A Systematic Review of Aripiprazole—Dose, Plasma Concentration, Receptor Occupancy, and Response: Implications for Therapeutic Drug Monitoring

Anna Sparshatt, MPharm, MRPharmS; David Taylor, MSc, PhD, MRPharmS; Maxine X. Patel, MBBS, MSc, MD, MRCPsych; and Shitij Kapur, MBBS, PhD, FRCPC

Objective: To evaluate relationships between aripiprazole dose, plasma level, pharmacologic activity, and clinical outcome in order to evaluate the potential for therapeutic drug monitoring.

Data Sources: In August 2008, we searched Embase, MEDLINE, and PubMed databases using the keywords *aripiprazole*, *plasma levels*, *plasma concentration*, and *therapeutic drug monitoring*.

Study Selection: Twenty-one reports were retrieved. Eight studies investigating the relationship between blood concentrations of aripiprazole and dose, dopamine D_2/D_3 occupancy, and/or outcome and adverse effects were then selected.

Data Extraction: All data concerning plasma or serum concentrations of aripiprazole were included if concentrations were reported in relation to a dose, dopamine occupancy, or clinical outcome. Those reports solely investigating drug interactions were not included.

Data Synthesis: A strong correlation exists between aripiprazole dose and plasma concentration. Positron emission tomography analyses suggest that there are significant relationships between dopamine receptor occupancy and both aripiprazole dose and blood concentration. Dopamine receptor occupancy appears to reach a plateau at doses above 10 mg, supporting the observation found in dose-response studies that 10 mg/d is the optimal dose for aripiprazole.

Conclusions: The dose range for aripiprazole is well defined, and it reliably predicts plasma level, dopamine receptor occupancy, and clinical response. Plasma level variation appears to have minimal impact on clinical response, but it may predict some adverse effects. A putative target plasma level range of between 150 and 210 ng/mL is suggested. Therapeutic drug monitoring has limited value in the clinical use of aripiprazole, but it may be useful in assuring adherence and optimizing response in individuals.

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Corresponding author: *David Taylor, MSc, PhD, MRPharmS, Pharmacy Department, Maudsley Hospital, Denmark Hill, London SE5 8AZ, UK (David.Taylor@slam.nhs.uk).*

Therapeutic drug monitoring (TDM) is an established, and in some cases essential, practice when prescribing and administering many drugs. It is the process by which plasma drug concentrations are measured in order to ensure beneficial effect in individual patients. Drugs that have a narrow therapeutic index and those drugs with an established relationship between plasma concentration and either efficacy or toxicity are those for which TDM is most appropriate. Although widely used in general medicine, there are relatively few drugs for which TDM is recommended in psychiatry.

Most common uses of TDM include assuring compliance (by monitoring to see if a given level is plausible for a prescribed dose) and ensuring consistency of plasma levels following a switch of formulation (eg, tablet to liquid). Therapeutic drug monitoring can also be used as a tool to guide dosing in the presence of drug interactions or physical illness, such as hepatic or renal disease. When a clear dose-response relationship cannot be established, but a correlation is found between plasma levels and clinical effect, TDM can be used to predict response, avoid relapse, and optimize symptom control. It is particularly useful when plasma concentrations show high variability between individual patients following exposure to equal doses.[1] Therapeutic drug monitoring thus allows the clinician to personalize treatment and ensure optimal use of the drug.

Aripiprazole is an atypical antipsychotic with a unique pharmacologic profile, acting as a partial agonist at dopamine D_2 receptors, an antagonist at 5-HT_{2A} receptors, and a partial agonist at 5-HT_{1A} receptors.[2,3] Attempts have been made to establish a dose-response range for aripiprazole[4,5] but little is known about plasma-level relationships. Pharmacokinetic studies in healthy male volunteers have shown steady-state plasma levels to be achieved only after approximately 14 to 16 days of continuous daily dosing owing to its long half-life of around 75 hours.[6,7] Aripiprazole's major active metabolite, dehydroaripiprazole, has a receptor binding profile similar to the parent compound, and therefore is expected to show similar pharmacologic activity.[7,8] At steady state, systemic exposure to the metabolite has been reported to represent 39% of that of the parent drug.[9] Plasma concentration of this metabolite may therefore be clinically relevant to both outcome and adverse effects, although its full effects have not yet been studied.[10] Further pharmacokinetic details are shown in Table 1.

In this review, our aim was to evaluate relationships between dose, plasma level, pharmacologic activity, and

clinical outcome in order to establish the role of TDM in patients receiving aripiprazole.

DATA SOURCES

In March 2008, we searched Embase, MEDLINE, and PubMed databases using the drug name *aripiprazole* alongside each of the terms *plasma levels*, *plasma concentration*, and *therapeutic drug monitoring*. The search was restricted to those articles written in English. All references were screened, then appropriate articles retrieved in full and the text examined for relevant citations. The search was repeated in April 2009 before final analysis of data. Graphs of pooled data from the various results were plotted using Stata software, version 10 (StataCorp LP, College Station, Texas). Linear regression lines were fitted to display the relationships between aripiprazole dose and aripiprazole concentration, aripiprazole dose and dehydroaripiprazole concentration, and aripiprazole concentration and dehydroaripiprazole concentration.

