National PBM Drug Monograph
Aripiprazole (Abilify®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Aripiprazole was approved on November 15, 2002 for the treatment of schizophrenia. At present, there is only 1 published clinical trial. The remainder of the information used in preparing this review was obtained from poster presentations and slide presentations prepared by Bristol Meyers Squibb. The use of aripiprazole in the treatment of acute mania has been presented as a poster and has not been included in this review.

PHARMACOKINETICS

Table 1. Pharmacokinetics

Bioavailability	87%
Mean Tmax	3 hours
Mean half-life	~ 75 hours
Protein binding	99% (mainly to albumin)
Metabolism	CYP 2D6, 3A4
Active metabolite	Dehydro-aripiprazole

RECEPTOR BINDING

Most of the efficacy of neuroleptics agents can be attributed to D_2 receptor blockade within limbic system. This results in improvement of positive symptoms. Neuroleptics also bind the D_2 receptors in the nigrostriatal pathway, which explains why parkinsonism and other extrapyramidal (EPS) side effects occur.

The mechanism of aripiprazole is considered to be different from that of the other atypical agents. It is referred to as "dopamine system stabilizer." Aripiprazole acts as a partial agonist at the dopamine (D_2) receptor. In areas of dopaminergic hyperactivity, it acts as an antagonist and in areas of dopaminergic hypoactivity, acts as an agonist.

The other atypical agents act as D_2 antagonists; however, they too have a low likelihood of extrapyramidal adverse effects because of limbic specificity, a favorable $5HT_{2A}$: D_2 profile, or short-acting blockade of the D2 receptor. Like the other atypical agents, aripiprazole has antagonist activity at the $5HT_{2A}$ receptor. In addition to contributing to the low EPS profile, $5HT_{2A}$ receptor antagonism may have a favorable effect on negative symptoms.

Table 2. Receptor binding

$5HT_{1A}$	Partial agonist
$5HT_{2A}$	Antagonist
Dopamine (D_2)	Partial agonist
Alpha-adrenergic (α_1)	Moderate
Histaminic (H_1)	Moderate
Muscarinic	Negligible

EFFICACY

Short-term studies

There are 4, short-term (4 weeks) placebo-controlled trials.[1-4] Three of these trials used haloperidol[1-3] as one of the treatment arms and the fourth used risperidone[4]. Patients included in these trials were inpatients with acute relapse of schizophrenia and have had a prior history of response to antipsychotic drugs. The primary comparisons were active treatment to placebo. There is also a 6-week trial comparing fixed-doses of aripiprazole to placebo; however, details on this study were unavailable.

Study 31-94-202 and Kane et al. were fixed-dose trials and used aripiprazole at doses of 2, 10, 15, and 30mg and haloperidol 10mg.[1, 3] Study 31-93-202 was a forced-titration trial.[2] Aripiprazole was titrated from 5-30mg over 13 days and haloperidol was titrated from 5-20mg over 7 days. Compared to placebo, aripiprazole and haloperidol resulted in statistically significant improvement as measured by PANSS-total and BPRS-total scores in all 3 studies. In Kane et al., the CGI-S and CGI-I scores improved in all active treatment groups compared to placebo. However in study 31-94-202, the improvement in CGI-S score was seen only in the group receiving aripiprazole 30mg. Kane et al. also evaluated percent responders which was defined as a $\geq$ 30% decrease in the PANSS or a CGI-I score = 1 or 2. The percent responders in the aripiprazole 15mg, 30mg, haloperidol, and placebo groups were 35%, 28%, 26%, and 17% respectively, with only the aripiprazole groups achieving statistical significance compared to placebo.

The PANSS-negative scale was used to evaluate negative symptomatology. In Kane et al., the negative score decreased in all active treatment groups, but statistical significance was achieved only with aripiprazole 15mg and haloperidol. This finding is interesting given that haloperidol is not usually considered effective in treating negative symptoms. In study 31-94-202, the PANSS-negative score decreased in all active treatment groups, but only the 30mg dose achieved statistical significance compared to placebo.

In study 97-202, aripiprazole 20mg, aripiprazole 30mg, and risperidone 6mg were compared to placebo. All active treatments resulted in significant improvement in the PANSS, PANSS-positive, PANSS-negative, and BPRS scales.

Comparator studies

Trial 98-213 is a 26-week randomized open-label study comparing aripiprazole 30mg and olanzapine 15mg in outpatients with stable psychosis receiving a typical agent, risperidone or quetiapine for at least 1 month.[5] Patients were randomized according to prior atypical versus typical use. The purpose of this study was to evaluate the efficacy of these agents at improving neurocognitive deficits and to evaluate tolerability. General cognitive factor, executive functioning, and secondary verbal memory factor were assessed at weeks 8 and 26. Both at weeks 8 and 26, aripiprazole resulted in significant improvement in the secondary verbal memory factor compared to olanzapine. Compared to baseline, the general cognitive factor improved for both agents at week 8, but was no longer significant at week 26. Neither group showed a significant change from baseline for the executive functioning factor.

