figure 3. Switching to aripiprazole in the inpatient setting.

inefficacy of the previous antipsychotic, in which case, weekly tapering is reasonable. It is generally recommended to discontinue benzodiazepine treatment, if added, after the discontinuation of the previous antipsychotic, but it can be done earlier.

Management of adverse symptoms during the switch

When switching from other antipsychotics to aripiprazole, withdrawal from the previous antipsychotic medication or initiation of aripiprazole may lead to undesired symptoms. In such cases, benzodiazepines, beta blockers, antihistamines and anticholinergics can be successfully used to suppress the undesired symptoms.[34,74–76] The adverse symptoms during switch and recommendations for managing the symptoms are summarized in Table 3.

Use of aripiprazole in first episode psychosis

The use of aripiprazole for first-episode psychosis is summarized in Figure 4. Generally, patients experiencing first attacks are more sensitive to antipsychotic effect and side effects. Therefore, lower doses are recommended for this patient group.[77] Initiating aripiprazole treatment is recommended at 2.5 mg/day. The dose can be increased to 5 mg/day by the end of the first week, and to 10 mg/day by the end of second week. Staying at 10 mg/day is recommended for at least 2 weeks, and if needed, the dose can be further increased to 15–20 mg/day. In severe cases, the dose can be increased to 30 mg/day. Before increasing the dose to 30 mg/day, staying at the 15–20 mg/day dose is recommended for at least 2 weeks.

If the patient requires sedation, addition of lorazepam (2.5–7.5 mg/day or clonazepam (1–2 mg/day) should be considered.

Use of aripiprazole in bipolar mania

The use of aripiprazole in bipolar mania is summarized in Figure 5. For treatment of acute mania, initiation of aripiprazole is recommended at 10 mg/day. The dose can be increased by 5–10 mg every 3–4 days, up to 20–30 mg/day and we recommend staying at 20 mg/day for at least 2 weeks before considering further titration. Addition of lorazepam (2.5–7.5 mg/day) or clonazepam (1–2 mg/day) can be considered, which should be tapered down slowly following stabilization. To prevent recurrent manic episodes, it is recommended keeping aripiprazole treatment at 15–30 mg/day.[78]

The use aripiprazole in patients with depression in the setting of inadequate response to antidepressants

The use of aripiprazole for treatment of depression is summarized in Figure 6. If response to

Table 3. Possible adverse effects during switch from other antipsychotics to aripiprazole and their management.

Symptom	Approach/additional drug
Akathisia	Decrease aripiprazole dose, slow down dose reduction of the previous antipsychotic; add benzodiazepine and possibly a beta-blocker and possibly anticholinergics
Mania, psychosis	Slow down dose reduction of the previous antipsychotic or reverse switch; increase aripiprazole dose Add benzodiazepine and possibly valproate (for bipolar disorder)
Agitation	Slow down dose reduction of the previous antipsychotic or reverse switch; increase aripiprazole dose Add benzodiazepine and possibly valproate (for bipolar disorder)
Anxiety	Slow down dose reduction of the previous antipsychotic or reverse switch; increase aripiprazole dose Add benzodiazepine
Insomnia	Slow down dose reduction of the previous antipsychotic Add benzodiazepine and possibly an antihistaminic and possibly a hypnotic
Nausea/ vomiting	Slow down dose reduction of the previous antipsychotic, reduce aripiprazole dose temporarily (2–3 days), split total daily dose in two Add antihistaminic and possibly an antiemetic
Hiccups	Slow down reduction of the previous antipsychotic; reduce aripiprazole dose (half dose) and wait for 2 weeks and increase the dose again; if hiccups occur again, stop aripiprazole

