A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder

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Abstract: Aripiprazole has been approved by regulatory agencies for the treatment of schizophrenia and bipolar I disorder. Although it is a dopamine partial agonist, it also has substantial binding affinity for the serotonin 5HT2A receptor. Several double-blind randomized clinical trials have established the efficacy and tolerability of aripiprazole within the dose range of 10–30 mg/day for schizophrenia, and 15–30 mg/day for manic or mixed states associated with bipolar I disorder. Relatively few comparative trials with other second-generation antipsychotics have been published for schizophrenia, with none available for bipolar disorder. The evidence so far suggests that in terms of efficacy for schizophrenia, aripiprazole is superior to placebo and haloperidol (long term), similar to perphenazine and risperidone, and inferior to olanzapine. Its tolerability profile in patients with schizophrenia appears superior to haloperidol, perphenazine, risperidone, and olanzapine. Efficacy in treating manic or mixed states was established in placebo-controlled trials. Among some patients with bipolar disorder, akathisia and gastrointestinal (GI) complaints can emerge at the start of treatment; however, the GI symptoms were time-limited in many instances. Appropriate dosing may also be important in individualizing therapy to improve tolerability, with lower starting doses becoming more important when adding to, or switching from, another antipsychotic. Aripiprazole appears to have a low propensity for weight gain, a favorable metabolic profile, and no association with hyperprolactinemia.

Keywords: aripiprazole, schizophrenia, bipolar disorder

Introduction

Aripiprazole was approved by the United States Food and Drug Administration in November 2002 for the treatment of schizophrenia. Its introduction was heralded by some as a "third-generation" antipsychotic, as it was the first dopamine partial agonist anti-schizophrenia drug to be marketed. Since then, there has been greater appreciation of the more complex nature of receptor binding affinities, and aripiprazole can also be classified as a medication with significant 5HT2A-antagonism, and with still other additional secondary binding characteristics which may be clinically important in individual patients. Other events since the product launch of aripiprazole have been the emergence of second-generation antipsychotics as mood stabilizers, with almost all of them, including aripiprazole, being approved by regulatory authorities for the indication of bipolar mania. This review will briefly examine the most current information on mechanism of action of aripiprazole and discuss in more detail the clinical trial evidence supporting its use in both schizophrenia and bipolar disorder. Reviewing studies has been made somewhat easier by the recent introduction of online clinical trial registries that provide information not always found in the published scientific literature; however, details are not consistently available for all

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registered studies. The efficacy and safety of aripiprazole is discussed separately for both schizophrenia and bipolar disorder, followed by a discussion on optimal dosing and general utility of this agent. In general, less information is available on the use of aripiprazole for bipolar disorder than it is for schizophrenia. Greater weight is placed on peer-reviewed publications, together with actual data provided from disclosures found in online registries. References to posters and abstracts, which are typically not subject to peer review, are made sparingly.

Mechanism of action

Aripiprazole is a quinolinone derivative with demonstrated partial agonist activity at D2 receptors (Burris et al 2002). This observation has led to the concept of aripiprazole being a "dopamine receptor stabilizer", decreasing dopamine activity when it is abnormally high, and increasing it when abnormally low. This has been used to explain aripiprazole's efficacy in reducing the symptoms of schizophrenia without causing much in the way of extrapyramidal effects. However, antagonist activity at serotonin 5HT2A receptors (Shapiro et al 2003) is also important in explaining the putative mechanism of action, and brings aripiprazole in line with the other second-generation antipsychotics as all being essentially serotonin-dopamine antagonists. Other receptor-binding activities, including at 5HT1A and D3 receptors, may become important in some patients at some doses, and reflect the complexities of attempting to predict specific therapeutic benefits from specific binding characteristics of antipsychotics, which may or may not be relevant to the individual being treated (Stahl 2002; Shayegan and Stahl 2004). Further discussion of receptor-binding characteristics for aripiprazole, including animal studies, as well as reviews of its chemistry and pharmacokinetic properties, can be found elsewhere (McGavin and Goa 2002; Harrison and Perry 2004; Bhati 2005; Fleishhacker 2005).

Partial agonism at the D2 receptor may have unintended consequences for some patients already being treated with another antipsychotic. DeQuardo (2004) described 2 cases of exacerbation of paranoia and anger in patients with schizophrenia when aripiprazole (at 15 mg/day and 10 mg/day) was added to stable doses of haloperidol decanoate and high doses of olanzapine (60 mg/day). The agonist effects of aripiprazole on dopamine neurotransmission in the limbic areas was proffered as an explanation for the exacerbation of psychosis, and the author recommended starting aripiprazole at lower doses (5 mg/day) when adding it to the regimens of chronically ill, tenuously controlled psychotic patients. A similar report was published of a patient with schizoaffective disorder experiencing a worsening of symptoms when aripiprazole 15 and then 30 mg/day was added to a regimen of quetiapine 800 mg/day (Reeves and Mack 2004). Worsening of psychosis was also reported in a case series of 4 patients with schizophrenia or schizoaffective disorder, where aripiprazole (15–30 mg/day) was added to second-generation antipsychotics (Ramaswamy et al 2004). Barnas et al (2005) report on a patient with schizoaffective disorder who experienced psychotic and manic symptoms, necessitating hospital admission, when her antipsychotic was switched from perphenazine to aripiprazole. Worsening psychotic symptoms with aripiprazole in two patients with chronic schizophrenia was also reported by Glick et al (2006). One of the patients described in that report initially did well with aripiprazole but then had an exacerbation requiring a change to another antipsychotic. The second patient experienced a worsening of psychotic symptoms upon the initiation of aripiprazole. A number of possible explanations were provided, including that this could be ascribed to the natural course of the disease. Other explanations included an increased dopamine effect owing to the addition of aripiprazole in patients who have been subject to chronic dopamine blockade, as well as the displacement of lower binding affinity antipsychotics by aripiprazole at the dopamine receptor, and pharmacokinetic interaction among multiple medications.

Efficacy

Schizophrenia (Table 1)

Almost all of the controlled clinical trials of aripiprazole have been conducted by its manufacturer. Some are published as peer-reviewed journal articles, some as articles in supplements to journals, and yet others as poster presentations at scientific meetings. Recently, additional information has become available on the world wide web in the form of clinical trial registries. Although the latter are not peer reviewed, they do contain substantially more information than the abstracts encountered at scientific meetings. Below are descriptions of the studies done that illuminate the efficacy of aripiprazole in the treatment of schizophrenia.

The first published report of a randomized clinical trial examining aripiprazole's efficacy in treating schizophrenia

was a double-blind 4-week study conducted in the USA comparing two doses of aripiprazole (15 mg/day and 30 mg/day) vs placebo, with haloperidol 10 mg/day acting as an active control (Kane et al 2002). A total of 414 patients with acute schizophrenia were randomized to each of the four groups, and 60% completed the entire 4 weeks (55% for placebo, 67% for aripiprazole 15 mg/day, 59% for aripiprazole 30 mg/day, and 60% for haloperidol). Patients

Table 1 Aripiprazole for the treatment of schizophrenia, randomized clinical trials

