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Aripiprazole: A Novel Atypical Antipsychotic Drug With a Uniquely Robust Pharmacology

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ABSTRACT

Aripiprazole (Abilify®) is an atypical antipsychotic drug that has been recently introduced for clinical use in the treatment of schizophrenia. Aripiprazole has a unique pharmacologic profile that includes partial agonism at several G-protein coupled receptors (GPCRs) [especially dopamine (D_2) and 5-HT_{1A}] and antagonistic action at others (especially 5-HT_{2A}). Clinical trials indicate that aripiprazole is effective in treating the positive and negative symptoms of schizophrenia. In short-term studies rapid onset of action (within one week) has been demonstrated. Preliminary data indicate that aripiprazole may also be effective in the treatment of manic symptoms of bipolar disorder. At recommended doses, aripiprazole appears to be safe and well tolerated in most adult patients with schizophrenia and schizoaffective disorder. There is only limited information available on the use of aripiprazole in children and adolescents, and pilot data suggest that a revised dosing strategy, based on weight, is indicated in this population. In the long-term studies, the use of aripiprazole was associated with continued efficacy, good compliance and increased time-to-relapse.

Aripiprazole represents the first functionally selective atypical antipsychotic drug.

INTRODUCTION

Affecting approximately 1% of the U.S. population, schizophrenia is a chronic mental illness that is characterized by positive symptoms (i.e., delusions and hallucinations), neg-

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ative symptoms (i.e., social withdrawal, poor hygiene and lack of motivation) and cognitive deficits (4,43,88). In addition to its symptom profile, schizophrenia is associated with significant social impairments. Over the past 50 years, two major breakthroughs in antipsychotic drug development have resulted in substantial advancements in the pharmacologic treatment of schizophrenia (31,55). The first breakthrough occurred in 1952 with the introduction of chlorpromazine, which became the standard typical antipsychotic drug. Like all typical antipsychotic drugs chlorpromazine exerts its main therapeutic action via D_2 receptor antagonism (78). Although they are effective in the treatment of positive symptoms of schizophrenia, typical antipsychotics (e.g., chlorpromazine, haloperidol, and fluphenazine) are only minimally effective in the treatment of negative symptoms and cognitive deficits associated with schizophrenia. Additionally, because of potent D_2 receptor blockade, typical antipsychotic drugs induce acute and chronic extrapyramidal side effects (EPS) and elevate serum prolactin. Given these limitations, there has been much interest in the development of better antipsychotic drugs for the treatment of schizophrenia.

The second breakthrough occurred with the introduction of clozapine, which was synthesized in 1958, but not formally approved for use in the US until the late 1980s (31). Clozapine, which is the standard atypical antipsychotic drug, is pharmacologically different from the typical antipsychotic drugs: it has extremely weak affinity for D_2 receptors and high affinity for 5-HT_{2A}-receptors. The pharmacologic criteria for "atypicality" were first proposed by Meltzer et al. (63); they were based on the relative affinities of the antipsychotic drugs at D_2-dopamine and 5-HT_{2A}-receptors. With the exception of quetiapine, other atypical antipsychotic drugs (i.e., clozapine, olanzapine, risperidone and ziprasidone) have 5-HT_{2A}/D_2 affinity ratios greater than 10 (62,63) Clinically, atypical antipsychotic drugs have been found to be effective in the treatment of positive as well as negative symptoms of schizophrenia. While originally tested in "treatment-resistant" patients, atypical antipsychotic drugs are now being used in patients throughout the course of schizophrenia. While their use is associated with less extrapyramidal syndrome (EPS) and prolactin level elevation than that of the typical antipsychotic drugs, some atypical antipsychotics cause weight gain and QT prolongation (delayed cardiac depolarization which can cause dysrhythmias and possible ventricular fibrillation) (6,33,47,55,61).

In November, 2002, aripiprazole (Abilify®), was approved by the U.S. FDA and introduced for the treatment of schizophrenia. Aripiprazole has been described as "the first next generation atypical antipsychotic" (15,40,47,71,82,91) because of its unique pharmacologic profile, which includes a lower 5-HT_{2A}/D_2 affinity ratio (73) and a different side effect profile (43,59) from all other atypical antipsychotic drugs. Additionally, recent pharmacologic evidence indicates that aripiprazole represents a "magic shotgun," being functionally selective at multiple biogenic amine receptors (72,80). This review article presents information on the pharmacodynamics, pharmacokinetics, clinical efficacy, safety and tolerability of aripiprazole. This article reviews receptor pharmacology of aripiprazole as well as the clinical studies that compare aripiprazole to placebo, typical antipsychotics or other atypical antipsychotic drugs. As this review does not include every preclinical study on aripiprazole, the reader is referred to other review articles for additional information on aripiprazole's development and preclinical profile (11,35,55,61,90).

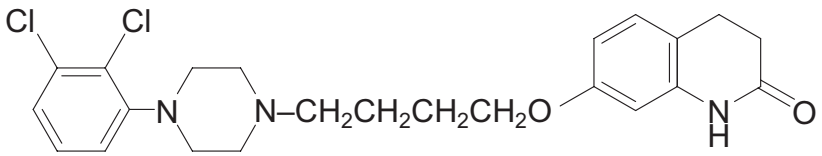

Fig. 1. The chemical structure of aripiprazole.

RECEPTOR PHARMACOLOGY

Aripiprazole, 7-{4-[-(2,3-dichlorophenyl)-1-piperazinyl]-butyloxy}-3,4-dihydro-2(1H)-quinolinone (Fig. 1), is a quinolinone derivative discovered by scientists at Otsuka Pharmaceuticals (49,66) and later licensed to Bristol-Myers Squibb Co. for further development for the treatment of schizophrenia and related disorders (13,38,54,66). Aripiprazole has a molecular weight of 448.38 (91) and a complex pharmacologic profile that includes activity at the dopaminergic and serotonergic receptors, along with activities at other receptors.

Dopamine (DA) Receptor Activity

Data from binding studies consistently indicate that aripiprazole has a high affinity for dopamine D_2 (15,49,54,80) and D_3 (15,54,80) receptors, a moderate affinity for D_4 receptors (54,60) and low affinity for D_1 and D_5 receptors (80). Lawler et al. (54) reported aripiprazole's high affinity for D_2-like dopamine receptors in rat striatum (K_i = 4.7 nM) and in Chinese Hamster Ovary (CHO) cells lines, each transfected with the D_{2S} and D_{2L} isoforms of the human dopamine receptor (K_{is} < 1.0 nM). Burris et al. (15) reported a somewhat higher affinity (K_i = 0.34 nM) for human cloned D_2 receptors, while Shapiro et al. (80) reported that aripiprazole had similar affinity at the human D_{2L} (K_i = 0.74 nM) and human D_3 (K_i = 1.0 nM) receptors, and had negligible affinity for the human D_1 (K_i = 1960 nM) and D_5 dopamine receptors (K_i = 2590 nM) and low affinity for the rat D_4 receptor (K_i = 510 nM). Taken together, these findings indicate that aripiprazole has high affinity for both D_2 and D_3 receptors and low affinity for other dopamine receptor subtypes.

