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# Aripiprazole: Review of its Pharmacology and Therapeutic Use in Psychiatric Disorders

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***The discovery of antipsychotic medications has revolutionized the treatment of schizophrenia and other psychotic disorders. However, side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), electrocardiogram (ECG) changes, weight gain, and metabolic disturbances indicate the continued need to develop new agents. The introduction of atypical drugs such as clozapine, risperidone, olanzapine, quetiapine, and ziprasidone has widened our choices. This article provides an overview of the pharmacology, efficacy, and techniques for the clinical use of aripiprazole, a novel agent with a unique pharmacological profile.***

**Keywords** Schizophrenia; Bipolar disorder; Aripiprazole; Antipsychotics.

## *INTRODUCTION*

Psychiatric practice was revolutionized following the introduction of antipsychotic agents ($D_2$ receptor antagonists) in the 1950s, beginning with chlorpromazine. Additional classes of the dopamine receptor blocking agents were subsequently developed, but side effects such as akathisia, acute dystonic reactions, drug-induced Parkinsonism, and hyperprolactinemia continue to be limiting factors (1–4). The appearance of tardive dyskinesia, for which there is no established treatment, has been an important source of concern in the use of antipsychotic agents (5,6). The "atypical" compounds developed in the mid 1990s combined $D_2$ blockade with antagonism of the serotonin 5-$HT_{2A}$ receptors and produced significantly less extrapyramidal symptoms (EPS) and hyperprolactinemia (except for risperidone) than the conventional antipsychotics. The prototype atypical agent, clozapine, is highly efficacious, but has the potential to cause serious side effects such as agranulocytosis and seizures (7,8). Clozapine and the other atypical agents are associated with different side-effect liabilities that include weight gain, somnolence, and possibly metabolic disturbances. Further, despite their established efficacy, up to 20% to 30% of patients treated with atypical antipsychotics remain treatment-refractory. Despite studies showing a differential cognitive effect of the atypical agents, the cognition does not improve sufficiently to put these patients back in gainful competitive employment (9). Hence, there is an ongoing need to develop new compounds with a side-effect profile that is "patient friendly" yet not compromising efficacy so as to further the field.

The use of dopamine $D_2$ partial agonists has been explored for the treatment of schizophrenia. The partial $D_2$ agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine (-3-PPP; preclamol) is the most studied (10,11). Preclamol is a phenylpiperidine derivate and a dopamine congener. Preclamol in a dosage of 300 mg twice daily (n = 10 subjects) decreased positive as well as negative symptoms of schizophrenia compared with placebo, but the actions were not sustained for longer than 1 week possibly because of tachyphylaxis (10).

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Aripiprazole is a novel agent with a unique pharmacologic profile that acts as a potent partial agonist at dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and an antagonist at 5-HT2A receptors (12–15).

This article will review the pharmacological profile and clinical trials of aripiprazole and present guidelines for prescribing aripiprazole. This medication was developed by Otsuka Pharmaceutical Company of Tokyo, Japan and is being distributed and marketed by Bristol-Meyers Squibb Co in the United States under the brand name Abilify™. Aripiprazole has been approved by the FDA for the treatment of schizophrenia in the United States.

## *1. OVERVIEW OF PHARMACODYNAMIC PROPERTIES*

### *Effects on Central Neurotransmitter Systems*

Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxyl]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}C_{l2}N_3O_2$. Aripiprazole exhibits a high affinity for dopamine $D_2$ and $D_3$, serotonin 5-$HT_{1A}$, and 5-$HT_{2A}$ receptors (Ki values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine $D_4$, serotonin 5-$HT_{2C}$ and 5-$HT_7$, alpha1-adrenergic and histamine $H_1$ receptors (Ki values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (Ki = 98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC50> 1000 nM) (15) (Table I).

Aripiprazole has been shown to be a partial agonist at the $D_2$ receptors (12,17). As a partial agonist, aripiprazole modulates dopamine according to the level of endogenous dopamine receptor activation (18). This translates into displacement of dopamine in hyperdopaminergic states resulting in decreased activation of the $D_2$ receptors. In hypodopaminergic states, when little or no dopamine is present, the binding of aripiprazole results in increased activation of $D_2$ receptors. Aripiprazole is also a partial agonist of the serotonin 5-$HT_{1A}$ receptors and an antagonist at the serotonin 5-$HT_{2A}$ receptor. Aripiprazole occupies 95% of the striatal $D_2$ –like receptors yet the incidence of EPS (greater than 80% occupancy results in EPS) in the trials was no higher than placebo. The most likely explanation for this finding is aripiprazole's weak partial agonism at the $D_2$-like receptors (19). Thus, the proposed mechanism of action is through partial agonist activity at the $D_2$ and 5-$HT_{1A}$ receptors and antagonist activity at 5-$HT_{2A}$ receptors. It is important to note that despite having greater affinity for the dopamine receptor aripiprazole still meets the criteria for an atypical agent as characterized by low EPS and miminmal if any prolactin elevation.

### *Supportive Pre-clinical Data*

Data from in vivo animal studies suggest that aripiprazole exhibits $D_2$ antagonistic properties in animal models simulating hyperdopaminergic states. It results in blockade of stereotypy induced by apomorphine (20). This drug inhibits increased 3,4-dihydroxyphenylalanine (DOPA) accumulation in reserpine-treated rats, which reflects $D_2$ agonist activity (20). The partial agonist activity at the 5-$HT_{1A}$ and antagonist activity at the 5-$HT_{2A}$ receptors is supported by binding and activity assays using recombinant human receptors (13). Aripiprazole exhibited potent, partial agonist activity at cloned human $D_2$ receptors using two independent biochemical assays of $D_2$ receptor-mediated signal transduction (21). These data support previous in vitro and in vivo evidence that aripiprazole is a partial agonist at $D_2$ receptors. In contrast, haloperidol, clozapine, risperidone, olanzapine, ziprasidone, did not display any agonist activity in either of these same assays. These data further demonstrate that aripiprazole is distinct from all other antipsychotic drugs, which are antagonists at $D_2$ receptors. In addition, aripiprazole displayed a potent, partial agonist profile at cloned human and rat hippocampal 5-$HT_{1A}$ receptors (21).