Long-term studies

The following data is from Bristol Meyers Squibb speakers slide presentation. There are 2 long-term trials with aripiprazole, the first one evaluating time to relapse and the second evaluating time to discontinuation for any reason.

Trial 1 was a 26-week study comparing aripiprazole 15mg to placebo (n=310 with 1:1 randomization) in stable patients with chronic schizophrenia. Patients underwent a 3-14 day washout prior to randomization. Relapse was defined as a CGI-Improvement score of $\geq$5 or a $\geq$20% increase in the PANSS-total score. The mean baseline PANSS score was 82. Forty-six percent of the aripiprazole group completed the trial versus 29% in the placebo group. A Kaplan-Meier plot was constructed showing time to relapse. A difference between the 2 groups could be seen after 20 days of treatment. At 180 days, 57% of the aripiprazole group had not relapsed versus 34% in the placebo group.

Trial 2 was a 52-week study comparing aripiprazole 30mg to haloperidol 10mg (n=1294 with 2:1 randomization aripiprazole: haloperidol) in patients with acute relapse of chronic schizophrenia. Prior to randomization patients underwent a washout for a minimum of 5 days. In case of intolerance, the dose of aripiprazole may be reduced to 20mg and haloperidol to 7mg. The mean baseline scores for the PANSS-total, PANSS-positive, PANSS-negative, and MADRS were 95, 24.2, 24.7, and 12.6 respectively. Table 3 shows the proportion remaining in the study at weeks 13, 26, 39, and 52.

Table 3. Proportion of patients remaining in the 52-week trial

	Week 13	Week 26	Week 39	Week 52
Aripiprazole	60%	50%	45%	43%
Haloperidol	50%	40%	32%	30%

The PANSS-positive, PANSS-negative, MADRS scores, and % responders were used to measured efficacy. Percent responders were defined as:

1.) 20% decrease in PANSS-total score without meeting relapse criteria at any single time point (primary outcome)

2.) 30% decrease in PANSS-total score without meeting relapse criteria maintained for at least 28days and one additional visit (secondary outcome)

Improvement in the PANSS-positive score was similar for both agents. From week 26-52, the decrease in the PANSS-negative score was significantly greater with aripiprazole. Significant differences in MADRS, favoring aripiprazole, were seen at weeks 6-10 and 26-52.

Table 4. Efficacy during 52-week trial

	PANSS-positive (Δ in score from baseline)	PANSS-negative (Δ in score from baseline)	MADRS (Δ in score from baseline)	20% improvement PANSS	30% improvement PANSS
Aripiprazole	-7	-5.5*	-2.5*	72%	52%*
Haloperidol	-7.5	-4.5	-1.7	69%	44%

*Significant versus haloperidol
Values for PANSS-positive, PANSS-negative, and MADRS estimated from graph

TOLERABILITY AND SAFETY

Extrapyramidal symptoms

The following data were obtained from the BMS speaker's slides. The incidence of any EPS adverse event reported during the short-term trials with haloperidol and placebo was 20% with aripiprazole, 43% with haloperidol, and 20% with placebo. When results from these trials are combined, the mean change from baseline using the Simpson-Angus Scale was –0.05 for aripiprazole and placebo, and +1.2 for haloperidol. The change for haloperidol was considered significant versus placebo. The mean change from baseline using the Barnes Akathisia Scale for aripiprazole, haloperidol, and placebo was +0.075, +0.4, and –0.05 respectively. The change in both active groups was considered significant compared to placebo. In the trial with risperidone, the change in Simpson-Angus and Barnes Akathisia scores were fairly comparable. For results from individual trials, please refer to the appendix located at the end of this document.

The mean change in the Simpson-Angus score during 52-weeks of therapy was –0.26 with aripiprazole 30mg and +1.88 with haloperidol 10mg. The change in the Barnes Akathisia score was -0.02 with aripiprazole 30mg and +0.44 with haloperidol 10mg.

Although not expected, it is too early to say whether aripiprazole has an effect on long-term movement disorders such as tardive dyskinesia.

Weight

In the 4-week trials, mean weight gain with clinically used doses of aripiprazole ranged from +0.4 to +1.8kg. The weight gain seen with haloperidol was +0.5kg and risperidone was +1.5kg. In the placebo groups, weight change ranged from –0.3kg to +1.1kg.[1-4]

In a meta-analysis performed by BMS (data from speaker's slides), the mean change in weight for aripiprazole all doses (n=852) was +0.75kg, for haloperidol 10mg (n=164) was +0.5kg, and placebo (n=379) was –0.1kg (all values estimated from graph). The percent of patients with ≥ 7% increase in weight with aripiprazole ranged from 4 –13% compared to 10% with haloperidol and risperidone, and 1- 4.5% with placebo.