Reference	Duration (weeks)	N	Aripiprazole, dose, N	Comparators, dose, N	Comments
Marder et al 2003	4	103	5–30 mg (N=34)	Placebo (N=35), haloperidol 5–20 mg (N=34)	Phase II study reported in a pooled safety analysis
Marder et al 2003	4	307	2 mg (n=59), 10 mg (N=60), 30 mg (N=61)	Placebo (N=64), haloperidol 10 mg (N=63)	Phase II study reported in a pooled safety analysis
Marder et al 2003	4	305	20 mg (N=101), 30 mg (N=101)	Placebo (N=103)	Phase III study reported in a pooled safety analysis
Kane et al 2002	4	414	15 mg (N=102), 30 mg (N=102)	Placebo (N=106), haloperidol 10 mg (N=104)	Haloperidol did not separate from placebo on the responder analysis; included in a pooled safety analysis (Marder et al 2003)
Potkin et al 2003	4	404	20 mg (N=101), 30 mg (N=101)	Placebo (N=103), risperidone 6mg (N=99)	
Bristol-Myers Squibb 2001 (CN138-001)	6	420	10 mg (N=103), 15 mg (N=103), 20 mg (N=97)	Placebo (N=107)	Conversion to open-label aripiprazole treatment at the end of week 3 for non-responders; included in a pooled safety analysis (Marder et al 2003)
Bristol-Myers Squibb 2005 (CN138-003)	6 (and 140)	703	15–30 mg (N=355)	Olanzapine 10–20 mg (N=348)	Not yet published
Saha et al 2002	15 days	40	30 mg (N=12), 45 mg (N=7), 60 mg (N=7), 75 mg (N=7), 90 mg (N=7)	None	Safety and tolerability study; available as a poster only
Bristol-Myers Squibb 2004a (CN138-002) and McQuade et al 2004	28–52	317	15 –30 mg (N=156)	Olanzapine 10–20 mg (N=161)	Safety and tolerability study; originally designed with a 12-week acute phase followed by a long-term extension phase, protocol amendment revised the endpoints to Week 26 (and 52) instead of Week 12
Bristol-Myers Squibb 2004b (CN138-032) and Kane et al 2003	6	300	15–30 mg (N=154)	Perphenazine 8–64 mg (N=146)	Not yet published; treatment failure to olanzapine or risperidone prospectively determined
Pigott et al 2003	26	310	15 mg (N=155)	Placebo (N=155)	
Kasper et al 2003	52	1294	30 mg (N=861)	Haloperidol 10 mg (N=433)	
Bristol-Myers Squibb 2004c (CN138-047)	52 (extension)	214	15–30 mg (N=104)	Olanzapine 10–20 mg (N=110)	Open-label extension to Pigott et al (2003)
Bristol-Myers Squibb 2004d (CN138-087) and Tandon et al 2006	8-24	1599	10–30 mg (N=1295)	Other antipsychotic (N=304)	Open-label "Broad Effectiveness Trial with Aripiprazole"

randomized to aripiprazole or haloperidol experienced reductions in their total Positive and Negative Syndrome Scale scores (PANSS) superior to that seen for placebo, but a responder analysis demonstrated no difference between haloperidol and placebo in terms of a 30% reduction in total PANSS from baseline. In terms of PANSS subscales, aripiprazole 15 mg/day and haloperidol, but not aripiprazole 30 mg/day, significantly improved the PANSS negative score compared with placebo. All three active treatment groups demonstrated superiority over placebo on the PANSS positive score.

The second key registration study was again 4 weeks in duration, but this time the active comparator was risperidone 6mg/day (Potkin et al 2003). A total of 404 patients with acute schizophrenia in the USA were randomized to one of two doses of aripiprazole (20 mg/day or 30 mg/day), placebo, or risperidone. As with the Kane et al study (2002), 60% completed the entire 4 weeks (50% for placebo, 60% for aripiprazole 20 mg/day, 66% for aripiprazole 30 mg/day, and 63% for risperidone). Patients randomized to aripiprazole or risperidone experienced reductions on the primary efficacy measures (PANSS total, PANSS positive, and Clinical Global Impressions-Severity [CGI-S]) superior to that seen for placebo. All three active treatment groups demonstrated superiority over placebo in the responder analysis (as defined by a 30% or more decrease from the baseline PANSS total score or a score of very much improved or much improved on the CGI-Improvement (CGI-I) scale).

Available on the Bristol-Myers Squibb Clinical Trials Disclosure Database (URL: http://ctr.bms.com/ctd/), are the results of study CN138-001, a Phase III multicenter randomized, double-blind, placebo-controlled study of 3 fixed doses of aripiprazole conducted in the USA and Canada with patients with acutely relapsed schizophrenia (Bristol-Myers Squibb 2001). A total of 420 patients were randomized to receive 1 of 3 doses of aripiprazole (10 mg/day, 15 mg/day, and 20 mg/day) or placebo for 6 weeks. Patients not responding by the end of Week 3, 4, or 5 were discontinued from blinded treatment and were offered open-label treatment with aripiprazole 20 mg/day for the remaining weeks. All participants were offered participation in a double-blind extension phase for an additional 46–134 weeks (where they were randomized to receive either 10–15 mg/day or 20–30 mg/day of aripiprazole). There was a large attrition rate, and only 34% of the randomized patients completed 6 weeks of double-blind treatment. All three active treatment groups showed statistically significantly greater improvement than placebo for the PANSS total, PANSS positive and negative, CGI-S, and CGI-I scores, and all active treatment groups were statistically significantly superior to placebo in the PANSS responder analysis (30% reduction).

These three short-term studies of aripiprazole (Kane et al 2002; Potkin et al 2003; Bristol-Myers Squibb 2001) established the acute efficacy of aripiprazole with demonstrated superiority over placebo. However, in the two studies that employed active controls, the protocols were not designed to directly compare aripiprazole with haloperidol (Kane et al 2002) or risperidone (Potkin et al 2003) per se. Thus additional double-blind studies are needed, particularly directly comparing aripiprazole with other second-generation antipsychotics. A multi-center, international, double-blind, randomized, comparative study of aripiprazole and olanzapine among patients with acute schizophrenia has recently been reported in the Bristol-Myers-Squibb Clinical Trials Disclosure Database as study CN138-003 (Bristol-Myers Squibb 2005). A total of 703 patients who were having an acute relapse were randomized to receive either olanzapine 10–20 mg/day or aripiprazole 10–20 mg/day for 6 weeks. At the conclusion of the 6 weeks, patients who demonstrated improvement were continued into an extended double-blind treatment period lasting up to 140 weeks. In all, 71% of the randomized patients in the aripiprazole group and 78% of the randomized patients in the olanzapine group completed the entire 6 weeks. Of the randomized subjects, 65% of the aripiprazole patients and 74% of the olanzapine patients entered the extension phase. At Week 6, patients in both treatment groups improved on their mean change from baseline PANSS total score, but the improvement was greater for olanzapine (–27.36) than aripiprazole (–22.15) (a minimum PANSS of 60 was required for randomization but the report does not provide the mean baseline PANSS scores for the participants). A prespecified criterion was set for noninferiority of aripiprazole, which was not met. At Week 6 statistically significant differences in favor of the olanzapine group were also observed in the mean change from baseline in the CGI-S, PANSS positive, PANSS negative, and Montgomery Asberg Depression Rating Scale (MADRS) scores. In addition, statistically significant differences in favor of the olanzapine group were demonstrated in the mean CGI-I and the percentage of responders at Week 6. When examining observed cases only, rather than last observation carried forward, statistically significant differences in favor of the olanzapine group were demonstrated in the mean change

from baseline on only the PANSS total, CGI-S, and MADRS. The mean change from baseline to Week 6 in the PANSS positive, PANSS negative, and the Week 6 mean CGI-I and the percentage of responders were not statistically significant among the observed cases.