### *Neuroendocrinological Effects*

The effect of aripiprazole on plasma prolactin has been measured after oral administration in both short-term and long-term studies. In a meta-analysis conducted by Carson and colleagues (2002) on the effect of aripiprazole on serum prolactin (random samples), data from 1343 patients enrolled in 4- to 6-week double-blind controlled studies were analyzed (22). In these short-term studies, serum

**Table I** Comparative Receptor Affinity of Aripiprazole and Other Antipsychotic Agents (affinity Ki [nM]) (15)

| Receptor | Aripiprazole | Haloperidol | Risperidone | Olanzapine | Quetiapine | Ziprasidone | Clozapine |
|---|---|---|---|---|---|---|---|
| $D_2$ | 0.34 | 1.4 | 2.2 | 20 | 180 | 3.1 | 130 |
| 5-$HT_{2A}$ | 3.4 | 120 | 0.29 | 3.3 | 220 | 0.39 | 8.9 |
| 5-$HT_{2C}$ | 15 | 4700 | 10 | 10 | 1400 | 0.72 | 17 |
| 5-$HT_{1A}$ | 1.7 | 3600 | 210 | 2100 | 230 | 2.5 | 140 |
| $a_1$ | 57 | 4.7 | 1.4 | 54 | 15 | 13 | 4.0 |
| $H_1$ | 61 | 440 | 19 | 2.8 | 8.7 | 47 | 1.8 |
| $M_1$ | > 10,000 | 1600 | 2800 | 4.7 | 100 | 5100 | 1.8 |

prolactin significantly decreased from baseline by 50% in patients treated with aripiprazole irrespective of dose. A likely cause may be the discontinuation of conventional antipsychotics, which elevate prolactin. In addition other atypical antipsychotics such as risperidone can cause prolactin elevation. In contrast, serum prolactin increased from baseline in patients treated with haloperidol or risperidone by 125% and 607%, respectively. Among patients who had normal prolactin levels at baseline, the incidence of increases in prolactin levels to greater than the upper limit of normal was 2% in the aripiprazole group, 7% in the placebo group, 54% in the haloperidol group, and 89% in the risperidone group. In patients with a baseline prolactin level greater than the upper limit of normal, 89% of the aripiprazole group had a decrease in prolactin to the normal range compared with 55% in the placebo group, 13% in the haloperidol group, and none in the risperidone group (22).

Carson and associates also analyzed data from two long-term studies. In a 26-week double-blind, placebo-controlled trial, aripiprazole ($n = 115$) and placebo ($n = 122$) groups were both associated with decreases in prolactin levels, there being no statistically significant differences between aripiprazole and the placebo group ($p < 0.07$ vs. placebo). In a 52-week double blind, haloperidol-controlled study, mean prolactin levels significantly ($p < 0.01$) decreased from baseline in the aripiprazole group ($n = 96$). In contrast, the haloperidol group ($n = 46$) demonstrated a significant ($p < 0.001$) increase in prolactin levels (22). Thus hyperprolactinemia is a nonissue with aripiprazole, which is a distinct advantage as hyperprolactinemia related side effects would not be expected with this agent.

## 2. PHARMACOKINETIC PROPERTIES

### Absorption and Plasma Concentrations

Aripiprazole, the parent drug, is responsible primarily for the pharmacological effects; its major metabolite, dehydro-aripiprazole (active), is responsible to a lesser extent. Aripiprazole is well absorbed with peak plasma concentrations occurring within 3 to 5 hours. The absolute bioavailability of the tablet formulation is 87%. The drug can be administered with or without food (15). Due to high plasma protein binding concomitant use of aripiprazole with drugs such as warfarin would need monitoring of PT, PTT, and INR.

### Tissue Distribution and Accumulation

At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to plasma proteins, primarily albumin. The steady state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution (15).

### Pregnancy and Lactation

Aripiprazole crosses the placenta, however there are currently no well-controlled trials in pregnant females. In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. In the case of rat studies, decreased fetal weight, undesended testes, and delayed skeletal ossification were observed at 30 mg/kg which is 10 times the maximum recommended human dosage. A low incidence of diaphragmatic hernia was also seen. In the case of pregnant rats an increase in stillbirths and decreases in pup weight and survival were noted at 30 mg/kg. In the case of pregnant rabbits increased abortions were seen at 100 mg/kg of aripiprazole. Aripiprazole was excreted in the milk of rats during lactation. Infants of those taking the drug should not be breast-fed. There are no reported clinical studies in humans as yet. The FDA lists Aripiprazole as pregnancy category C.

### Metabolism and Excretion

Aripiprazole is metabolized mainly by three biotransformation pathways: dehydration, hydroxylation, and N-dealkylation. The cytochrome $P_{450}$ system enzymes CYP3A4 and CYP2D6 are responsible for dehydration and hydroxylation of the drug. N-dealkylation is catalyzed by CYP3A4. At steady state, dehydro-aripiprazole, the active metabolite, is responsible for 40% of aripiprazole AUC in the plasma (15). Genetic polymorphism determines the rate of hydroxylation of the drug to its active metabolite. Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are considered slow metabolizers, whereas the rest are extensive metabolizers. Slow metabolizers have 60% higher exposure to the total active moieties from a given dose of the aripiprazole. Coadministration of aripiprazole with inhibitors of CYP2D6 such as quinidine can raise aripiprazole levels 112% (15). A dosage adjustment is needed in this group of patients.

### Special Populations

No dosage adjustment is suggested based on a patient's age, gender, race, smoking status, or hepatic or renal function (15,23). In the case of the geriatric and pediatric populations starting low and titrating slowly is recommended.

## *3. THERAPEUTIC USE IN SCHIZOPHRENIA*

### *Open-Label Studies*

In a 26-week, open-label study the neurocognitive benefits, safety, and tolerability of aripiprazole and olanzapine were compared in outpatients with stable schizophrenia (24). Patients were randomized to daily treatment with aripiprazole 30 mg (n = 128) or olanzapine 15 mg (n = 127) and assessed at baseline, week 8, and week 26. Clinical improvement was not significantly different between the two groups. Both aripiprazole and olanzapine produced a significant improvement at week 8 in general cognitive functioning ($p < 0.05$) with a trend toward improvement at week 26 ($p < 0.10$). Aripiprazole significantly improved secondary verbal memory at weeks 8 and 26 (both $p < 0.001$).

### *Comparisons with Placebo and Other Antipsychotics*

Aripiprazole was evaluated in the treatment of schizophrenia in five short-term, 4- to 6-week, placebo-controlled phase II and phase III studies. These trials included patients with schizophrenia and schizoaffective disorder (N = 1648). An active control arm using risperidone was included in one study (22) and haloperidol was included in three studies (23–25). A total of 932 patients received aripiprazole, 416 received placebo, 201 received haloperidol, and 99 received risperidone. In all trials, comparisons were performed between the active treatments and placebo (Table II).