Table 5. Weight gain during 4-week trials

	A2	A10	A15	A20	A30		Risp6	HAL10	PL	
Mean weight gain (kg)	+1.1 (M) -2.2 (F)	+0.4 (M) +0.1(F)	+0.4	+1.2	#31-94-202 #97-202 #97-201	+1.6 (M) / +1.8 (F) +0.75 +0.9	+1.5	#97-201 +0.5	#31-94-202 #97-202 #97-201	+0.2 (M)/ +1.1 (F) -0.3 +0.2
≥7% ↑ weight	10%	11.5%	7.2%	13%	#31-94-202 #97-202 #97-201	11% 9% 4%	10%	#31-94-202 14% #97-201 10%	#31-94-202 #97-202 #97-201	4.5% 1.2% 1%

In the 26-week comparative trial with olanzapine, mean weight decreased by 1kg with aripiprazole and increased by approximately 3.5-4.5kg with olanzapine. The percent of patients with ≥ 7% increase in weight was 7% for

aripiprazole and 35% for olanzapine. Fifty percent of the aripiprazole group experienced weight loss compared to 20% in the olanzapine group.[5]

In an open-label follow-up of studies #31-93-202 and #31-94-202, weight change with aripiprazole at 24 weeks was –1.5kg for females and –0.4kg for males.[2]

In the 52-week trial, weight change was stratified according to baseline body mass index. Thirty percent of patients with a baseline BMI <23 had a ≥7% increase in weight compared to 19% with a baseline BMI of 23-27, and 8% with a BMI>27. Therefore, the risk of weight gain was greatest for individuals with low BMI and least likely for patients who were overweight at baseline.

Lipids
Effect on lipids was assessed in the 26-week long-term placebo-controlled trial and in the comparator trial with olanzapine. In the placebo-controlled trial, fasting triglycerides and LDL decreased by a median value of 12mg/dL and 5mg/dl respectively with aripiprazole and by 4mg/dl and 3mg/dl respectively with placebo. HDL increased by a mean of 2mg/dl with aripiprazole and 1mg/dl with placebo (estimated from graph from slide presentation).

In the comparator trial with olanzapine, total cholesterol was evaluated in non-fasting blood samples. A median increase of 8mg/dl was observed with olanzapine compared to a 10mg/dl decrease with aripiprazole. For these values to be more meaningful, fractionated cholesterol values and triglycerides using fasting samples will be needed.

Prolactin
Aripiprazole has a favorable prolactin profile. When combining the results from the short-term studies with haloperidol, prolactin concentration decreased with aripiprazole and increased with haloperidol. Only 1 patient had a value outside the normal range. (Data from slide presentation)

Table 6. Change in serum prolactin concentration

	Aripiprazole	Haloperidol	Placebo
Baseline prolactin (ng/mL)	10	10	8.5
End point prolactin (ng/mL)	5	22	8.5

In the comparative trial with risperidone, the prolactin level increased by 5ng/mL with both aripiprazole doses, by 55ng/ml with risperidone 6mg, and by 10ng/ml with placebo.[4]

QTc interval
In the short-term studies with haloperidol, approximately 4% of aripiprazole, 8% of haloperidol, and 6% of placebo patients had a ≥ 30msec in the QTc interval. QTc interval > 450msec occurred in 2 patients receiving aripiprazole and in 2 patients receiving haloperidol. No patient had a QTc interval >500msec. (Data from slide presentation) Mean changes from studies ranged from –6.6msec to +3.7msec. [2-4] There is no mention of when the ECG was obtained relative to serum concentration of drug.

In the long-term studies, the mean QTc interval decreased from baseline. The 52-week trial did show that 19.3% of the patients taking aripiprazole and 25.1% of those taking haloperidol had an increase in QTc interval of ≥ 30%.

Table 7. QTc interval -mean change from baseline in long-term trials

	Aripiprazole	Olanzapine	Haloperidol	Placebo
26-week placebo-controlled trial	-5.51msec			0.86 msec
26 week aripiprazole vs. olanzapine trial	-4.61 msec	+1.35 msec		
52-week aripiprazole vs. haloperidol trial	-7.4 msec		-4.0 msec	

General Adverse Events
The following table presents the treatment-emergent adverse events, with an incidence greater than 5%, noted during the 4-week trials.[1-4]