The above trials represent evidence for acute treatment. However, patients with schizophrenia typically require treatment with antipsychotics indefinitely. Moreover, long-term treatment is expected to result in further amelioration of not only positive symptoms, but also negative symptoms and cognitive symptoms (DeQuardo and Tandon 1998). Long-term treatment of schizophrenia with aripiprazole was established in 2 pivotal reports (Kasper et al 2003; Pigott et al 2003). In the first, a 26-week randomized, double-blind, multicenter study conducted internationally, 310 patients with stable schizophrenia were randomized to aripiprazole 15 mg/day or placebo (Pigott et al 2003). Stability was defined as no significant improvement or worsening of symptoms within the past 3 months, but patients enrolled in the study were still experiencing significant symptomatology as evidenced by a mean baseline PANSS of 82 (a score of at least 60 was needed for study entry). Patients also had to score no more than 4 (moderately ill) on the CGI-S and not be hostile or uncooperative based on the pertinent PANSS items being less than or equal to 4 (moderately ill). Overall, 37% completed the entire 26-week study (46% for aripiprazole and 29% for placebo). The time to relapse following randomization was significantly longer for aripiprazole than placebo. Aripiprazole was significantly superior to placebo from baseline to endpoint in PANSS total, PANSS positive, and CGI-S scores. A 52-week open-label extension was offered to patients (study CN138-047) (Bristol-Myers Squibb 2004c) where a total of 214 patients were randomized to either aripiprazole 15–30 mg/day or olanzapine 10–20 mg/day. A total of 69% completed the open-label extension (63% for aripiprazole and 74% for olanzapine). There were no statistically significant differences on the efficacy measures between the two treatment arms.

The second report of a double-blind long-term clinical trial of aripiprazole in patients with schizophrenia was a pooled analysis of two similar protocols (Kasper et al 2003). A total of 1294 patients in acute relapse who had previously responded to antipsychotic medications were randomized to receive either aripiprazole 30 mg/day or haloperidol 10 mg/day for 52 weeks. Overall, 38% of patients completed the entire 52-week study (43% for aripiprazole and 30% for haloperidol). Aripiprazole demonstrated significantly greater improvements for PANSS negative and MADRS scores than haloperidol. The time to discontinuation for any reason was significantly greater with aripiprazole than with haloperidol.

Thus, two published double-blind studies have demonstrated the long-term efficacy of aripiprazole, one (Pigott et al 2003) showing superiority to placebo, the other (Kasper et al 2003) showing superiority to haloperidol. Long-term, double-blind studies comparing aripiprazole with other second-generation antipsychotics are needed. The multi-center, international, double-blind, randomized, comparative study of aripiprazole and olanzapine (Bristol-Myers Squibb 2005) allowed for an extended double-blind treatment period lasting up to 140 weeks for patients who had a response in the first 6 weeks, as defined by a CGI-I of 3 or less, or a PANSS total improvement of 20% or greater from baseline. Data for up to Week 52 are available. Attrition was high, with 61% of the randomized patients in the aripiprazole group and 53% of the randomized patients in the olanzapine group discontinuing the study before Week 52. The discontinuation rate over time was statistically significantly higher in the aripiprazole group than in the olanzapine group for the period up to Week 52. For the PANSS total, statistical differences favoring olanzapine were seen in the last observation carried forward dataset, while no significant differences were observed in the observed cases analyses. The efficacy scores for patients who were not eligible to continue in the extension phase because of only partial response at Week 6 were also carried forward to Week 52, and contributed to the differences in efficacy observed between the two treatment groups after Week 6 on the last observation carried forward analysis.

Additional information on the comparative efficacy of aripiprazole and olanzapine is available from a safety and tolerability study, part of which has been published in a journal supplement (McQuade et al 2004), and part can be found in the Bristol-Myers Squibb Clinical Trials Disclosure Database as study CN138-002 (Bristol-Myers Squibb 2004a). In this international study, 317 patients with schizophrenia in acute relapse and who required hospitalization were randomized to receive either aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day) for 52 weeks. Patients were required to have at least a score of 60 on the PANSS total. Patients remained hospitalized until at least the Day 4 visit. Patients with a CGI-I of 1–3 could be discharged, based on clinical judgment. Patients with a CGI-I score of at least 4 (no improvement or

worsening) at Week 6 were discontinued from the study. Patients unable to tolerate the lowest dose of study medication and patients who required rehospitalization for worsening schizophrenia were also discontinued from the study. At the end of 12 weeks of study therapy, patients with a CGI-I of 1–3 or a at least 20% decrease from baseline in PANSS total were given the option to continue in the study on blinded treatment for 40 additional weeks. A protocol amendment changed the primary and secondary endpoints from Week 12 to Week 26; the reason provided was that long-term weight gain data could be captured. Attrition rates were high. Only 28% of the 317 randomized patients completed 26 weeks of the protocol, with 16% completing 52 weeks (87% of the aripiprazole patients and 81% of the olanzapine patients discontinued on or before Week 52). The responder analysis showed that aripiprazole and olanzapine had similar improvement at Week 52 using the observed cases data set, 20/21 (95%) of aripiprazole patients meeting the definition of response vs 29/30 (97%) of olanzapine patients. Aripiprazole and olanzapine had similar improvement on the PANSS total, PANSS positive, PANSS negative, CGI-S, and CGI-I scores. The treatment groups also had similar results on the MADRS. The major shortcoming of this trial in terms of assessing efficacy is that no information was provided on comparative efficacy at Week 12, before enrollment into the extension phase for responders. In addition, comparison of the completers focuses on patients who have done relatively well and differences between treatment arms would have been difficult to detect, particularly with the small numbers of patients for which data were available.

Patients with treatment-refractory schizophrenia form a subgroup that is usually excluded from registration studies. Few controlled studies are available (Citrome et al 2002), and meta-analyses have generally supported clozapine as the gold standard for these difficult-to-treat patients (Wahlbeck et al 1999; Chakos et al 2001). Available on the Bristol-Myers Squibb Clinical Trials Disclosure Database as study CN138-032 (Bristol-Myers Squibb 2004b) and presented as a poster (Kane et al 2003), is a Phase III randomized double-blind clinical trial conducted in the US and Canada that tested the hypothesis that aripiprazole is superior to perphenazine in treatment-resistant schizophrenia. Patients were considered treatment resistant if they had not experienced satisfactory symptom relief despite at least 2 periods of treatment during the past 2 years, each lasting at least 6 weeks, with adequate doses of antipsychotic medication agents (of which at least 1 was a first-generation antipsychotic). Patients were required to have a PANSS total of at least 75 and a score of at least 4 (moderately ill) on at least 2 of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behavior, or delusions; and a score of at least 4 (moderately ill) on the CGI-S. Eligible patients underwent a 4- to 6-week, prospective, open-label treatment trial with either olanzapine (10–20 mg/day) or risperidone (2–8 mg/day), depending on their previous treatment history, to confirm treatment-resistance. Patients were required to receive at least 15 mg olanzapine or 6 mg risperidone per day for a minimum of 3 weeks during this phase in order to be considered for continuation in the study. Patients with improvement as defined by a reduction in the PANSS total score of at least 20% and a CGI-S of 1–3 (normal to mildly ill) at any time during this phase were discontinued from the study. Patients who failed to show this improvement were randomized to receive flexible doses of either perphenazine (8–64 mg/day) or aripiprazole (15–30 mg/day) for 6 weeks. At the completion of the double-blind phase, patients were provided the option to receive open-label aripiprazole for an additional 98–109 weeks. A total of 416 patients were enrolled into the phase confirming treatment resistance to olanzapine or risperidone, and a total of 300 patients categorized as treatment resistant were subsequently randomized to aripiprazole or perphenazine. Overall, 75% of patients completed the double-blind phase (71% for aripiprazole and 79% for perphenazine). Overall, 27% and 25% of patients responded to aripiprazole and perphenazine, respectively, based on a CGI-I of 1–2, or at least a 30% decrease in PANSS total. There was no significant difference between the perphenazine and aripiprazole groups in the primary efficacy measure, mean change from baseline to Week 6 in the PANSS total (improvements of 9.8 for aripiprazole and 10.5 for perphenazine). Neither were there any statistically significant differences on the secondary efficacy measures, PANSS positive and negative scores, CGI-S, CGI-I, percentage of categorical responders, and the rate of discontinuation owing to lack of efficacy.

Thus efficacy of aripiprazole for the treatment of acute schizophrenia was demonstrated in short-term clinical trials comparing it with placebo. Superiority to haloperidol was demonstrated in a longer-term trial, but the efficacy of aripiprazole appears inferior to that of olanzapine in short- and long-term trials. Among treatment-resistant patients, aripiprazole demonstrated similar improvement to that seen with perphenazine. Tolerability will be discussed later.

