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Brief review

Aripiprazole in patients with bipolar mania and beyond: an update of practical guidance

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Abstract

Background:
Aripiprazole is an atypical antipsychotic with a pharmacological and clinical profile distinct from other atypical antipsychotics.

Scope:
A European multidisciplinary advisory panel of university-based experts in bipolar disorders convened in April 2010 to review new clinical guidelines for the management of mania and the role of aripiprazole in its treatment. This report describes the consensus reached on how best to use aripiprazole in the treatment of mania.

Findings:
Current guidelines recommending aripiprazole for first-line treatment of mania have not generally translated to clinical practice. The panel agreed that clinicians may not feel sufficiently knowledgeable on how to use aripiprazole effectively in mania, and that the perception that aripiprazole is less sedating than other antipschotics may hamper its use. There was consensus about the importance of ensuring that clinicians understood the distinction between antimanic efficacy and sedation. Most acutely manic patients may require night-time sedation, but continuous daytime sedation is not necessarily indicated and may interfere with long-term compliance. If sedation is necessary, guidelines recommend the use of adjunctive benzodiazepines only for a short-time.

Conclusions:
Clinical practice guidelines widely recommend aripiprazole as a first-line treatment for mania. Although clinical trials may not represent all patient subpopulations, they show that aripiprazole is well tolerated and has a long-term stabilizing potential. The successful use of aripiprazole rests on using the appropriate initial dose, titrating and adjusting the dose as needed and using appropriate concomitant medication to minimize any short-term adverse events. Low incidence of sedation makes aripiprazole a reasonable long-term treatment choice. If short-term sedation is required an adjunctive sedative agent can be added and removed when no longer needed. Clinical considerations should influence treatment choice, and a better distinction between sedation and antimanic effects should be an educational target aimed to overcome potential barriers for using non-sedative antimanic agents such as aripiprazole.

Introduction

Bipolar I disorder is a chronic illness that is characterized by episodes of mania and depression. The lifetime prevalence is around 1%, with a 12-month prevalence of 0.6%[1]. Although effective treatment of acute episodes is obviously necessary, the greater challenge is probably to stabilize the patient in the long term. The balance of various factors, notably medication and lifestyle regulation, play a large part in the long-term effectiveness of treatment.

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Therapeutic options for the treatment of acute episodes and for maintenance have multiplied with the availability of atypical antipsychotics, which over the past few years have become widely used for the treatment of bipolar disorder. In most developed countries, olanzapine, risperidone, quetiapine, ziprasidone, asenapine, aripiprazole, and a number of conventional antipsychotics are approved for the treatment of acute mania; quetiapine and olanzapine–fluoxetine combination (in the United States) are approved for the treatment of acute bipolar depression; and olanzapine, quetiapine and aripiprazole are approved for maintenance treatment (prevention of mania in Europe)[2], ziprasidone and long-acting risperidone being recently approved in some specific countries.

Existing guidelines on the efficacy of these agents offer some direction when making treatment decisions for patients with bipolar disorder. In 2009, three major sets of guidelines were updated from the British Association of Psychopharmacology (BAP)[3]; the World Federation of Societies of Biological Psychiatry (WFSBP)[4]; and the Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders (CANMAT)[5]. They provide evidence-based suggestions derived from systematic reviews of bipolar treatment data. Of note, the current revisions provide guidance on both the efficacy of antimanic agents and their overall risk–benefit profile. Efficacy will always be the critical factor guiding acute treatment decisions but the need to consider the acceptability of short-term treatment effects and patients' long-term physical health is also reflected in this new guidance. A joint statement from the European Psychiatric Association/European Association for the Study of Diabetes/European Society of Cardiology (EPA/EASD/ESC), also published in 2009, provides guidance on the medical management of patients with severe mental illness, a population whose physical health may be compromised by antipsychotic therapies[6].

Among the new options for treating mania, the majority of new agents are antipsychotics that bind directly to dopamine receptors. In the case of aripiprazole, it has been shown to be effective in placebo-controlled trials for the treatment of acute manic episodes[7–9] and in the prevention of recurrence of manic episodes in patients responding acutely to the drug[10,11] and also in the treatment of psychotic features in the frame of a manic episode[12]. Indeed, the recently published guidelines recommend aripiprazole as a first-line agent for the treatment of mania. The perception has been, however, that clinicians find its use a challenge in ordinary practice. We convened as a European multidisciplinary expert panel in April 2010 to identify the underlying reasons for this and provide support to clinicians in this respect. Aripiprazole has novel properties both in terms of its pharmacology and its clinical profile, most notably a relative absence of sedation. The expert group concluded that it would be useful to provide a detailed and balanced perspective on sedation in the treatment of mania because its value may often be uncritically assumed to be obvious.

Accordingly, the aim of this publication is to supplement the guidelines available to European clinicians on the treatment of mania and review the evidence base for the use of aripiprazole in bipolar inpatients and outpatients presenting with mania.

Aripiprazole pharmacodynamics

Aripiprazole has a pharmacology that is distinct from other antipsychotics currently in use. Its efficacy is assumed to be mediated through a combination of partial agonist activity at dopamine D_2, D_3 and 5-HT_{1A} receptors,

and antagonist activity at 5-HT_{2A} receptors[13–15]. Partial agonism implies occupancy of dopamine receptors, so preventing the actions of the endogenous agonist, dopamine, but causing a partial receptor activation. Transmission at dopamine D_2 receptors will be reduced in hyperdopaminergic regions of the brain, but maintained at a tonic low level rather than simply blocked completely, as with an antagonist. It therefore results in a reduced potential for EPS and hyperprolactinemia, but the partial agonist properties of aripiprazole may not protect against akathisia[16]. In addition, prolonged administration of antipsychotics with strong dopamine antagonist effects prior to the introduction of aripiprazole has been associated with dopamine D_2 receptor hypersensitivity, which can be manifested as dystonic symptoms[17].

Compared with agents such as clozapine, olanzapine and quetiapine, aripiprazole also has a relatively low affinity for H_1 (histamine) receptors, which is the likely reason for its lower potential to cause sedation and weight gain[15,18]. Studies in a variety of different patient populations have now established aripiprazole's balance between its efficacy and its relative lack of impact on physical health parameters such as lipid levels[19–20].

Aripiprazole's key pharmacological characteristics and associated outcomes are summarized in Table 1.

Table 1. Pharmacological and clinical profile of aripiprazole.

Characteristic	Aripiprazole property
Pharmacological*	
Receptor profile	
Dopamine D_2 and D_3	• Partial agonist, high affinity: - Low potential to cause EPS - Low potential to cause hyperprolactinemia - Some potential to cause akathisia
Serotonin 5-HT_{1A}	• Partial agonist, high affinity: - May benefit mood
Serotonin 5-HT_{2A}	• Antagonist, high affinity: - Low potential to cause EPS
Histamine H_1	• Antagonist, moderate affinity: - Relatively low potential to cause sedation - Low potential to cause weight gain
Acetylcholine muscarinic α_1	• Antagonist, negligible affinity: - Low potential to cause cognitive impairment - Can be associated with orthostatic hypotension but this is uncommon (Abilify SmPC)
Pharmacokinetic	
Half-life	• 75 hours
Time to steady-state	• 2 weeks
Clinical†	
Formulation	• Oral tablet, solution, intramuscular
Recommended dose (oral)	• 15–30 mg/day
Recommended time of administration	• Morning
Onset of action	• Antimanic response as early as Day 2 following oral administration versus 2 hours following IM administration
Usual adverse effects	• Commonly observed (≥1/100 to <1/10) adverse events include restlessness, insomnia, anxiety, extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache, blurred vision, dyspepsia, vomiting, nausea, constipation, salivary hypersecretion and fatigue • For akathisia, tremor and insomnia, first occurrence is more likely early in treatment; if not observed in the first 3–6 weeks following initiation, occurrence is much less likely later in treatment

EPS = extrapyramidal symptoms.
*Modified from Kroeze *et al.* (2003)[22] and Lieberman (2004)[19].
†In bipolar mania.

