

Aripiprazole, a “Dopamine-Serotonin System Stabilizer” in the Treatment of Psychosis

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Abstract

Aripiprazole, a novel antipsychotic agent, is assumed to be a “dopamine-serotonin system stabilizer”. According to preclinical studies, aripiprazole exerts partial agonistic action on D_2 and 5-HT_{1A} receptors. Thus, it may block a receptor if it is overstimulated and stimulate a receptor when activity is needed. It also has antagonist properties at 5-HT_{2A} receptors.

In randomized double-blind studies, aripiprazole was significantly more effective than placebo in controlling positive and negative symptoms of schizophrenia. It showed antipsychotic efficacy comparable to haloperidol, olanzapine and risperidone. Negative and depressive symptoms responded better to aripiprazole than to haloperidol. In an open-label study comparing olanzapine to aripiprazole, aripiprazole showed beneficial effects on cognitive dysfunctions in schizophrenic patients. Also, aripiprazole was effective in patients with mania.

Under aripiprazole the rate of extrapyramidal side effects was less than under haloperidol treatment, and did not differ from the placebo and risperidone arms. Clinically significant weight gain occurred less frequently with aripiprazole than with olanzapine. Aripiprazole also demonstrated a significant reduction in cholesterol levels, while haloperidol and olanzapine increased cholesterol levels in comparative trials. Prolactin levels increased 5-fold over placebo levels with risperidone, no increase was seen with aripiprazole.

While risperidone treatment was associated with a significantly prolonged mean QTC interval when compared with placebo, aripiprazole treatment did not differ from placebo level. The three most common adverse effects attributed to aripiprazole included headache, anxiety and insomnia. Due to its metabolism process, the risk for interactions of aripiprazole with other cytochrome P 450 dependent drugs is minimal (German J Psychiatry 2003; 6: 9-16).

Keywords aripiprazole, antipsychotics, atypical, schizophrenia, mania, clinical studies

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Introduction

It is assumed that antipsychotics reduce psychotic symptoms by blocking dopamine D_2 receptors (Carlsson, 1988). Classical antipsychotics unspecifically block both mesolimbic A_{10} dopamine pathways, resulting in antipsychotic efficacy, and nigrostriatal A_9 pathways, resulting in unwanted extrapyramidal side effects (EPS). Also, tardive dyskinesia and neurocognitive deficits have been associated with dopamine blockade. The blockade of receptors in the

tubero-infundibular dopamine system results in prolactin elevations and sexual dysfunctions.

So-called “second generation” antipsychotics, also known as atypical antipsychotics, possess a lower EPS liability, and show a better efficacy in the treatment of negative and depressive symptoms, as well as cognitive disorders associated with schizophrenia. These unique features have been attributed to a higher affinity to serotonin receptors, or to a differential blockade of A_{10} vs. A_9 pathways, respectively.

However, while atypical antipsychotics were designed to reduce EPS, they brought about other side effects, which have not been an issue in the era of the classical neuroleptics. These include substantial weight gain, hyperglykemia, cholesterol level elevation, and QT interval prolongation. Thus, there is still an unmet need for novel antipsychotics that are better tolerated than currently available atypical drugs.

Recently, aripiprazole, a novel antipsychotic agent with a mechanism of action different from all currently marketed typical and atypical antipsychotics, has been approved in the U.S. and is waiting for approval in other countries. Aripiprazole claims to be the first agent of a third generation of antipsychotics, the so-called “dopamine-serotonin system stabilizers”. Preclinical studies have provided evi-

dence that aripiprazole possesses potent partial agonistic properties at D_2 receptors and also exhibits partial agonism at $5-HT_{1A}$ receptors, as well as antagonistic properties at $5-HT_{2A}$ receptors. The promising features of this new antipsychotic may be associated with its unique pharmacological receptor profile.