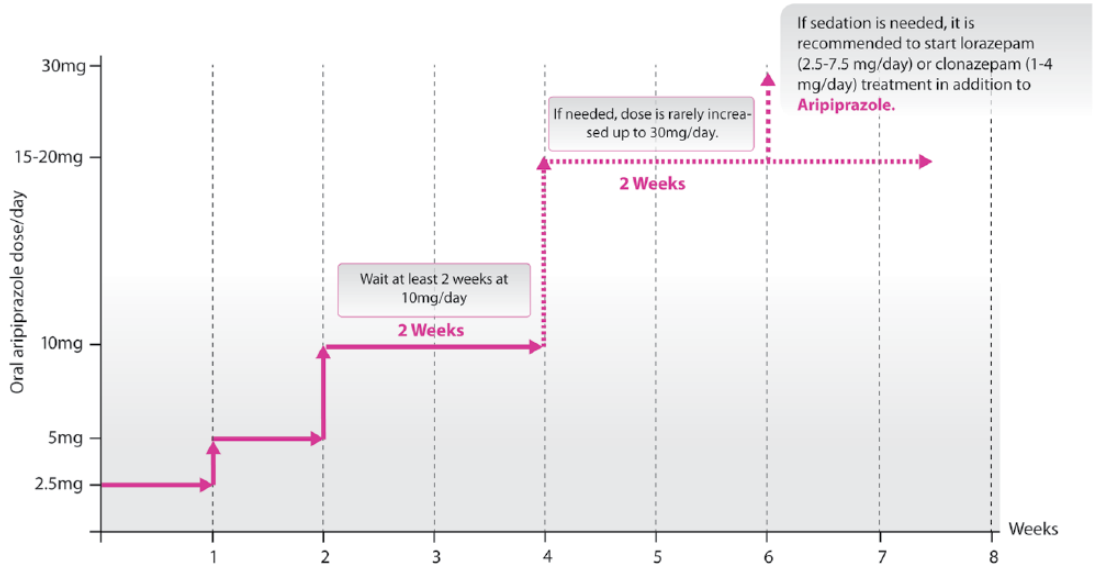

Figure 4. Use of aripiprazole for treatment of first-episode psychosis.

antidepressant treatment is inadequate, addition of an atypical antipsychotic (e.g. aripiprazole, quetiapine or olanzapine) is considered the most common and effective augmentation strategy.[30] For augmentation purposes, using aripiprazole within a dose range of 2.5–10 mg/day is recommended. In this patient group, it is reasonable to start aripiprazole at 2.5 mg/day (in addition to antidepressant treatment); if needed, the dose can be increased to a maximum level of 10 mg/day, by increasing 2.5 mg every 2 weeks.

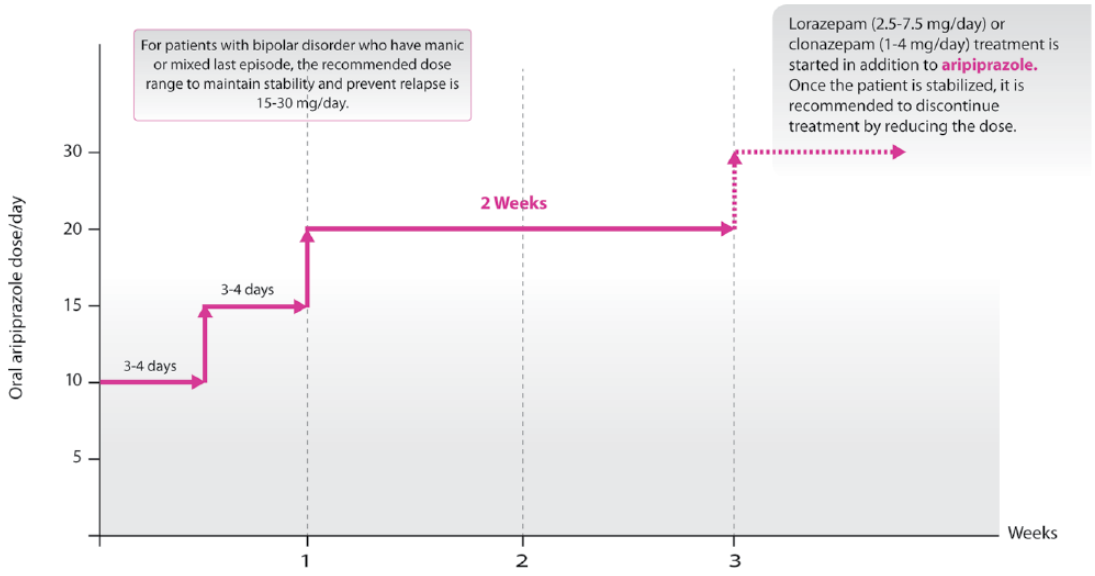

Figure 5. The use of aripiprazole for treatment of acute bipolar episodes.