Functionally, aripiprazole has demonstrated both agonist and antagonist properties at the D_2 receptor, which fits a partial agonist pharmacologic profile (2,50,55,66,87). While aripiprazole has high affinity for D_2 receptors, it has low intrinsic efficacy (15,89). Aripiprazole has been touted as a "dopamine system stabilizer" (48,79,82) because *in vivo* studies demonstrate that it reduces dopamine release via presynaptic agonism (49) to behave as a functional antagonist of some postsynaptic D_2- receptors (49) and as an agonist at others (38).

Several studies focused on aripiprazole's binding affinity and partial agonistic action in various cell lines transfected with isoforms of the human D_2 receptors. One *in vitro* study (15) examined the affinity values and the ability of aripiprazole to activate D_2 receptors in CHO cells transfected with human recombinant D_{2L} receptors. Under conditions that promoted coupling (agonist-labeled) or uncoupling (antagonist-labeled) of receptors to G proteins aripiprazole displayed high affinity for both states of the D_2 receptors (K_i = 0.34 vs. 0.70 nM). The ratio of affinity ($K_{i\,Low}/K_{i\,High}$) of aripiprazole was intermediate between two full agonists (quinpirole and dopamine) and two antagonists (butaclamol and

haloperidol), suggesting that aripiprazole is a low efficacy D_2 receptor partial agonist. In the paper by Burris et al. (15) aripiprazole is reported to potently inhibit forskolin-stimulated adenylate cyclase activity with a maximum efficacy of ~85% that of dopamine.

A recent study (2) examined the action of aripiprazole on prolactin (PRL) release and cAMP accumulation by retrovirally transducing the short (D_{2S}) and the long (D_{2L}) isoforms of the human D_2 receptor gene into GH4Cl, a rat pituitary cell line. The maximal binding capacity at the D_{2S} receptor-expressing GCH4Cl cell membrane was approximately four-fold higher than at D_{2L} receptor-expressing GCH4Cl cell membrane. The K_d and B_{max} for [^{3}H]raclopride was 2182 pM and 26.6 pmol/mg protein for D_{2S} compared to 1898 pM and 6.58 pmol/mg protein for D_{2L}. Affinity characteristics for the two isoforms were similar in these cells. Aripiprazole dose-dependently inhibited the forskolin-stimulated increase in PRL secretion in D_{2L}- as well as D_{2S}-receptor-expressing GH4Cl cells. The maximal inhibition of PRL release by aripiprazole for D_{2S}-receptor-expressing cells was greater than for D_{2L}-receptor-expressing cells. In the D_{2S} cells, the maximal inhibition by aripiprazole was 82.1%, compared to 118% for the full agonist, dopamine (DA). In the D_{2L} cells, the maximal inhibition by aripiprazole was 38.0%, compared to 93.6% for DA. Assays for cAMP accumulation within cells indicated that aripiprazole inhibited dose-dependent forskolin-induced cAMP accumulation in both D_{2L} and D_{2S} receptor-expressing cells. For the D_{2S}, the maximal inhibition was 77.6%, compared to 85.1% for DA. For the D_{2L}, the maximal inhibition was 64.6%, compared to 93.0% for DA.

By contrast, Lawler et al. (54) and Shapiro et al. (80) reported that the partial agonist actions of aripiprazole vary widely depending upon the cellular milieu. Thus, nearly full agonism, weak partial agonism and frank antagonism, have all been reported, depending upon the assay system and cellular background. Shapiro et al. (80) also reported that aripiprazole is a highly efficacious D_3 agonist and a D_4 partial agonist. It is well known from classical pharmacology that partial agonists may exert a variety of actions depending upon the receptor and G-protein expression levels (48). Thus, the most parsimonious explanation of the multiple actions of aripiprazole at D_2 receptors is that the agonist actions are simply due to different levels of receptor expression. Shapiro et al. (80) directly examined this possibility and found that aripiprazole's actions could not be explained by various levels of receptor expression because aripiprazole behaved as a neutral antagonist in the cell line with the highest level of receptor expression. This was most pronounced when GTPγS binding studies were performed under conditions of high levels of receptor reserve (e.g., 'spare receptors') in HEK-293 cells (80) and where aripiprazole behaved as a neutral antagonist—findings that are not compatible with aripiprazole being a simple partial agonist. These findings led to the suggestion that aripiprazole displays 'functional selectivity' being an agonist, partial agonist and antagonist depending on the cellular milieu (72).

In vitro and *in vivo* animal studies provide further evidence of aripiprazole's unique actions at dopamine receptors. In rat striatum, Inoue and colleagues (38) found that aripiprazole had an approximately 100-fold higher affinity for D_2 receptors than D_1 receptors (K_{is} = 38 vs. 5100 nM, respectively). Behaviorally, aripiprazole, like all antipsychotic drugs, antagonized apomorphine-induced stereotyped behavior and hyperlocomotion (49), thus suggesting antagonist activity at mesocortical and mesolimbic D_2 receptors or agonism of presynaptic D_2-dopamine receptors. Aripiprazole had no cataleptogenic activity even at the highest dose tested (40 mg/kg) (79). This finding was consistent with its partial agonist activity at striatal D_2 receptors. Neurochemically, *in vivo* microdialysis (79)

indicated that aripiprazole decreased extracellular DA in the rat striatum and frontal cortex — an effect consistent with D_2 autoreceptor agonism.

In mice, Nakai et al. (64) investigated whether acute or repeated administration of aripiprazole, haloperidol, or risperidone produced a cataleptic response (a model for EPS in humans) or increased dopamine metabolism in the striatum and olfactory tubercle (a model for D_2 antagonism). Acute treatment with higher doses of aripiprazole (30 mg/kg p.o.), risperidone (10 mg/kg p.o.) or haloperidol (3 mg/kg p.o.) resulted in increased duration of catalepsy. In contrast to haloperidol, risperidone and aripiprazole, by chronic (for 21 days) administration, attenuated cataleptic response. Data on the effects of acute administration of these drugs on dopamine and its metabolites in the olfactory tubercle indicated that at all doses tested aripiprazole produced a modest increase in dihydroxyphenylacetic acid (DOPAC) levels. Homovanillic acid (HVA) levels were affected by aripiprazole only at the 10 mg/kg dose. In contrast, haloperidol elevated DOPAC and HVA at 1 and 3 mg/kg doses. Only at the highest dose used (10 mg/kg) risperidone decreased dopamine levels while it produced significant increases in DOPAC and HVA at all doses tested.