#### *Trial 1*

Kane and colleagues (2002) compared two dosages of aripiprazole (15 and 30 mg/day) with haloperidol (10 mg/day) and placebo in 414 patients with a primary diagnosis of schizophrenia or schizoaffective disorder (27). In this 4-week, multicenter, double-blind trial, efficacy measures included the Positive and Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS negative, PANSS-derived Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI)-Severity of illness, and CGI-Improvement. All three treatment arms showed statistically significant ($p < 0.05$) improvement from baseline on the PANSS positive, PANSS total, PANSS-derived BPRS, CGI-S, and CGI-I scores compared with placebo. Aripiprazole 15 mg/day and haloperidol 10 mg/day also significantly improved PANSS negative scores compared with placebo. Aripiprazole was well tolerated with no evidence of serum prolactin elevations or a marked potential for EPS, weight gain, or QTc prolongation.

#### *Trial 2*

In another fixed-dose, double-blind trial, two doses of aripiprazole (20 and 30 mg/day) were compared with risperidone (6 mg/day) or placebo (25). A total of 404 patients with an acute exacerbation of schizophrenia or schizoaffective disorder were randomized to treatment for 4 weeks. All three active treatment arms fared significantly better than placebo as determined by change from baseline in PANSS positive, PANSS negative, PANSS total, CGI-S, and CGI-I scores ($p < 0.05$). No statistically significant differences were observed between the placebo groups and either of the aripiprazole groups in serum prolactin levels, worsening of EPS, or mean change from baseline in QTc interval.

#### *Trial 3*

This 6-week, phase III, double-blind study (N = 420) compared three fixed dosages of aripiprazole (10, 15, and 20 mg/day) with placebo (29). All three dosages were noted to be statistically significantly superior to placebo in the PANSS total, PANSS negative, and PANSS positive scores ($p = 0.05$).

#### *Trial 4*

This was a 4-week, phase II, double-blind, placebo-controlled study (N=103) comparing aripiprazole in a range of 5 to 30 mg/day or haloperidol 5 mg to 20 mg to placebo, haloperidol was superior to placebo in the BPRS and responder analysis based on CGI severity score (28). The aripiprazole group was significantly different from the placebo group, showing improvement only in the responder analysis based CGI-severity score.

#### *Trial 5*

In another 4-week, phase II, multicenter, double-blind trial, 307 patients were randomized to one of five treatment groups: aripiprazole 2, 10, or 30 mg, haloperidol 10 mg, or placebo (26). Among the three aripiprazole doses, only the 30 mg demonstrated statistically significant effects on all clinical assessments including PANSS total, PANSS positive, PANSS negative, CGI-S, CGI-I, and BRPS. The 30 mg aripiprazole dose was clearly more effective than the 2 and 10 mg doses, and demonstrated early onset of efficacy from week 1 on all efficacy variables including the PANSS negative subscale. All aripiprazole doses were well tolerated. With aripiprazole treatment, the incidence of EPS was comparable to placebo and serum prolactin levels did not increase.

**Table II** Efficacy of Aripiprazole in Schizophrenia and Acute Mania

| Study | Patient population | Duration (weeks) | N | Treatment and daily dose (n) |
|---|---|---|---|---|
| Daniel et al., 2000 | Acute schizophrenia | 4 | 307 | Placebo (64)<br>Aripiprazole 2 mg (59)<br>Aripiprazole 10 mg (60)<br>Aripiprazole 30 mg (61)<br>Haloperidol 10 mg (63) |
| Petrie et al., 1997 | Acute schizophrenia | 4 | 103 | Placebo<br>Aripiprazole titrated from 5 to 30 mg over 13 days<br>Haloperidol titrated from 5 to 20 mg over 7 days |
| Kane et al., 2002 | Acute schizophrenia and schizoaffective disorder | 4 | 414 | Placebo (106)<br>Aripiprazole 15 mg (102)<br>Aripiprazole 30 mg (102)<br>Haloperidol 10 mg (104) |
| Potkin et al., 2003 | Acute schizophrenia and schizoaffective disorder | 4 | 404 | Placebo (103)<br>Aripiprazole 20 mg (101)<br>Aripiprazole 30 mg (101)<br>Risperidone 6 mg (99) |
| Lieberman et al., 2002 | Acute schizophrenia | 6 | 420 | Placebo<br>Aripiprazole 10 mg<br>Aripiprazole 15 mg<br>Aripiprazole 20 mg |
| Carson et al., 2002 | Stable chronic schizophrenia | 26 | 310 | Placebo (155)<br>Aripiprazole 15 mg (155) |
| Kujawa et al., 2002 | Schizophrenia with acute exacerbation | 52 | 1294 | Aripiprazole 30 mg (861)<br>Haloperidol 10 mg (433) |
| Cornblatt et al., 2002 | Schizophrenia and schizoaffective disorder | 26 | 255 | Aripiprazole 30 mg (128)<br>Olanzapine 15 mg (127) |
| Kane et al., 2003 | Treatment-resistant schizophrenia | 6 | 300 | Aripiprazole 15 or 30 mg (154)<br>Perphenazine 8–64 mg (146) |
| Jody et al., 2002a | Bipolar 1 disorder, manic or mixed episode | 3 | 262 | Placebo (132)<br>Aripiprazole 30 mg (130) |
| Bourin et al., 2003 | Bipolar 1 disorder, manic or mixed episode | 12 | 347 | Aripiprazole 15–30 mg (175)<br>Haloperidol 10–15 mg (172) |

### *Long-term Efficacy of Aripiprazole*

A multicenter, randomized, double-blind, placebo-controlled study was conducted in 310 patients with stable chronic schizophrenia (30). Patients were randomized to aripiprazole 15 mg/day or placebo and treated for 26 weeks. Efficacy measures included time to relapse, number of relapses, and PANSS total score. The majority of the patients (those randomized to aripiprazole or placebo) were on perphenazine (N = 75), haloperidol (N = 66), risperidone (N = 33), olanzapine (N = 29), thioridazine (N = 20), Chlorpromazine (N = 9), clozapine (N = 8), terazine (N = 9), methotrimeperazine (N = 8), zuclopenthixol (N = 7), sulpiride (N = 5), quetiapine (N = 4) and other agents with numbers less than five subjects. Compared with placebo, aripiprazole treatment effectively increased time to relapse and resulted in fewer patients relapsing at endpoint (34% of aripiprazole group vs. 57% of placebo group; $p < 0.001$). Patients treated with aripiprazole had significantly greater improvement in PANSS total and positive subscale scores and showed continuing stability on the PANSS negative subscale score. Aripiprazole was generally well tolerated with a side-effect profile comparable to placebo. Compared with placebo, there were no elevations in plasma prolactin levels and no clinically important cardiac risks in the aripiprazole group. In addition, weight gain and EPS adverse effects associated with aripiprazole were comparable to placebo.