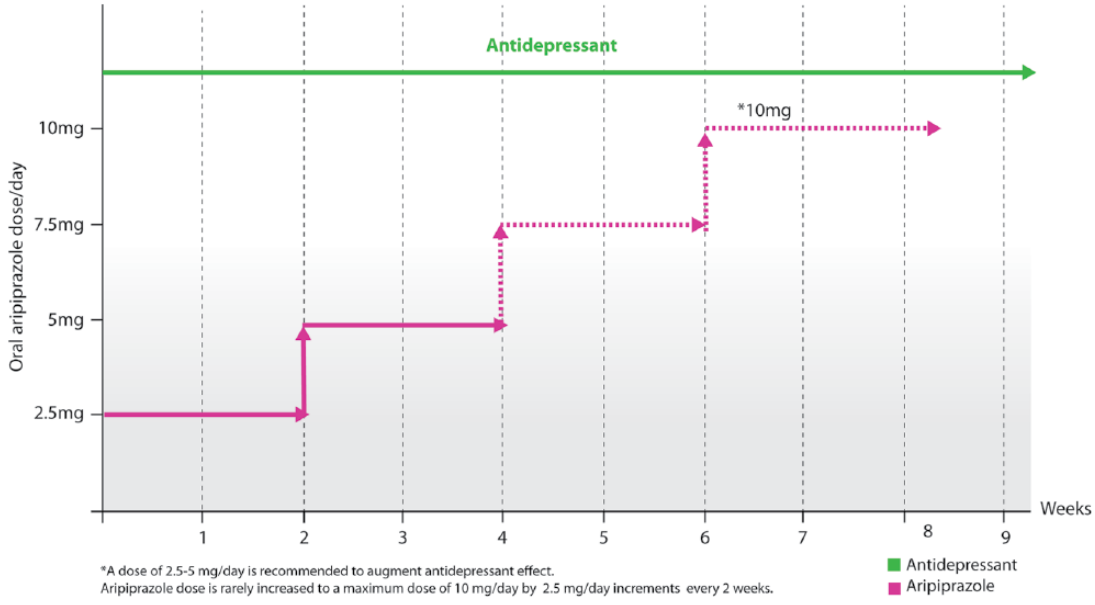

Figure 6. Addition of aripiprazole in the setting of poor response to antidepressants.

The use of aripiprazole in patients with antipsychotic-induced hyperprolactinemia

The use of aripiprazole for treatment of antipsychotic-induced hyperprolactinemia is summarized in Figure 7. Hyperprolactinemia is a major adverse effect of second-generation antipsychotics, which can lead to amenorrhea and galactorrhea in women, and gynecomastia in men. Moreover, it can also cause sexual side effects and osteoporosis in both men and women.[79] In the setting of hyperprolactinemia associated with antipsychotic administration, switching to aripiprazole should be considered, particularly when the response to the existing antipsychotic is limited. When the existing regimen is sufficiently controlling the symptoms, addition of aripiprazole to the existing treatment can also be considered. In such cases, it is reasonable to add low-dose aripiprazole (e.g. 2.5 mg/day) to the current regimen, and if needed, it can be titrated up to 10 mg/day.[80] On the other hand, in the setting of hyperprolactinemia associated with

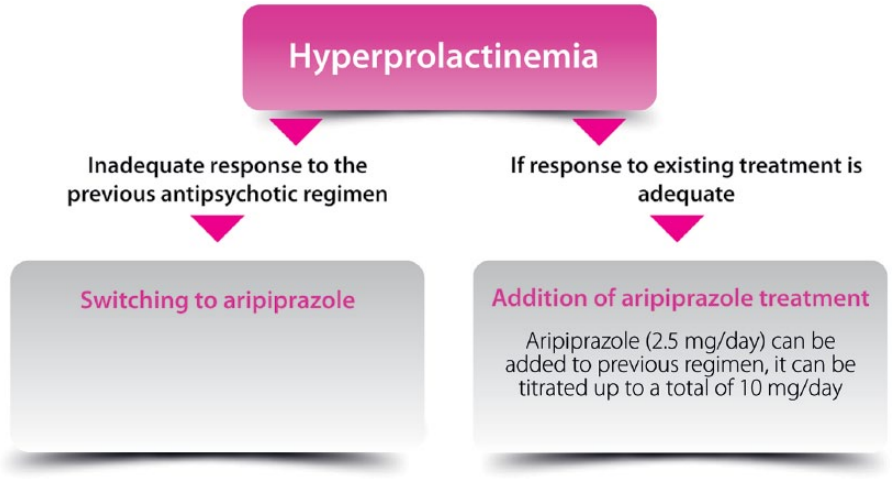

Figure 7. The use of aripiprazole in the setting of hyperprolactinemia associated with antipsychotics.

