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The Effect of CYP2D6/3A5 Genotypes on Plasma Concentrations of Haloperidol after Adjunctive Treatment of Aripiprazole

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Objectives To evaluate the drug interactions between aripiprazole and haloperidol, authors investigated plasma concentrations of those drugs by genotypes.

Method Fifty six patients with a confirmed Diagnostic and Statistical Manual of Mental Disorders 4th edition diagnosis of schizophrenia were enrolled in this eight-week, double blind, placebo-controlled study. Twenty-eight patients received adjunctive aripiprazole treatment and twenty-eight patients received placebo while being maintained on haloperidol treatment. Aripiprazole was dosed at 15 mg/day for the first 4 weeks, and then 30 mg for the next 4 weeks. The haloperidol dose remained fixed throughout the study. Plasma concentrations of haloperidol and aripiprazole were measured by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) at baseline, week 1, 2, 4 and 8. *1, *5, and *10 B alleles of CYP2D6 and *1 and *3 alleles of CYP3A5 were determined. The Student's T-test, Pearson's Chi-square test, Wilcoxon Rank Sum test and Logistic Regression analysis were used for data analysis. All tests were two-tailed and significance was defined as an alpha < 0.05.

Results In the frequency of CYP2D6 genotype, *1/*10 B type was most frequent (36.5%) and *1/*1 (30.8%), *10B/*10B (17.3%) types followed. In the frequency of CYP3A5 genotype, *3/*3 type was found in 63.5% of subjects, and *1/*3 type and *1/*1 were 30.8% and 5.8% respectively. The plasma levels of haloperidol and its metabolites did not demonstrate significant time effects and time-group interactions after adjunctive treatment of aripiprazole. The genotypes of CYP2D6 and 3A5 did not affect the plasma concentration of haloperidol in this trial. No serious adverse event was found after adding aripiprazole to haloperidol.

Conclusion No significant drug interaction was found between haloperidol and aripiprazole. Genotypes of CYP2D6 and 3A5 did not affect the concentration of haloperidol after adding aripiprazole.

Key Words Aripiprazole · Haloperidol · Drug interaction · Cytochrome P450.

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Introduction

Combined treatment with more than two antipsychotic drugs is common in clinical practice for treating schizophrenia patients.[1)] Aripiprazole is a potentially attractive augmentation agent because of its unique pharmacological profile [partial agonist at dopamine (D2) receptors][2)] and good tolerability.[3)] Aripiprazole acts as a functional antagonist in the mesolimbic dopamine pathway, where excessive dopamine activity is thought to cause positive symptoms but acts as a functional agonist in the mesocortical pathway, where reduced dopamine activity is thought to be associated with negative symptoms and cognitive impairment.[4)5)] Recently several studies have demonstrated that aripiprazole augmentation enhanced antipsychotic benefit by improving residual symptoms in patients treated with clozapine[6)] as well as by reducing daily dose of clozapine.[7)] Aripiprazole augmentation treatment has also tried in other psychiatric disorders such as major depressive disorder and obsessive compulsive disorder which had shown an incomplete response to antidepressant and anti-obsessional drugs.[8)9)]

Aripiprazole adjunctive treatment is also effective in the

treatment of antipsychotic drug induced hyperprolactinemia. Recently Shim et al[10] reported that eight weeks of adjunctive aripiprazole treatment was effective, safe and well tolerated in reducing elevated prolactin levels and restoring menstruation in many chronic schizophrenia patients stabilized and maintained on haloperidol.

Aripiprazole is metabolized by the human cytochrome P450 isozymes CYP3A4 and CYP2D6.[11] It indicates that comedication with drugs inhibiting or inducing CYP2D6 or CYP3A4 affects the serum concentrations of aripiprazole.[12] In an interaction study with the potent CYP2D6 inhibitor quinidine, the aripiprazole area under the plasma concentration versus time curve (AUC) increased by 110%, whereas that of dehydroaripiprazole decreased by 35%. Moreover, CYP2D6 poor metabolizers have been shown to obtain 80% higher and 30% lower AUCs of aripiprazole and dehydroaripiprazole, respectively, as compared with extensive metabolizers.[13]

Haloperidol is widely used in the treatment of schizophrenia and other psychiatric disorders and commonly coadministered with other antipsychotic medications. Haloperidol combined with aripiprazole can be a useful strategy for the treatment of schizophrenia, because two drugs have their own unique actions on different receptor profiles and the combined treatment may result in an additional effect on improving schizophrenic symptoms.[14]

Although second generation antipsychotic drugs are most commonly prescribed, a conventional drug, haloperidol, is still widely prescribed for alleviating psychotic symptoms in patients with schizophrenia. A number of studies have shown that CYP2D6 and 3A4/5 are associated with metabolism of haloperidol and aripiprazole.[11][15] There are several evidences that aripiprazole augmentation with haloperidol can enhance outcome of pharmacological treatment of schizophrenia as well as reduce side effects of haloperidol.[16] However, few data on drug interactions between those drugs have been reported.