Bipolar disorder (Table 2)

The first published pivotal trial of aripiprazole for the treatment of bipolar disorder was a multi-center study conducted in the US and reported by Keck et al (2003). A total of 262 patients with bipolar I disorder, manic or mixed episode, who were experiencing an acute relapse that required hospitalization, were randomized to either aripiprazole 30 mg/day or placebo for 3 weeks. Subjects were required to have a minimum Young Mania Rating Scale (YMRS) score of at least 20. Patients not responding at the end of Week 2 were discontinued from double-blind treatment and offered open-label treatment with aripiprazole. Overall, 31% of the patients completed the study (42% for aripiprazole and 21% for placebo). Although the starting dose of aripiprazole was 30 mg/day, the dose could be reduced to 15 mg/day for tolerability if required. The majority of patients (86%) randomized to aripiprazole remained on the 30 mg/day dose for the entire study. The mean dose of aripiprazole at endpoint was 27.9 mg/day. Patients receiving aripiprazole demonstrated significant improvement on the YMRS compared with placebo. Response, defined as a 50% reduction in the YMRS, was greater for aripiprazole than placebo at all time points, with endpoint response rates of 40% and 19% respectively. Other measures corroborated the advantage of aripiprazole vs placebo, including measures of severity of illness.

A second positive controlled 3-week trial of aripiprazole compared with placebo for acute manic or mixed episodes in patients with bipolar I disorder was recently reported by Sachs et al (2006). The design was similar to the study reported by Keck et al (2003), and was also conducted in the US. A total of 272 hospitalized patients were randomized to receive either aripiprazole 30 mg/day or placebo. Overall, 53% of the patients completed the study (55% for aripiprazole and 52% for placebo), thus the attrition rate was substantially lower than in the Keck et al (2003) study. The majority of patients (85%) randomized to aripiprazole remained on the 30 mg/day dose for the entire study. The mean dose of aripiprazole at endpoint was 27.7 mg/day. Patients receiving aripiprazole demonstrated significant improvement on the YMRS compared with placebo. Response, defined as a 50% reduction in the YMRS, was greater for aripiprazole than placebo at all time points, with endpoint response rates of 53% and 32% respectively. Other measures supported the advantage of aripiprazole vs placebo, including measures of severity of illness.

Not published and never publicly presented, was a third double-blind, randomized clinical trial of aripiprazole in patients with bipolar I mania. Some information on this trial was included in a press release from the manufacturer (Bristol-Myers Squibb 2003b). In this study, aripiprazole did not show a statistically significant separation from placebo. The press release noted that aripiprazole demonstrated symptom improvement comparable with that of the other studies, but that there was a high placebo response rate (approximately 40%). Further details are not available, other than patients in the study were randomized to receive aripiprazole 15 or 30 mg/day or placebo (Lyseng-Williamson and Perry 2004).

Table 2 Aripiprazole for the treatment of bipolar mania, randomized double-blind clinical trials

Reference	Duration (weeks)	N	Aripiprazole, dose, N	Comparators, dose, N	Comments
Keck et al 2003	3	262	30 mg (N=130)	Placebo (N=132)	
Vieta et al 2005	12	347	15–30 mg (N=175)	Haloperidol 10–15mg (N=172)	Benztropine or other anticholinergics were not permitted
Bristol-Myers Squibb 2003b	?	?	15 mg (N=?), 30 mg (N=?)	Placebo (N=?)	Response to aripiprazole did not separate from placebo; data not published, nor posted in the Bristol-Myers Squibb Clinical Trials Disclosure Database
Sachs et al 2006	3	272	30 mg (N=137)	Placebo (N=135)	
Bristol-Myers Squibb 2003a (CN138-010), and Keck et al 2006	26	161	15–30 mg (N=77)	Placebo (N=83)	

Thus, data from 2 out of 3 short-term double-blind trials support the use of aripiprazole for the treatment of acute manic or mixed episodes. These trials did not address what the utility of aripiprazole was after the first 3 weeks of treatment. Moreover, no active comparator (or active control) was employed. Additional information comes from an international, 12-week, double-blind, randomized clinical trial comparing aripiprazole with haloperidol (Vieta et al 2005). In contrast to the 3-week studies involving placebo, patients in this trial could participate regardless of whether they were inpatients or outpatients, as long as they were experiencing an acute manic or mixed episode and had a YMRS score of at least 20. Patients were randomized to receive aripiprazole 15 mg/day or haloperidol 10 mg/day. There were 2 phases to the trial: phase 1 included the first 3 weeks and represented an acute phase of treatment, and phase 2 which consisted of Weeks 4–12. At the end of Week 1 or 2, patients showing a poor response to therapy had the option to have their dose of aripiprazole increased to 30 mg/day or haloperidol to 15 mg/day. Patients intolerant of the higher dose could return to their initial lower dose. Anticholinergic medications were not permitted at any time during the trial. Patients unable to tolerate 15 mg/day of aripiprazole or 10 mg/day of haloperidol at any time, and patients who remained significantly symptomatic at the end of Week 3 were discontinued from the trial. Thus, Weeks 4–12 could be viewed as an evaluation of maintenance of response. A total of 347 patients were randomized to aripiprazole or haloperidol. At Week 3, the average daily dose of aripiprazole was 22.6 mg/day and haloperidol 11.6 mg/day. At Week 12, average daily doses were 21.6 mg and 11.1 mg respectively. Overall, 66% of the patients completed the first 3 weeks of treatment (77% for aripiprazole and 55% for haloperidol). Overall, 40% of the patients completed the entire 12 weeks of the study (51% for aripiprazole and 29% for haloperidol). Response rate to treatment showed no statistically significant differences between aripiprazole and haloperidol at 3 weeks, but a difference emerged at 12 weeks (response rate was 50% for aripiprazole and 28% for haloperidol). Both aripiprazole and haloperidol treatment resulted in marked improvement in the YMRS from baseline to Week 12 (mean reductions of 19.9 for aripiprazole and 18.2 for haloperidol, from mean baselines of 31.1 and 31.5, respectively). Among completers the reductions in YMRS were larger, 29.0 for aripiprazole and 27.4 for haloperidol. Among completers, more patients on aripiprazole were in remission (defined as YMRS less than 12) at Week 12 than patients receiving haloperidol, with remission rates of 50% and 27% respectively. Both treatments demonstrated similar reductions on measures of disease severity. Of additional interest were measures of depression. Reductions in depressive symptoms observed with aripiprazole were larger than with haloperidol and this was statistically significant at Week 3, but not at Week 12. Significantly more patients on aripiprazole than with haloperidol demonstrated a 50% or greater decrease on the MADRS at Weeks 3 and 12.