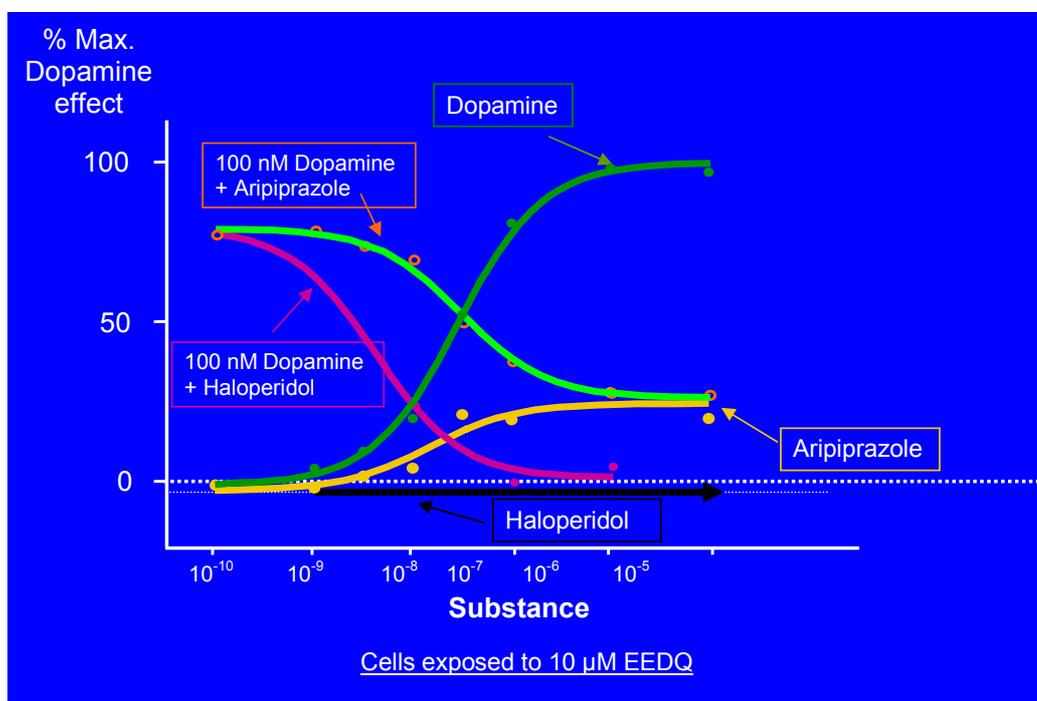
Pharmacodynamics

Aripiprazole is a quinolinone derivative, which is a potent partial agonist for dopamine D_2 receptors (Burris et al., 2002; Lawler et al., 1999). In receptor binding studies using cloned human D_{2L} receptors, aripiprazole acted as an ago-

Figure 1. Dopamine receptor activation of aripiprazole. Aripiprazole was evaluated for its intrinsic activity in Chinese hamster ovary cells that were transfected to express cloned human D_2 dopamine receptors (CHO- D_2). The exposure of these cells to forskolin leads to accumulation of cAMP; this accumulation is inhibited by the stimulation of D_2 receptors by dopamine or other agonists. The degree of inhibition of cAMP accumulation is directly dependent on the degree of receptor activation. The data are presented here as a percent of the maximal response, corresponding to the maximal inhibition of forskolin-stimulated cAMP accumulation by dopamine.

1. Dopamine or another full agonist activates the receptors in a dose-dependent manner until the saturation point is reached—the maximal receptor activation is reached at $\sim 10^{-6}$ M of dopamine. (100%)
2. Haloperidol is a full antagonist, and even at high concentrations when all the receptors are bound, there is no activation of the receptor.
3. Aripiprazole produced a dose-dependent stimulation of the D_2 receptors that was quantitatively and significantly less than that of dopamine alone. When fully saturating the receptors, the intrinsic activity of aripiprazole was approximately 25% that of dopamine in this particular experimental system.

Therefore, in the absence of dopamine, aripiprazole behaves as an agonist, partially activating the receptor.



nist with lower intrinsic activity than dopamine itself (Gründer et al., 2002). Partial agonism refers to the ability to both block a receptor if it is overstimulated and to stimulate a receptor when higher activity is needed (Figure 1).