Aripiprazole pharmacokinetics

Aripiprazole is available as an oral tablet or solution or intramuscular (IM) formulations. The oral aripiprazole tablet, administered once daily, exhibits linear pharmacokinetics at doses between 15 and 30 mg[21]. Peak plasma concentrations (C_{max}) are reached 3–5 hours after ingestion, with aripiprazole demonstrating a half-life of 75 hours. This is significantly longer than many other oral antipsychotics, so steady-state plasma concentrations for aripiprazole are only achieved after 2 weeks. Nevertheless, the time course of effect observed with aripiprazole is similar to other members of its class. The long half-life of aripiprazole offers a potential advantage to patients with bipolar disorder in maintaining therapeutic blood levels, in the event of patients forgetting to take their medication on time. With respect to potential interactions, aripiprazole does not inhibit or induce the cytochrome P450 CYP3A4 or CYP2D6 enzymes, and has not been shown to influence the pharmacokinetics of lithium or valproate[21]. However, it is important to note that CYP3A4 or CYP2D6 inhibitors may increase aripiprazole concentrations, whereas CYP3A4 inducers such as carbamazapine may decrease aripiprazole concentrations, thus creating a need to adjust the aripiprazole dose.

Treatment choices in guidelines for the treatment of bipolar disorder

BAP

The BAP guidelines[3] categorized recommendations based on evidence. Their guidelines recommend a treatment scheme for acute manic and mixed episodes whereby, for patients not already on long-term treatment for bipolar disorder, oral administration of an antipsychotic or valproate is recommended because of their rapid antimanic

effects compared with lithium. Antipsychotics, lithium and valproate all have antimanic actions with levels of evidence I or II. Treatment selection should be guided where possible by the clinical context and, wherever possible, by patient preference and experience.

The BAP guidelines comment that the older antipsychotics have been widely and appropriately used for the treatment of highly active and/or agitated patients with mania. However, doses of such agents producing extrapyramidal side-effects or other adverse symptoms should only be tolerated for the shortest necessary period of time and, if possible, avoided altogether (level of evidence I). Atypical antipsychotics should be considered because of their generally more favorable short-term adverse-effect profile, especially in relation to motor side-effects and the evidence of their efficacy as antimanic agents. Atypical antipsychotics are less likely to produce extrapyramidal symptoms (EPS) than typical antipsychotics used at conventional doses (level of evidence I), which is of particular significance in bipolar disorder because of an apparently greater risk of motor side-effects, including tardive dyskinesia (level of evidence III). The atypical antipsychotics aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone have shown efficacy in placebo-controlled monotherapy trials in mania (level of evidence I).

In general, the BAP approach is to identify those treatments that meet adequate levels of evidence for efficacy, without making definitive distinctions between them on the basis of differential efficacy. Side effects are more predictable and so may guide treatment preference. Ultimately, treatment success is judged at the level of the individual patient. Since these guidelines were published in 2009, asenapine has been licensed for the treatment of bipolar disorder in Europe.

CANMAT/ISBD

The CANMAT and ISBD have also published updated guidelines for the management of bipolar disorder[5]. Aripiprazole is recommended as first-line treatment for mania both as monotherapy treatment and in combination with lithium/divalproex (Table 2).

The CANMAT approach is to identify multiple treatment levels such as first line and second line. This categorization follows rules, but risks being arbitrary in how it weights the efficacy of a medicine against its association with particular side effects. It might be judged surprising, given its high efficacy and good performance in many head-to-head trials with other antipsychotics, that haloperidol is a 'third-line' treatment (behind carbamazepine and ECT), even if its side-effect profile may require vigilance in practice. Some of the areas where CANMAT's recommendations potentially conflict with clinical practice in Europe have been reviewed elsewhere[23].

Table 2. CANMAT recommendations for first-line treatment of acute mania[5].

Monotherapy	Combination therapy
Aripiprazole	Aripiprazole + lithium or divalproex
Divalproex	Olanzapine + lithium or divalproex
Lithium	Quetiapine + lithium or divalproex
Olanzapine	Risperidone + lithium or divalproex
Quetiapine	
Quetiapine XR	
Risperidone	
Ziprasidone	

CANMAT = Canadian Network for Mood and Anxiety Treatments; XR = extended release.

WFSBP

The WFSBP guidelines for acute mania[4] analyzed efficacy data extracted from a variety of sources, which were categorized into six levels of evidence (category of evidence for efficacy based on scientific rigor). Recommendation grades were then derived from the category of evidence and from additional aspects such as safety, tolerability and interaction potential. Based on available evidence, aripiprazole fulfils category of evidence A (highest level; directly based on evidence from meta-analysis of randomized controlled trials [RCTs], at least two large, good-quality RCTs showing superiority to placebo and at least one showing superiority or equivalent efficacy to a comparator) for antimanic efficacy and recommendation grade 1 (highest level) for overall clinical effectiveness, which includes efficacy, safety, tolerability and practicability of use, which is the highest recommendation available (Table 3).

Aripiprazole use in clinical practice

Aripiprazole is a recommended acute treatment for mania in all these guidelines, based on the evidence supporting its efficacy and safety/tolerability profile. The continued use of a drug such as aripiprazole with a relatively favorable metabolic safety profile to prevent recurrence of manic episodes[11] could also be an advantage in the long term. However, despite these guideline recommendations, aripiprazole is not used as frequently in mania as other antipsychotics. Prescribing data from France, Germany, Italy, Spain and the United Kingdom for 2010 show that only 13% ($n = 1014$) of patients were prescribed aripiprazole for the first-line treatment of bipolar disorder, with 18% ($n = 999$) of patients receiving aripiprazole for second-line treatment and 21% ($n = 364$) for third-line treatment (BMS data on file). In part, this may be because cost factors contribute to clinical decision-making in many European countries. However, the group considered that the low incidence of sedation seen with aripiprazole treatment

Table 3. WFSBP guidelines 2009: CE and RG for antimanic monotherapy efficacy and safety.

Antimanic agent	Category of evidence (CE)†	Recommendation Grade (RG)±	Licensed for relapse/ recurrence prevention*
Aripiprazole	A	1	Yes
Risperidone	A	1	No
Valproate[a]	A	1	No
Ziprasidone[b]	A	1/2	No
Asenapine	A	2	No
Carbamazepine	A	2	No
Haloperidol	A	2	No
Lithium[c]	A	2	Yes
Olanzapine	A	2	Yes
Quetiapine	A	2	Yes

WFSBP = World Federation of Societies of Biological Psychiatry; CE = category of evidence; RG = Recommendation Grade.
Adapted from Grunze *et al.* (2009)[4].
†Criteria for evidence level A: two or more double-blind, parallel group RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo' in a study with adequate blinding) AND one or more positive RCTs showing superiority to equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all evaluable studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
±Criteria for RG 1: category A evidence and good risk–benefit ratio; for RG 2: category A evidence and moderate risk–benefit ratio.
*Currently licensed by the European Medicines Agency (European Medicines Compendium, Dec 2010).
[a]Valproate is not recommended as first choice treatment (RG 1) in women of child-bearing age.
[b]The RG for ziprasidone is 2 in countries where its use is restricted due to regulatory order.
[c]If long-term treatment is considered at the same time, the RG for lithium is 1.

may reduce its appeal in ordinary practice. The reports of akathisia in acute studies may be another deterrent factor and, indeed, aggressive dosing may predispose to akathisia. There is an inevitable gap between what we can speculate to occur in real-life prescribing and what actually happens, but it seems possible that an important reason for clinicians not choosing aripiprazole may relate primarily to their desire for rapid antimanic efficacy, which is confounded with visible effects such as sedation. However, such an approach could expose more patients than necessary to the risks associated with excessive sedation.