Recently published (Keck et al 2006), and available in the Bristol-Myers Squibb Clinical Trials Disclosure Database as study CN138-010 (Bristol-Myers Squibb 2003a), is a 26-week, double-blind, placebo-controlled, international study comparing aripiprazole with placebo for maintaining the stability of patients with bipolar I disorder. The primary outcome measure was time to relapse (time to discontinuation owing to lack of efficacy). Patients were considered as relapsing if they were hospitalized for manic or depressive symptoms, or required changes in their medications. Patients who had recently completed a 3-week acute mania study of aripiprazole were eligible to enter, but patients who had recently received inpatient treatment for a manic or mixed episode and had not participated in a 3-week aripiprazole study were also eligible. Patients entered the study as inpatients or as outpatients. The study had 3 phases: a stabilization phase lasting 6–18 weeks, a maintenance phase lasting 26 weeks (the main phase of the study), and an optional extension phase lasting up to 74 additional weeks. During the stabilization phase, patients received open-label treatment with aripiprazole at a starting dose of 30 mg/day, with a possible dose reduction to 15 mg/day in case tolerability issues emerged. The mean dose of aripiprazole during the stabilization phase was 25.3 mg/day. Patients would continue in this phase until their bipolar symptoms were considered stable, defined by a YMRS of less than or equal to 10, and a MADRS of less than or equal to 13 for 4 consecutive visits over a minimum of 6 weeks. The mean duration of the stabilization phase was 89 days (median 85 days). Once stable, patients were randomized to receive either aripiprazole or placebo. The dose of aripiprazole remained at the same amount as they had been receiving during open-label treatment, either 15 mg/day or 30 mg/day, and could be changed at any time during the study, as necessary, based on efficacy and tolerability. The mean dose of aripiprazole in the double-blind (maintenance) phase was 24.3 mg/day. Patients who completed 26 weeks of the maintenance phase without a relapse were initially invited to continue on their current double-blind study drug

treatment in an extension phase for up to an additional 74 weeks. However, enrollment in the study was stopped after 45 patients had relapsed, and patients were allowed to continue in the study only until the last randomized patient had completed the maintenance phase, at which time the study was terminated. A total of 567 patients entered the stabilization phase (59% from a previous aripiprazole acute mania trial). Overall, 37% of patients completed the stabilization phase. A total of 196 patients were randomized to either aripiprazole or placebo, but because of operational problems, only 161 patients could be included in the analysis of the primary outcome measure. Attrition was high. Overall, 42% completed the study (50% for aripiprazole and 34% for placebo). The time to relapse of symptoms was significantly longer with aripiprazole treatment than with placebo. In addition, significantly fewer aripiprazole-treated patients experienced relapse (manic, mixed, or depressive symptoms) than those receiving placebo (25% for aripiprazole and 43% for placebo). Aripiprazole was found to be superior to placebo in delaying the time to a manic relapse but no difference between the treatment groups was observed in time to a depressive relapse. This was consistent with the finding of lower YMRS scores and lack of differences in the MADRS when comparing aripiprazole with placebo.

Thus, efficacy in the short-term management of acute manic or mixed episodes was established in comparison with placebo, and a 12-week controlled trial revealed comparable efficacy of aripiprazole with haloperidol after 3 weeks of acute treatment, but superiority after 12 weeks. A 26-week relapse prevention study demonstrated that aripiprazole was superior to placebo in preventing relapse into mania, but not depression.

Safety and tolerability

Schizophrenia

Marder et al (2003) reviewed safety and tolerability in a pooled analysis of 5 of the short-term (4- to 6-week), placebo-controlled trials of aripiprazole. Of the 1509 randomized patients, 932 received aripiprazole (dose range 2–30 mg/day), 416 placebo, and 201 haloperidol. Two of the studies were Phase II, 3 were Phase III. The discontinuation rate owing to adverse events with aripiprazole treatment was similar to that for haloperidol and placebo (7%, 8%, and 10% respectively). The most frequent adverse events leading to discontinuation from placebo, aripiprazole, or haloperidol included: psychosis (6.1%, 3.6%, and 1.5% respectively), agitation (1.9%, 0.6%, and 0% respectively), anxiety (0.2%, 0.5%, and 0% respectively), and akathisia (0%, 0.6%, and 1.5% respectively). A dose–response relationship with aripiprazole for treatment-emergent adverse events was not found, with the exception of somnolence, but the overall incidence of somnolence was comparable with placebo (11.0% vs 8.0%). In addition, the somnolence with aripiprazole decreased over time: 7.7% during Days 1–7 vs 2.2% from Day 29 onwards. This was similar with placebo (Days 1–7, 4.8% vs Day 29 onwards, 1.6%). Overall, the adverse event rates with aripiprazole were comparable with placebo, and lower than haloperidol for akathisia, extrapyramidal syndrome, and somnolence. There were no significant differences between aripiprazole and placebo on Simpson–Angus Scale scores, no dose-dependent effects on Barnes Akathisia scores, and significant reductions in Abnormal Involuntary Movement Scale scores from baseline vs placebo. Mean weight change with aripiprazole (+0.71 kg) and haloperidol (+0.56 kg) were similar. QTc prolongation was not observed. Serum prolactin increased with haloperidol, but not aripiprazole. The low propensity of aripiprazole to be associated with extrapyramidal effects was also demonstrated over a longer period of time. In the 52-week study by Kasper et al (2003) aripiprazole had significantly lower scores on all extrapyramidal symptoms assessments than haloperidol. When comparing safety and tolerability of aripiprazole with another first-generation antipsychotic, perphenazine, among patients with treatment-resistant schizophrenia (Bristol-Myers Squibb 2004b), the incidence of elevated prolactin was substantially higher in the perphenazine group compared with the aripiprazole group. In addition, aripiprazole was less likely than perphenazine to be associated with extrapyramidal side-effects.

In the 26-week study by Pigott et al (2003) comparing aripiprazole with placebo, aripiprazole was well tolerated, with no evidence of marked sedation, hyperprolactinemia, or prolonged QTc. Extrapyramidal symptoms were comparable in the aripiprazole and placebo groups. Modest mean weight loss at endpoint was evident in both groups. In the 52-week, open-label, randomized extension (Bristol-Myers Squibb 2004c), more patients receiving olanzapine than patients receiving aripiprazole experienced significant weight gain (at least 7% increase in weight) at all measured time points, as well as greater mean change and mean percentage change from baseline in weight. Although there were no statistically significant differences between the two

treatment groups for changes in extrapyramidal rating scales, patients in the olanzapine group had a higher incidence of extrapyramidal-related adverse events compared with aripiprazole (18% vs 10%). Prolactin elevation was more frequently encountered for patients receiving olanzapine than aripiprazole. Potentially clinically significant levels of prolactin (above the upper limit of normal) were recorded more frequently for patients in the olanzapine group than for the aripiprazole group. Although there were no statistically significant differences between the two groups in terms of fasting glucose, patients receiving olanzapine were more likely to have elevations in cholesterol and triglycerides. In another comparison of olanzapine and aripiprazole, this time double-blind and specifically designed to compare safety and tolerability (Bristol-Myers Squibb 2004a; McQuade et al 2004), by Week 26, 37% of olanzapine-treated patients had experienced significant weight gain compared with 14% of aripiprazole-treated patients. Statistically significant differences in mean weight change were observed between treatments beginning at Week 1 and sustained throughout the study. Changes in fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were significantly different in the two treatment groups, with worsening of the lipid profile among patients treated with olanzapine. In the observed cases data set analysis, 6/21 (29%) patients in the aripiprazole group and 17/31 (55%) patients in the olanzapine group had a significant weight gain at Week 52. Patients treated with aripiprazole had a mean weight change of –1.43 kg and a mean percent change of –0.1% at Week 52. Patients treated with olanzapine had a mean weight increase of +5.55 kg and a mean percent increase of 6.9% at Week 52.