Table 8. Treatment-emergent adverse events during 4-week trials

	Studies 31-93-202 and 31-94-202 ARI / HAL / PL	Kane et.al. (Study 97-201) ARI 15 / ARI 30 / HAL 10 / PL	Study 97-202 ARI 20 / ARI 30 / R6 / PL
Headache (%)	26.6 / 27.8 / 23.2	24 / 29 / 25 / 23	28 / 35 / 31 / 27
Insomnia (%)	24.3 / 22.7 / 17.2	19 / 22 / 24 / 17	31 / 22 / 20 / 22
Somnolence (%)	14.5 / 27.8 / 12.1	5 / 10 / 13 / 4	4 / 19 / 14 / 11
Dyspepsia (%)	12.1 / 10.3/ 11.1	-	16 / 16 / 12 / 21
Constipation (%)	11.2/ 9.3 / 3.0	-	7 / 11 / 11 / 3
Pain (%)	11.2 / 9.3 / 4.0	-	6 / 6 /2 / 4
Nausea (%)	10.3 / 15.5 / 13.1	15 / 14 / 6 / 7	13 / 4 / 12/ 10
Vomiting (%)	11.2 / 12.4 / 9.1	8 / 17 / 10 / 10	15 / 8 / 8 / 6
Asthenia (%)	10.7 / 14.4 / 7.1	3 / 6 / 5 / 3	8 / 8 / 6 / 5
Dizziness (%)	10.7 / 11.3 / 8.1	13 / 17 / 6 / 6	12 / 9 / 11 / 9
Abdominal pain (%)	7.9 / 2.1 / 6.1	9 / 6 / 6 / 5	-
Dry mouth (%)	5.1 / 5.2 / 7.1	-	6 / 6 / 7 / 6
Anxiety (%)	-	23 / 17 / 19 / 15	21 / 20 / 18 / 17
Akathisia (%)	-	8 / 12 / 23 / 11	20 / 20 / 14 / 9
Orthostatic hypotension (%)	-	2 / 7 / 1 / 3	-
Hypertonia (%)	-	2 / 8/ 3 / 5	-
Tremor (%)	-	2 / 3 / 7 / 3	7 / 12 / 2 / 5
Blurred vision (%)	-	1 / 2 / 8 / 1	-

SWITCH STUDY

The data for this study were obtained from the speaker's slide presentation. Three different switching strategies were evaluated over an 8-week period. Patients receiving prior treatment with olanzapine, risperidone, or haloperidol were switched to aripiprazole using 1 of 3 strategies. For strategy 1, the current antipsychotic was immediately stopped and aripiprazole 30mg was immediately started. Strategy 2 involved a 2-week taper of the current antipsychotic with the immediate start of aripiprazole 30mg. The third strategy involved a 2-week taper of the current antipsychotic with start of aripiprazole titrated to 30mg over a 2 week period. The mean baseline PANSS-total score was approximately 69 for the 3 groups. There was no significant difference in improvement in the PANSS-total score between the groups at any of the time points measured.

Table 9. Results based on switch strategy

	Strategy 1 (n=97)	Strategy 2 (n=100)	Strategy 3 (n=101)
% completers	70%	66%	82%
d/c due to worsening schizophrenia	10%	10%	7.5%
d/c to due other adverse events	6%	10%	6%
PANSS-total at endpoint	59	56	57

Values estimated from graph

Change in PANSS-total score, weight and serum prolactin concentration were evaluated when stratified by prior antipsychotic therapy. When switched to aripiprazole, the PANSS-total score decreased for all 3 groups. The greatest decrease in weight was seen in those previously receiving olanzapine followed by risperidone. Weight increased minimally in those receiving prior haloperidol. Serum prolactin concentration decreased most in those on prior risperidone and haloperidol.

Table 10. Results stratified by prior antipsychotic therapy

	Olanzapine (n=172)	Risperidone (n=109)	Haloperidol (n=15)
Baseline PANSS-total	69.4	69.9	68.8
Change in PANSS-total	-7	-10.5	-9.5
Baseline weight (kg)	92.7	87.8	87.7
Change in weight (kg)	-2	-0.6	+0.1
Baseline serum prolactin (ng/ml)	11.8	40.0	38.5
Change in serum prolactin (ng/ml)	-5	-35	-32

DRUG INTERACTIONS

Pharmacokinetic

Aripiprazole is metabolized by the CYP2D6 and CYP3A4 isoenzymes; therefore, it would be important to know how other drugs inhibiting or inducing these enzymes affect the metabolism of aripiprazole. Aripiprazole does not appear to induce or inhibit the CYP450 enzymes.

There was a 63% increase in the plasma concentration of aripiprazole when the potent CYP3A4 inhibitor ketoconazole (20mg/d x 14 days), and a single dose of aripiprazole 15mg were concurrently administered. When the CYP2D6 inhibitor quinidine (166mg/d x 13 days) and aripiprazole (10mg single dose) were co-administered the plasma concentration of aripiprazole increased by 112%. Carbamazepine, a CYP3A4 inducer, resulted in a 70% decrease in the plasma concentration of aripiprazole. The manufacturer recommends that the dose of aripiprazole be reduced by 50% when co-administered with a strong CYP3A4 or 2D6 inhibitor or be doubled if administered with a strong 3A4 inducer.