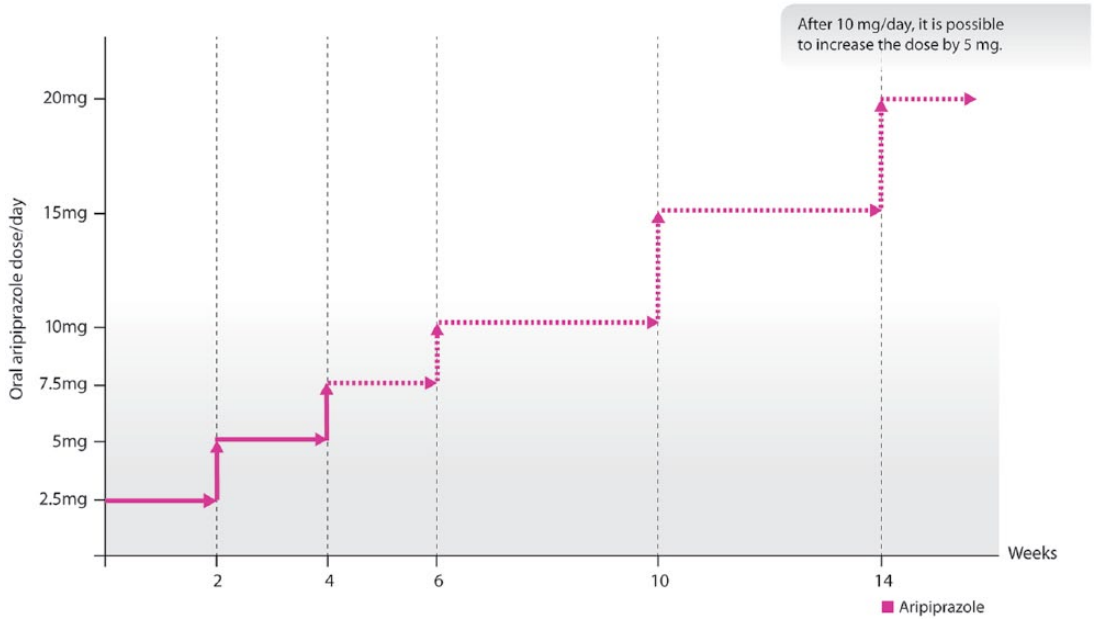

Figure 8. The use of aripiprazole in the setting of treatment resistant obsessive–compulsive disorder.

benzamide-derivative antipsychotics (sulpiride and amisulpride), addition of aripiprazole has no demonstrated effect on prolactin levels.[81]

The use of aripiprazole in the setting of treatment-resistant obsessive–compulsive disorder

The use of aripiprazole for OCD is summarized in Figure 8. Antipsychotic augmentation of the serotonin reuptake inhibitor (SRI) or clomipramine use in patients with treatment-resistant OCD is a recommended option according to the NICE treatment guidelines.[82] Additionally, a systematic review and meta-analysis on augmentation treatment of SRI-resistant OCD with antipsychotics have suggested that aripiprazole is an effective agent for augmentation.[61] In this patient group, in addition to SRI or clomipramine, initiating aripiprazole treatment at 2.5 mg/day is recommended, and then titrating up to 10 mg/day with 2.5 mg increases every 2 weeks. For this patient group, increasing the dose up to a maximum of 20 mg/day is recommended. If a dose $>$ 10 mg/day is considered, staying at least 4 weeks at 10 mg/day is recommended and 15 mg/day subsequently, before titrating further.