Long-term safety data are also available from a large, randomized, efficacy study of aripiprazole and olanzapine (Bristol-Myers Squibb 2005). More patients in the aripiprazole group (19.2%) than in the olanzapine group (14.9%) discontinued before Week 52 for reasons of adverse event. The adverse events with rates of at least 10% in at least 1 treatment group were weight gain (21% for olanzapine and 6% for aripiprazole), insomnia (21% for olanzapine and 27% for aripiprazole), headache (8% for olanzapine and 15% for aripiprazole), anxiety (13% for olanzapine and 16% for aripiprazole), and somnolence (11% for olanzapine and 4% for aripiprazole). The major differences between olanzapine and aripiprazole in terms of tolerability were related to weight gain and metabolic effects. At Week 26, a significantly higher proportion of patients in the olanzapine group experienced clinically significant (at least 7%) weight gain than in the aripiprazole group (31.5% and 12.5% in the olanzapine and aripiprazole groups, respectively). This difference in weight gain was also observed in all cohorts stratified by patients' baseline body mass index (BMI). Patients receiving olanzapine had increases in mean total cholesterol, LDL-cholesterol, and triglycerides levels, whereas they decreased in patients randomized to aripiprazole at all time points to Week 52. The differences in mean change from baseline to Week 52 in these levels for patients treated with olanzapine and aripiprazole were statistically significant in favor of aripiprazole. Serum glucose levels and glycosylated hemoglobin levels decreased in both treatment groups. Patients randomized to aripiprazole experienced mean reductions from baseline in serum prolactin that were significantly greater than patients in the olanzapine treatment group. There was no significant difference between treatment groups for tardive dyskinesia at Week 52. Although the differences were small, statistically significant treatment differences were seen in favor of olanzapine on extrapyramidal rating scales, including the Barnes Akathisia Global Clinical Assessment at Week 52. In contrast to the open-label randomized extension study reported earlier (Bristol-Myers Squibb 2004c), in this trial, more extrapyramidal-related adverse events occurred in the aripiprazole group than in the olanzapine group. These extrapyramidal adverse events rarely led to discontinuation from the 52-week study (1% of olanzapine-treated patients and 2% of aripiprazole-treated patients). Nevertheless, more aripiprazole patients received concomitant anticholinergic medications (16%) than olanzapine patients (9%).

Information on the comparative safety of aripiprazole and risperidone is limited to the single short-term study by Potkin et al (2003). Overall, both 20 mg/day and 30 mg/day of aripiprazole were well tolerated. A total of 44 (11%) of 403 patients in the safety sample were discontinued from the study owing to adverse events (17% for placebo, 8% for risperidone, 11% for aripiprazole 20 mg/day, and 8% for aripiprazole 30 mg/day). The number of patients with treatment-related adverse events was similar as well. The most common adverse events were headache (27%, 31%, 28%, and 35% respectively), agitation (23%, 22%, 27%, and 29% respectively), insomnia (22%, 20%, 31%, and 22% respectively), anxiety (18%, 18%, 21%, and 20% respectively), akathisia (9%, 14%, 20%, and 20% respectively), somnolence (11%, 14%, 4%, and 19% respectively), and dyspepsia (21%, 12%, 16%, and 16%

respectively). Measures of extrapyramidal symptoms, including akathisia, revealed no statistically significant differences between active treatments and placebo, and the use of benztropine was comparable across the three active treatment groups. Clinically significant weight gain (at least 7%) was observed in 2% of patients given placebo, 11% for risperidone, 13% for aripiprazole 15mg/day, and 9% for aripiprazole 30 mg/day, and statistical significance compared with placebo on this measure was observed for all three active arms. Serum prolactin levels decreased in patients assigned to aripiprazole (both groups), increased minimally in the placebo group (0.1 ng/mL), and increased by a mean of 47.9 ng/mL in the risperidone group (the latter statistically significantly greater than the change observed with placebo). Categorical change in prolactin levels, defined as the percentage of patients with an increase in serum prolactin level above the upper limit of the reference range of 23 ng/mL was 10.3% for placebo, 4.1% for aripiprazole 20 mg/day, 3.3% for aripiprazole 30 mg/day, and 90.5% for risperidone. Mean changes in QTc interval were –2.18 milliseconds for placebo, 0.97 milliseconds for aripiprazole 20 mg/day, –2.35 milliseconds for aripiprazole 30 mg/day, and 6.31 milliseconds for risperidone. Although no patients receiving aripiprazole or placebo had a QTc of 450 milliseconds or more and a 10% or greater increase from baseline, this occurred in 3% of those receiving risperidone. There were no clinical differences in vital signs or laboratory abnormalities (except for prolactin) among the four groups.

Because clinical trials include a relatively small number of patients, and furthermore have stringent inclusion and exclusion criteria that usually exclude patients with comorbid conditions, information on some of the more uncommon adverse events come from isolated case reports. For example, neuroleptic malignant syndrome in association with aripiprazole was reported in a case report of an antipsychotic-naïve person with a history of methamphetamine and cannabis abuse (Srephichit et al 2006), in a case of a person with depression also treated with fluoxetine (Duggal and Kithas 2005), in a 17-year-old adolescent with schizophrenia who had already been exposed to other second-generation antipsychotics (Spalding et al 2004), and in a 42-year-old male with a 28-year history of schizophrenia (Chakraborty and Johnston 2004). Dew et al (2005) report on a 13-year-old girl with established neuroleptic malignant syndrome after receiving olanzapine and haloperidol. After a protracted course where she received treatment with dantrolene, bromocriptine, and electroconvulsive therapy, she was given aripiprazole to alleviate her symptoms of agitation and potential psychosis, with resultant worsening of tachycardia and rise in serum creatinine kinase level.

Galactorrhea has been reported in a 29-year-old woman with schizoaffective disorder when aripiprazole was started and haloperidol dose was decreased (Ruffatti et al 2005), and in a 36-year-old woman with schizophreniform disorder who had received trifluoperazine 3 years previously without incident (Mendhekar and Andrade 2005). On the other hand, aripiprazole was successfully used to resolve antipsychotic induced symptomatic hyperprolactinemia, including galactorrhea, in female patients with schizophrenia age 19–40 years (Lee et al 2006).

In summary, aripiprazole was well tolerated among the patients with schizophrenia who participated in the acute and long-term studies. Aripiprazole was associated with lower rates of elevated prolactin than risperidone, haloperidol, perphenazine, and olanzapine, and consistently lower rates of extrapyramidal effects than haloperidol or perphenazine. Weight and metabolic adverse effects were observed more often with olanzapine than with aripiprazole. Aripiprazole had a more favorable profile than risperidone for QTc prolongation. Rare occurrences of neuroleptic malignant syndrome have been reported, as well as case reports of galactorrhea, although the latter has also been reported to resolve with the use of aripiprazole.

Bipolar disorder

In the clinical trials comparing aripiprazole with placebo among patients with bipolar disorder, aripiprazole appeared to be well tolerated. In the study reported by Keck et al (2003), there were no differences in discontinuation rates between aripiprazole and placebo attributable to adverse events. However, gastrointestinal (GI) adverse events including nausea, dyspepsia, vomiting, and constipation, were more common with aripiprazole than with placebo (23%, 22%, 16%, and 13% vs 10%, 10%, 5%, and 6%, respectively). Somnolence was reported in 20% of patients receiving aripiprazole and in 5% of patients on placebo. Anxiety was reported in 18% of aripiprazole patients and in 10% of patients randomized to placebo. Akathisia was reported in 11% of the patients receiving aripiprazole, and in 3% of patients assigned to placebo. Changes from baseline on the scales measuring extrapyramidal effects, including akathisia, were small, but statistically greater among those receiving aripiprazole than placebo. No problems were identified for bodyweight, prolactin elevation, QTc

prolongation, vital signs, or laboratory analyses. Similar tolerability outcomes were seen in the study report from Sachs et al (2006); however, the incidence of treatment-emergent akathisia was higher at 17.6% for aripiprazole and 4.5% for placebo. A significant difference was observed between the two groups at endpoint in mean change from baseline in akathisia rating scores, but this was small in magnitude. At endpoint, there was no significant difference between aripiprazole and placebo in the number of patients with clinically significant akathisia rating scale scores. The spontaneous reports of akathisia among the patients receiving aripiprazole were generally mild to moderate in severity and primarily occurred early in treatment, and rarely led to discontinuations or reduction in dose. The report by Sachs et al (2006) also described the time course of somnolence, nausea, dyspepsia, and constipation as being limited mainly to the first week of treatment.