Drugs used to augment the response to antipsychotics may sometimes become necessary; therefore, it is important to know if these agents have the potential to interact with aripiprazole. Aripiprazole 30mg was administered on days 1-14 followed by combination therapy with either valproate (serum concentration 5.0-12.5mcg/ml) or lithium (1.0-1.4mmol/L) on days 15-36. A slight change in aripiprazole serum concentration was noted; however, dosage adjustment is unnecessary.

To test for protein binding displacement interactions and interactions with CYP2C9and CYP2C19, aripiprazole 10mg was administered for 14 days with warfarin. There was no observed change in warfarin kinetics.

When aripiprazole was administered with dextromethorphan, a substrate for CYP2D6 and CYP3A4, no changes in the kinetics of dextromethorphan were noted.

Because aripiprazole can inhibit the alpha-adrenergic (α_1) receptor, use caution when using certain antihypertensive agents.

DOSE

Both the initial and target dose is 10-15mg once daily. The dose may be increased to a maximum of 30mg daily. The dose may be taken without regard to meals. Dosage adjustment is not needed for patients with renal insufficiency, hepatic insufficiency, or the elderly. Aripiprazole is available as 10mg, 15mg, 20mg, and 30mg unscored tablets in bottles of 30 and 100.

COST

The price of aripiprazole is $6.29 for the 10 and 15mg tablets and $8.90 for the 20 and 30mg tablets. It is unknown at this time what the average daily dose and monthly cost for aripiprazole will be within the VA. However, if one were to use the 15mg daily dose as an example, the monthly cost would be $188.70, which is only slightly, less than olanzapine.

Table 11. VA 4QFY02 data

	Average daily dose	Average monthly cost
Quetiapine	217.44mg	$72.92
Risperidone	2.86mg	$98.33
Ziprasidone	97.40mg	$136.81
Olanzapine	12.14mg	$194.86

Table 12. Price per unit

Olanzapine		Quetiapine		Risperidone		Ziprasidone	
2.5mg	$3.10	25mg	$0.72	0.25mg	$1.65	20mg	Flat-
5mg	$3.66	100mg	$1.28	0.5mg	$1.60	40mg	priced at
7.5mg	$3.71	200mg	$2.59	1mg	$1.60	60mg	$2.31
10mg	$5.56	300mg	$3.71	2mg	$2.65	80mg	
15mg	$7.40			3mg	$3.15		
20mg	$11.08			4mg	$4.13		

SUMMARY

Unfortunately, there is only 1 peer-reviewed published clinical trial; so much of the data presented in this review comes from poster presentations and speakers slides prepared by BMS. Based on the available data, efficacy is probably similar to risperidone and olanzapine. Aripiprazole is dosed once daily, has no significant adverse effect on QTc prolongation, prolactin, serum lipids, and has a low potential for weight gain. The EPS side effect profile is improved compared to haloperidol and probably similar to that of risperidone. Like the other atypical agents, it is metabolized via the CYP450 system and requires dosage adjustment when administered with certain drugs.

Table 13. Comparison of atypical agents

	Aripiprazole	Risperidone	Olanzapine	Quetiapine	Ziprasidone
CYP450	2D6, 3A4	2D6	1A2, 2D6 (minor)	3A4	3A4 (1/3)
Dosing frequency	QD	QD-BID	QD	BID-TID	BID
% of patients with $\geq$ 7% increase in weight during short-term trials (drug/placebo)	4-13%/1-4.5%	18%/9%	29%/3%	23%/6%	10%/4%
QTc interval prolongation precaution	No	No	No	No	Yes
Increase serum prolactin	None-low	Low	None-low	None-low	None-low
Total cholesterol/triglycerides	Slight decrease	Slight decrease	Slight increase	↑ 11%/17%	Slight decrease
Binding to D2 receptor	Partial agonist	Antagonist	Antagonist	Antagonist	Antagonist
Binding to 5HT2A receptor	Antagonist	Antagonist	Antagonist	Antagonist	Antagonist
Muscarinic receptor affinity	Negligible	Negligible	High	Negligible	Negligible
Alpha-1 receptor affinity	Moderate	High	High	High	High
Histamine-1 receptor affinity	Moderate	High	High	High	Moderate