Unlike older atypical antipsychotics, which reduce positive symptoms of psychosis by blocking D₂ receptors, aripiprazole stabilizes or modulates these binding sites. If there is an excessive supply of dopamine, which is associated with occurrence of positive symptoms, aripiprazole binds with high affinity to D₂ receptors and decreases overstimulation (Stahl, 2001).

The result is a stabilized signal near to normal physiological function (Byars et al., 2002), resulting in a reduction of psychotic symptoms. In a study employing positron emission tomography, administration of aripiprazole over 14 days resulted in a dose-dependent receptor occupancy between 40-95% after the administration of 0.5-30 mg per day. Interestingly, even with striatal D₂ receptor occupancy values above 90%, which occurred at higher doses of aripiprazole, extrapyramidal side effects (EPS) were not observed (Yokoi et al., 2002). Previous theories on the mechanism of action of atypical antipsychotics claimed that a D₂ receptor occupancy higher than 70-89% would lead to EPS (Farde et al., 1994). However, the aripiprazole data suggest that this association may only be true for full antagonists, but not for partial agonists.

If, however, dopaminergic transmission is reduced, aripiprazole may enhance transmission due to its own intrinsic activity. This unique quality may be relevant for the treatment of negative symptoms which have been correlated with a low dopaminergic tone (Byars et al., 2002).

Aripiprazole also shows partial agonism at 5HT_{1A} serotonin receptors and antagonism at 5HT_{2A} receptors. 5HT_{1A} receptors are known to exert anxiolytic effects (Rickels et al., 1982). Antagonism at 5HT_{2A} receptors may confer a

favorable effect on negative symptoms (Millan, 2000).

These explanations of the unique mechanism of action of aripiprazole may remain theoretical. However, clinical studies seem to support this concept.

Among the atypical antipsychotics, aripiprazole displays the lowest affinity for histamine (H₁), and muscarinic (M₁) receptors (Goodnick and Jerry, 2002). The blockade of α_1 -adrenergic receptors has been associated with orthostatic hypotension.

Pharmacokinetics

In a preclinical study investigating the pharmacokinetic attributes of aripiprazole, the mean plasma concentration peak (T_{max}) occurred 3 hours after oral application (Mallickarjun et al., 2000). The mean elimination half-life (t_{1/2}) was approximately 75 hours. A steady state was achieved on day 14. The oral bioavailability was found to be 87%. Aripiprazole can be administered with or without food.

Clinical Studies

The clinical studies with aripiprazole are summarized in Table 1.

Table 1. Double-Blind Studies with Aripiprazole

Authors	Diagnosis	Patients N	Comparison	Efficacy
Acute studies				
Carson et al., 2002b	Schizophrenia	420	vs. Placebo	Aripiprazole > placebo
Kane et al., 2002	Schizophrenia or schizoaffective disorder	414	Haloperidol, placebo	Aripiprazole = haloperidol > placebo
Petrie et al., 2002	Schizophrenia	103	Haloperidol, placebo (dose-titration study)	Haloperidol > placebo Aripiprazole > placebo (only CGI-severity responders)
Saha et al., 2001	Schizophrenia	404	Risperidone, placebo	Aripiprazole = risperidone > placebo
Long-term studies				
Pigott et al., 2002	Schizophrenia	310	Placebo	Aripiprazole > placebo
McQuade et al., 2002a	Schizophrenia	1,294	Haloperidol, placebo	Positive symptoms: aripiprazole = haloperidol > placebo Drop-outs: aripiprazole < haloperidol Negative and depressive symptoms: aripiprazole > haloperidol Aripiprazole > placebo
Marcus et al., 2002	Mania	262	Placebo	Aripiprazole > placebo

Schizophrenia

Short-term studies

In a 6-week trial with 420 schizophrenic patients comparing three fixed doses of aripiprazole (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score, the PANSS positive subscale, and the PANSS negative subscale (Carson et al., 2002b).