In the present study, we investigated the drug interactions between aripiprazole and haloperidol and the effect of CYP2D6/3A5 genotypes on plasma concentration of haloperidol and aripiprazole.

Methods

Subjects

Fifty six patients with a confirmed Diagnostic and Statistical Manual of Mental Disorders 4th edition diagnosis of schizophrenia were enrolled in this eight-week, double blind, placebo-controlled study. The inclusion criteria included : male and female subjects, aged 18 to 45, clinically stable, who have been treated with haloperidol monotherapy and taking the same dosage of haloperidol for at least 3 months. Subjects also had no documented medical and/or neurological illness and no past history of drug or alcohol abuse.

Medications

Twenty eight patients received adjunctive aripiprazole treatment and twenty eight patients received placebo while being maintained on haloperidol treatment. Aripiprazole was dosed at 15 mg/day for the first 4 weeks then 30 mg for next 4 weeks if it was clinically tolerated. The haloperidol dose remained fixed throughout the study and no other medications were permitted during the study. Lorazepam PRN for anxiety or insomnia was permitted. All patients were enrolled into this study after giving written consent. This study was approved by the Institutional Review Board of Inje University.

Assay of plasma concentration of drugs and its metabolites

Serum haloperidol and aripiprazole levels were measured at baseline, week 1, 2, 4 and 8. Plasma concentrations of haloperidol, its 6 metabolites (reduced haloperidol, HPTP (4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-1, 2, 3, 6-tetrahydropyridine), RHPTP (4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-1, 2, 3, 6-tetrahydropyridine), CPHP (4-(4-chlorophenyl)-4-piperidinol/4-(4-Chloropheny)-4-hydroxypiperidine), HPP^+ (4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-pyridinium), $RHPP^+$ (4-(4-(chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-pyridinium), and aripiprazole were determined by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described,[17-19] with modifications. In brief, the Waters C18 Sepak cartridge column (100 mg), set on a Visiprep SPE vacuum manifold (Supelco, St. Louis, MO, USA) connected to a vacuum pump, was successively washed with 1 mL of methanol and 30 mm ammonium acetate solution, respectively. Then, 0.5 mL of plasma and 20 L of the IS (chlorohaloperidol, 100 ng/mL) were applied to the column. After washing with 1 mL of 100 mM ammonium acetate solution, drugs were eluted with 1 mL of methanol. The eluate was evaporated to dryness at ambient temperature in a Speed-Vac (Savant, Holbrook, NY, USA) ; the residue was dissolved in 0.1 mL of mobile phase and injected into the LC-MS/MS system. A QTrap 4000 LC-MS/MS system (Applied Biosystems, Foster City, CA, USA) equipped with an Agilent 1100 series H-PLC system (Agilent, Wilmington, DE, USA) was used. Chromatographic separation of the compound was accomplished by a Luna C18 column (2.0 50 mm, 3 m ; Phenomenex, Torrance, CA, USA), with use of a mobile phase consisting of water and acetonitrile mixture (70/30, v/v) containing 0.1%

formic acid, delivered at a flow rate of 0.2 mL/min. The MS/MS system was operated using an electrospray in positive ionization mode. For haloperidol, reduced haloperidol, aripiprazole, and chlorohaloperidol, the precursor-to-product ion reactions monitored were *m/z* 376165, 378149, 448285, and 392181, respectively. Approximate retention times for haloperidol, reduced haloperidol, aripiprazole, and chlorohaloperidol were 1.9, 1.5, 3.8, and 2.8 minutes, respectively. The lower limits of quantification for haloperidol, reduced haloperidol, and aripiprazole were 0.1, 0.1 and 1.0 ng/mL. The interassay precision for all analytes were less than 14.3%.

Side effect Checklist were performed at baseline and at weeks, 1 2, 4, 6 and 8. Two experienced psychiatrists performed research ratings independently.