Aripiprazole was compared with haloperidol in a multicenter, randomized, double-blind study conducted in 1294 patients with acute relapse of chronic schizophrenia (31). Patients were randomized to aripiprazole 30 (n = 861) or haloperidol 10 mg (n = 433) daily for 52 weeks. A one-time dose reduction was allowed to aripiprazole 20 mg or haloperidol 7 mg. A significantly greater proportion of aripiprazole-treated patients responded and remained on treatment at weeks 8, 26, and 52 compared with haloperidol-treated patients. At week 52, 40% of the aripiprazole

group and 27% of the haloperidol group were on treatment and in response ($p < 0.001$). Aripiprazole was comparable to haloperidol in improvement of PANSS total and positive scores and significantly more effective than haloperidol for reduction of negative and depressive symptoms as measured on the PANSS negative subscale ($p < 0.03$) and the Montgomery Asberg Depression Rating Scale (MADRS) ($p < 0.03$). The discontinuation rate due to an adverse event was significantly lower in aripiprazole-treated patients than in the haloperidol-treated patients ($p < 0.001$). In addition, the incidence of EPS-related adverse events was significantly lower with aripiprazole than with haloperidol ($p < 0.001$). There was no significant difference between groups in weight gain or QTc interval prolongation.

There was no evidence in any study that higher dose groups offered any advantage over the lowest dose group. An examination of the population subgroups did not reveal clear evidence of differential responsiveness on the basis of gender, race, or age.

### *Use in Treatment - Resistant Schizophrenia*

The role of aripiprazole in patients with confirmed treatment-resistant schizophrenia has been explored in a multicenter, double-blind study (32). Following failure on olanzapine or risperidone, patients were randomized to a 6-week, double-blind treatment phase with aripiprazole 15 or 30 mg/day ($n = 154$) or the typical antipsychotic, perphenazine, 8 to 64 mg/day ($n = 146$). Assessments of PANSS, CGI, safety, and the Quality of Life Scale (QLS) were done. Patients treated with either aripiprazole or perphenazine showed improvement in PANSS total (−9.8 and −10.5, respectively), negative and positive subscale scores, and CGI Improvement scores. Overall, 27% and 25% of patients responded to aripiprazole and perphenazine, respectively, based on a CGI-I score of 1 or 2 or a 30% or greater decrease in PANSS total. Fewer aripiprazole-treated patients experienced extrapyramidal symptoms (EPS), electrocardiogram (ECG) abnormalities, or elevations in plasma prolactin levels.

### *Effects on Neurocognition*

Cognitive impairment is an important cause of functional disability in schizophrenia and other psychotic disorders. In a study comparing olanzapine and aripiprazole using a neurocognitive battery in which measured variables were reduced to three factors which included verbal learning, working memory, problem solving, the aripiprazole treated patients did better on verbal learning while both groups demonstrated improvement on working memory tasks (24). This neurocognitive study provides evidence that both drugs were alike overall in the area of cognition, though there was some advantage in the aripiprazole group in verbal learning.

### *Studies in Bipolar Disorder*

In a phase III, multicenter, double-blind (study 1) study, 262 patients with acute mania were randomized to treatment with aripiprazole 30 mg ($n = 130$) or placebo ($n = 132$) for 3 weeks (33,34). Aripiprazole produced a statistically significant improvement in Young Mania Rating Scale (Y-MRS) scores beginning on day 4 ($p < 0.005$), which was maintained throughout the 3-week study. Twice as many aripiprazole-treated patients responded to treatment as did placebo-treated patients (40% vs. 19%, respectively; $p = 0.01$). Discontinuations due to adverse events were similar between the aripiprazole and placebo groups (11% and 13%, respectively). Aripiprazole was efficacious, safe, and well tolerated for patients with bipolar disorder experiencing an acute manic or mixed episode. A second study (study 2 $N = 272$; aripiprazole $n = 135$, placebo $n = 129$) comparing aripiprazole with placebo revealed the drug group to be no different from the placebo group (38% placebo response) (35). The 15 mg aripiprazole group had a 41% response rate while the 30 mg aripiprazole group had a 45% response rate. It should be noted that this study has a high placebo response rate while the response rate in the aripiprazole group was comparable to other studies. In another 3-week inpatient study (study 3) aripiprazole tested against placebo with a start dosage of 30 mg with option to go down to 20 mg daily. This study noted a drug response rate of 40% versus a placebo response of 19%. Significant drug placebo differences were noted as early as day 4 (36). This study noted a 15% prevalence of akathisia.

A 12-week, multicenter, double-blind trial compared response rates with aripiprazole and haloperidol in patients with bipolar disorder who were experiencing an acute manic or mixed episode (37). A total of 347 patients were randomized to treatment with aripiprazole 15 mg/day or haloperidol 10 mg/day; doses could be titrated in weeks 1–3 to improve response or tolerability. The primary efficacy measure was response at week 12, defined as 50% or greater improvement from baseline in Y-MRS score and continuation of therapy. After 12 weeks of therapy, 50% of aripiprazole-treated patients continued to respond to treatment compared with 28.4% of haloperidol-treated patients ($p < 0.001$). There also were marked differences in long-term continuation rates between the groups; 29.1% of patients remained on haloperidol compared with 50.9% on aripiprazole.

### *Aripiprazole and Negative Symptoms*

In the study by Kane and colleagues, patients treated with aripiprazole 15 mg/day or haloperidol 10 mg/day demonstrated significant improvement on the PANSS negative subscale compared with placebo ($p = 0.006$ and $p = 0.043$, respectively) (27). This study did not compare the two drugs against each other with regard to negative symptoms, which is a limiting factor in our opinion. A meta-analysis of four short-term, fixed-dose, placebo-controlled studies also found aripiprazole to be effective in reducing negative symptoms as assessed by the PANSS negative subscale (29). Changes in PANSS negative subscale were assessed over 52 weeks in a multicenter, double-blind trial (38). Patients with acute relapse of chronic schizophrenia were randomized to treatment with aripiprazole 30 mg/day ($n = 861$) or haloperidol 10 mg/day ($n = 433$). The overall mean reduction in PANSS negative score was significantly greater among patients treated with aripiprazole than among those treated with haloperidol (−4.57 vs. −3.59, respectively; $p = 0.011$). Effects of aripiprazole were especially evident among patients with more prominent negative symptoms at baseline (PANSS negative score > 24). In this group of patients, mean changes in PANSS score were −6.97 in the aripiprazole group and −5.25 in the haloperidol group ($p = 0.005$). Thus, it appears that aripiprazole improves both positive and negative symptoms of schizophrenia.