A 4-week, double-blind, randomized, fixed-dose study compared aripiprazole (15 or 30 mg/day) to haloperidol (10 mg/day) and placebo. A total of 414 patients with schizophrenia or schizoaffective disorders were randomized. Both doses of aripiprazole and haloperidol produced statistically significant improvements from baseline on the PANSS total, PANSS positive, PANSS-derived BPRS score, and Clinical Global Impression (CGI)-Severity scores, and significantly lower CGI-Improvement scores at endpoint when compared with placebo. Aripiprazole (15 mg) and haloperidol (10 mg) significantly improved the PANSS negative score compared with placebo. Both aripiprazole doses and haloperidol were significantly different from placebo for PANSS total scores from week 2 through week 4 (Kane et al., 2002).

In a 4-week trial with 404 schizophrenic patients, two fixed doses of aripiprazole (20 or 30 mg/day) and risperidone (6 mg/day) were compared to placebo. Both doses of aripiprazole were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score (Potkin et al., 2003).

Long-term relapse prevention studies

A 26-week study with 310 schizophrenic patients demonstrated that aripiprazole was significantly superior to placebo in the prevention of relapses ($p < 0.001$) (Pigott et al., 2002).

In a 52-week study with 1,294 schizophrenic patients, aripiprazole was compared with the typical neuroleptic haloperidol. Both drugs were similar in reducing positive symptoms as measured by the PANSS total score. Compared to the haloperidol cohort, a much larger percentage of patients treated with aripiprazole showed a therapeutic response and remained in treatment at weeks 8, 26, and 52 (week 52: 40 percent vs. 27 percent, $p < 0.001$). In this study, a cessation of the treatment response was defined as either a worsening of the GCI score (higher or equal 6), worsening of psychosis as a serious adverse event, or worsening of scores (higher or equal 5) on one of the following items of the PANSS positive subscale: delusion, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution. Furthermore, patients treated with aripiprazole reported significantly greater improvements in negative and depressive symptoms in the PANSS negative subscale and

the Montgomery Åsberg Depression Rating Scale (MADRS) (McQuade et al., 2002a). Patients treated with aripiprazole experienced significantly fewer extrapyramidal side effects and showed a greater response (defined as 30% improvement in the PANSS total score) than haloperidol-treated patients. In the same group, significantly fewer patients discontinued treatment due to lack of efficacy or adverse events.

Open studies

An open study with 311 patients was designed to assess the safety and tolerability of switching patients from their current antipsychotic medication (i.e. haloperidol, olanzapine, or risperidone) to aripiprazole (Casey et al., 2003). Three switching strategies were employed: (1) switch to aripiprazole at full dose (without titration) from prior antipsychotic treatment; (2) switch to aripiprazole at full dose along with tapering off prior treatment for two weeks; and (3) switch to aripiprazole with titration to full dose while simultaneously tapering previous treatment for two weeks. Results were similar across all three switching strategies, and switching was generally safe and well tolerated in all groups. Thus, it seems justified to use an effective dose of aripiprazole immediately without gradually increasing the dose. In all groups, an improvement was seen from baseline on PANSS total, PANSS negative and positive subscales, and CGI-improvement scores after four and eight weeks.

Aripiprazole (30mg/day) was compared with olanzapine (15mg/day) with regard to neurocognitive functions in an open-label multicenter study in 255 randomized patients with stable psychosis (Carson et al., 2002a). Significant improvements in secondary verbal memory could be shown for aripiprazole, but not for olanzapine.

Mania

In a double-blind study including 262 patients with acute mania, aripiprazole treatment (mean dosage 27.9 mg/d) resulted in statistically significant improvements on the Young Mania Rating Scale (Y-MRS), and in a higher response rate (40% vs 19%) compared to placebo (Jody et al., 2002a).

Dosage

Aripiprazole is administered as a once-daily oral tablet and can be taken with or without food. The effective dose range is 10 to 30 mg. The recommended starting and maintenance dose of 15 mg daily enables physicians to initiate therapy at an effective dose without the need for titration (Daniel et al., 2000). Dosage can be subsequently adjusted to optimize individual patient response. Aripiprazole is

currently available in 10 mg, 15 mg, 20 mg, and 30 mg tablets in the USA.