Determination of CYP3A and CYP2D6 genotype

The CYP3A5*3 allele was detected using a previously published method.[20] The 293-bp DNA fragment containing CYP3A5*3 allele was amplified with the specific primers, 5'-CATGACTTAGTAGACAGATGA-3' and 5'-GGTCCAAACAGGGAAGAAATA-3', and digested with SspI. The presence of CYP3A5*3 allele was detected by fragments of 168 and 125-bp, whereas the wild-type allele was 148, 125 and 20-bp fragments. In order to detect CYP2D6*5 allele, 200−300 ng of genomic DNA was amplified with LA Taq polymerase (TaKaRa, Shiga, Japan) in a 2400 thermal cycler (PE Applied Biosystems, Foster city, CA, USA). PCR condition was an initial denaturation at 94℃ for 1 min, followed by 30 cycles of 98℃ for 20 s, 68℃ for 20 s, 68℃ for 5 min, and a final elongation at 72℃ for 10 min. The deletion of CYP2D6*5 allele were identified using primer 5'-CACCAGGCACCTGTACTCCTC-3' (located in CYP2D7) and 5'-CAGGCATGAGCTAAGGCACCCAGAC-3' (3'-flanking region of CYP2D6). CYP2D6 gene was amplified using primers 5'-CCAGAAGCCTTTGCAGGCTTC-3' and 5'-ACTGAGCCCTGGGAGGTGGTA-3'.[21] PCR products of CYP2D6 and CYP2D6*5 were separated by agarose gel electrophoresis. The PCR products of CYP2D6*5 and CYP2D6 were 3.5 kb and 5.1 kb in size, respectively. Genotyping of CYP2D6*10 was determined by allele specific PCR and restriction fragment length polymorphism as described elsewhere.[22] Using 5.1 kb CYP2D6 PCR product as a template, 534 bp-long fragment including C-188T position (*10) was amplified with primers 5'-ACCAGGCCCCTCCACCGG-3' and 5'-TCTGGTAGGGGAGCCTCAGC-3'. The PCR reaction was according to the method described by Johansson et al.[22] The PCR condition was pre-denaturation at 94℃ for 5 min and 30 cycles of 94℃ for 1 min, 64℃ for 1 min and 72℃ for 1 min. The post-extension was carried out at 72℃ for 5 min. The PCR product was digested with HphI restriction enzyme and separated by agarose gel electrophoresis. CYP2D6*10 allele (188T) was obtained from digested fragments of 376 bp, 98 bp and 60 bp while 188C allele was from fragments of 474 bp and 60 bp. The CYP2D6*1 allele was assigned from the absence of CYP2D6*5 and *10 alleles.

Statistical analysis

The Student's T-test, Pearson's Chi-square test, Wilcoxon Rank Sum test and Logistic Regression analysis were used for data analysis. All tests were two-tailed and significance was defined as an alpha < 0.05.

Results

Clinical characteristics

Fifty six patients with schizophrenia were enrolled into this study. Three patients who were assigned to the aripiprazole group were discharged just after randomization. Another one patient withdrew a written consent without any reason before taking a research medication. Thus, 52 patients (24 aripiprazole and 28 placebo group) were analyzed. Among the 52 patients, 50 patients completed the study (22 patients in aripiprazole and 28 in placebo groups) and two patients in the aripiprazole group withdrew from the study due to aggravation of clinical symptoms. The sex ratio, age, body mass index, and daily dose of haloperidsol did not significantly differ between the aripiprazole and placebo groups (Table 1).

Genotype subgroups of Cytochrome 2D6 and 3A5 in the subjects

We could evaluate genotypes of 52 patients. In alleles of CYP2D6 of 52 subjects, the frequency of *1, *10B and *5 was 67.9%, 54.7% and 15.1%. In the frequency of CYP2D6 genotype, *1/*10 B type was the most frequent genotype of CYP2D6 (36.5%, 19/52) and *1/*1 (30.8%, 16/52), *10B/*10B (17.3%, 9/52), *5/*10B