Low potential for sedation: a positive or a negative feature?

Although studies on the symptom of sedation are scarce, it has received some attention in the palliative care literature where a consensus seems to accept that the primary aim of sedation is symptom amelioration and that it is a measure of last resort to lower the level of consciousness deliberately after other treatments have failed. Its use in psychiatry appears to be less clearly targeted. There is an element of the same desire to palliate manic symptoms, which when severe can be distressing to patient, carers and nursing staff. From such a perspective, sedation can be an option to consider after other treatments have failed. However, these may introduce into clinical management a simple desire to increase behavioral control through sedation or perhaps, more defensibly, to facilitate sleep in very sleep-deprived patients. Where these objectives are legitimate, guidelines usually suggest that the combination of a potent benzodiazepine with an antipsychotic is the best strategy[24]. In general, the use of sedative antipsychotics rather than non-sedative antipsychotics in mania has not shown superiority, even on short-term outcomes. In fact, haloperidol (non-sedative) was significantly superior to quetiapine (sedative) in a randomized clinical trial in acute mania at the 3-week primary endpoint[25].

Data about the efficacy of drugs, including data about aripiprazole, come from RCTs that have a number of requirements (e.g. need to sign an informed consent, exclusion criteria such as current substance misuse or severe suicide risk, the ability to undergo a research assessment). Therefore, clinical trials represent a subpopulation of more stable and compliant subjects. This could be one of the reasons why clinical experience may not fully mirror results from aripiprazole RCTs. Manic patients very often require behavioral control, particularly during the first 7–10 days (i.e. an earlier time point than the one usually utilized to assess primary endpoints), not only because of possible danger of physical harm directly or indirectly to self and/or others, and reduced need/inability to sleep but also because patients may be aggressive, impulsive, overactive, confused, or dangerously psychotic. The non-sedating properties of aripiprazole are certainly an advantageous characteristic of this drug but may also account for difficulty in controlling severe psychomotor agitation with oral aripiprazole in monotherapy. Such symptoms would be better controlled through the administration of IM aripiprazole and/or when an adequate dose of an adjunctive agent, such as a benzodiazepine, an antihistamine or a 'sedating' antipsychotic is prescribed and then discontinued when agitation is no longer present.

How often is a significant sedative effect believed to be required in acute mania? According to a systematic survey carried out among the expert panel and their nursing staff, around 60% of inpatients may require some degree of short-term sedation. In the case of manic patients seen on an outpatient basis, opinion was divided: overall, the panel considered that the percentage of

patients who required sedation lay in the range 0–30%; however, some clinicians in the panel expressed the strong opinion that, in fact, 0% was the true number of patients actually requiring sedation in an outpatient setting.

Some agents used in the treatment of mania, such as haloperidol, are associated with relatively low sedation at the doses routinely used. However, clinicians' prior experience with older antipsychotics in the treatment of mania, many of which are sedating, may have created the opinion or tradition that sedation is a necessary and desirable component of treatment. The widespread use of olanzapine may also have contributed to this. The panel considered that, in clinical practice, there might be too little differentiation made between the need for a true antimanic effect (i.e. attenuation of motor and mental activity by blockade of the dopaminergic limbic pathways achieved with antipsychotics) and a consciousness-lowering effect (mediated via other transmitter pathways such as histamine). It was advocated that clinicians critically examine their prescribing decisions about when and for how long a consciousness-lowering effect is ever really required[26–29].

The expert panel felt that the only manic symptoms that would specifically require sedation (i.e. a deliberate consciousness-lowering effect) were as follows: danger of physical harm directly or indirectly to self and/or others (including destructive or aggressive behavior), and reduced need/inability to sleep. A sedative effect is generally only required for a matter of hours and therefore sedatives should be used for a minimal time (hours/days but a maximum of 2 weeks may be acceptable). Sedatives should be initiated as soon as possible, when required.

When such a sedative effect is required, an adjunctive sedative agent could be administered in short-term combination with a non-sedating antipsychotic. This may be a more logical and beneficial approach compared with prescribing a sedating antipsychotic because an adjunctive sedative can be withdrawn once the sedative effect is no longer required, and is easier to manage with regard to individual patients' differences in tolerance to sedation. This is important in the long term, given that sedation/somnolence is frequently associated with stigmatization and a negative impact on quality of life[30].

The choice of consciousness-lowering agent would probably be a benzodiazepine, e.g. starting dose 1 mg dose of clonazepam or 1–2 mg dose of lorazepam; final doses should be flexible within maximum doses permitted as per licensing instructions. However, considering some of the problems associated with benzodiazepines (i.e. risk of misuse), other short-term adjuncts for sleep disturbance that may work effectively include antihistamines and sedating antipsychotics (e.g. quetiapine or chlorpromazine).

Akathisia and other side effects associated with aripiprazole

A concise overview of the common side-effects associated with aripiprazole use in bipolar disorder and appropriate management strategies has been provided recently by Fagiolini (2008) and the expert group broadly concurred with this guidance[31]. The Summary of Product Characteristics for aripiprazole states that the most commonly reported adverse events (AEs) occurring in placebo-controlled trials are akathisia and nausea, each in >3% of patients treated with oral aripiprazole[20].

Results of a 52-week study with aripiprazole adjunctive to lithium or valproate by Vieta *et al.* (6-week double-blind phase followed by a 46-week open-label extension phase)[32,33] showed that the most commonly occurring AEs observed during the 46-week extension phase were (aripiprazole + lithium or aripiprazole + valproate, respectively): tremor (17.0% vs. 12.1%); akathisia (6.6% vs. 8.6%); headache (6.6% vs. 4.0%); insomnia (9.4% vs. 10.3%); depression (7.5% vs. 9.2%); and weight increase (11.3% vs. 8.6%). If akathisia, tremor and insomnia occur, this tends to happen predominantly in the first few weeks following aripiprazole initiation, with very low likelihood of a first incidence thereafter (Figure 1). It is therefore important to monitor for these effects early in treatment and respond accordingly.

We are still uncertain whether akathisia is the appropriate term for the motor symptoms associated with starting patients on aripiprazole. The incidence of akathisia given in the preceding section reflects side effects coded in clinical trials, not necessarily a systematic clinical evaluation. Scores on a defined scale do not confirm such effects; therefore, they should be better characterized in future studies. We judge that, for many clinicians, akathisia is difficult to diagnose and may be confused with agitation due to the manic episode itself. Table 4 summarizes how to differentiate akathisia from agitation. A *post-hoc* analysis of pooled data on the incidence of akathisia observed in aripiprazole clinical trials is summarized in Table 5. Although the clinical trials with aripiprazole do not demonstrate an effect of dose on the risk of akathisia, it was thought clinically wise to start aripiprazole at 15 mg/day in acute inpatients and, in outpatients, it may be advisable to start at an even lower dose for a few days before increasing to 15 mg. Patients with a previous history of akathisia occurrence should also receive a lower dose. If a lower initial dose is required, aripiprazole could also be used in combination with valproate – aripiprazole is licensed for use in combination with lithium or valproate from the start of therapy. Short-term administration of a benzodiazepine