### *Aripiprazole and Tardive Dyskinesia*

Whether aripiprazole can be used to treat tardive dyskinesia (TD) needs further investigation. At present, it is impossible to determine if aripiprazole induces TD, since most patients receiving the drug have already been exposed to conventional antipsychotics, all known to cause TD. In the clinical trials using aripiprazole the AIMS scores compared were not different in the aripiprazole group compared to placebo (27–30). The aim should always be to minimize the risk of TD by using the lowest effective dosage, monitoring for TD every 3 months, using antipsychotic agents only when potentially less harmful alternatives have not yielded good results or are not available, and restricting long-term use of this agent to patients with chronic illnesses. It is very important to discuss TD with the patient and document informed consent (39).

### *Aripiprazole and Neuroleptic Malignant Syndrome (NMS)*

Two possible cases of NMS that occurred during treatment with aripiprazole are in the preclinical worldwide clinical database (15). For more detailed information on NMS contact the NMS hotline at 1888 NMS TEMP. If a patient on aripiprazole develops symptoms and signs of NMS the drug should be discontinued and the patient be treated by supported measures, which include hydration as well as maintenance of vital signs. The patient should be kept antipsychotic free preferably for 2 weeks. If rechallenged a drug from a different class should be used. The degree of fever, as well as the severity of rigidity, determine the use of drugs to counteract these side effects.

## *4. ADVERSE EFFECTS*

Aripiprazole treatment has been well tolerated with minimal adverse events, which have not been treatment limiting. No clinically meaningful changes in vital signs have been noted.

### *Serum Lipids*

In short-term studies, there was no statistically significant difference in changes in total cholesterol between aripiprazole and placebo groups (40). In a long-term study, median changes in total cholesterol for the aripiprazole groups were comparable to the placebo group (40). In a 26-week, open-label, comparative study, there was a significant increase in median total serum cholesterol in the olanzapine group (202 to 210 mg/dL), whereas there was a decrease in median total cholesterol (197 to 187 mg/dL) in the aripiprazole group (24). In a 26-week, randomized, placebo-controlled study in patients with stable chronic schizophrenia, improvement in lipid profiles was observed with both aripiprazole 15 mg/day and placebo (41). In both groups, small decreases in levels of fasting total and low-density lipoprotein cholesterol and slight increases in plasma high-density lipoprotein levels were noted. Mean fasting plasma triglycerides levels were reduced by 37 mg/dL and 3 mg/dL from baseline in the aripiprazole and placebo groups, respectively. It should be noted that the patients as a group may have a high prevalence of increased triglycerides and glucose which is known to be associated with the chronic psychiatric disease state. The FDA has issued guidance recommending the screening of all patients for diabetes before starting atypical antipsychotics as well as ongoing monitoring.

## *EFFECTS ON WEIGHT*

A meta-analysis assessed the short-term and long-term effects of aripiprazole on weight gain. In short-term trials, patients on aripiprazole, haloperidol, and risperidone had mean weight gains of 0.7, 0.6, and 1.3 kg, respectively; patients in the placebo group had a mean weight loss of 0.05 kg (39). Approximately 8% of patients treated with aripiprazole and 3% of patients on placebo met the criteria

for clinically significant weight gain (i.e., weight gain of > 7% of body weight). With aripiprazole, the weight increase was not dose-dependent. In a 26-week, placebo-controlled trial (29), aripiprazole was comparable to placebo in mean changes in weight and the percentages of patients who showed significant weight gain. In another 26-week, open-label study (24), olanzapine was associated with a greater incidence of weight gain (29%) than aripiprazole (7%). The aripiprazole group had a mean weight decrease of 0.9 kg in contrast to the olanzapine group, which had a mean weight increase of 3.6 kg.

### *Effects on Glucose and on the Development of Diabetes Mellitus and the Metabolic Syndrome*

Based on a 26-week, placebo-controlled study (41), aripiprazole does not appear to have a potential to increase the risk of diabetes. Mean fasting glucose did not change significantly in either group over the course of the trial. From baseline to study endpoint, increases in mean fasting glucose were 0.1 mg/dL in the aripiprazole group (n = 75) and 2.1 mg/dL in the placebo group (n = 75). Glycosylated hemoglobin (A1C) values decreased by 0.11% and 0.17% in the aripiprazole and placebo groups, respectively.

Weiden and colleagues (2003) used risk factor data from 306 patients who entered a 26-week, double-blind, placebo-controlled trial of aripiprazole for maintenance treatment of schizophrenia to model long-term changes in the risk for type 2 diabetes mellitus. The investigators found that the overall effect of 6 months of treatment with aripiprazole on systolic blood pressure, high-density lipoprotein (HDL) cholesterol, fasting blood glucose, and body mass index (BMI) was similar to that of placebo (42). Furthermore, the effect of aripiprazole on predicted 7.5-year risk for diabetes mellitus also was similar to that of placebo.

Data from two 26-week, double-blind, randomized, controlled clinical trials designed to evaluate the efficacy of aripiprazole were used to compare the incidence of the metabolic syndrome in acute schizophrenic patients (43). One trial enrolled 306 stable patients with chronic schizophrenia who were randomized to treatment with aripiprazole or placebo. The other trial enrolled 314 patients who were experiencing acute episodes of schizophrenia and were randomized to aripiprazole or olanzapine. Using criteria developed by the National Cholesterol Education Program Expert Panel (44), investigators found that relative to placebo, treatment with aripiprazole does not increase the likelihood of developing or exacerbating the metabolic syndrome. However, therapy with olanzapine significantly increases the likelihood of developing or exacerbating the metabolic syndrome relative to aripiprazole (43). It should be noted that patients with schizophrenia have a higher prevalence of diabetes, hyperlipidemia and should be screened annually at the minimum.

### *Extrapyramidal Symptoms*

Data from clinical trials and preclinical pharmacology suggest that aripiprazole has an extremely favorable EPS profile. In short-term trials (25,27), the incidence of EPS was similar in patients treated with aripiprazole 15 to 30 mg/day, risperidone 6 mg/day, or placebo. However, haloperidol was associated with a higher incidence of such effects and more haloperidol-treated patients needed benztropine to manage their symptoms compared with aripiprazole-treated patients. The overall incidence of EPS was significantly lower with aripiprazole than with haloperidol in the 52-week maintenance trial ($p < 0.001$) (31). A meta-analysis was conducted of five 4- to 6-week, double-blind, multicenter studies in 1648 patients with acute relapse of schizophrenia or schizoaffective disorder (45). In these trials, patients were randomized to aripiprazole, haloperidol, risperidone, or placebo. The overall incidence of EPS was 21% and 44% with aripiprazole and haloperidol, respectively, compared with 19% with placebo. The difference between aripiprazole and placebo was not significant; in contrast, the difference between haloperidol and placebo was significant ($p < 0.001$). In addition, there was no apparent relationship between the incidence of EPS and dose of aripiprazole.