In the 26-week maintenance phase of the double-blind study comparing aripiprazole with placebo (Bristol-Myers Squibb 2003a; Keck et al 2006), there were no adverse events in the aripiprazole group with at least a 10% incidence and twice the incidence of the placebo group. Treatment-emergent adverse events reported by patients receiving aripiprazole at an incidence of at least 5% and twice the incidence of placebo were tremor, akathisia, vaginitis, and pain in the extremities. The analysis of movement disorder scales demonstrated no significant differences between aripiprazole and placebo. There was a statistically significant difference in favor of aripiprazole in mean change from randomization to endpoint in prolactin level. Although the incidence of elevated creatine phosphokinase (CPK) was slightly higher in patients receiving aripiprazole (6.76% vs 4.11%) and there were 5 patients receiving aripiprazole with potentially clinically significant elevated CPK levels, none of these patients had associated symptoms consistent with neuroleptic malignant syndrome. There were no problems identified regarding QTc, vital signs, weight, or physical examinations.

In the comparison of aripiprazole and haloperidol (Vieta et al 2005), the most frequent treatment-emergent adverse events were extrapyramidal syndrome, akathisia, and depression for haloperidol (35.5%, 23.1%, and 14.2% respectively), and insomnia, akathisia, and depression for aripiprazole (13.7%, 11.4%, and 11.4% respectively). It should be emphasized that anticholinergic agents were not permitted for symptomatic or prophylactic treatment of extrapyramidal symptoms during the study, contributing to the rates of extrapyramidal syndrome reported in the study, and contributing to the high discontinuation rate for patients receiving haloperidol. Other differences between aripiprazole and haloperidol include serum prolactin elevations (mean decrease for aripiprazole but a mean increase for haloperidol). No differences were seen for mean change in bodyweight, except when the data were stratified by initial BMI, resulting in the observation that patients in the high baseline BMI category lost an average of 0.86 kg on aripiprazole, but gained an average of 0.41 kg on haloperidol. There were no differences observed in QTc, vital signs, or laboratory measures.

In summary, aripiprazole appears to be well tolerated in patients with bipolar disorder. Although akathisia and GI complaints emerged at the start of treatment in some patients, GI symptoms in particular may be time-limited in many instances. Haloperidol was associated with greater rates of extrapyramidal symptoms than aripiprazole. There is a lack of comparative safety data with other second-generation antipsychotics among patients with bipolar disorder.

Optimal dose

Dosing in schizophrenia

The recommended starting and target dose of aripiprazole for patients with schizophrenia, as approved by regulatory agencies, is 10 or 15 mg/day, taken once a day without regard to meals (Bristol-Myers Squibb 2006). The product labeling provides the following additional information: "…doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state". Because these recommendations are the result of registration studies that were used in evaluating aripiprazole for commercialization, these recommendations may not always apply in actual clinical practice. The patients enrolled in such trials may not be representative of the general clinical population in need of treatment – patients in registration trials need to provide informed consent, be free of alcohol or substance abuse, be in good physical health, be able to tolerate a washout off medication, be able to be treated with a monotherapy, and not be treatment resistant (Citrome and Volavka 2002; Citrome et al 2005b, 2005c). Dosing of antipsychotics in more challenging clinical populations may be quite different than the dosing used in registration trials. For example, among patients (80% diagnosed with schizophrenia or schizoaffective disorder) hospitalized within facilities operated by the New York State Office of

Mental Health in the second quarter of 2003, the average dose of aripiprazole was 22.4 mg/day (standard deviation 11.0). Over half of the patients receiving aripiprazole were receiving doses in excess of 15 mg/day (Citrome et al 2005c), and 11.4% were receiving doses in excess of the product label maximum of 30 mg/day (unpublished).

Although the registration studies of aripiprazole have failed to demonstrate a dose-response relationship for efficacy, and there are no fixed-dose studies of aripiprazole examining efficacy of doses in excess of 30 mg/day, there have been other studies that may help in evaluating dose. The Bristol-Myers Squibb Clinical Trials Disclosure Database and a report in press (Tandon et al 2006) describe a study (CN138-087) that randomized (in a 4:1 ratio) 1599 patients with schizophrenia to receive either aripiprazole open label within the range of 10–30 mg/day or "standard of care" treatment consisting of a single new antipsychotic medication based on the investigator's judgment and dosed according to the package insert (Bristol-Myers Squibb 2004d). The study was conducted in a general psychiatric practice environment at 292 different sites and each patient could participate up to 24 weeks or until aripiprazole became commercially available (whichever was sooner). The study had very broad inclusion criteria: diagnosis of schizophrenia or schizoaffective disorder for whom an alteration in medication was clinically reasonable or initiation of antipsychotic treatment was required. A total of 1295 patients were randomized to aripiprazole, and 65% completed 8 weeks of treatment. The mean dose of aripiprazole at endpoint was 20 mg/day; at Week 8, 47% who completed the study were receiving 15 mg/day and 29% were receiving 30 mg/day. Thus, results from a broad effectiveness trial indicate that many completers required dosing of aripiprazole that was higher than what was recommended in the product label, and in line with data from an in-patient public psychiatric hospital setting. Systematic studies on dose of aripiprazole greater than 30 mg/day are not available with the exception of one report presented as a poster (Saha et al 2002). The safety, tolerability, and pharmacokinetics of escalating doses of aripiprazole from 30 to 90 mg/day were evaluated among 40 patients with stable schizophrenia or schizoaffective disorder. Patients were randomized to 30 mg/day (N=12), 45 mg/day (N=7), 60 mg/day (N=7), 75 mg/day (N=7), and 90 mg/day (N=7) for 15 days of treatment at that dose. Linear pharmacokinetics was observed. Incidence of adverse events was similar across dose groups, with the exception of akathisia and tachycardia which appeared higher at 90 mg/day (frequency of 57% and 71% respectively). Patients in all dose groups maintained a stable symptom profile. Thus, dosing above 30 mg/day appears generally tolerable. More information is required regarding efficacy, but higher doses may be helpful for some patients. A recent case report describes the use of aripiprazole 75 mg/day in a 21-year-old woman with paranoid schizophrenia (Duggal and Mendhekar 2006) where symptomatic improvement occurred when the dose was gradually increased in several steps. On the other hand, reports of worsening psychosis when aripiprazole is added to the antipsychotic regimen for some patients is of concern (DeQuardo 2004; Ramaswamy et al 2004; Reeves and Mack 2004), and careful titration upwards may be the best course of action to minimize this risk. When aripiprazole was first introduced in 2002, the smallest dosage strength available was 10 mg. Since then, a 5-mg tablet and an oral solution (1 mg/mL) have become available (Bristol-Myers Squibb 2006), allowing for a smaller starting dose when tolerability is a concern. Double-blind, randomized, fixed-dosed studies of adequate length are desirable to address the utility of higher dosing for patients with schizophrenia.

Dosing in bipolar disorder

The recommended dose of aripiprazole for patients with bipolar disorder, as approved by regulatory agencies, is 30 mg/day (Bristol-Myers Squibb, 2006). The product labeling further adds: "approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability". The recommended starting dose of 30 mg/day stems directly from the registration trials where this strategy was employed. Little information is known about the relative merits of higher or lower dosing in terms of efficacy in controlling manic symptoms. Complicating dose selection for aripiprazole is the observation that for many patients with bipolar disorder, combination treatment with lithium or an anticonvulsant is commonly prescribed. Although not approved by regulatory agencies for combination with lithium or valproate, pharmacokinetic studies of aripiprazole in combination with lithium or valproate do not indicate any need for dose adjustment based on concerns about alterations in plasma levels of aripiprazole or its main active metabolite (Citrome et al 2005d).

Is aripiprazole worth using?