One clinical study (92) used positron emission tomography (PET) to characterize the relationship between doses of aripiprazole and its (striatal) D_2/D_3 dopamine receptor occupancy in humans. PET was performed on 15 healthy males before and after two weeks of administration of aripiprazole. Aripiprazole was administered orally once per day in the morning to the subjects at 30 mg ($n = 4$), 10 mg ($n = 2$), 2 mg ($n = 3$), 1 mg ($n = 3$), and 0.5 mg ($n = 3$) doses. The plasma concentrations of aripiprazole were determined just before administration of the last dose and at intervals between 3.5 and 180 h after day 14 of administration. Measures of plasma concentrations and D_2/D_3 receptor occupancy in the putamen and corpus striatum of the human brains indicated that increasing doses of aripiprazole correlated with a proportional increase in the plasma concentration of the drug and a decrease in the binding potential of [^{11}C]raclopride. D_2/D_3 receptor occupancy ranged from 40% (at 0.5 mg/day) to 95% (at 30 mg/day). Grunder et al. (36) noted that these data did not match the concept of "therapeutic window" proposed by Farde et al. (29), which suggests that the efficacy of antipsychotics occurs within 60–80% occupancy and EPS is associated with values above the 80% threshold. Because aripiprazole lacks EPS in humans these data are consistent with the notion that aripiprazole is a D_2/D_3 partial agonist in human striatum.

Several *in vivo* studies (1,69,70) consistently reveal that aripiprazole suppresses serum prolactin in humans — an effect likely to be mediated by D_2-partial agonism. Potkin et al. (69) presented data from a short-term (4-weeks) trial involving 404 patients that indicate that neither at 20 nor at 30 mg/day does aripiprazole increase prolactin levels. In fact, mean serum prolactin levels decreased from baseline levels in both groups (20 mg/day: –6.6 ng/mL and 30 mg/day: –6.4 ng/mL). In contrast, patients who were randomized to risperidone demonstrated significant increases in mean prolactin levels (+47.9 ng/mL). Data from five preclinical studies (1) involving 1,648 patients indicated that aripiprazole increased prolactin levels above the upper limit of normal in only 1.8% of patients, compared to substantial increases in prolactin levels with either haloperidol or risperidone (54 and 89%, respectively).

Serotonin (5-HT) Receptor Activity

In the first preclinical study on the effects of aripiprazole on 5-HT receptor activity, Lawler et al. (54) used transfected Human Embryonic Kidney (HEK) cells and reported the binding affinities of aripiprazole at the human cloned 5-HT_6 and 5-HT_7 receptors ($K_{0.5}$ = 161 and 14.5 nM, respectively). Using recombinant CHO cell membranes, Shapiro et al., (80) found that aripiprazole had highest affinity for h5-HT_{2B} receptors (0.36 nM), significant affinity (5-30 nM) for h5-HT_{1A}, r5-HT_{2A}, h5-HT_{2A}, h5-HT_{2C}, and h5-HT_7 and low affinity (570–1240 nM) for h5-HT_{1B}, r5-HT_3, h5-HT_{5A}, and h5-HT_6 receptors. Thus, aripiprazole has a highly complex serotonergic pharmacology with significant activity at a number of 5-HT receptors.

Functionally, Shapiro et al. (80) reported that aripiprazole was a potent (EC_{50} = = 8.67 ± 0.16) partial agonist (E_{max} = 68.1% of effect of 10 μM 5-HT) of h5-HT_{1A} receptors. Similar results have been reported by others (41). Shapiro et al. (80) also reported that aripiprazole was a weak partial agonist at 5-HT_{2C} and 5-HT_7 receptors and a functional antagonist at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_6 receptors. Using the chimeric G-protein to functionally characterize 5-HT_6 ligands in HEK cells, Zhang et al. (93) presented data indicating that aripiprazole was a weak 5-HT_6 antagonist. In their *in vivo* study, Marona-Lewicka and Nicols (60) used a drug discrimination procedure on thirteen male Sprague Dawley rats to evaluate the discriminative stimulus effect and relative potency of aripiprazole relative to the selective 5-HT_{1A} agonist, [(-)-4R-6-acetyl-4-(di-*n*-propylamino)-1,3,4,5-tetrahydrobenz(c,d) indole; LY293284]. The results indicated that aripiprazole was less potent than LY 293284 (ED_{50} = 1.39 vs. 0.024 μmol/kg) and it acted as an agonist at the 5-HT_{1A} receptor *in vivo*.

Activity at Other Receptors

Comprehensive pharmacological profiling of aripiprazole (80) indicates that *in vitro* aripiprazole displays a moderate-to-high affinity for a large number of human cloned biogenic amine G-protein-coupled receptors (GPCRs) (see selected K_i values in Table 1). Aripiprazole has modest affinity for the human H_1 histamine receptor (25.1 nM) and α_1-adrenergic receptors, which could explain its minimal propensity to induce short-term weight gain (51). Aripiprazole has low affinity for guinea pig H_3 histamine receptors (224 nM) but negligible affinities (K_i > 10,000 nM) for the human H_2 and human H_4 histamine receptors. Within the adrenergic system, aripiprazole displays moderate affinity at many adrenergic receptors (Table 1). Aripiprazole does not have appreciable affinity for any of the five human muscarinic receptor subtypes (13,65,80).

Kalkman and Loetscher (42) examined the antagonistic potencies of many antipsychotics, including aripiprazole, at human α_{2A} and α_{2C} adrenoceptors expressed in CHO cells and at the D_{2L} receptors stably expressed in HEK 293 cells. At concentrations of 0.01–1000 nM all of the antipsychotics tested, including aripiprazole, were silent antagonists and did not interact potently with the human α_{2A} or α_{2C} receptors. In the HEK 293 cell system, aripiprazole has full agonist action at D_{2L} receptors. While it was as efficacious as the endogenous dopamine, aripiprazole had an approximately 40-fold higher affinity. In contrast, all other antipsychotics tested were antagonists at the D_{2L} receptor; their potency was reported as: risperidone > chlorpromazine > iloperidine > ziprasidone > clozapine > quetiapine > yohimbine > idazoxan.

Putative Mechanisms of Action

Several groups of investigators have examined a variety of hypotheses relating to "atypicality," in attempts to understand the actions of aripiprazole at dopamine and 5-HT receptors. These include, most prominently, aripiprazole's specific actions as a dopamine partial agonist, the possibility of dopaminergic functional selectivity and the possibility that aripiprazole may exhibit functionally selective non-selectivity.