### *ECG*

Between-group comparisons for pooled placebo-controlled trials do not reveal any significant issues with regard to aripiprazole. The data suggest that in the dosage range of 10–30 mg/day, aripiprazole does not cause significant QTc interval prolongations. In a meta-analysis of both short- and long-term studies (46), clinical trial data was analyzed. Short-term studies revealed no differences in QTc among patients treated with aripiprazole and placebo, whereas risperidone treatment was associated with a statistically significant increase in QTc compared with placebo ($p < 0.01$). Mean changes in QTc were –4.4 msec for aripiprazole, –3.5 msec for placebo, –1.04 msec for haloperidol, and +2.15 msec for risperidone. No dose-dependent effect on the QTc interval was observed with aripiprazole. None of the aripiprazole treated patients had a QTc = 500 msec or a = 60 msec increase from baseline.

In the 26-week, open-label trial comparing aripiprazole and olanzapine, the olanzapine group had a mean QTc increase from baseline of 1.35 msec while the aripiprazole group had a mean QTc decline of –4.61 msec ($p < 0.05$) (45). In the 26-week, placebo-controlled trial, no significant

differences between placebo and aripiprazole were observed. In a 52-week trial, aripiprazole was associated with a statistically greater decrease in mean change from baseline in QTc at study endpoint (−7.4 msec for aripiprazole and −4.0 msec for haloperidol; $p < 0.05$). In addition, 19.3% of the aripiprazole group and 25.1% of the haloperidol group experienced a QTc increase of 30 msec or greater (46).

The ECG data suggests that aripiprazole has a greater safety margin than some of the available drugs, and QTc interval prolongation does not appear to be an issue with aripiprazole.

### *5. INFORMED CONSENT*

The decision to use aripiprazole should be discussed with the patient. Side effects, potential benefits, other treatment options, and reasons for its selection should be explored. The physician should ensure that the patient understands the implications of treatment with aripiprazole, has the capacity and is legally competent to give informed consent. Any off label use of the drug or the use of a higher than the maximum recommended dosage should also be discussed to obtain consent. Family involvement is important and, if available, spouses or other close relatives or significant others should participate in discussions. Informed consent should be documented in the medical record.

### *6. TREATMENT IMPLEMENTATION*

Aripiprazole can be used as a first-line drug in treating patients with schizophrenia or those suffering from other forms of psychoses. Before initiating treatment with aripiprazole, the patient should have a thorough psychiatric assessment, a complete medical history (including assessment of other medical illnesses and concomitant medications), a physical examination, and laboratory tests including a general health panel (i.e., complete blood count, serum electrolytes, liver enzymes, and urine analysis) and an electrocardiogram if indicated. A pregnancy test should be performed in women of child-bearing potential which is important when prescribing psychotropic agents.

Antipsychotic efficacy for aripiprazole has been shown for dosages between 15 to 30 mg/day in clinical trials. The drug is started at a dosage of 15 mg daily and can be titrated to 30 mg daily, while monitoring for side effects, such as EPS. When switching to aripiprazole, the other antipsychotic should preferably be discontinued after a sufficient overlap period of 6-8 weeks. In patients taking depot antipsychotics, oral aripiprazole should be started at the time of the next scheduled depot injection. During the switch over, medications for EPS should be used as needed (e.g, benztropine 2 to 6 mg/day). Agitation during the initial period may be managed with lorazepam (e.g., 1 to 2 mg oral/parenteral). If akathisia is observed propranolol can be used successfully at dosages of 40 mg twice daily.

Caution is recommended for the use of aripiprazole in the elderly, children and adolescents, the physically debilitated, and in persons predisposed to hypotension, until more data and experience is obtained with this agent.

### *7. SIDE EFFECT MONITORING AND MANAGEMENT*

Patients taking aripiprazole should be monitored for drug-induced Parkinsonism, sedation, restlessness, orthostatic hypotension (OH), and other common side effects (Table III). Lorazepam (1 to 2 mg) can be administered for insomnia, and on an as needed basis for daytime agitation (oral/intramuscular). Sedation is a dosage-related side effect of aripiprazole. Individuals should be warned not to operate heavy machinery or drive until this effect has abated.

Orthostatic hypotension can occur with aripiprazole because of alpha 1-adrenergic antagonism. Orthostatic blood pressures should be measured when initiating treatment if the patient complains of dizziness; however, clinical trials show no difference between aripiprazole and placebo. If OH is a significant problem for a particular patient, upward dose titration can be slowed, or the dosage can be reduced. Increasing the patient's sodium intake and support stockings may be helpful. Fludrocortisone (Florinef) may be helpful in some patients in whom OH is a significant problem, although this appears unlikely (47,48). Caution should be exercised in patients predisposed to hypotension such as those with dehydration, diabetes mellitus, myocardial infarction, and those taking antihypertensive medications.

**Table III** Most Frequent Adverse Effects Reported with Aripiprazole in Short-term, Placebo-controlled Trials (14)

| | Percentage of Patients Reporting Effect | |
|---|---|---|
| Adverse effect | Aripiprazole (n = 926) | Placebo (n = 413) |
| Headache | 32 | 25 |
| Asthenia | 7 | 5 |
| Fever | 2 | 1 |
| Nausea | 14 | 10 |
| Vomiting | 12 | 7 |
| Constipation | 10 | 8 |
| Anxiety | 25 | 24 |
| Insomnia | 24 | 19 |
| Lightheadedness | 11 | 7 |
| Somnolence | 11 | 8 |
| Akathisia | 10 | 7 |
| Tremor | 3 | 2 |
| Rhinitis | 4 | 3 |
| Coughing | 3 | 2 |
| Rash | 6 | 5 |
| Blurred vision | 3 | 1 |

There are no current published data regarding interactions of aripiprazole with lithium, antidepressants, and benzodiazepines. Fluoxetine and other cytochrome P450IID6 inhibitors (e.g., quinidine and paroxetine) might increase the blood level of aripiprazole because of its inhibitory effect on cytochrome P450IID6, and this might result in an increased incidence of side effects. In such cases, it is suggested that the aripiprazole dosage be reduced to one-half the normal dose. In patients taking potent cytochrome P4503A4 inducers, such as carbamazepine, the aripiprazole dosage should be doubled (15).