Receptor binding information obtained from product package insert

APPENDIX: Aripiprazole Clinical Trials

<table>
<tr><th>Study</th><th>Inclusion</th><th>Dose</th><th>Demographics</th><th>Efficacy</th><th>Safety and tolerability</th></tr>
<tr>
<td>Study #31-93-202 (phase 2)
R, DB, PC, multicenter
Aripiprazole or haloperidol vs. placebo
N=103
4 weeks
ITT, LOCF</td>
<td>Tx-responsive adults in acute relapse of schizophrenia
Inpatients
BPRS-total score ≥ 30
Score ≥ 4 on any 2 items of psychotic subscale</td>
<td>5-day washout from previous antipsychotic
ARI titrated from 5-30mg over 13 days
HAL 5-20mg titrated over 7 days
Placebo</td>
<td>BPRS 50-53</td>
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<tr><th></th><th>ARI</th><th>HAL</th><th>PL</th></tr>
<tr><td>BPRS total</td><td>-7.5*</td><td>-8.5*</td><td>-2</td></tr>
<tr><td>CGI-S</td><td>-0.5*</td><td>-0.75*</td><td>0</td></tr>
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<tr><td>PANSS negative</td><td>-3*</td><td>-3.5*</td><td>-1</td></tr>
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Mean values estimated from graph
*Significant vs. placebo
</td>
<td>
<table>
<tr><th></th><th>ARI</th><th>HAL</th><th>PL</th></tr>
<tr><td>Simpson-Angus</td><td>+0.25</td><td>+1.25</td><td>-0.2</td></tr>
<tr><td>Barnes</td><td>+0.4</td><td>+0.7</td><td>+0.05</td></tr>
<tr><td>AIMS</td><td>-0.5</td><td>-0.1</td><td>-0.2</td></tr>
<tr><td>Prolactin</td><td>-13.64</td><td>Not shown</td><td>Not shown</td></tr>
</table>
Mean values estimated from graph
</td>
</tr>
<tr>
<td>Study #31-94-202 (phase 2)
R, DB, PC, multicenter
Aripiprazole or haloperidol vs. placebo
N=307
4 weeks
ITT, LOCF</td>
<td>Tx-responsive adults in acute relapse of schizophrenia
Inpatients
BPRS-total score ≥ 36
Score ≥ 4 on any 2 items of psychotic subscale</td>
<td>3-7-day washout from previous antipsychotic

<u>Fixed-dose:</u>
ARI 2mg
ARI 10mg
ARI 30mg
HAL 10mg
Placebo</td>
<td>BPRS 51.9 – 53
PANSS 89-92
CGI-S 4.7 – 4.8
% Males 80.5%
51.8% white, 37.5% black
% Paranoid 60-70%
%Undifferentiated 22-35%
% Disorganized 1.7-4.8%</td>
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<tr><td>BPRS total</td><td>-8*</td><td>-7*</td><td>-10*</td><td>-6*</td><td>-0.1</td></tr>
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<tr><td>PANSS total</td><td>-11*</td><td>-11*</td><td>-15*</td><td>-10*</td><td>-0.5</td></tr>
<tr><td>PANSS negative</td><td>-2.75</td><td>-3</td><td>-3.75*</td><td>-2</td><td>-0.75</td></tr>
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Mean change from baseline
*Significant vs. placebo
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<tr><th></th><th>A2</th><th>A10</th><th>A30</th><th>H10</th><th>PL</th></tr>
<tr><td>All d/c</td><td>37.2%</td><td>41.6%</td><td>32.8%</td><td>46%</td><td>54.7%</td></tr>