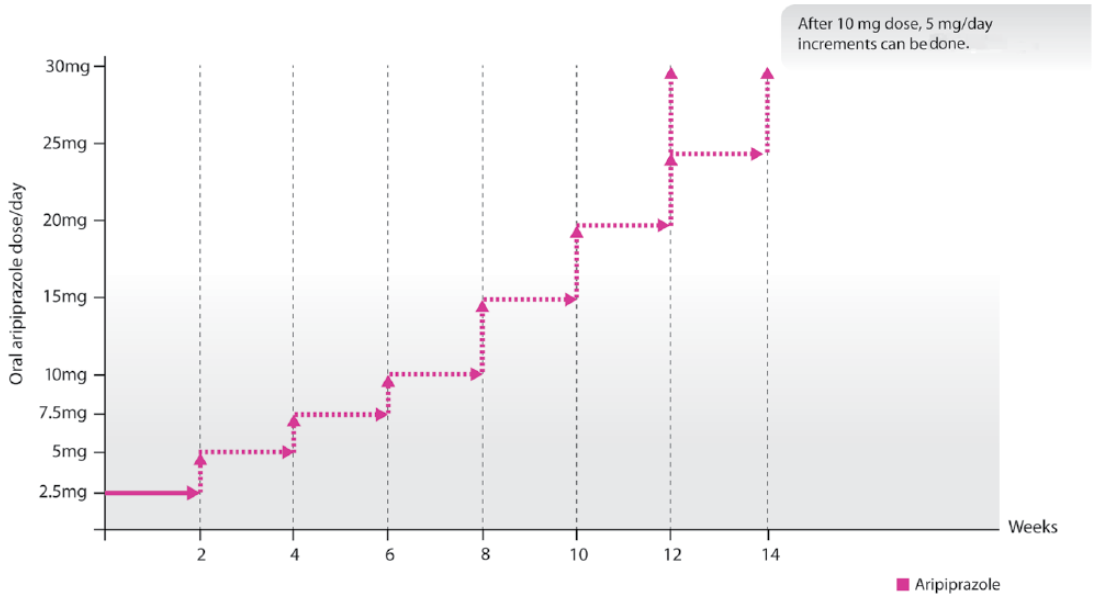

Figure 9. The use of aripiprazole for treatment of tic disorders.

The use of aripiprazole for tic disorders

The use of aripiprazole for treatment of tic disorders is summarized in Figure 9. Aripiprazole is suggested as a treatment option for tic disorders by the Canada treatment guidelines.[83] Aripiprazole has been reported as effective for comorbid conditions in tic disorders, including OCD, depression, anxiety, and attention-deficit hyperactivity disorder.[84] Another study has reported that 82 of 100 patients with Tourette syndrome responded to aripiprazole treatment.[85]

For tic disorders, initiating aripiprazole treatment at 2.5 mg/day is recommended, which should be increased to 10 mg by 2.5 mg increments every 2 weeks. Where further titration is appropriate, 5 mg per day increase every 2 weeks for a target dose of 30 mg/day can be considered. It is also acceptable to make a rapid increase from 20 mg/day to 30 mg/day, where clinically justified. When a sufficient response is achieved at a dose within the 2.5–30 mg range, the dose should not be increased further.

Summary and conclusion

In this review, we have attempted to share our 10-year clinical experience with aripiprazole use and switching from other antipsychotics to aripiprazole. Aripiprazole has some unique receptor binding qualities which provides some advantages over other antipsychotics in certain clinical situations. We have covered potential clinical scenarios for aripiprazole use as a single agent and switching from other agents in inpatient and outpatient settings. Our goal is to create an aid for clinicians on most appropriate use of aripiprazole in different clinical situations.

Key points

(1) The management of switching from atypical antipsychotics to aripiprazole is critical because of the pharmacological properties.
(2) The duration of the steady state is 2 weeks. Waiting for 2 weeks to decide about increasing the dose is recommended.
(3) OCD and tic disorders are the most common psychiatric diseases that psychiatrists prefer in their prescriptions.

Acknowledgements

Contributors to the Turkish aripiprazole consensus group meeting and report:
Prof. Mesut Cetin
Prof. Murat Atmaca
Prof. Haluk Savas
Dr Canan Tinaz
Dr Ulas Camsari

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The consensus group meeting for the development of this publication was organized and funded by Nobel Pharmaceuticals. This publication is based on the discussions from the consensus group meeting, with all authors contributing to all drafts of the article. The opinions expressed in this article are the independent consensus views of the authors and have not been influenced by third-party sponsorship.

Prof. Dilbaz has received speaker honoraria, been invited member of advisory boards and participated in clinical trials on behalf of several pharmaceutical companies including Nobel, Abdi İbrahim, Janssen Cilag, Lundbeck, Generica, Santa Pharma and Pfizer.

Prof. Veznedaroglu has received speaker honoraria, been invited member of advisory boards and participated in clinical trials on behalf of several pharmaceutical companies including, Abdi İbrahim Otsuka, Bilim İlaç, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Cilag, Lilly, Nobel, Sanofi-Synthelabo, Sanovel.

Prof. Uzun has received speaker honoraria, been invited as a member of advisory boards and participated in clinical trials on behalf of several pharmaceutical companies including Janssen Cilag and Nobel.

Prof. Isik has received speaker honoraria from Nobel and Lundbeck and been invited as a member of advisory boards of Nobel and Lundbeck.

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