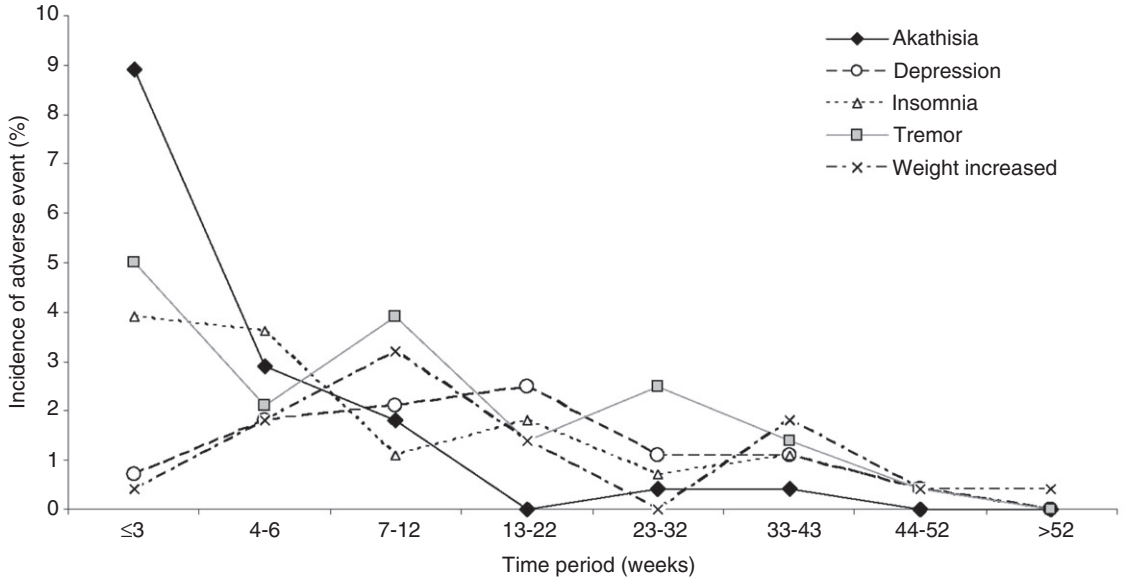


Figure 1. Temporal pattern of adverse events by period of first onset following addition of aripiprazole to lithium/valproate[32].
For patients treated with placebo during the short-term phase, the time of occurrence of the adverse event is based on the first day of aripiprazole use in the open-label extension phase.
For patients treated with aripiprazole during the short-term phase, the time of occurrence is based on the first day of aripiprazole use in the short-term phase.
The percentage incidence is based on the number of patients in the open-label safety sample ($n = 280$).

Table 4. Differentiation of akathisia from agitation.

	Akathisia	Agitation
Subjective feeling of inner restlessness or tension[a]	Present (but patient might not always be able to articulate it)	Present
Physical sensation felt by patient due to muscle quivering, which gives rise to an irresistible urge to move[a]	Yes, notably in the legs. Patient finds it almost impossible to stay still. Can usually stay still if requested but this leads to significant discomfort	Patient will not describe such a physical sensation or the physical need to move
Increasing dose of antipsychotic[b]	Likely to make symptoms worse[c]	Likely to make symptoms better
Adjunctive beta-blockers	Very likely to ameliorate symptoms[b,c]	Will not ameliorate symptoms
Adjunctive benzodiazepines[b]	Likely to ameliorate symptoms[c]	Very likely to ameliorate symptoms

[a]Day (1999)[34].
[b]APA. Practice guidelines for the treatment of patients with schizophrenia (2004)[35].
[c]Hirose (2003)[36].

at the start of treatment may also be beneficial for managing akathisia, if it occurs.

If symptoms of akathisia are observed, recommended management strategies include the co-administration of beta-blockers (e.g. propranolol up to 60 mg/day; 20 mg three times daily) or benzodiazepines (e.g. lorazepam or equivalent up to 4 mg/day; usually 0.5 mg three times daily is sufficient)[37]. Although anticholinergics (e.g. benztropine or equivalents up to 6 mg/day) are sometimes used, evidence to support the use of anticholinergics is limited and many clinicians do not find it particularly useful for managing akathisia[38].

The 52-week study of adjunctive aripiprazole to lithium or valproate found that, in patients where akathisia occurred (40 out of 280 patients), it was generally mild to moderate in severity. In half of the cases, it resolved completely either spontaneously or with intervention by Week 52 and, of those cases that did not resolve, 80% were mild or moderate in severity[32].

Strategies for the prevention/management of nausea and vomiting in aripiprazole-treated patients include reducing the aripiprazole dose until the side effect has resolved, before returning to the target dose after 2–3 days.

For insomnia in aripiprazole-treated patients, strategies for prevention and/or management include administration of aripiprazole in the morning rather than later in the day[40]. In addition, co-medication with

Table 5. *Post-hoc* analysis of pooled akathisia data from aripiprazole trials.

	Short-term schizophrenia trials§		Short-term bipolar trials		Long-term schizophrenia trials§			
	ARI (*n* = 1170)	PLA (*n* = 465)	ARI (*n* = 597)	PLA (*n* = 436)	ARI (*n* = 859)	HAL (*n* = 431)	ARI (*n* = 504)	OLA (*n* = 505)
Incidence of reported akathisia, *n* (%)*	105 (9.0)	29 (6.2)	107 (17.9)	22 (5)	96 (11.2)	96 (22.3)	51 (10.1)	28 (5.5)
Time to first onset (mean/median in days)	8.5/7	9/5	6.5/6	9/10	22/16	17/11	19/13	17/16
Mean/median duration (days)	12.5/5	4.2/1.5	10/6	4/2	40/13	44/17	23/7	8/7
% patients reporting akathisia as mild or moderate	91%	93%	90%	96%	99%	95%	98%	100%
Patients reporting akathisia with no subsequent action taken, *n* (%)	101 (96.7)	29 (100)	80 (74.8)	13 (59.1)	75 (78.1)	56 (58.3)	39 (76.5)	25 (89.3)
Dose reduction† due to reported akathisia‡, *n* (%)	0 (0)	0 (0)	13 (2.2)	0 (0)	16 (16.7)	31 (32.3)	5 (9.8)	1 (3.6)
Discontinuation due to reported akathisia, *n* (%)	4 (0.3)	0 (0)	14 (2.3)	0 (0)	8 (0.9)	12 (2.8)	6 (1.2)	1 (0.2)

*In short-term schizophrenia trials, incidence includes low (2 and 5 mg) doses of aripiprazole. In long-term schizophrenia trials, incidence is reported for events occurring in the first 12 weeks.
†As the short-term schizophrenia protocols did not allow down-titration to manage akathisia, the percentage of patients showing decreased doses due to akathisia was 0% in this data set.
‡Denominator is number of patients reporting akathisia.
§Includes both schizophrenia and schizoaffective disorder trials.
ARI = aripiprazole; PLA = placebo; HAL = haloperidol; OLA = olanzapine.
Adapted from Kane *et al.* (2010)[39].

benzodiazepines (e.g. lorazepam or equivalents up to 2 mg/day), or other hypnotics, can be considered[40].

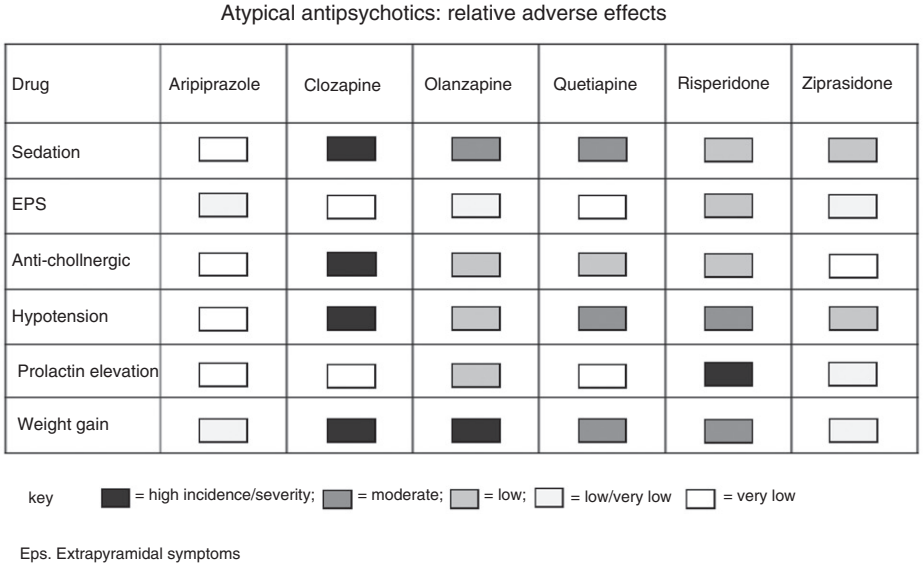
Aripiprazole used both as monotherapy and in combination with lithium or valproate has not been found to have a significant negative effect on metabolic parameters (cholesterol, triglycerides, glucose or prolactin) either in the short or long term[11,32,33]. Metabolic syndrome (including obesity, insulin-resistant diabetes, dyslipidemia, and hypertension) occurs at a higher incidence in patients with bipolar disorder than in the general population[41]. Among existing atypical antipsychotics, aripiprazole is associated with a lower risk of cardiometabolic factors, such as weight gain, diabetes, and dyslipidemia[42]. Indeed, results from a *post-hoc* analysis of a 26-week study showed that the effects of aripiprazole on the prevalence of metabolic syndrome were comparable with placebo in patients with bipolar disorder[43]. Nevertheless, professional organizations advocate long-term monitoring of metabolic parameters in patients receiving any atypical antipsychotic to circumvent the likelihood of developing metabolic conditions[42] and more extensive naturalistic long-term data will be desirable.