Dose-ranging studies in schizophrenia showed superior qualities of orally administered 2, 10, and 30 mg aripiprazole per day over placebo (Daniel et al., 2000). During the acute phase, a once daily dose of 15-30 mg seems to be sufficient, according to the available data. For long term maintenance treatment and relapse prevention, a once daily dose of 20-30 mg was used in the haloperidol controlled study (McQuade et al., 2002a).

In the treatment of patients with acute bipolar mania (Jody et al., 2002a), a daily dose of 30 mg aripiprazole was shown to be superior to placebo.

Increasing aripiprazole from oral doses of 30 mg/day to 90 mg/day did not result in a dose-dependent increase of adverse events (Auby et al., 2002).

Side Effects

The frequency of adverse events is shown in Table 2.

In short-term, placebo-controlled trials, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The most common adverse events spontaneously reported during treatment with aripiprazole were headache, insomnia, agitation, dyspepsia, nausea and anxiety (McQuade et al., 2002b).

In contrast to haloperidol, aripiprazole did not show any significant differences to placebo with regard to the frequency of extrapyramidal side effects assessed via the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) (Marder et al., 2003; McQuade et al., 2002b).

Table 2. Side Effects. Incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses >2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo (taken from US Prescribing Information).

Side effect	Aripiprazole %	Placebo %
Headache	32	25
Anxiety	25	24
Insomnia	24	19
Nausea	14	10
Vomiting	12	7
Lightheadedness	11	7
Somnolence	11	8
Akathisia	10	7
Constipation	10	8
Asthenia	7	5

In a comparison of aripiprazole and risperidone, neither treatment produced significant extrapyramidal side effects (Potkin et al., 2003). Mean plasma prolactin levels increased 5-fold over placebo with risperidone, while no such change could be seen in the aripiprazole group. While risperidone treatment was associated with a significant increase in the QTC interval, aripiprazole treatment did not increase the QTC-interval (Potkin et al., 2003).

In a 52-week haloperidol-controlled study, treatment with aripiprazole was associated with a minimal increase in body weight in patients with a baseline body mass index (BMI) <23, while patients with a baseline BMI >27 experienced weight loss (McQuade et al., 2002a). Also, aripiprazole was associated with a mean weight loss of 0.9 kg in a 26 week open-label study, while olanzapine lead to a mean weight gain of 3.6 kg (Jody et al., 2002b).

Aripiprazole treatment also resulted in a significant reduction in mean cholesterol levels, while olanzapine, risperidone, and haloperidol produced a significant cholesterol increase (Jody et al., 2002b; McQuade et al., 2002a; Saha et al., 2001).

In contrast to haloperidol and risperidone, which both showed a significant increase in serum prolactin levels of 120% and 600% from baseline respectively, aripiprazole did not increase serum prolactin levels (Marder et al., 2003; McQuade et al., 2002b).

Interactions

The cytochrome P 450 enzymes CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism (McGavin and Goa, 2002). Agents that induce CYP3A4 (e.g. *carbamazepine*) could cause an increase in aripiprazole clearance and lower plasma levels. Inhibitors of CYP3A4 (e.g. *ketoconazole*) or CYP2D6 (e.g. *quinidine*, *fluoxetine*, or *paroxetine*) can theoretically inhibit aripiprazole elimination, and cause elevated plasma levels.

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In in vivo studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (*dextromethorphan*), CYP2C9 (*warfarin*), CYP2C19 (*omeprazole*, *warfarin*), and CYP3A4 (*dextromethorphan*) substrates. In addition, aripiprazole and dehydro-aripiprazole did not show any potential for altering CYP1A2-mediated metabolism in vitro (US Prescribing Information Abilify™).