TABLE 1. K_i values for aripiprazole at multiple receptors

Receptors			
Type	Subtype		Average K_i of aripiprazole (nM)
Dopaminergic	D_1		1173.5
	D_2		1.64
	D_{2L}		0.74
	D_3		7.1
	D_4		512
	D_5		2133
	Dopamine transporter		3215.5
Cholinergic, muscarinic	M_1		6778
	M_2		3508.5
	M_3		4678
	M_4		1520
	M_5		2328.5
Serotoninergic	5-HT transporter		1081
	5-HT_{1A}		5.59
	5-HT_{1B}		831.5
	5-HT_{2A}		8.7
	5-HT_{2A}		35
	5-HT_{2A}	(rat)	4.6
	5-HT_{2A}	(rat)	22
	5-HT_{2B}		0.36
	5-HT_{2C}	(rat)	76
	5-HT_{2C}	(rat)	181
	5-HT_{2C}		628
	5-HT_3	(rat)	630
	5-HT_5		1241
	5-HT_6		642.6
	5-HT_7		9.97
Adrenergic	α_{1A}		25.85
	α_{1B}		34.4
	α_{2B}		102.33
	α_{2C}		37.63
	β_1	(rat)	>10,000
	β_1		141
	β_2	(rat)	>10,000
	β_2		163
Histaminergic	H_1		27.93
	H_2		>10,000
	H_3	(guinea pig)	>10,000
	H_3	(guinea pig)	2242
	H_4		>10,000

* Unless otherwise indicated all receptors are human.

Dopamine partial agonism and 'dopamine-serotonin system stabilizer'

Aripiprazole has been advertised as "a dopamine-serotonin system stabilizer" due to its partial agonistic action at D_2 and 5-HT_{1A} and its functional antagonism at the 5-HT_{2A} receptors. Data from several studies lend support to this model. Byars et al. (16) used CHO cells expressed in human recombinant D_2, D_3, 5-HT_{1A}, and 5-HT_{2A} receptors and found that aripiprazole acted as a partial agonist at D_2 and 5-HT_{1A} receptors and an antagonist at r5-HT_{2A} receptors. Another *in vivo* study (41) used microdialysis to examine the effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function in active rats. Extracellular concentrations of dopamine and its major metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were determined along with its effect on a major metabolite of 5-HT, 5-hydroxyindole acetic acid (5HIAA) in the medial prefrontal cortex and striatum. In these brain areas acute administration of aripiprazole did not affect extracellular dopamine levels, but moderately increased DOPAC and HVA levels, and was associated with a significant decrease in 5-HIAA levels. Since these systems have been prominently implicated in the pathology of schizophrenia, such a diminution of their global activity could be salutary for treating at least some symptoms of schizophrenia. As previously mentioned, however, mere partial agonism at D_2 and 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors cannot explain the myriad actions of aripiprazole *in vitro* and *in vivo*.

Functional selectivity

The notion of "functional selectivity" emphasizes that the characteristics of the expression system (local membrane environment and cellular milieu) are important in defining pharmacological properties of drugs (54). This model suggests that aripiprazole is not simply a partial agonist at the D_2 receptor, but a drug whose variable potencies and efficacies (at D_2 and other receptors) are determined by cellular location, expression level and relative complement of a variety of signaling proteins. Supporting this hypothesis are studies (37,80) demonstrating variable receptor binding affinities and functional properties of aripiprazole in different cell lines and in environments with different levels of receptor reserve. Lawler et al. (54) found that the receptor binding profile of aripiprazole for D_{2L} receptors was lower in CHO cells than in C-6 glioma cells ($K_{0.5}$ = 0.59 vs. 1.71 nM, respectively). In the C-6 glioma cells, aripiprazole produced dose-dependent partial inhibition of cAMP synthesis, with maximal inhibition of 30%. In contrast, in the CHO cells, at the maximal concentration (10 μM) aripiprazole did not inhibit cAMP synthesis. Shapiro et al. (80) demonstrated that, in the 5-HT_{1A} receptor stably expressed in CHO cells, aripiprazole had a lower potency (EC_{50} = 329 nM) than serotonin (EC_{50} = 4.5 nM) at inhibiting forskolin-stimulated cAMP production. In C-6-glioma cells that expressed 5-HT_{2A} receptors without receptor reserve, aripiprazole demonstrated even lower intrinsic activity by causing increases in PI hydrolysis only at the highest concentration tested (10 μM). In GF62 cells expressing rat 5-HT_{2A} receptor with substantial receptor reserve, aripiprazole was a partial agonist (EC_{50} = 48 nM) and had an intrinsic activity that was 12.7% that of the full agonist 5-HT. Aripiprazole's affinities in HEK 293 cells in an assay buffer containing NaCl were significantly lower than values obtained earlier by Lawler et al. (54) who used stable, transfected CHO cells assayed in a Na^+-free buffer. Other diverse effects of aripiprazole were seen at 5-HT_{2B} (inverse agonist), 5-HT_{2C} (partial agonist),

5-HT_6 (antagonist) and 5-HT_7 (weak partial agonist) receptors. Aripiprazole acted as a pure antagonist in MES-23.5 cells and in CHO cells with stably transfected D_{2L} receptors.

Additionally, as already mentioned, *in vivo* studies with aripiprazole display a variety of actions at D_2-like receptors behaving in some cases as a partial agonist and other times as an antagonist (38,49). These varied actions cannot be explained simply by the assumption that aripiprazole is a partial agonist and are most parsimoniously explained by the notion that aripiprazole displays functional selectivity.

Other mechanisms

Another model, which has attempted to provide a unified explanation for "atypicality," is the "rapid dissociation rate" hypothesis. According to this hypothesis (45) atypical antipsychotic drugs are characterized by low affinities and, hence, rapid dissociation rates from D_2 receptors. Recently, Meltzer et al. (62) and Roth et al. (72) examined the theory proposed by Kapur and Seeman (45) that suggests that the profile of atypical antipsychotic drugs can be attributed to their relatively weak affinities and subsequent fast dissociation rates (K_{off}) from D_2 receptors. Unlike clozapine and quetiapine (but similar to olanzapine, risperidone and ziprasidone), aripiprazole is predicted to dissociate slowly from the D_2 receptor (72). Aripiprazole's extremely high affinity at D_2 receptors is not consistent with the "rapid dissociation hypothesis."

Shapiro et al. (80) explored the D_2/D_3 hypothesis of "atypicality" (22,76), which suggests that the clinical efficacy of some atypical antipsychotic drugs (such as amilsulpride and remoxipride) could be related to high affinity for D_2- and D_3-receptors and negligible affinity for 5-HT_{2A} receptors. While aripiprazole does have a high affinity for the D_2 and D_3 receptors, it also has a high affinity for 5-HT_{2A} receptors. More recently, we have proposed (72) that aripiprazole and other atypical antipsychotic drugs display functionally selective non-selectivity. Thus, the beneficial actions of aripiprazole and similar agents are likely to be due to the accumulated actions of aripiprazole at the variety of biogenic amine receptors. This model also proposes that no single molecular target is likely to be solely responsible for the actions of clinically effective atypical antipsychotic drugs (Fig. 2).