A summary of the relative adverse effects seen with atypical antipsychotics is shown in Figure 2, as detailed in the Maudsley Prescribing Guidelines (10th edition, 2009)[44].

When to select and how to use aripiprazole as treatment for mania

Acute manic episode

Aripiprazole is available both as oral and IM formulations. Where a faster onset of action is required in acute mania, the IM formulation of aripiprazole is a reliable option, with demonstrated ability to reduce agitation significantly in less than 2 hours[45]. The IM formulation may also be useful for patients who refuse oral medication. The recommended initial dose of IM aripiprazole is 9.75 mg (1.3 mL), administered as a single injection, and up to three doses may be given in any 24-hour period[46]. Co-administration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects did not result in clinically important changes in the pharmacokinetics of either drug. While clinical trials have not evaluated aripiprazole and lorazepam administered in a single syringe, an in-vitro study on the physical stability of IM aripiprazole solution and IM lorazepam solution 30 minutes after mixing indicated no signs of instability (color changes, precipitation, cloudiness or changes in pH; BMS data on file). No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation observed in healthy subjects was greater with the



Adapted from Maudsley prescribing guidelines. Taylor et al. (2009)[44].

Figure 2. Relative adverse effects of atypical antipsychotics.

combination compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater with the combination compared to that observed with lorazepam alone[46].

The recommended starting dose of oral aripiprazole in patients with acute manic and mixed episodes is 15 mg/day administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy. Some patients may benefit from a higher dose but the maximum daily dose should not exceed 30 mg/day, based on evidence from controlled clinical trials[46,47]. Compared with placebo, a significant antimanic response was observed as early as Day 2[7,9] or Day 4 of oral aripiprazole administration[8,48]. Initiation of 15 mg/day is effective in clinical practice, followed by titration to 30 mg/day, if required. For example, if there is uncertainty as to whether behavioral problems are agitation or akathisia, a dose increase from 15 to 30 mg/day may be relevant under careful observation. Initiation at 15 mg/day may also minimize the risk of short-term, dose-related adverse effects, such as nausea and akathisia. Conversely, initiation at a dose of 30 mg/day may work well in patients who are agitated and who have not already been administered IM aripiprazole. If the patient has previous dose-related tolerability issues, a lower starting dose is recommended (10 mg/day). Overall, any required dose adjustment of oral aripiprazole should be based on tolerability, whereby doses may be adjusted to between 15 and 30 mg/day[20]. To stabilize manic symptoms in an acute episode, aripiprazole therapy should be initiated immediately upon onset of symptoms (Figure 3). A temporal pattern for the emergence of some AEs has been noted with aripiprazole treatment – specifically, akathisia, tremor and insomnia occurred mainly in the first few weeks after aripiprazole initiation, with low incidences thereafter. Therefore, monitoring and intervention is advised during the first few weeks following initiation to minimize the impact of these AEs; however, if these AEs are not observed in the first 3–6 weeks of treatment, they are generally unlikely to occur later in treatment.

Inadequate response to mood stabilizer monotherapy

Less acute clinical situations may favor the considered use of a medicine such as aripiprazole with a somewhat unfamiliar pharmacology. Thus, antipsychotics can be used as an add-on therapy in patients who show inadequate response to lithium or valproate and the advice of guidelines emphasizes the weight of evidence behind such combination treatment for mania. Of course, caution must be warranted in interpretation of all clinical studies as study design aspects such as the study population, prior treatments, and endpoint parameters can influence outcomes. The addition of aripiprazole to lithium or valproate in these circumstances is illustrated (Figure 3). Thus, the expert panel agreed that add-on aripiprazole therapy is an appropriate option in patients who are partially non-responsive to mood stabilizer monotherapy.

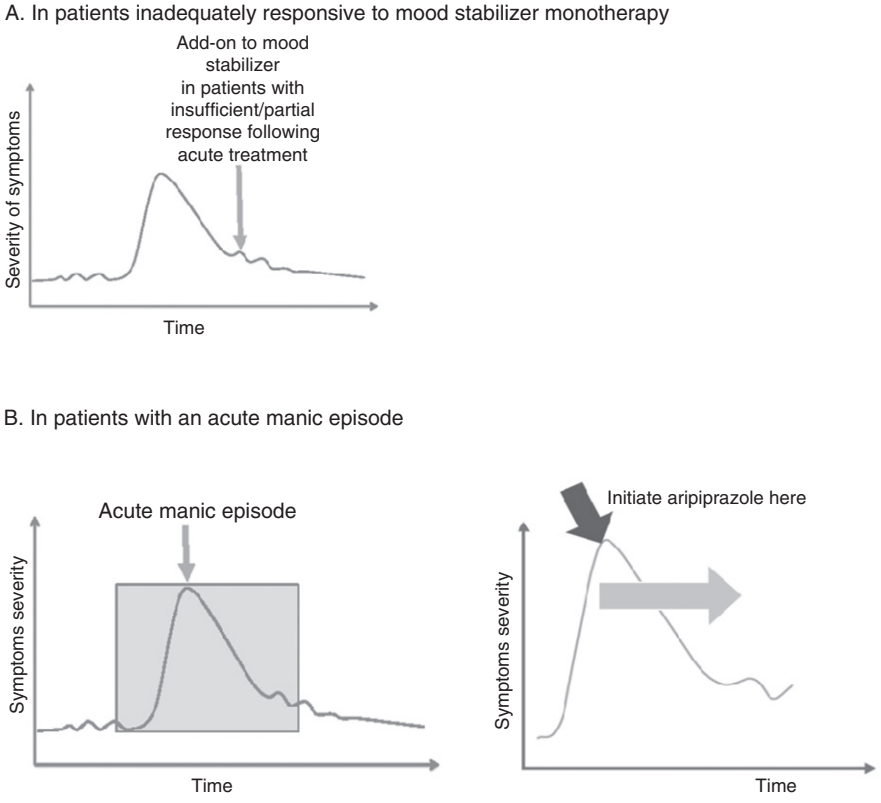


Figure 3. Timing of aripiprazole initiation.

Based on their clinical experience, the expert group estimated that 30–60% of patients treated for an acute manic episode will continue to have significant symptoms of mania in the weeks after initial treatment, which compromises patient wellbeing and, if left untreated, could lead to relapse and another manic episode. It is important to adjust the medication regimen when insufficient response is recognized, in order to prevent a manic relapse. Regarding the timeframe for addition of an antipsychotic, the panel recommended modification of therapy within 1 week of identification of insufficient response to monotherapy.