The interactions with the following drugs are not clinically relevant and no dosage adjustment is required if these drugs are administered concomitantly with aripiprazole: *Famotidine*: Coadministration of aripiprazole with the H2 antagonist famotidine, a potent gastric acid blocker, de-

creased the solubility of aripiprazole, and hence its rate and extent of absorption. *Valproate*: When valproate and aripiprazole were coadministered at steady state, the C_{max} and AUC of aripiprazole were decreased by 25% (US Prescribing Information Abilify™). In another study, aripiprazole was coadministered with valproate (Citrome et al., 2002), which had no clinically significant effect on the steady state pharmacokinetics of aripiprazole. *Lithium*: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not metabolized and bound to plasma proteins, and is almost entirely excreted unchanged in the urine. Coadministration of therapeutic doses of lithium with aripiprazole did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite dehydro-aripiprazole (Citrome et al., 2002). *Dextromethorphan*: Aripiprazole had no effect on the O-dealkylation of dextromethorphan into its major metabolite dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on the N-demethylation of dextromethorphan into its metabolite 3-methoxymorphan, a pathway known to be dependent on CYP3A4 activity (US Prescribing Information Abilify™). *Warfarin*: Aripiprazole had no effect on the pharmacokinetics of R- and S-warfarin (US Prescribing Information Abilify™). *Omeprazole*: Aripiprazole had no effect on the pharmacokinetics of omeprazole, a CYP2C19 substrate, in healthy subjects (US Prescribing Information Abilify™).

Contraindications

Aripiprazole is contraindicated in patients with a known hypersensitivity to the drug. Aripiprazole has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction, or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

As experiences are lacking, aripiprazole should not be used during pregnancy or while breast-feeding.

Precautions

Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database (US Prescribing Information Abilify™). Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α 1-adrenergic receptor antagonism. Aripiprazole should be used with caution in patients with known cardiovascular diseases (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular diseases, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures

occurred in 0.1% (1/926) of aripiprazole-treated patients in short-term, placebo-controlled trials. Like other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (e.g. Alzheimer's dementia).

Aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills, although some cognitive functions have been improved in patients with schizophrenia in clinical studies. Patients should be cautioned about operating hazardous machinery, including automobiles when taking aripiprazole.

Use in Elderly Patients

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established. Vigilance should be exercised, particularly for the emergence of orthostatic hypotension, swallowing difficulties, or excessive somnolence, which could predispose to accidental injury or aspiration.

Conclusions

Currently available data suggests that aripiprazole has the potential to become a promising addition to our armament of antipsychotic drugs. It may be an alternative to existing drugs in the treatment of schizophrenia and mania, as it has equal or even superior efficacy as typical and atypical reference drugs with regard to positive, negative, depressive, and cognitive functions, and is well tolerated. Known problems with other atypical drugs, such as weight gain, hyperglycemia, cholesterol increase, prolactin elevation or QT prolongation are not an issue with aripiprazole treatment.

References

- Auby P, Saha AR, Mirza A, et al. Safety and tolerability of aripiprazole at doses higher than 30 mg. *Eur. Neuropsychopharmacol.* 2002;12 (Suppl. 3):S288.
- 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(1):381-9.