PHARMACOKINETICS

In two randomized, placebo-controlled, double-blind studies involving 48 normal volunteers (57) the mean peak plasma levels of aripiprazole of 55 ng/mL (at 5 mg/day dose) and 302 ng/mL (at 20 mg/day dose) were obtained at 3 to 5 h after treatment Steady-state concentrations were reported after two weeks of daily dosing. The mean elimination half-lives of aripiprazole and its major metabolite, dehydro-aripiprazole, are 75 and 95 h, respectively (13). Aripiprazole is, thus, usually taken orally in tablet form once a day. Neither the timing of drug administration (morning or evening) nor mealtime (with or without) affects the metabolism of the drug (57). Effective clinical doses of aripiprazole generally range from 10 to 30 mg.

Aripiprazole is extensively metabolized by the cytochrome P450 3A4 and 2D6 systems in the liver and its terminal elimination half-life ranges from 48–68 h (13,57). The clearance of dehydro-aripiprazole is reduced 20% in the elderly as compared to younger adult subjects. Approximately 8% of Caucasians are poor metabolizers (PM) of the drug, whereas the rest are extensive metabolizers (EM). No dosage adjustment for aripiprazole

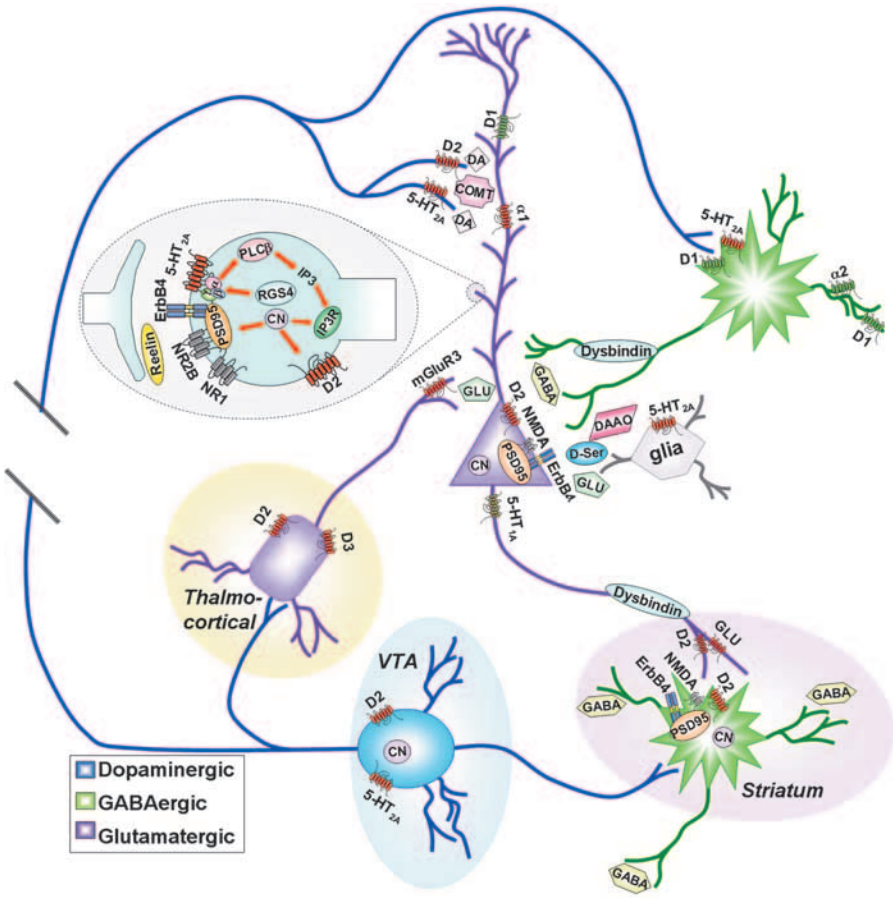

Fig. 2. Aripiprazole's site of action reveals a complex mixture of effects at a variety of cellular targets. Shown is a schematic 'wiring diagram' of prefrontal cortical glutamate neurons which likely represent a final common pathway in the pathogenesis of schizophrenia (72,73). The diagram also shows many of the molecules implicated in the pathogenesis of schizophrenia, including dysbindin, reelin, RGS-4, 5-HT_{2A}-serotonin, D_2-dopamine, calcineurin and NMDA receptors. Aripiprazole is suggested to have a variety of actions at dopaminergic and non-dopaminergic receptors leading to a normalization of glutamatergic neurotransmission. These may include antagonism at 5-HT_{2A} and α_1-adrenergic receptors and partial agonism at 5-HT_{1A} receptors to diminish glutamatergic neurotransmission (72,73). Additionally, partial agonism of presynaptic D_2-receptors might diminish dopaminergic neurotransmission in critical dopaminergic fields while antagonism at other receptors might directly diminish glutamatergic neurotransmission. The close physical proximity of D_2- and 5-HT_{2A}-receptors and many of the molecules implicated in the pathogenesis of schizophrenia suggests that modulating the activity of either of these receptors may alter the functional activity of many of the mediators, including reelin, dysbindin, calcineurin and ERB-4.

is required on the basis of a person's gender, race, or smoking status. Two studies (55) evaluated the effects of renal and hepatic impairment on the pharmacokinetics of a single dose of aripiprazole (15 mg). In the first study, serial blood and urine specimens were collected and analyzed for aripiprazole and its metabolites in 19 subjects with varying degrees of liver cirrhosis and six healthy volunteers. In the second study, specimens were collected from six subjects with severe renal impairment and six healthy volunteers. Re-

sults indicated that neither renal nor hepatic impairment had a clinically meaningful impact on aripiprazole's pharmacokinetics.

Findling et al. (30) conducted a pilot study aimed at evaluating the pharmacokinetics, safety and optimal dosing regimen of aripiprazole in children and adolescents. Their "revised" dosing strategy was based on weight: 1 mg/day for <25 kg; 2 mg/day for 25–50 kg; 5 mg/day for 50–70 kg, and 10 mg/day for >70 kg. Steady-state aripiprazole concentrations were attained within 14 days in both children and adolescents.