Some patients develop akathisia while on aripirazole. This should be treated with propranolol or clonazepam.

No fatalities have been reported from an aripiprazole overdose. The signs and symptoms reported were those resulting from exaggeration of drug induced side effects. The management of an aripiprazole overdose is the same as for other antipsychotics, that is, maintaining patency of the airway, gastric lavage, ECG, and the use of activated charcoal in addition to other life support measures (15).

## *8. UTILITY OF DRUG PLASMA CONCENTRATIONS*

Plasma concentrations of aripiprazole and its active metabolite have not shown correlation with clinical response and hence levels do not have a clinical role.

## *9. MAINTENANCE TREATMENT*

The guidelines for maintenance treatment with aripiprazole are similar to those for other antipsychotics. The dosage that controls symptoms adequately should be continued to prevent relapse of symptoms. Patients should be periodically assessed to determine the need for continued therapy. In chronic illnesses, long-term therapy is indicated to avoid relapse.

## *10. PLACE OF ARIPIPRAZOLE IN THERAPY*

Aripiprazole is a dopamine system stabilizer that is highly effective and well tolerated. It has the potential for a significant role in the current treatment of psychotic disorders. It should be used as a first line drug because of the low frequency of side effects, or can be an alternative in patients unable to tolerate conventional or other atypical antipsychotics. Patients on conventional antipsychotics who develop tardive dyskinesia may benefit from a switch to aripiprazole. The difficult question is whether to switch patients to aripiprazole who are well-controlled on an atypical antipsychotic or clozapine who have few or minimal side effects. This decision will be influenced by a multitude of factors such as: 1) problematic side effects of other atypicals including weight gain or metabolic abnormalities; 2) risk of relapse; 3) cost effectiveness of treatment; and 4) refusal of weekly blood work (for patients on clozapine) and other side effects associated with clozapine. Before switching medications, these issues, including the possibility of relapse, should be thoroughly discussed with the patients and their families, so an informed decision can be made.

### *Clinical Indications Other Than Schizophrenia*

Aripiprazole can be used for other disorders just as the other atypical antipsychotics. The drug can be used in bipolar disorder to treat acute mania but there are no studies in maintenance treatment or for bipolar depression. Other clinical uses include the treatment of psychotic symptoms associated with dementia. In a double-blind placebo-controlled 10 week study in Alzheimer's dementia patients with psychosis (N = 256) in the skilled nursing facilities aripiprazole produced a statistically significant improvement on secondary measures of agitation, neuropsychiatric inventory nursing home version (NPI-NH), BPRS, and clinical global impression of improvement (CGI-I) compared with the placebo group. The two groups did not separate on the primary efficacy measures, which included the NPI psychosis subscale (49). The drug and placebo group did not separate significantly based on adverse event reporting. In another study looking at adverse event in a pooled analysis using data from the nursing home study and a study focused on community residing elderly patients with psychosis of Alzheimer's dementia, safety and tolerability were addressed. Safety and tolerability issues overall were low and there were no statistically significant differences between the two groups with regard to EPS, orthostasis, accidental injury, anticholinergic events, cardiac abnormalities, and stroke. In the trials in dementia patients, aripiprazole was started at 2 mg daily and increased as clinically indicated to a maximum of 10 mg daily (50). In the geriatric population, the starting dosage based on clinical experience should be 5 mg daily; the dose can be adjusted based on response with increments of 5 mg with a possible maximum of 10–15 mg daily determined by efficacy and tolerability.

In the pediatric population there is emerging data to suggest the drug may be well tolerated. An open label pilot study demonstrated the safety and efficacy of aripiprazole in conduct disorder. The study included 12 children and 11 adolescents, initial dosing being between 1–15 mg based on body weight. As initial use in this population suggested sensitivity to vomiting and sedation a schedule based on weight was followed with much improved tolerability. The dosing schedule was adjusted based on weight <25 kg (1 mg), weight 25–50 kg (2 mg), weight 50–75 kg (5 mg), weight > 70 kg (10 mg). The pharmacokinetics was noted to be similar and consistent with adults (35).

Aripiprazole may also be used as an augmentation strategy in treatment resistant depression in conjunction with antidepressant medications. Another use of this agent could be difficult to treat obsessive-compulsive disorder. In the near future we should see studies using aripiprazole in these disorders. Currently the prescription of aripiprazole for disorders other than schizophrenia is considered off label use, which requires a discussion with the patient followed by documentation.

Aripiprazole has ushered in an exciting new era in the treatment of schizophrenia and other psychotic illnesses and appears to be a step up from its predecessors, the atypical agents. As with any new medication, time and experience will be needed for us to determine its place in therapy. Psychiatrists and other physicians now have another effective agent with a favorable side-effect profile.