Aripiprazole can be used relatively easily and safely in combination with valproate or lithium because there is no pharmacokinetic interaction between these agents. Therefore, when adding aripiprazole to the treatment regimen for patients with insufficient response to lithium or valproate therapy, the recommended dose range is the same as that used in monotherapy, i.e. 15–30 mg once daily. It may be beneficial to decrease the dose to 10 mg/day to minimize any short-term adverse effects, should they occur, and titrate upwards again after a few days to 15 mg or 30 mg. Administration of aripiprazole in the morning should lower the likelihood of insomnia.

Table 1 presents an overview of the pharmacological and clinical profile of aripiprazole to guide clinical decision. In addition, patients who are obese (or with other characteristics indicating susceptibility to metabolic syndrome), EPS-prone, intoxicated, cognitively impaired or with elevated prolactin levels, may be deemed more suitable for aripiprazole than other treatments.

Summary overview of aripiprazole comparative data in acute mania and prevention of relapse as monotherapy or combination therapy

Aripiprazole has been shown to be efficacious in mania in short- and long-term clinical trials. The clinical trial data summarized below includes studies carried out in multiple countries and with differing prescribing indications. Therefore, clinicians are strongly encouraged to review their local prescribing information as some of the doses reported below may not be consistent with the product label in certain countries.

Data in monotherapy

Trials assessing the efficacy of aripiprazole as monotherapy are individually summarized below.

In one study, manic patients requiring hospitalization were randomized to double-blind aripiprazole (15 mg/day, up to 30 mg/day after Day 4 based on tolerability and clinical response; $n = 155$), placebo ($n = 165$) or lithium (900 mg/day, up to 1200 mg/day at Day 4 or up to 1500 mg/day after Day 7; $n = 160$) for 3 weeks. Lithium doses could be altered based on lithium serum concentrations to ensure that patients were maintained within the target therapeutic serum level of 0.60–1.20 mEq/L)[9]. Aripiprazole-treated and lithium-treated patients remained on blinded treatment for a further 9 weeks. Aripiprazole provided statistically significant improvement of acute mania within 2 days, continuing over 3 weeks and sustained over 12 weeks. The magnitude of improvement to Week 12 was similar with aripiprazole and lithium.

In another 12-week randomized trial, patients experiencing a manic or mixed episode requiring hospitalization were randomized to double-blind aripiprazole (15 mg/day, up to 30 mg/day after Day 4 based on tolerability and clinical response; $n = 167$), placebo ($n = 153$) or haloperidol (5 mg/day, up to 10 mg/day after Day 4 or up to 15 mg/day after Day 7; $n = 165$) for 3 weeks[7]. Aripiprazole- and haloperidol-treated patients remained on masked treatment for a further 9 weeks. Clinical improvements with aripiprazole were sustained to Week 12, demonstrated by an improvement in Young Mania Rating Scale (YMRS) total score from baseline. Improvement was similar to that seen with haloperidol therapy. Aripiprazole was well tolerated; extrapyramidal adverse events were more frequent in the haloperidol treatment group (53.3% vs. 23.5%).

Two 3-week, randomized, placebo-controlled studies evaluated the efficacy and safety of aripiprazole (30 mg/day, reduced to 15 mg/day for tolerability if needed) in 262[48] and 272[8] patients with bipolar I disorder experiencing an acute relapse of manic/mixed episode that required hospitalization, and observed significant improvements in symptoms of mania and response, as measured by YMRS, for aripiprazole compared with placebo.

Another fixed-dose trial of hospitalized acute mania patients failed to demonstrate an advantage over placebo for both 15 mg/day and 30 mg/day aripiprazole. Potential reasons for study failure are further addressed in the original report[49].

A clinical study in patients initially presenting with acute mania requiring hospitalization, followed up, on an outpatient basis, those who responded to acute treatment with aripiprazole, to compare long-term aripiprazole therapy (15 or 30 mg/day) versus placebo in the prevention of recurrence of any mood episodes over 100 weeks (initial 26-week double-blind relapse-prevention phase followed by a further 74-week double-blind extension phase). The study showed that aripiprazole was superior to placebo in delaying time to any mood episode and was generally well tolerated[11]. Further analysis of the study revealed that the overall prophylactic effect of aripiprazole versus placebo was due to the prevention of new manic episodes, but not depression.

Adjunctive aripiprazole in patients partially non-responsive to mood stabilizer monotherapy

In a 6-week, placebo-controlled study of adjunctive aripiprazole in outpatients partially non-responsive after 2 weeks of lithium or valproate monotherapy at therapeutic levels (lithium 0.6–1.0 mmol/L or valproate 50–125 μg/mL), patients received either adjunctive aripiprazole at a dose of 15 mg/day that could be increased to 30 mg/day after Week 1 or adjunctive placebo. Adjunctive aripiprazole therapy improved manic symptoms by Week 1 and at all subsequent time points to the study endpoint at Week 6. In addition, adjunctive aripiprazole also resulted in greater remission rates compared with adjunctive placebo[33]. In the open-label, 46-week extension of this 6-week study, all patients received lithium + aripiprazole or valproate + aripiprazole. Lithium was administered at a dose range of 500–1500 mg/day (600–1500 mg/day in US) and valproate was administered at a dose range of 500–2500 mg/day. Aripiprazole was administered at 15 or 30 mg/day. Lithium and valproate remained at stable doses sufficient to maintain therapeutic serum levels of 0.6–1.0 mmol/L and 50–125 mg/mL, respectively. Analysis showed that both subgroups experienced significant improvement versus baseline in YMRS and Montgomery–Åsberg Depression Rating Scale (MADRS) total scores to the end of the 46-week extension phase. A Kaplan–Meier survival analysis of patients who had achieved remission on lithium/valproate plus aripiprazole at Week 6 showed that both drug combinations, aripiprazole + lithium and aripiprazole + valproate, were effective in maintaining remission (YMRS total score ≤ 12 and MADRS ≤ 8) over the 46-week follow-up, with at least two-thirds of patients in either subgroup maintaining remission 40 weeks after the end of the double-blind study[32].

Two placebo-controlled studies of aripiprazole in combination with mood stabilizers in patients with manic or mixed bipolar I disorder who were stabilized on the aripiprazole combination regimen have recently been completed. The first study compared the time to relapse in patients on aripiprazole or placebo adjunctive to lithium/valproate and the second study evaluated aripiprazole or placebo in combination with lamotrigine. In the first study, 337 patients were randomized to either aripiprazole adjunctive to lithium/valproate or placebo with lithium/valproate and followed up for 52 weeks. The target

therapeutic serum levels of mood stabilizers were 0.6–1.0 mmol/L for lithium and 50–125 μg/mL for valproate. Aripiprazole was initiated at 15 mg/day, with the option to increase to 30 mg/day or to decrease to 10 mg/day after Day 4. Adjunctive aripiprazole significantly delayed the time to any relapse as compared with placebo plus lithium/valproate (hazard ratio = 0.544 [95% CI: 0.33–0.89], log-rank $p = 0.014$). In addition, adjunctive aripiprazole decreased the risk for manic relapse by 65% (hazard ratio = 0.35 [95% CI: 1.46–0.829], log rank $p = 0.01$)[50]. In the second study, 351 patients were randomized and followed up for 52 weeks. Patients were started on 10 mg/day of aripiprazole, with a target dose of 15 mg/day, in combination with open-label lamotrigine, which was started at 25 mg/day and titrated over 6 weeks (Week 1–2: 25 mg/day; Week 3–4: 50 mg/day; Week 5: 100 mg/day; and Week 6: 200 mg/day), with a target dose of 200 mg/day. Stable patients were randomized to continue aripiprazole plus lamotrigine or switch to placebo plus lamotrigine and evaluated over 52 weeks. The aripiprazole combination treatment arm showed a longer time to relapse to manic or mixed episodes (study primary endpoint) than the lamotrigine monotherapy arm, but this treatment effect did not reach statistical significance (hazard ratio = 0.55 [95% CI: 0.30–1.03], log-rank $p = 0.058$). Findings were similar for time to relapse due to any episode (hazard ratio of 0.67 [95% CI: 0.45–1.01], log rank $p = 0.055$). In addition, a *post-hoc* analysis revealed that time to relapse to a manic episode only was significantly longer for aripiprazole + lamotrigine vs. placebo + lamotrigine (hazard ratio of 0.45 [95% CI: 0.20–1.00], log-rank $p = 0.044$)[51].