Table 1. Characteristics of subjects

Variables	Aripiprazole (n = 24)	Placebo (n = 28)
Sex		
M	10 (41.7%)	11 (39.3%)
F	14 (58.3%)	17 (60.7%)
Age (years)	38.2 ± 5.3	40.5 ± 4.1
BMI (kg/m^2)	23.5 ± 3.5	23.0 ± 3.6
Education (years)	9.1 ± 2.9	10.1 ± 2.6
Age of onset (years)	22.9 ± 6.1	24.2 ± 6.1
Duration of illness (years)	15.3 ± 6.1	15.4 ± 6.4
Number of psychiatric hospitalizations	3.1 ± 2.2	3.2 ± 1.9
Dose of haloperidol (mg/day)	21.4 ± 12.4	24.8 ± 14.1

BMI : body mass index

(9.6%, 5/52) and *1/*5 (5.8%, 3/52) followed. In the frequency of CYP3A5 genotype, *3/*3 type was found in 63.5% (33/52) of subjects and *1/*3 type and *1/*1 were 30.8% (16/52) and 5.8% (3/52) respectively (Table 2).

Plasma level of drugs

The mean dose of haloperidol was not significantly different between aripiprazole and placebo groups (21.4 ± 12.4 mg/day vs. 24.8 ± 14.1 mg/day). The baseline plasma levels of haloperidol and its metabolites were not significantly different between two groups. In a repeated measures analysis of variance design, the plasma levels of haloperidol and its metabolites did not demonstrate significant time effects and time-group interactions after adjunctive treatment of aripiprazole (Fig. 1). The plasma levels of aripiprazole were 102.0 ± 60.8 nM/mg at week 4 and 183.2 ± 79.2 nM/mg at week 8.

Plasma concentration of drugs and genotypes of CYP2D6 and 3A5

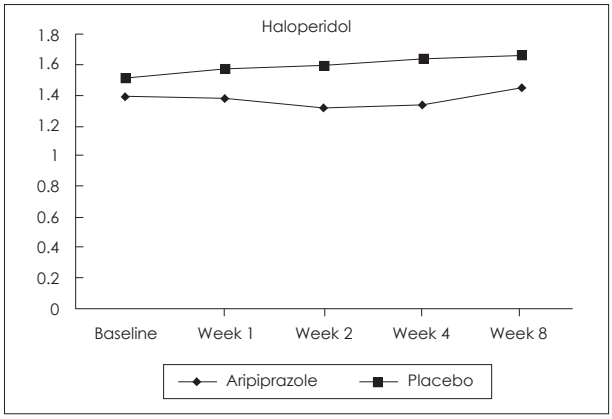
Plasma concentrations of drug were compared among three genotypes of CYP2D6 (*1/*1, *1/*10B, and *10B/*10B) and two genotypes of CYP3A5 (*1/*3 and *3/*3). Others were excluded in data analysis because of too small a sample size. The plasma concentrations of haloperidol and its metabolite (reduced haloperidol, HPTP, RHPTP, CPHP, HPP^+, and $RHPP^+$) were not significantly different among genotypes of CYP2D6 and 3A5 (Table 3).

Plasma concentration of drug and side effects

Cumulative side effects in the study for patients randomized to aripiprazole were as follows insomnia (42%), dry mouth (31%), headache (23%), sedation (12%) and weakness (8%). In the placebo group side effects were dry mouth (21%), sedation (18%) and insomnia (18%). The side effects were not correlated with the change of plasma level of drugs.

Discussion

In this study, we determined *1, *5, and *10B allele of CYD 2D6 and *1 and*3 alleles of CYP3A5, because those alleles account for most of the total CYP2D6 and 3A5 found in Korean. Among CYP2D6 genotypes, *1/*10B type was a most frequent (36.5%, 19/52). The frequencies of CYP2D6 alleles in our study were similar with that identified in our previous study (40.6%).[23] *1 of CYP2D6 has a normal enzyme activity, while *5 is nonfunctional allele of CYP2D6 and *10B is an unstable variant with decreased catalytic activity. With comparison of expected enzyme activity of CYP2D6 *1/*1, those of CYP2D6 *5/*5, *5/*10B and *10B/*10B are 0%, 25% and 50%.[24] CYP2D6 EMs with either homozygous or heterozygous CYP2D6*10B had a significantly lower clearance of paroxetine, an antidepressant, than the EMs.[25] An steady-state concentrations (Css) of them were significantly higher in Japanese with either 1 or 2 CYP2D6