DRUG INTERACTIONS

CYP3A4 and CYP2D6 are responsible for aripiprazole's metabolism. Therefore, inhibitors and inducers of these enzymes are likely to affect the metabolism of this drug (91). Because ketoconazole and nefazodone (inhibitors of CYP3A4) and quinidine, fluoxetine and paroxetine (inhibitors of CYP2D6) may inhibit aripiprazole's metabolism and increase its blood levels, the manufacturer (13) recommends that the dose of aripiprazole should be lowered by one-half when administered concomitantly with these drugs. In contrast, carbamezapine and phenytoin (inducers of CYP3A4) may induce aripiprazole metabolism and lower its blood levels, thus requiring dosage adjustment based on clinical evaluations.

To date, there are no reports of significant metabolic changes when aripiprazole is co-administered with drugs metabolized by other cytochrome P450 enzymes (such as famotidine, dextramethorphan, warfarin, or omeprazole). Also, no dosage adjustment is required with the co-administration of aripiprazole with valproate (which showed a 25% decrease in C_{max} and AUC of aripiprazole) or lithium (which showed no appreciable interaction) (6,13,91).

CLINICAL EFFICACY

Aripiprazole was developed for the treatment of schizophrenia (13), and it has been shown to be effective in treating both positive and negative symptoms. Data are limited regarding aripiprazole's effect on neurocognitive deficits in schizophrenia. Recently published data from two studies indicate that aripiprazole may be effective in the treatment of patients with acute bipolar mania.

Schizophrenia and Related Disorders

Five short-term (4 weeks) clinical trials were conducted to evaluate the effectiveness of aripiprazole in inpatients with an acute relapse of schizophrenia or schizoaffective disorder (19,23,43,67,69,70). A brief summary of short-term clinical trials is presented in Table 2. In the three haloperidol-controlled studies, after a 3–5 day washout period, patients were randomly assigned to either placebo, aripiprazole 15 mg/day, aripiprazole 30 mg/day, or haloperidol 5-10 mg/day. Results indicated that aripiprazole was not significantly different from haloperidol in the response rates. It produced an approximately 30% decrease from baseline in Positive and Negative Symptom Scale (PANSS) total score at last visit with either drug. Data also indicated that aripiprazole as well as haloperidol were effective as measured by the PANNS negative and positive scores and the CGI-S score. Improvement in efficacy measures occurred within one week; these improvements

were maintained through the end of the 4-week studies. In one risperidone-controlled study (69), 404 patients from 40 medical centers in the United States underwent a 5-day placebo washout period before their assignment to either aripiprazole (20 or 30 mg/day), risperidone (6 mg/day), or placebo. Results indicated that at either dose aripiprazole was superior to placebo and comparable to risperidone in efficacy. In the fifth trial, aripiprazole (10, 15, or 20 mg/day) was compared to placebo. Results indicated that aripiprazole was superior to placebo in the efficacy parameters of interest. In short-term studies, rapid onset of efficacy (within one week) was demonstrated in the aripiprazole groups. These results indicate that aripiprazole is at least as effective as haloperidol or risperidone in the short-term treatment of schizophrenia. These studies did not reveal any intrinsic advantage of aripiprazole over either a conventional antipsychotic drug (e.g., haloperidol) or a commonly prescribed atypical antipsychotic drug (e.g., risperidone). It is not clear whether this study was adequately powered to reveal subtle advantages or whether the appropriate secondary measures were used which could have revealed either advantages or disadvantages of the comparator. Additionally, there is a continued controversy regarding the appropriate dose of haloperidol, the conventional antipsychotic drug, and further studies using this drug at a variety of doses are needed.

One multicenter, open-label study (17) involving 255 stable outpatients focused on the neurocognitive effects of aripiprazole (30 mg/day) vs. olanzapine (15 mg/day). Patients were assessed on a three factor neurocognitive battery of tests (general cognitive ability, executive functioning, and secondary verbal memory) at baseline, and at weeks 8 and 26 (last visit). Compared to olanzapine, aripiprazole showed similar improvement in general cognitive function and produced significantly greater improvement from baseline in secondary verbal memory at weeks 8 and 26. Neither medication showed improvement in executive functioning. These studies indicate that aripiprazole may be superior to olanzapine on selected cognitive areas, although the open-label design of the study places limitations on these conclusions.

Schizophrenia usually presents during late adolescence or early adulthood (4). To date, only one pilot study (14) presented data on the clinical efficacy and tolerability of aripiprazole in patients with first-episode schizophrenia. Twenty patients (mean age 22 years) (duration less than 1 year) participated in a multicenter, fixed dose, open-label 28-day study of aripiprazole. Following a washout period, patients received aripiprazole 15 mg/day ($N = 14$), 20 mg/day ($N = 5$) and 30 mg/day ($N = 1$). Efficacy was determined by the Positive and Negative Symptom Scale (PANSS) — total score and the Clinical Global Index (CGI) score. This pilot study demonstrated that first-episode patients showed significant clinical improvement across all doses of aripiprazole. Again, the open label design limits the potential impact of this study.

Data from two studies (18,45,58,68) were used to evaluate the longer-term (26 and 52 weeks) efficacy of aripiprazole. In a placebo-controlled study of 310 outpatients with chronic, stable schizophrenia, Carson et al. (18) examined the effects of aripiprazole treatment over a 26 week period. Compared with placebo, aripiprazole (15 mg/day) was significantly more effective in increasing time-to-relapse, as well as in reducing the number of relapses and improving PANSS total scores and PANSS positive subscale scores. A 52-week, double-blind comparison study (58) involving 1,294 acute, relapsing patients demonstrated that, compared to haloperidol (10 mg/day), patients on aripiprazole (30 mg/day) demonstrated significant improvement in PANNS negative scores and in depressive symptoms as measured by Montgomery-Åsburg Depression Rating Scale

(MADRS) scores. Time to relapse was similar for both groups (5,45,68). These results indicate the sustained efficacy of aripiprazole in stabilized patients with chronic schizophrenia.

As aripiprazole becomes more widely prescribed, it is likely that case reports will emerge regarding its clinical efficacy in other domains of schizophrenia treatment. To date, one case report (27) presented the effective use of aripiprazole in a treatment-resistant patient with schizoaffective disorder who had significant tardive dyskinesia (TD). The patient was started on 15 mg daily and raised to 30 mg daily after two weeks. The patient's Abnormal Involuntary Movement Scale (AIMS) improved from 12 to 2 after four weeks on aripiprazole. In contrast, another case report (26) describes two chronically ill patients with schizophrenia who experienced exacerbation of paranoia and anger when aripiprazole (15 and 10 mg/day) was added to stable doses of antipsychotic medication (haloperidol and olanzapine, respectively).