Overall, aripiprazole, both in combination with lithium/valproate or as monotherapy, has demonstrated consistent efficacy in resolving symptoms of acute mania and significantly delaying time to any relapse in patients responding acutely to aripiprazole in pivotal short- and long-term studies of patients with bipolar disorder. A summary of representative studies is presented in Table 6.

Summary

Although recent guidelines suggest equivalent general indications for the antipsychotics approved for the treatment of mania, aripiprazole appears to be relatively rarely employed as a first-line choice. The consensus of an expert group asked to consider this finding was sought. It was suggested that this underuse could be related to its perceived clinical profile as a non-sedative medicine, together with other factors like its novelty or the reports of akathisia in clinical samples.

Aripiprazole is an antipsychotic with a unique pharmacological profile that is available in oral tablets, solution and IM formulations. Oral aripiprazole can be initiated as add-on or monotherapy in patients with acute bipolar mania at doses of 15 or 30 mg/day. Aripiprazole, administered as a single IM injection of 9.75 mg, may be an appropriate option for more rapid control of manic symptoms in the acute phase (under 2 hours).

Using an appropriate initial dose and titration, adjusting this dose as needed and using appropriate concomitant medication to minimize any short-term AEs will all be important in the success of aripiprazole therapy in mania. Aripiprazole has also been demonstrated to have short-term (6 weeks) efficacy as adjunctive therapy in manic patients partially non-responsive to lithium or valproate monotherapy and in the prevention of mood event recurrence both as monotherapy[11] and in combination with lithium or valproate[50].

Unlike some other atypical and typical antipsychotic agents, aripiprazole does not lead to significant increases in metabolic parameters (such as lipids and glucose) or importantly to hyperprolactinemia. Aripiprazole is associated with a relatively low incidence of weight gain in the short and long term, compared to agents such as olanzapine and quetiapine, both as monotherapy and in combination with mood stabilizers. The panel concluded that early use of aripiprazole may also be an appropriate choice for patients with subsyndromal symptoms that suggest the potential for relapse to an acute episode. The main difficulty relating to subsyndromal symptoms is that clinicians usually fail to recognize these in time to initiate treatment before the onset of a full manic episode. This is due to the fact that subsyndromal symptoms – which very often include sleep disturbance – are difficult to identify accurately and quickly in an outpatient setting. Therefore, a major challenge for clinicians is to improve symptom identification – for example, through the use of patient diaries or other more innovative information relay systems, and providing psychoeducation to patients[52] and relatives[53] so breakthrough early symptoms can be identified and treated.

Low propensity to cause sedation may make aripiprazole a reasonable choice to use in the long term, as treatment is less likely to interfere with the patient's functionality or impact on quality of life in relation to sedation. It remains important to distinguish between antimanic efficacy and sedation as a consciousness-lowering side effect and to alert clinicians to this distinction. Where sedation would be beneficial in the short term, this can be achieved, if required, by adding a sedative to the treatment regimen – it can then be removed when a sedative effect is no longer desired.

The group were mindful that many clinical considerations do and should influence choice of treatment for individual patients, but would advise caution if a

Table 6. Randomized controlled trials of aripiprazole both in combination with lithium/valproate or as monotherapy in the treatment of bipolar I disorder with manic, depressive or mixed episodes.

Study	Bipolar I diagnosis	Design type	Trial length (Weeks)	Efficacy measures at study endpoint
Keck *et al.*, 2003[48]	Mixed/manic	Flexible dose, placebo-controlled	3	Reduction in YMRS: −8.2 aripiprazole vs. −3.4 placebo ($p<0.005$) Response rate: 40% aripiprazole vs. 19% placebo ($p\leq0.005$)
Vieta *et al.*, 2005[54]	Mania	Flexible dose (15–30 mg/day), haloperidol-controlled	12 (acute)	Effectiveness response (Week 12): 49.7% aripiprazole vs. 28.4% haloperidol ($p<0.001$) Time to discontinuation: favored aripiprazole vs haloperidol ($p<0.001$)
Keck *et al.*, 2006[55]	Mixed/manic	Flexible dose (15–30 mg/day), placebo-controlled	26 (maintenance)	Time to relapse: favored aripiprazole ($p=0.02$) Time to manic relapse: favored aripiprazole ($p=0.008$) Time to depressive relapse: not significant Relapse rate: 25% aripiprazole vs. 43% placebo ($p=0.013$)
Sachs *et al.*, 2006[8]	Mixed/manic	Flexible dose (15–30 mg/day), placebo-controlled	3	Reduction in YMRS: −12.5 aripiprazole vs. −7.2 placebo ($p\leq0.001$) Response rate: 53% aripiprazole vs. 32% placebo ($p=0.001$)
Keck *et al.*, 2007[11]	Mixed/manic	Flexible dose (15–30 mg/day), placebo-controlled	74 (extension)	Time to relapse: longer for aripiprazole vs. placebo ($p=0.011$) Time to manic relapse: favored aripiprazole vs. placebo ($p=0.005$) Time to depressive relapse: not significantly different
Thase *et al.*, 2008[56]	Depressive	Flexible dose (5–30 mg/day), placebo-controlled	8	Reduction in MADRS total score: not significant (aripiprazole vs. placebo) Discontinuation rates: favored placebo vs. aripiprazole ($p=0.02$)
Vieta *et al.*, 2008[33]	Mixed/manic	Flexible dose (15 or 30 mg/day), placebo-controlled adjunctive to lithium or valproate	6	Reduction in YMRS: −13.3 aripiprazole vs. −10.7 placebo ($p<0.01$) Response rate: 62.8% aripiprazole vs. 48.5% placebo ($p<0.01$), LOCF Remission rate: 66.0% aripiprazole vs. 50.8% placebo ($p<0.01$), LOCF
Keck *et al.*, 2009[9]	Mixed/manic, mania	Flexible dose (15–30 mg/day), placebo-controlled	3	Reduction in YMRS: −12.6 aripiprazole vs. −9.0 placebo ($p<0.001$) Reduction in YMRS: −12.0 lithium vs. −9.0 placebo ($p=0.005$) Response rate: 46.8% aripiprazole/45.8% lithium vs. 34.4% placebo ($p<0.05$)
	Mixed/manic, mania	Flexible dose (15–30 mg/day)	9 (extension)	Reduction in YMRS (Week 12): −14.5 aripiprazole/−12.7 lithium Response rate (Week 12): 56.5% aripiprazole/49.0% lithium
Young *et al.*, 2009[7]	Mania	Fixed dose (15 or 30 mg/day), haloperidol (5–15 mg/day), placebo-controlled	3	Reduction in YMRS (Week 3): −12.0 aripiprazole ($p<0.005$ vs placebo) and −12.8 haloperidol ($p<0.001$ vs placebo), −9.7 placebo Response and remission rates (Week 3): not significant vs placebo for aripiprazole or haloperidol
	Mania	Fixed dose (15 or 30 mg/day), haloperidol (5–15 mg/day)	9 (extension)	YMRS (Week 12): −17.2 aripiprazole and −17.8 haloperidol ($p=0.564$, from baseline) Response and remission rates (Week 12): not significant vs placebo for aripiprazole or haloperidol
El Mallakh *et al.*, 2010[49]	Mixed/manic	Fixed dose (15 or 30 mg/day), placebo-controlled	3	Reduction in YMRS: −10.0 (15 mg/day) and −10.8 (30 mg/day) vs. −10.1 (placebo) Response rate: not significant (aripiprazole vs. placebo)
Vieta *et al.*, 2010[32]	Mixed/manic	Open label, aripiprazole (15 or 30 mg/day) adjunctive to lithium or valproate	46 (extension)	Reduction in YMRS (Week 52): −16.5 aripiprazole + lithium and −17.6 aripiprazole + valproate (both $p<0.001$ vs. baseline)
Marcus *et al.*, 2011[50]	Mixed/manic	Flexible-dose, placebo-controlled, aripiprazole adjunctive to either lithium or valproate	52 or relapse	Reduction in YMRS (Week 52): −0.1 aripiprazole combination, 2.9 placebo combination ($p<0.001$) Relapse rate (Week 52): 17% aripiprazole combination, 29% placebo combination Time to any relapse: favored aripiprazole + lithium/valproate (hazard ratio = 0.54, 95% CI [0.33–0.89]; $p=0.014$)
Carlson *et al.*, 2011[51]	Mixed/manic	Flexible-dose, placebo-controlled, aripiprazole in combination with lamotrigine	52 or relapse	Reduction in YMRS (Week 52): favored aripiprazole combination (treatment difference = −2.3; 95% CI [−3.91−0.67]; $p=0.006$) Relapse rate (Week 52): 11% aripiprazole combination, 23% placebo combination Time to manic/mixed relapse: numerically favored aripiprazole combination (hazard ratio = 0.55; 95% CI [0.30–1.03]; $p=0.058$)