Schizophrenia

Efficacy needs drive antipsychotic selection, tempered by safety and tolerability issues. Attempts to place aripiprazole

into clinical perspective have included a Cochrane Collaboration review (El-Sayeh and Morganti 2004). All randomized clinical trials available at the time comparing aripiprazole with placebo and/or first- or second-generation antipsychotics for schizophrenia were analyzed. Absent from the analyses were some data that have only recently become available, such as what has been posted on the Bristol-Myers Squibb Clinical Trials Disclosure Database (for example, study CN138-003). Thus the Cochrane meta-analysis did not include all information now available on comparisons of olanzapine and aripiprazole. Nevertheless, the meta-analysis did calculate clinically relevant measures such as relative risk (RR), 95% confidence intervals (CI), and numbers needed to treat (NNT) (Kraemer and Kupfer 2006). Data were presented for 4125 people in 10 randomized studies. Compared with placebo, aripiprazole significantly decreased relapse in both the short and medium term (n=300, 1 study, RR 0.66 CI 0.53– 0.81, NNT 5 CI 4–8). Compared with first-generation antipsychotics, there were no significant benefits for aripiprazole for global state, mental state, quality of life, or leaving the study early. When compared with olanzapine and risperidone, aripiprazole was no better or worse on outcomes of global state and leaving the study early. On safety and tolerability, the authors reported that aripiprazole might decrease prolactin levels below that expected from placebo (n=305, 1 RCT, RR 0.32 CI 0.13–0.81, NNT 14 CI 11–50). Both aripiprazole and first-generation antipsychotics demonstrated similar rates of adverse effects, including akathisia (RR 0.44 CI 0.17–1.12) and general extrapyramidal effects (RR 0.53 CI 0.18–1.53). Aripiprazole did, however, cause more insomnia than perphenazine (n=300, 1 study, RR 2.23 CI 1.57–3.18, NNH 4 CI 3–9) and less need for antiparkinson drugs than 10–20 mg/day of haloperidol (n=1854, 4 studies, RR 0.45 CI 0.33–0.60, NNT 4 CI 3–5). The rates of adverse effects were also similar between aripiprazole and second-generation antipsychotics (olanzapine and risperidone), with the exception of less elevation of prolactin (n=301, 1 study, RR 0.04 CI 0.02–0.08, NNT 2) and less prolongation of the mean QTc (30 mg/day) (n=200, 1 study, weighted mean difference –10.0, CI –16.99 to –3.01) compared with risperidone. The reviewers concluded that aripiprazole may be effective for the treatment of schizophrenia, but it is not much different from first-generation antipsychotics and second-generation antipsychotics in treatment response, efficacy, or tolerability, and the authors recommended additional pragmatic short-, medium-, and long-term randomized, controlled trials to determine its position in everyday clinical practice. Another critical review was not so charitable (Prescrire 2005), stating that "in practice, there is no sound reason to prescribe aripiprazole: its advantages and disadvantages are not clearly established, and we already have several treatment alternatives".

The above reviews, which were clearly independent of influence by the manufacturer of aripiprazole, address the difficulty in seeing advantages for new antipsychotics that, on the whole, are not so different from their predecessors when compared among groups of patients. What is missing is consideration of the common clinical observation that response, both in terms of efficacy and tolerability, to a specific antipsychotic, varies greatly from individual to individual and that practitioners need to be able to craft individually tailored medication regimens. New information about aripiprazole, not included in the Cochrane meta-analysis, accentuates this issue. Namely, a large study (CN138-003) demonstrated overall differences between olanzapine and aripiprazole (Bristol-Myers Squibb 2005) – olanzapine was superior to aripiprazole in efficacy but not as well tolerated in terms of metabolic issues. In most cases, this is not a therapeutic dilemma per se – not all patients receiving olanzapine develop significant metabolic problems, and many patients respond quite well to aripiprazole. In a consensus panel report supported by the manufacturer of aripiprazole (Travis et al 2005), aripiprazole was noted to be at least as effective as other antipsychotics in the treatment of patients with schizophrenia aged 18–65 years, and that its favorable side-effect profile may make it an appealing choice for patients with first onset of psychosis or patients who have experienced problems with side-effects while receiving other antipsychotic medications. Thus, aripiprazole can be considered a first-line treatment. It appears that aripiprazole may be a useful option when switching patients from a poorly tolerated antipsychotic, but it is unclear how useful it would be for patients who require a switch because of poor efficacy with another antipsychotic. It is anticipated that the Phase 3 results of the Clinical Antipsychotic Trials of Intervention Effectiveness (Lieberman et al 2005) will provide additional information on switching to open-label aripiprazole from a variety of blinded antipsychotics or from open-label clozapine. The issue of using aripiprazole as an augmenting agent to other antipsychotics has not yet been reported in a randomized, double-blind, clinical trial, although case reports exist of combinations of olanzapine or clozapine with aripiprazole resulting in increased efficacy or

tolerability (Duggal 2004; Lim et al 2004; Ziegenbein et al 2005; Clarke et al 2006; Henderson et al 2006). However, addition of aripiprazole to first- and second-generation antipsychotics has also been associated with exacerbation of symptoms (DeQuardo 2004; Reeves and Mack 2004; Ramaswamy et al 2004; Barnas et al 2005; Glick et al 2006). Thus, at the present time, caution should be exercised when using aripiprazole in combination with other antipsychotics.

Bipolar disorder

Second-generation antipsychotics have emerged as "mood stabilizers", rivaling classic agents such as lithium and certain anticonvulsants such as valproate and carbamazepine (Citrome et al 2005a). The second-generation antipsychotics, as monotherapies, can successfully treat bipolar mania, even in the absence of psychotic symptoms, as demonstrated by many clinical trials. Safety and tolerability issues can drive treatment selection, particularly for the bipolar patient who appears to respond well to a wide array of agents. For example, because of the potential teratogenic effects of valproate and lithium, second-generation antipsychotics are perhaps more desirable alternatives for female patients who are actively seeking to bear children. The occurrence of adverse effects on one agent, for example weight gain with olanzapine, may prompt a switch to another agent. Aripiprazole appears to have a low propensity for weight gain, a favorable metabolic profile, and no association with hyperprolactinemia. Clinical trials that directly compare aripiprazole with other second-generation antipsychotics, as well as lithium, valproate, and carbamazepine, would provide additional perspectives on the utility of aripiprazole for the treatment of bipolar disorder, including issues such as suitability as a first-choice treatment.

Conclusions

Aripiprazole is approved by regulatory agencies for the treatment of schizophrenia and bipolar disorder. Among the second-generation antipsychotics it has the unique property of being a dopamine partial agonist; however, aripiprazole shares with the rest of this antipsychotic class substantial antagonist activity at the serotonin 5HT2A receptor. Efficacy in the short- and long-term treatment of schizophrenia has been established in placebo-controlled trials, and aripiprazole appears superior in efficacy to haloperidol (long term), similar to perphenazine and risperidone, and inferior to olanzapine. The tolerability profile of aripiprazole among patients with schizophrenia appears superior to haloperidol, perphenazine, risperidone, and olanzapine. Aripiprazole has a low propensity for weight gain, a favorable metabolic profile, and no association with hyperprolactinemia. Information on the efficacy of aripiprazole in the treatment of bipolar disorder is more limited, particularly in terms of comparisons with other second-generation antipsychotics for which there are no reported trials. Compared with placebo, aripiprazole is efficacious in treating acute manic or mixed episodes associated with bipolar I disorder, is superior to placebo for preventing relapse to mania (but not depression), and superior to haloperidol in maintenance of response. Tolerability of aripiprazole among patients with bipolar disorder is generally good; however, some patients can develop treatment-emergent akathisia and GI symptoms, with the latter usually resolving with time in many instances. Dosing of aripiprazole for schizophrenia is unclear, with product labeling suggesting a starting and target dose of 10 or 15 mg/day but broader-based clinical trials and clinical practice demonstrate general use of aripiprazole at higher doses. However, lower dosing may be important in individualizing therapy to improve tolerability, with lower starting doses becoming more important when adding to, or switching from, another antipsychotic. Dosing of aripiprazole for treatment of manic or mixed episodes was set at 30 mg/day in the registration trials for that indication, and there are no data currently available for review from studies that used multiple fixed doses that would address the question if different dose regimens would be any more or less efficacious than 30 mg/day. The overall favorable tolerability profile of aripiprazole makes it an attractive option for the treatment of both schizophrenia and bipolar disorder.

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