<tr><td>D/c due to LOE</td><td>18.6%</td><td>11.7%</td><td>10%</td><td>19%</td><td>31.2%</td></tr>
<tr><td>D/c due to AE</td><td>6.8%</td><td>3.3%</td><td>6.5%</td><td>6.3%</td><td>1.6%</td></tr>
<tr><td>Simpson-Angus</td><td>-0.25</td><td>+0.2</td><td>+0.1</td><td>+1.6</td><td>+0.9</td></tr>
<tr><td>Barnes</td><td>0</td><td>0</td><td>+0.1</td><td>+0.3</td><td>0</td></tr>
<tr><td>AIMS</td><td>-0.4</td><td>+0.15</td><td>-0.5</td><td>-0.9</td><td>-0.1</td></tr>
<tr><td>QTc (msec)</td><td>-1.1</td><td>3.7</td><td>-6.6</td><td>-0.7</td><td>-4.5</td></tr>
<tr><td>Prolactin (ng/ml)</td><td>-7</td><td>-4</td><td>-6</td><td>+12</td><td>-1</td></tr>
<tr><td>≥7% ↑ wt.</td><td>10%</td><td>11.5%</td><td>11%</td><td>14%</td><td>4.5%</td></tr>
<tr><td>Wt. (male/ female)</td><td>+1.1/ -2.2kg</td><td>+0.4/ +0.1kg</td><td>+1.6/ +1.8kg</td><td>Not shown</td><td>+0.2/ +1.1kg</td></tr>
</table>
Mean values estimated from graph
</td>
</tr>
<tr>
<td>Study 97-202
R, DB, PC
U.S.
multicenter
Aripiprazole or risperidone vs. placebo
N=404
4 weeks
ITT, LOCF</td>
<td>DSM-IV schizophrenia or schizoaffect with acute relapse
Hospitalized
Prior h/o antipsychotic response
18-65y/o</td>
<td>3-5 day washout
ARI 20mg QD
ARI 30mgQD
RISP 3mg BID (began 1mg BID x 1 day, 2mg BID x1 day, then full dose
Placebo</td>
<td>70% males
Mean PANSS 92-95
Schizophrenia 65-76%
Schizoaffective 24-35%</td>
<td>
<table>
<tr><th></th><th>ARI 20 N=101</th><th>ARI 30 N=101</th><th>RISP 6 N=99</th><th>PL N=103</th></tr>
<tr><td>PANSS</td><td>-14*</td><td>-13*</td><td>-15*</td><td>-5</td></tr>
<tr><td>PANSS positive</td><td>-5*</td><td>-4*</td><td>-5.2*</td><td>-1.8</td></tr>
<tr><td>PANSS negative</td><td>-3*</td><td>-3.1*</td><td>-3.3*</td><td>-0.5</td></tr>
<tr><td>BPRS</td><td>-3.6*</td><td>-3.1*</td><td>-4*</td><td>-1.75</td></tr>
</table>
Mean change from baseline
*Significant vs. placebo
Values estimated from graph
</td>
<td>
<table>
<tr><th></th><th>ARI 20</th><th>ARI 30</th><th>RISP 6</th><th>PL</th></tr>
<tr><td>Dropouts</td><td>39.6%</td><td>33.6%</td><td>37.4%</td><td>49.5%</td></tr>
<tr><td>LOE/AE</td><td>19.8%/1%</td><td>16.8%/3%</td><td>18.2%/3%</td><td>30%/7.8%</td></tr>
<tr><td>Simpson Angus</td><td>-0.16</td><td>-0.09</td><td>-0.18</td><td>-0.29</td></tr>
<tr><td>Barnes Akathisia</td><td>0.15</td><td>0.18</td><td>0.14</td><td>0.11</td></tr>
<tr><td>Weight</td><td>+1.2kg</td><td>+0.75kg</td><td>+1.5kg</td><td>-0.3kg</td></tr>
<tr><td>↑Wt ≥7%</td><td>13%</td><td>9%</td><td>10%</td><td>1.2%</td></tr>
<tr><td>Prolactin ng/ml</td><td>+5</td><td>+5</td><td>+55</td><td>+10</td></tr>
<tr><td>ΔQTc</td><td>1msec</td><td>-2msec</td><td>+6.5msec</td><td>-2msec</td></tr>
</table>
Mean values estimated from graph
</td>
</tr>
</table>