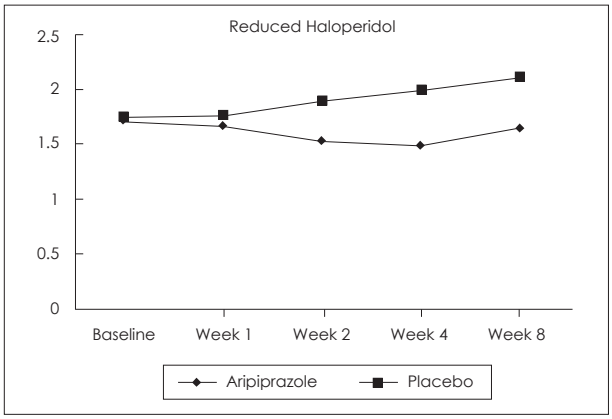


Fig. 1. Changes of plasma concentration of haloperidol and its metabolites.

Table 2. Distribution of subjects by CYP2D6 and 3A5 genotypes

		Aripiprazole (n = 24)	Placebo (n = 28)	Total (n = 52)
CYP2D6	*1/*1	25.0% (6/24)	35.7% (10/28)	30.8% (16/52)
	*1/*5	4.2% (1/24)	7.1% (2/28)	5.8% (3/52)
	*1/*10B	41.7% (10/24)	32.1% (9/28)	36.5% (19/52)
	*5/*10B	12.5% (3/24)	7.1% (2/28)	9.6% (5/52)
	*10B/*10B	16.7% (4/24)	17.9% (5/28)	17.3% (9/52)
CYP3A5	*1/*1	8.3% (2/24)	3.6% (1/28)	5.8% (3/52)
	*1/*3	20.8% (5/24)	39.3% (11/28)	30.8% (16/52)
	*3/*3	70.8% (17/24)	57.1% (16/28)	63.5% (33/52)

Table 3. Plasma concentration (nM/mg) of aripiprazole, haloperidol and its metabolites by CYP2D6/3A5 genotypes

	CYP2D6			CYP3A5	
	*1/*1	*1/*10B	*10B/*10B	*1/*3	*3/*3
ARP	42.71 ± 19.69	35.34 ± 19.35	53.27 ± 31.44	63.54 ± 19.35	40.43 ± 20.24
HAL	1.57 ± 0.83	1.42 ± 0.64	1.28 ± 0.82	1.83 ± 0.72	1.36 ± 0.65
RHAL	2.17 ± 2.50	1.35 ± 1.21	0.99 ± 0.87	2.92 ± 2.21	1.36 ± 1.40
HPTP	0.003 ± 0.002	0.003 ± 0.002	0.002 ± 0.002	0.009 ± 0.003	0.007 ± 0.003
RHPTP	0.003 ± 0.003	0.002 ± 0.002	0.001 ± 0.002	0.003 ± 0.003	0.002 ± 0.002
CPHP	0.65 ± 0.60	0.45 ± 0.36	0.30 ± 0.30	0.64 ± 0.57	0.46 ± 0.38
HPP^+	0.16 ± 0.21	0.11 ± 0.13	0.12 ± 0.09	0.17 ± 0.21	0.14 ± 0.13
$RHPP^+$	0.19 ± 0.26	0.08 ± 0.07	0.09 ± 0.06	0.22 ± 0.26	0.11 ± 0.13

ARP : Aripiprazole, HAL : Haloperidol, RHAL : Reduced Haloperidol, HPTP : 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-1, 2, 3, 6-tetrahydropyridine, RHPTP : 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-1, 2, 3, 6-tetrahydropyridine, CPHP : 4-(4-chlorophenyl)-4-piperidinol/4-(4-Chloropheny)-4-hydroxypiperidine, HPP^+ : 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-pyridinium, $RHPP^+$: 4-(4-(chlorophenyl)-1-[4-(4-fluorophenyl)-4-hydroxybutyl]-pyridinium

*10 than in those without this variant. The Css of haloperidol in Koreans was significantly different among CYP2D6 genotype groups when doses lower than 20 mg were given, but no differences were observed at higher doses.[26] The individual variation is found in metabolism of antipsychotic drugs.[27] In previous study treated with therapeutic dose of aripiprazole, interindividual variability in ratio of dose adjusted serum concentration of aripiprazole was 37-fold for aripiprazole and 78-fold for the active metabolite dehydroaripiprazole.[28] In our study, no significant change of plasma concentration of haloperidol after adding aripiprazole was found and also their concentrations were significantly different among genotypes of CYP2D6. Our finding should be confirmed in future study with large sample size.