## *REFERENCES*


1. Ayd FJJ: A survey of neuroleptic-induced extrapyramidal reactions. *JAMA* 1961; 175:1054–1061.
2. Rupniak NMJ, Jenner P, Marsden CD: Acute dystonia induced by neuroleptic drugs. *Psychopharmacol* 1986; 88:403–419.
3. Van Putten T: The many faces of akathisia. *Comprehensive Psychiatry* 1975; 16:43–47.
4. Van Putten T, May PRA, Marder SR: Why do schizophrenic patients refuse to take their drugs? *Arch Gen Psychiatry* 1974; 31:67–72.
5. Kane JM, Smith JM: Tardive dyskinesia: Prevalence and risk factors, 1959–1979. *Arch Gen Psychiatry* 1982; 39:473–481.
6. Jeste DV, Wyatt RJ: *Understanding and treating Tardive Dyskinesia*. New York: Guilford Press; 1982.
7. Kane JM: Clinical efficacy of clozapine in treatment-refractory schizophrenia: An overview. *Br J Psychiatry* 1992; 160(suppl.17):41–45.
8. Krupp P, Barnes P: Clozapine-associated agranulocytosis: Risk and aetiology. *Br J Psychiatry* 1992; 160 (suppl. 17): 38–40.
9. Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Brier A, Tollefson GD. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Archives of General Psychiatry* 2000; 57:249–258.
10. Lahti AC, Weiler MA, Corey PK, et al. Antipsychotic properties of the partial dopamine agonist (-)-3(3-hydroxyphenyl)-N-n-propylpiperidine (preclamol) in schizophrenia. *Biol Psychiatry* 1998; 43:2–11.
11. Sramek JJ, Eldon MA, Posvar E, et al. Initial safety, tolerability, pharmacodynamics, and pharmacokinetics of CI-1007 in patients with schizophrenia. *Psychopharmacol Bull* 1998; 34:93–99.
12. 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; 302:381–389.
13. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *Eur J Pharmacol* 2002; 441:137–140.
14. McQuade RD, Burris KD, Jordan S, Tottori K, Kurahashi N, Kikuchi T. Aripiprazole: A dopamine-serotonin system stabilizer. *Int J Neuropsychopharmacol* 2002; 5(Suppl 1):S176.
15. Abilify™ prescribing information. Bristol-Myers Squibb Company, Princeton, New Jersey; November 2002.
16. Goodnick and Jerry. *Expert Opin Pharmacother* 2002; 3:1773–1781.
17. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacol* 1999; 20:612–627.
18. Inoue A, Nakata Y. Strategy for modulation of central dopamine transmission based on partial agonist concept in schizophrenia. *Jpn J Pharmacol* 2001; 86:376–380.
19. Grunder G, Carlsson A, Wong D. Mechanism of action of new antipsychotic medications. *Arch Gen Psychiatry* 2003; 60:974–977.
20. Kikuchi T, Tottori K, Uwahodo Y, et al. 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic $D_2$ receptor antagositic activity. *J Pharmacol Exp Ther* 1995; 274:329–336.
21. Jordan S, Tadori Y, McQuade R, Yocca F, Kostic D, Kikuchi T. *Definitive evidence that aripiprazole is a $D_2$ and 5-$HT_{1A}$ partial agonist*. Presented at the 2003 APA Annual Meeting, San Francisco, CA; May 17–22, 2003.
22. Carson WH, Saha AR, Iwamoto T, Lin C, Kujawa MJ. Meta-analysis of prolactin effects with aripiprazole. *Int J Neuropsychopharmacol* 2002b; 5(Suppl 1):S186.
23. Bramer S, Shoaf S, Salazar DE, Mallikaarjun S. *Effects of renal and hepatic impairment on the pharmacokinetics of aripiprazole*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
24. Cornblatt B, Kern RS, Carson WH, Ali MW, Luo X, Green M. Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis. *Int J Neuropsychopharmacol* 2002; 5(Suppl 1):S185.
25. Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with

schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 2003; 60:681–690.
26. Daniel DG, Saha AR, Ingenito G, Carson WH, Dunbar G. Aripiprazole, a novel antipsychotic: Overview of a phase II study result. *Int J Neuropsychopharmacol* 2000; 3(Suppl 1):S157.
27. Kane JM, Carson WH, Saha A, McQuade RD, Ingenito GG, Zimbroff DL, Ali MW. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002; 63:763–771.
28. Petrie JL, Saha AR, McEvoy JP. Aripiprazole, a new atypical antipsychotic: phase II clinical trial result. *Eur Neuropsychopharm* 1997; 7(Suppl 2):S227.
29. Lieberman J, Carson WH, Saha AR, et al. Meta-analysis of the efficacy of aripiprazole in schizophrenia. *Int J Neuropsychopharmacol* 2002; 5(Suppl 1):S186.
30. Carson WH, Pigott TA, Saha AR, et al. Aripiprazole vs placebo in the treatment of chronic schizophrenia. *Int J Neuropsychopharmacol* 2002a; 5(Suppl 1):S187.
31. Kujawa M, Saha AR, Ingenito GG, et al. Aripiprazole for long-term maintenance treatment of schizophrenia. *Int J Neuropsychopharmacol* 2002; 5(Suppl 1):S186.
32. Kane J, Carson W, Kujawa M, et al. *Aripiprazole vs perphenazine in treatment-resistant schizophrenia*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
33. Jody D, Marcus R, Keck P, et al. Aripiprazole vs placebo in acute mania. *Int J Neuropsychopharmacol* 2002a; 5(Suppl 1):S57.
34. Keck Jr. 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. *American Journal of Psychiatry* 2003; 160:1651–1658.
35. Bristol Meyers Squibb/Otsuka America Pharmaceuticals. Data on file.
36. Marcus et al. *Aripiprazole for acute mania*. Presented at the 5th International Conference on Bipolar Disorder, June 11–14, 2003 Pittsburgh, PA.
37. Bourin M, Auby P, Swanink R, et al. *Aripiprazole vs haloperidol for maintained treatment effect in acute mania*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
38. Manos G, McQuade R, Stock E, et al. *Long-term effects of aripiprazole on the negative symptoms of schizophrenia*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
39. Gupta S, Frank BL, Madhusoodanan S: Tardive dyskinesia: Legal issues and consent. *Psychiatric Annals* 2002; 32:245–248.
40. Jody D, Saha AR, Iwamoto T, et al. Meta-analysis of weight effects with aripiprazole. *Int J Neuropsychopharmacol* 2002b; 5(Suppl 1):S186.
41. Marder SR, Jody D, Kaplita S, et al. *Glycemic control and plasma lipids in long-term treatment with aripiprazole*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
42. Weiden P, Waldeck R, Tafesse E, Cislo P, L'Italien G, Carson W. *Aripiprazole is not associated with increased diabetes risk: A long-term model*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
43. Casey D, L'Italien GL, Waldeck R, Cislo P, Carson W. *Metabolic syndrome comparison between olanzapine, aripiprazole, and placebo*. Presented at the 2003 APA Annual Meeting, May 17–22, 2003; San Francisco, CA.
44. Grundy SM, Becker D, Clark LT, et al. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–2497.
45. Stock E, Marder SR, Saha AR, et al. Safety and tolerability meta-analysis of aripiprazole in schizophrenia. *Int J Neuropsychopharmacol* 2002a; 5(Suppl 1):S186.
46. Stock E, Marder SR, Saha AR, et al. Meta-analysis of cardiac safety with aripiprazole. *Int J Neuropsychopharmacol* 2002b; 5(Suppl 1):S186.
47. Schatz IJ: Orthostatic Hypotension II. Clinical diagnosis, testing, and treatment. *Arch Intern Med* 1984; 144:1037–1041.
48. Pollack MH, Rosenbaum JF: Management of antidepressant-induced side effects. A practical guide for the clinician. *J Clinical Psychiatry* 1987; 48:3–8.
49. Streim JE, McQuade RD, Stock E et al. *Aripiprazole treatment of institutionalized patients with psychosis of Alzheimer's dementia*. Presented at 17 Annual meeting of the American Association of Geriatric Psychiatry, February 21–24, 2004; Baltimore, MD.
50. Kujawa MJ and Bristol Meyers Squibb. *Safety and tolerability of aripiprazole in elderly patients with psychosis of Alzheimer's dementia*: *A pooled analysis.* Presented at 17 Annual meeting of the American Association of Geriatric Psychiatry, February 21–24, 2004; Baltimore, MD.