- Byars A, Burris K, Jordan S, Tottori K, Kikuchi T, McQuade R. Aripiprazole: A dopamine-serotonin system stabilizer. *European Neuropsychopharmacology* 2002;12:S290-S291.
- Carlsson A. The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1988;1(3):179-86.
- Carson W, Cornblatt B, Saha A, Ali M, Kern R, Green M. Neurocognitive benefits of aripiprazole versus olanzapine in stable psychosis. *European Neuropsychopharmacology* 2002a;12:S291-S291.
- Carson W, McQuade R, Saha A, Torbeyns A, Stock E. Aripiprazole versus placebo for re-lapse prevention in patients with chronic schizophrenia. *European Neuropsychopharmacology* 2002b;12:S288-S288.
- Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology (Berl)* 2003.
- Citrome L, Josiassen R, Bark N, Brown KS, Mallikaarjun S, Salazar DE. Pharmacokinetics and safety of aripiprazole and concomitant mood stabilizers. *Int. J. Neuropsychopharmacol.* 2002;5 (Suppl. 1):S187.
- Daniel DG, Saha A, Ingenito G, Carson WH, Dunbar G. Aripiprazole, a novel antipsychotic: overview of a phase 2 study result. *Int. J. Neuropsychopharmacol.* 2000;3 (Suppl. 1):157.
- Farde L, Nordstrom AL, Nyberg S, Halldin C, Sedvall G. D1-, D2-, and 5-HT₂-receptor occupancy in clozapine-treated patients. *J Clin Psychiatry* 1994;55 Suppl B:67-9.
- Goodnick PJ, Jerry JM. Aripiprazole: profile on efficacy and safety. *Expert Opin Pharmacother* 2002;3(12):1773-81.
- Gründer G, Medori M, Kungel M, McQuade, R.Kikuchi T. Aripiprazole: Pharmacology of a new antipsychotic. *Eur. Arch. Psychiatry Clin. Neurosci.* 2002;252 (Suppl. 1):51.
- Jody D, Marcus R, Keck P, et al. Aripiprazole versus placebo in acute mania. *Int. J. Neuropsychopharmacol.* 2002a;5 (Suppl. 1):S57.
- Jody D, Saha A, Iwamoto T, et al. Meta-analysis of weight effects with aripiprazole. *European Neuropsychopharmacology* 2002b;12:S290-S290.
- Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002;63(9):763-71.
- Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 1999;20(6):612-27.
- Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability and safety of aripiprazole following single and multiple oral dose administration. *Eur. Neuropharmacol.* 2000;10 (Suppl. 3):306.
- Marcus R, Saha A, Jody D, Tourkodimitris S, Archibald D, Iwamoto T. Aripiprazole versus placebo in acute mania. *European Neuropsychopharmacology* 2002;12:S289-S289.
- Marder SR, R.D. M, Stock E, et al. Aripiprazole in the treatment of schizophrenia: Safety and tolerability in short-term placebo-controlled trials. *Schizophrenia Res.* 2003;in press.
- McGavin JK, Goa KL. Aripiprazole. *CNS Drugs* 2002;16(11):779-86; discussion 787-8.
- McQuade R, Carson W, Saha A, Ingenito G, Ali M, Archibald D. Aripiprazole for long-term maintenance treatment of schizophrenia. *European Neuropsychopharmacology* 2002a;12:S288-S288.
- McQuade R, Saha A, Kaplita S, Archibald D, Iwamoto T, Stock E. Meta-analysis of the safety and tolerability profile of aripiprazole in schizophrenia. *European Neuropsychopharmacology* 2002b;12:S290-S290.
- Millan MJ. Improving the treatment of schizophrenia: focus on serotonin (5-HT)_{1A} receptors. *J Pharmacol Exp Ther* 2000;295(3):853-61.
- Petrie J, Saha AR, McEvoy JP. Aripiprazole, a new atypical antipsychotic: phase 2 clinical trial results. *Eur. Neuropsychopharmacol.* 2002;7 (Suppl. 2):S227.
- Pigott TA, Saha A, Ali M, et al. Aripiprazole vs. placebo in the treatment of stable, chronic schizophrenia. *APA Annual Meeting, Philadelphia; Abstract NR314* 2002.
- Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder. *Arch. Gen. Psychiatry* 2003;(in press).
- Rickels K, Weisman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry* 1982;43(12 Pt 2):81-6.
- Saha A, Carson WH, Ali M, Dunbar GC, Ingenito G. Efficacy and safety of aripiprazole and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder. *World J. Biol. Psychiatry* 2001;2(Suppl. 1):305.
- Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. *J Clin Psychiatry* 2001;62(12):923-4.

US Prescribing Information Abilify™.

Yokoi F, Grunder G, Biziere K, et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC

14597): a study using positron emission tomography and [11C]raclopride. *Neuropsychopharmacology* 2002;27(2):248-59.