CYP3A enzymes are the most abundantly expressed cytochrome P450 enzymes in liver and are responsible for the metabolism of over 50% of all clinically used drugs, including substances as diverse as steroids, antidepressants, benzodiazepines, and antipsychotic drug[29][30] CYP3A enzymes involve in the metabolism of haloperidol and aripiprazole. However, limited studies on genotypes of CYP3A in human have been investigated. In this study we did not find significant different in plasma concentration of haloperidol among CYP3A5 genotypes. It needs the further study with large sample size to clarify the relationship between drug and CYP3A5 genetype.

In a previous study, comedication with the CYP3A4 inducer carbamazepine lowered the dose-adjusted aripiprazole concentration by 88%. Comedication with CYP2D6 inhibitors gave a mean concentration 44% higher than in the monotherapy group.[31] Although the combined aripiprazole with other drugs is commonly used and of benefit to improving schizophrenic symptoms as well as adverse events such as hyperprolactinemia,[32] few studies were reported about drug-drug interaction between aripiprazole and other psychiatric drugs. In this study, the plasma concentrations of haloperidol and its metabolite did not changed significantly after adding arirpiprazole to a fixed dose of haloperidol (some of this data were presented in our previous study). Aripiprazole reached the peak plasma concentration (tmax) at 3−5 hours after taking drug and its elimination half-life (t1/2) is approximately 75 hours.[33] It suggested that taking aripiprazole for 4 weeks is enough to reach a steady state concentration. The plasma concentration of aripiprazole at 8 week was significantly higher than those at week 4 ; 102.0±60.8 nM/mg at week 4 and 183.2±79.2 nM/mg at week 8. However, in most patients, aripiprazole increased up to 30 mg/day at week 8, so it was difficult to find clinical significance of this finding.

In this study, two patients experienced symptoms of insomnia, anxiety, and irritability, though no serious adverse events were noted in majority of subjects. It is recommended that more attention should be paid to monitoring for symptoms of insomnia, anxiety and irritability when one considers adjunctive aripiprazole treatment on haloperidol.

The limitations of our study should be considered. First, the sample size was small to determine the drug interaction between aripiprazole, haloperidol and to evaluate the influence of CYP2D6, 3A5 genotype on their interactions. Second, just limited number of CYP2D6/3A5 genotypes, which frequently are found in Korean, was evaluated, so more extensive numbers of CYP2D6/3A5 genotypes should be investigated for understanding the association between CYP2D6/3A5 genotypes and drug interaction.

Conflicts of interest

The authors have no financial conflicts of interest.

REFERENCES

1) **Mouaffak F, Tranulis C, Gourevitch R, Poirier MF, Douki S, Olié JP, et al.** Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. Clin Neuropharmacol 2006;29:28-33.