Response = proportion of patients showing ≥50% decrease in YMRS total score from baseline, except in Vieta *et al.* (2005)[54] where response was defined as an effectiveness measure of the proportion of patients with a ≥50% decrease in YMRS total score from baseline still remaining on therapy by Week 12; YMRS = Young Mania Rating Scale total score.

prescriber's perceived requirement for continuous sedation was the over-riding clinical consideration.

Transparency

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References

1. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543-52
2. Fountoulakis KN, Vieta E. Efficacy and safety of aripiprazole in the treatment of bipolar disorder: a systematic review. Ann Gen Psychiatry 2009;8:16
3. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2009;23:346-88
4. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry 2009;10:85-116
5. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009;11:225-55
6. De Hert M, Dekker JM, Wood D, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 2009;24:412-24
7. Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry 2009;194:40-8
8. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol 2006;20:536-46
9. Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord 2009;112:36-49
10. Keck PE, Calabrese J, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006;67:626-37
11. Keck PE, Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007;68:1480-91
12. Fountoulakis KN, Gonda X, Vieta E, et al. Treatment of psychotic symptoms in bipolar disorder with aripiprazole monotherapy: a meta-analysis. Ann Gen Psychiatry 2009;8:27
13. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002;302:381-9
14. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT(1A) receptor. Eur J Pharmacol 2002;441:137-40
15. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacol 2003;28:1400-11

16. Poyurovsky M, Weizman R, Weizman A. Aripiprazole's receptor pharmacology and extrapyramidal side effects. Am J Psychiatry 2008;165:398; author reply 98-9
17. Koener B, Hermans E, Maloteaux JM, et al. Paradoxical motor syndrome following a switch from atypical neuroleptics to aripiprazole. Am J Psychiatry 2007;164:1437-8
18. Miller D. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry 2004;6(Suppl 2):3-7
19. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004;18:251-67
20. Bristol-Myers-Squibb, Ltd. OPE. Abilify (aripiprazole) Summary of Product Characteristics. September 2011
21. McIntyre RS, Soczynska JK, Woldeyohannes HO, et al. Aripiprazole: pharmacology and evidence in bipolar disorder. Expert Opin Pharmacother 2007;8:1001-9
22. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:519-26
23. Vieta E, Nolen WA, Grunze H, et al. A European perspective on the Canadian guidelines for bipolar disorder. Bipolar Disord 2005;7(Suppl 3):73-6
24. Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. Emerg Med J 2003;20:339-46
25. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania-a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol 2005;15:573-85
26. Meehan K, Zhang F, David S, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. J Clin Psychopharmacol 2001;21:389-97
27. Kane JM, Sharif ZA. Atypical antipsychotics: sedation versus efficacy. J Clin Psychiatry 2008;69(Suppl 1):18-31
28. Allen MH, Currier GW, Carpenter D, et al. Introduction: methods, commentary, summary. J Psychiatr Pract 2005;11(S1):5-25
29. Canas F. Management of agitation in the acute psychotic patient – efficacy without excessive sedation. Eur Neuropsychopharmacol 2007;17(Suppl 2):S108-14
30. Angermeyer MC, Matschinger H. [Neuroleptics and quality of life. A patient survey]. Psychiatr Prax 2000;27:64-8
31. Fagiolini A. Practical guidance for prescribing with aripiprazole in bipolar disorder. Curr Med Res Opin 2008;24:2691-702
32. Vieta E, Owen R, Baudelet C, et al. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. Curr Med Res Opin 2010;26:1485-96
33. Vieta E, T'joen C, McQuade RD, et al. Adjunctive aripiprazole in bipolar mania partially non-responsive to valproate/lithium: a placebo-controlled study (CN138-134). Am J Psych 2008;165:1316-25
34. Day RK. Psychomotor agitation: poorly defined and badly measured. J Affect Disord 1999;55:89-98
35. APA. Practice guidelines for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161:1-56
36. Hirose S. The causes of underdiagnosing akathisia. Schizophr Bull 2003;29:547-58
37. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000;22:73-81
38. Rathbone J, Soares-Weiser K. Anticholinergics for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 2006(4):CD003727
39. Kane JM, Barnes TRE, Correll CU, et al. Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials. J Psychopharmacol 2010;24:1019-29
40. Aitchison KJ, Bienroth M, Cookson J, et al. A UK consensus on the administration of aripiprazole for the treatment of mania. J Psychopharmacol 2009;23:231-40
41. Fagiolini A, Frank E, Scott JA, et al. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005;7:424-30
42. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596-601
43. Kemp D, Calabrese J, Tran Q, et al. Metabolic syndrome in patients enrolled in a clinical trial of aripiprazole in the maintenance treatment of bipolar I disorder. J Clin Psychiatry; 2010;71:1138-44
44. Taylor D, Paton C, Kapur S. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust Prescribing Guidelines, 10th edn, 2009
45. Zimbroff DL, Marcus RN, Manos G, et al. Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. J Clin Psychopharmacol 2007;27:171-6
46. Bristol-Myers Squibb. Abilify prescribing information. 2011. Available at: http://packageinserts.bms.com/pi/pi_abilify.pdf [Last accessed September 2011]
47. European Medicines Agency E. Abilify – European Public Assessment Report (EPAR). 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000471/WC500020171.pdf [Last accessed 2011]
48. Keck PE, Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003;160:1651-8
49. El Mallakh RS, Vieta E, Rollin L, et al. A comparison of two fixed doses of aripiprazole with placebo in acutely relapsed, hospitalized patients with bipolar disorder I (manic or mixed) in subpopulations (CN138-007). European neuropsychopharmacology: J Eur College Neuropsychopharmacol 2010;20:776-83
50. Marcus R, Khan A, Rollin L, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord 2011;13:133-44
51. Carlson B, Ketter T, Sun W *et al.* Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disord 2011;In Press
52. Colom F, Vieta E, Sanchez-Moreno J, et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial. Br J Psychiatry 2009;194:260-5
53. Reinares M, Colom F, Sanchez-Moreno J, et al. Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial. Bipolar Disord 2008;10:511-19
54. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry 2005;187:235-42
55. Keck PE, Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006;67:626-37
56. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008;28:13-20