Mood Disorders

To date, two studies indicate that aripiprazole is effective and well tolerated in patients with acute bipolar mania (Table 2). The first study (46,58) involved 262 patients with acute mania in a Phase III double-blind, placebo-controlled 3 week trial of aripiprazole (30 mg) vs. placebo. The primary measure of efficacy was the change in Young Mania Rating Scale (YMRS). Total score with response was defined as a 50% or greater reduction. Patients treated with aripiprazole had a significantly better response than patients on placebo (40 vs. 19%). Also, 42% of the patients treated with aripiprazole completed the trial compared with 21% in the placebo group. The second study (69,70) involved 347 patients with acute mania in a 12-week flexibly dosed trial of aripiprazole (15 to 30 mg/day) vs. haloperidol (10 to 15 mg/day). Again, response was primarily defined as a 50% or greater reduction in the YMRS total scores. While reductions in the YMRS were similar for the two groups, continuation rates with aripiprazole were significantly higher when compared with haloperidol (50.9 vs. 29.1%). In both studies, data indicated higher levels of compliance in patients randomized to aripiprazole; these findings are important given the high rate of medication noncompliance in patients with bipolar disorder (75). These results indicate that aripiprazole is effective as a single agent in acute mania with an efficacy similar to that of haloperidol at a flexible but moderately high dose.

Other Disorders

There are few published studies regarding the use of aripiprazole in individuals with other disorders. Attia (7) is conducting a study that compares aripiprazole to olanzapine in the treatment of anorexia nervosa. Shapiro et al. (80) predicted on the basis of its 5-HT_{2A}/5-HT_{2C} profile that aripiprazole would have anorectic actions in humans. Aripiprazole is also being investigated in psychosis associated with Alzheimer's disease (24). A report from the multicenter, double-blind placebo-controlled trial involving 208 outpatients (mean age 81.5 years) indicated that aripiprazole may cause improvements in the Neuropsychiatric Inventory (NPI) Psychosis scale and in a subscale (delusions and hallucinations) of The Brief Psychiatric Rating Scale (BPRS). The mean aripiprazole dose used was 10 mg/day and ratings were conducted at the 10th week.

One case report (77) describes a severe exacerbation of Parkinson's disease without improvement of psychosis in a 70-year-old man with a 16-year history of Parkinson's

disease. Another case report (83) describes successful treatment with aripiprazole of a 37-year-old man with a 20 year history of Asperger's disorder.

Findling et al. (30) presented data from a 15 day, open-label study of aripiprazole (2–15 mg/day) involving 12 children (aged 6–12 years) and 11 adolescents (aged 13–17

TABLE 2. Short term clinical studies with aripiprazole

Study, authors, year of publication (reference)	DSM-IV criteria/dosing strategy, number of patients (*N*)	Design (duration in weeks)	Outcome, efficacy compared to placebo
Petrie et al., 1997 (67)	SCZ or SchAff, acute relapse Aripiprazole: 5-30 ascending (35) Haloperidol: 5-10 ascending (34) Placebo (34)	Double-blind (4)	Aripiprazole and haloperidol equally effective in improving BPRS-total, BPRS-score, CGI-severity and PANSS total
Daniel et al., 2000 (23)	SCZ or SchzAff, acute relapse Aripiprazole: 2 mg (59), 10 mg (60), 30 mg (61) Haloperidol: 10 mg (63) Placebo: (64)	Double-blind (4)	Aripiprazole and haloperidol more effective than placebo Aripiprazole 30 mg. more effective in treating negative symptoms
Kane et al., 2002 (43)	SCZ, SchzAff, acute relapse Aripiprazole: 15 mg (102), 30 mg (102) Haloperidol: 10 mg (104) Placebo: (106)	Double-blind (4)	Both aripiprazole and haloperidol effective in improving PANSS total, PANSS positive, PANSS-derived BPRS score and CGI scale
Potkin et al., 2003 (70)	SCZ, SchAff, acute relapse Aripiprazole: 20 mg (101), 30 mg (101) Risperidone: 6 mg (99) Placebo (103)	Double-blind (4)	Aripiprazole and risperdone significantly effective in improving PANSS-total, PANSS positive and negative subscales and CGI subscales
Brown et al., 2003 (14)	First-episode, SCZ, Aripiprazole: 15, 20, 30 mg	Fixed-dose (4)	Across all doses, patients on aripiprazole showed clinical improvement on PANSS-total and CGI score
Carson et al., 2002 (17)	SCZ, stable outpatients Aripiprazole: 30 mg (128) Olanzapine: 30 mg (127)	Open-labeled (8)	No significant change in executive function. Aripiprazole superior to olanzapine in secondary verbal memory
Keck et al., 2003 (46)	Bipolar, acute mania Aripiprazole: 30 mg (130) Placebo: (132)	Double-blind (3)	Aripiprazole produced significant improvement in Total score on Young Mania Rating Scale and CGI-Bipolar Version scores
Sachez et al., 2003 (74)	Bipolar, acute mania Aripiprazole: 15 – 30 mg (n.s.) Haloperidol: 10–15 mg (n.s.)	Flexibly dosed (12)	Aripiprazole treatment led to higher response rate (improvement in Young Mania Scale) and improved tolerability (staying in treatment)

Abbreviations. SCZ, Schizophrenia; SchAff, Schizoaffective; PANSS, Positive And Negative Symptom Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Index; DSM IV, Diagnostic and Statistical Manual of Mental Diseases, 4th Edition.

years) with a primary diagnosis of conduct disorder and a score of 2 or greater on the Rating of Aggression against People and/or Property (RAPP) Scale. This pilot study found that aripiprazole was effective in reducing aggressive behavior in children and adolescents with conduct disorder. Currently, the NIMH is recruiting children and adolescents (ages 8–18) for a Phase II clinical trial (81) that will evaluate the effectiveness, safety and tolerability of aripiprazole (compared to risperidone) in schizophrenia and psychosis. Lastly, Blumer (9) is conducting an investigation, which examines the effects of aripiprazole on the behavioral sequelae of children who sustain severe traumatic brain injury. Taken together these reports indicate that aripiprazole is being actively investigated as a treatment for many conditions, although firm data regarding its effectiveness in illnesses other than schizophrenia or bipolar disorder are lacking.

SAFETY AND TOLERABILITY

In animals, the safety and tolerability of aripiprazole have been compared with those of haloperidol with results indicating that aripiprazole induces fewer EPS than haloperidol, a typical antipsychotic drug (54). Sugiyama et al. (86) reported that at clinically relevant doses (0.003–0.3 mg/kg) aripiprazole was less potent than haloperidol on cardiovascular parameters in dogs. These preclinical studies, along with the receptor profile of aripiprazole, predict that aripiprazole will be well tolerated in humans. Importantly, the receptor profile predicts that aripiprazole will have minimal cardiovascular and metabolic side effects. Side effects that are seen appear to be due mainly to partial agonism at D_2 receptors (e.g., nausea, vomiting, agitation, insomnia, exacerbation of psychosis).