2) **Hirose T, Uwahodo Y, Yamada S, Miwa T, Kikuchi T, Kitagawa H, et al.** Mechanism of action of aripiprazole predicts clinical efficacy and a favourable side-effect profile. J Psychopharmacol 2004;18:375-383.
3) **Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al.** Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63:763-771.
4) **Cada DJ, Levien T, Baker DE.** Aripiprazole. Hospital Pharmacy 2003;38:247-256.
5) **Swainston Harrison T, Perry CM.** Aripiprazole: a review of its use in schizophrenia and schizoaffective disorder. Drugs 2004;64:1715-1736.
6) **Clarke LA, Lindenmayer JP, Kaushik S.** Clozapine augmentation with aripiprazole for negative symptoms. J Clin Psychiatry 2006;67:675-676.
7) **Keller Ashton A.** Indexing of reports on aripiprazole augmentation of clozapine. J Clin Psychiatry 2007;68:334-335; author reply 335.
8) **Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al.** The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68:843-853.
9) **Simon JS, Nemeroff CB.** Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. J Clin Psychiatry 2005;66:1216-1220.
10) **Shim JC, Shin JG, Kelly DL, Jung DU, Seo YS, Liu KH, et al.** Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry 2007;164:1404-1410.
11) **Kubo M, Koue T, Inaba A, Takeda H, Maune H, Fukuda T, et al.** Influence of itraconazole co-administration and CYP2D6 genotype on the pharmacokinetics of the new antipsychotic ARIPIPRAZOLE. Drug Metab Pharmacokinet 2005;20:55-64.
12) **Citrome L, Macher JP, Salazar DE, Mallikaarjun S, Boulton DW.** Pharmacokinetics of aripiprazole and concomitant carbamazepine. J Clin Psychopharmacol 2007;27:279-283.
13) **Molden E, Lunde H, Lunder N, Refsum H.** Pharmacokinetic variability of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients. Ther Drug Monit 2006;28:744-749.
14) **Kuo J, Hwu HG.** Aripiprazole and haloperidol: beneficial combination antipsychotic therapy for a schizophrenic patient. Clin Neuropharmacol 2008;31:173-175.
15) **Urichuk L, Prior TI, Dursun S, Baker G.** Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. Curr Drug Metab 2008;9:410-418.
16) **Kubo M, Mizooku Y, Hirao Y, Osumi T.** Development and validation of an LC-MS/MS method for the quantitative determination of aripiprazole and its main metabolite, OPC-14857, in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2005;822:294-299.
17) **Hempenius J, Steenvoorden RJ, Lagerwerf FM, Wieling J, Jonkman JH.** 'High throughput' solid-phase extraction technology and turbo ionspray LC-MS-MS applied to the determination of haloperidol in human plasma. J Pharm Biomed Anal 1999;20:889-898.
18) **Hoja H, Marquet P, Verneuil B, Lotfi H, Dupuy JL, Pénicaut B, et al.** Determination of haloperidol and its reduced metabolite in human plasma by liquid chromatography-mass spectrometry with electrospray ionization. J Chromatogr B Biomed Sci Appl 1997;688:275-280.
19) **Roy JN, Lajoie J, Zijenah LS, Barama A, Poirier C, Ward BJ, et al.** CYP3A5 genetic polymorphisms in different ethnic populations. Drug Metab Dispos 2005;33:884-887.
20) **Gaedigk A, Gotschall RR, Forbes NS, Simon SD, Kearns GL, Leeder JS.** Optimization of cytochrome P4502D6 (CYP2D6) phenotype assignment using a genotyping algorithm based on allele frequency data. Pharmacogenetics 1999;9:669-682.
21) **Johansson I, Oscarson M, Yue QY, Bertilsson L, Sjöqvist F, Ingelman-Sundberg M.** Genetic analysis of the Chinese cytochrome P45-02D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. Mol Pharmacol 1994;46:452-459.
22) **Nikoloff D, Shim JC, Fairchild M, Patten N, Fijal BA, Koch WH, et al.** Association between CYP2D6 genotype and tardive dyskinesia in Korean schizophrenics. Pharmacogenomics J 2002;2:400-407.
23) **Lee SY, Sohn KM, Ryu JY, Yoon YR, Shin JG, Kim JW.** Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit 2006;28:382-387.
24) **Yoon YR, Cha IJ, Shon JH, Kim KA, Cha YN, Jang IJ, et al.** Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6*10 genotype of Korean subjects. Clin Pharmacol Ther 2000;67:567-576.
25) **Kim K, Johnson JA, Derendorf H.** Differences in drug pharmacokinetics between East Asians and Caucasians and the role of genetic polymorphisms. J Clin Pharmacol 2004;44:1083-1105.
26) **Darby JK, Pasta DJ, Dabiri L, Clark L, Mosbacher D.** Haloperidol dose and blood level variability: toxicity and interindividual and intraindividual variability in the nonresponder patient in the clinical practice setting. J Clin Psychopharmacol 1995;15:334-340.
27) **Molden E, Lunde H, Lunder N, Refsum H.** Pharmacokinetic variability of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients. Ther Drug Monit 2006;28:744-749.
28) **Hashimoto H, Toide K, Kitamura R, Fujita M, Tagawa S, Itoh S, et al.** Gene structure of CYP3A4, an adult-specific form of cytochrome P450 in human livers, and its transcriptional control. Eur J Biochem 1993;218:585-595.
29) **Hustert E, Haberl M, Burk O, Wolbold R, He YQ, Klein K, et al.** The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics 2001;11:773-779.
30) **Castberg I, Spigset O.** Effects of comedication on the serum levels of aripiprazole: evidence from a routine therapeutic drug monitoring service. Pharmacopsychiatry 2007;40:107-110.
31) **Travis MJ, Burns T, Dursun S, Fahy T, Frangou S, Gray R, et al.** Aripiprazole in schizophrenia: consensus guidelines. Int J Clin Pract 2005;59:485-495.
32) **de Leon J.** Atypical antipsychotic dosing: the effect of smoking and caffeine. Psychiatr Serv 2004;55:491-493.