<table>
<tr>
<td>Kane 2002
Study 97-201
R, DB, PC
U.S.
multicenter
Aripiprazole or haloperidol vs. placebo
N=414
4 weeks
ITT, LOCF</td>
<td>DSM-IV schizophrenia or schizoaffect with acute relapse
Hospitalized
Prior h/o antipsychotic response
18-65y/o
PANSS ≥ 60
Score ≥ 4 on ≥ 2 items on psychotic subscale</td>
<td>Minimum 5-day placebo washout

Fixed-dose:
ARI 15mg
ARI 30mg
HAL 10mg
Placebo

Other psychotropic meds prohibited except lorazepam for agitation and benztropine for EPS (max dose 6mg/day)</td>
<td>70% males
Age 38.6 ± 0.5
PANSS: A15 98.5; A30 99.0; H10 99.3; PL 100.2
PANSS positive: A15 24.8; A30 24.5; H10 25.2; PL 25
PANSS negative A15 25.1; A30 25.5; H10 25.6; PL 25.8
CGI-S: A15 4.9; A30 4.8; H10 4.8; PL 4.9
%Schizophrenia: A15 74%; A30 72%; H10 61%; PL 75%</td>
<td>
<table>
<tr><th></th><th>ARI 15 N=102</th><th>ARI 30 N=102</th><th>H 10 N=104</th><th>PL N=106</th></tr>
<tr><td>PANSS</td><td>-15.5*</td><td>-11.4*</td><td>-13.8*</td><td>-2.9</td></tr>
<tr><td>PANSS Positive</td><td>-4.2*</td><td>-3.8*</td><td>-4.4*</td><td>-0.6</td></tr>
<tr><td>PANSS Negative</td><td>-3.6*</td><td>-2.3</td><td>-2.9*</td><td>-1.2</td></tr>
<tr><td>BPRS</td><td>-3.1*</td><td>-3.0*</td><td>-3.5*</td><td>-1.1</td></tr>
<tr><td>CGI-S</td><td>-0.6*</td><td>-0.4*</td><td>-0.5*</td><td>-0.1</td></tr>
<tr><td>CGI-I</td><td>3.5*</td><td>3.8*</td><td>3.7*</td><td>4.3</td></tr>
<tr><td>% respond</td><td>35%*</td><td>28%*</td><td>26%</td><td>17%</td></tr>
</table>
Responder = ≥ 30% ↓ PANSS or CGI-I = 1 or 2
Mean values
* Significant versus placebo
</td>
<td>
<table>
<tr><th></th><th>ARI 15</th><th>ARI 30</th><th>HAL 10</th><th>PL</th></tr>
<tr><td>All dropouts</td><td>33.3%</td><td>41.2%</td><td>40.4%</td><td>45.3%</td></tr>
<tr><td>D/c 2° LOE/AE</td><td>5%/ 9%</td><td>15%/ 8%</td><td>6%/ 11%</td><td>14%/ 16%</td></tr>
<tr><td>Simpson Angus</td><td>-0.3</td><td>+0.2</td><td>+1.1*</td><td>-0.5</td></tr>
<tr><td>Barnes Akathisia</td><td>+0.1</td><td>-0.1</td><td>+0.3*</td><td>-0.1</td></tr>
<tr><td>AIMS</td><td>-0.4</td><td>-0.4</td><td>-0.4</td><td>-0.2</td></tr>
<tr><td>% using benz ≥ 1x</td><td>8</td><td>15</td><td>30</td><td>12</td></tr>
<tr><td>Weight</td><td>+0.4kg</td><td>+0.9kg</td><td>+0.5kg</td><td>+0.2kg</td></tr>
<tr><td>↑Wt ≥7%</td><td>7.2%*</td><td>4%</td><td>10%*</td><td>1%</td></tr>
<tr><td>Prolactin ng/ml</td><td>-7.0</td><td>-7.1</td><td>+22.5*</td><td>-1.8</td></tr>
<tr><td>ΔQTc >10%</td><td>6%</td><td>6.4%</td><td>8%</td><td>6%</td></tr>
<tr><td>ΔQTc msec</td><td>-2.02</td><td>-3.38</td><td>+1.67</td><td>-3.45</td></tr>
</table>
Mean values unless otherwise indicated
* Significant versus placebo
</td>
</tr>
<tr>
<td>Study 98-213
R, open label
Aripiprazole vs. olanzapine
26 weeks
N=255
ITT/LOCF
VA MIRECC</td>
<td>Outpatients
Stable psychosis
18-65y/o
DSM-IV schizophrenia or schizoaffec
Stable dose of a typical agent, risperidone or quetiapine ≥ 1mo.
No hosp ≥ 2 mos.</td>
<td>ARI 30mg QD
OLZ 15mg QD
(10mg x 7 days)

Randomization stratified to prior atypical vs. typical</td>
<td>68% males ARI, 66% OLZ
Mean age 40y/o
Vocabulary score: ARI 32.46; OLZ 31.39
Block design score: ARI 30.11; OLZ 30.68
Info score: ARI 13.66; OLZ 13.01
PANSS: ARI 73.06; OLZ 72.46
PANSS negative: ARI 17.56; OLZ 17.81
PANSS positive: ARI 18.88; OLZ 19.11</td>
<td>
<table>
<tr><th></th><th>ARI N=128</th><th>OLZ N=127</th></tr>
<tr><td>General cognitive factor (Week 8/ week 26)</td><td>0.14*/ 0.1</td><td>0.16*/ 0.13</td></tr>
<tr><td>Executive functioning factor (week 8/ week 26)</td><td>0.13/ 0.08</td><td>0.1/ 0.13</td></tr>
<tr><td>2° verbal memory factor (Week 8/ week 26)</td><td>0.5*^/ 0.4*^</td><td>0.15/0.15</td></tr>
</table>
*Significant versus baseline
^Significant versus olanzapine
Values estimated from graph
</td>
<td>
<table>
<tr><th></th><th>ARI</th><th>OLZ</th></tr>
<tr><td>Mean weight Δ</td><td>-1kg</td><td>+4.5kg*</td></tr>
<tr><td>↑Wt ≥7%</td><td>7%</td><td>35%</td></tr>
<tr><td>Wt. loss</td><td>50%</td><td>20%</td></tr>
<tr><td>Total cholesterol</td><td>-8mg/dl</td><td>+12mg/dl</td></tr>
</table>
</td>
</tr>
</table>

AE=adverse event, ARI= aripiprazole, BPRS=Brief Psychiatric Rating Scale, CGI-S=Clinical global impression-severity, CGI-I=clinical global impression-improvement, DB= double-blind, D/C= discontinued, ESRS=Extrapyramidal Symptom Rating Scale, HAL= haloperidol, ITT= intent-to-treat, LOCF= last observation carried forward, LOE=lack of efficacy, OLZ= olanzapine, PANSS=Positive and negative syndrome scale, PC= placebo-controlled, PR= parallel, R=randomized, RISP= risperidone

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