Data from the short-term pre-registration clinical trials indicate that aripiprazole is a safe and a "well-tolerated" antipsychotic (20,43,53,59,92). Aripiprazole's long-term (26 or 52 weeks) safety and tolerability studies are also favorable (39,45,50). Stock et al. (84) reported no adverse metabolic changes during long-term (26 week) aripiprazole therapy in patients with schizophrenia. In another trial, aripiprazole has been found to be safe and well tolerated at doses of 30 to 90 mg/day (8).

Adverse Events (AE) and Side Effects

The short-term (4- or 6-weeks), placebo- or haloperidol-controlled, clinical trials involved 1,549 inpatients with schizophrenia or schizoaffective disorder who were randomly assigned to aripiprazole ($N = 932$), haloperidol ($N = 201$) or to placebo ($N = 416$). Aripiprazole had similar AE rates to placebo, with headache (31.7%), agitation (31%), anxiety (25%), insomnia (24.1%), nausea (14%), and vomiting (12%) among reported events (6). Agitation, anxiety, nausea and insomnia are predictable because of partial agonism of aripiprazole at D_2 receptors.

In 20 patients with first-episode schizophrenia (14) who were randomized to 15, 20, or 30 mg of aripiprazole per day the most common AEs (>10% of patients) included anxiety, akithesia, tachycardia, dizziness, postural hypotension, nervousness, somnolence, and nausea. There were no clinically significant QTc or laboratory findings and there was only minimal change in body weight. In two 14-day, placebo-controlled, double-blind studies involving 48 normal volunteers (57) AEs of aripiprazole were mild to moderate in severity. In the first study, 37 healthy male subjects were randomly assigned to 5, 10, or and 15 mg/day of aripiprazole or to placebo. In the second study, 11 healthy male subjects

were randomized to aripiprazole, titrated from 10 to 30 mg/day, or placebo. Data from both studies indicated that the most commonly reported AEs were nausea and vomiting ($N = 3$), postural dizziness ($N = 4$), somnolence ($N = 1$) and asthenia ($N = 1$). Serious AEs occurred on Day 1 and resolved over the 14-days of the trials. There were no increases in QTc intervals and there were no increases in prolactin levels.

In their pilot study of 23 children and adolescents (aged 6–18 years) with conduct disorder, Findling et al. (30) reported a need to revise their dosing strategy for aripiprazole because the first 4 children reported vomiting and somnolence. There were no reports of serious AEs reported during this study.

In the preregistration clinical trials, aripiprazole was associated with low rates of sedation (11%), EPS (6%), weight gain (8.1%), QTc interval prolongation (0.2%) and hyperprolactinemia (1.8%) (1,59). The majority of somnolence occurred early in the study period; the rate decreased to 2.2% by the end of trials.

While the side effect profile of aripiprazole will become better known as this drug is used more widely in clinical populations, there are early indications that one of the benefits of aripiprazole is its different side effect profile in comparison to other atypical antipsychotics (Table 3). To date, available literature indicates that, aripiprazole demonstrates less risk of EPS, weight gain, raised prolactin levels and prolongation of the QTc interval (1,3,11,28,32–35,39,51,59,69).

Now that aripiprazole is widely available, there will likely be reports about its safety and tolerability in more "average" patients with schizophrenia. For example, deJohn (25) cautions physicians about interactions between some anticonvulsants and atypical antipsychotics that may require correction of dosing for atypical antipsychotics. A case report (56) described severe EPS in a 16-year-old girl with a history of moderate to severe retardation and schizophrenia who was given aripiprazole 10 mg/once a day. The girl had a history of EPS.

Switching Strategies

A study of three switching strategies (1 — immediate initiation of aripiprazole and discontinuation of current antipsychotic monotherapy; 2 — immediate initiation of aripiprazole and titration of current antipsychotic; and 3 — titration of aripiprazole while tapering off antipsychotic) indicated that all three strategies were safe and well tolerated (21,52).

TABLE 3. Side effect profile of aripiprazole as compared to other atypical antipsychotics

Drugs	EPS	Weight gain	Prolactin levels	QT Interval prolongation (short term use)
Aripiprazole	Minimal	Low	Decreased or no change	Reduced or no significant effect
Risperidone	Dose-dependent EPS	Moderate	Dose dependent increase	No significant effect
Clozapine	None	Substantial	No elevation	Little risk
Quetiapine	Minimal	Substantial	No elevation	Negligible
Olanzapine	Low risk	Substantial	Transient increase	Negligible
Ziprasidone	Low risk	Low	Minimal	Moderate risk

CONCLUSIONS

Aripiprazole appears to be unique by virtue of its partial agonism at several GPCRs (especially, D_2, D_3, and D_4, and 5-HT_{1A}, 5-HT_{2C}, and 5-HT_7) and its antagonistic action at others (especially, 5-HT_{2A} and 5-HT_6). The complex pharmacological profile of aripiprazole suggests that it will be difficult to replicate its actions via the sort of large-scale random screening approaches currently in vogue in the pharmaceutical company. Instead, as we have recently suggested (72), it is more likely that behavioral and/or genomic approaches will be more successful in identifying drugs that mimic aripiprazole's unique actions.

To date, well-designed, placebo-controlled trials involving adults demonstrate the efficacy of aripiprazole in adult patients with schizophrenia and schizoaffective disorders. Its effectiveness in children and adolescents with schizophrenia is still not adequately documented. Efficacy of aripiprazole has been usually observed after 1 week of therapy. The improvements in positive and negative symptoms of schizophrenia were sustained in long-term (26 and 52 week) trials. Two short-term studies in patients with bipolar disorder indicate that aripiprazole is also efficacious in the treatment of adults with acute mania. Across all published clinical trials, aripiprazole was determined to be safe and well tolerated with minimal side effects. A key feature of aripiprazole's side effect profile is that nearly all of the observed side effects can be reliably predicted from a detailed examination of its receptor pharmacology. Thus, aripiprazole is suggested to be devoid of EPS and to be relatively devoid of cardiovascular and metabolic side effects. These predictions have been largely verified by the large-scale clinical trials. On the other hand, because of its varying degree of $D_2/D_3/D_4$ partial agonism, aripiprazole is predicted to have primarily dopaminergic side effects. These would include such side effects as activation, nausea and vomiting. To date, the main side effects of aripiprazole appear to be insomnia, akathisia/activation, nausea and vomiting.

In conclusion, aripiprazole is a novel atypical antipsychotic drug with a unique robust pharmacology. Its complex mode of action is dominated by functionally selective actions at a variety of biogenic amine receptors. This unique profile is likely to yield novel indications for aripiprazole in diseases other than schizophrenia and related disorders.

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