STUDY SELECTION

Twenty-one published articles were retrieved from the initial literature search. Those articles selected were reports investigating, in multiple participants, the relationship between plasma/serum concentrations of aripiprazole and dose, dopamine D_2/D_3 occupancy, and/or outcome and adverse effects. Review articles were also obtained and included for discussion.

DATA EXTRACTION

All published reports of plasma or serum concentrations of aripiprazole were included if plasma or serum aripiprazole concentrations were reported in relation to a dose, dopamine D_2/D_3 occupancy m or clinical outcome (measured by a suitable efficacy measure such as the Brief Psychiatric Rating Scale[11] and the Positive and Negative Syndrome Scale [PANSS][12]). Investigations into the effects of age and sex were also selected. Those reports solely investigating drug interactions were not included here. Data from both randomized controlled trials and naturalistic TDM studies were selected in order to ensure that a varied and large sample of participants was studied. Mens and women of any age were included, regardless of psychiatric diagnosis, comorbidity, and bed status.

DATA SYNTHESIS

Description of Studies

Twenty-one published articles were retrieved from the initial literature search. Eight studies with data available for 651 participants were selected. Excluded studies are shown in Table 2. Selected articles included 4 positron emission tomography (PET) studies, one of which included a naturalistic TDM sample; and a further 4 naturalistic TDM studies. The included studies came from a range of health care systems across Europe, North America, the United Kingdom, and Canada. These studies were published from 2002 to 2008. Details of the various study designs including methods of plasma/serum concentration detection, are shown in Tables 3 and 4. Mean aripiprazole plasma/serum concentrations and doses found in each study are shown in Figure 1A. Five studies combined display a strong positive correlation between aripiprazole daily dose and plasma level ($r^2 = 0.8707$, $P < .0001$; Figure 1A). There was also a moderate correlation between aripiprazole dose and dehydroaripiprazole plasma concentration ($r^2 = 0.6211$, $P = .035$; Figure 1B) and between the concentrations of the parent and metabolite ($r^2 = 0.6193$, $P = .035$; Figure 1C).

Table 1. Dosing Recommendations and Pharmacokinetic Properties of Aripiprazole[a,b]

Recommended dosing	10–15 mg once daily, maximum 30 mg once daily[a]
Recommended time of sampling	Trough concentration (from once-daily dosing)
Units of plasma concentration	ng/mL or µg/L (equivalent units)
Approximate elimination half-life, h	75 in extensive metabolizers of CYP2D6 and approximately 146 in poor metabolizers of CYP2D6[b]
Time to steady state, d	16 (based on half-life of 75 h)
Plasma protein binding, %	99, bound to serum proteins; binds primarily to albumin[b]
Absolute bioavailability, %	87[b]
Apparent volume of distribution, L/kg	4.9[b]
Peak absorption, h	3–5 postdose[b]
Metabolism	Aripiprazole is extensively hepatically metabolized, primarily by dehydrogenation, hydroxylation (via CYP3A4 and CYP2D6), and *N*-dealkylation (CYP3A4)[b]
Active metabolite	Dehydroaripiprazole[b]

[a]Data from Joint Formulary Committee.[32]
[b]Data from Otsuka and Bristol-Myers Squibb.[2]
Abbreviation: CYP = cytochrome P450.

Table 2. Excluded Studies

Study	Reason for Exclusion
Mallikaarjun et al,[6] 2004	Healthy volunteer study to investigate pharmacokinetic parameters; trough concentrations not reported
Citrome et al,[9] 2005	Medication interaction study
Kubo et al,[33] 2005	Study of analytic method
Kubo et al,[34] 2005	Medication interaction study
Zuo et al,[35] 2006	Pharmacokinetic profile study; trough concentrations not reported
Mallikaarjun et al,[36] 2006	Plasma levels not reported
Hendset et al,[31] 2007	Genotype comparison study
Citrome et al,[37] 2007	Medication interaction study
Castberg et al,[38] 2007	Comedication interaction study
Kubo et al, [39] 2007	Pharmacokinetic profile study
Musenga et al,[40] 2008	Study of analytic method
Boulton et al,[10] 2008	Healthy volunteer pharmacokinetic profile study of intramuscular/intravenous aripiprazole
Waade et al,[41] 2009	Comedication interaction study

Plasma/Serum Concentration Studies

The relationship between both aripiprazole and dehydroaripiprazole serum concentration and dose was investigated

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Table 3. Serum Aripiprazole Concentration Studies

Design	Subjects[a]	Exclusion Criteria	Mean Dose (mg/d)[a]	Concentration (ng/mL)[a]			Main Outcomes[a]			Ref
				Aripiprazole	Dehydroaripiprazole	Total Moiety	Aripiprazole	Dehydroaripiprazole	Total Moiety	
TDM data collected from patients dosed according to clinician decision. Trough, steady-state serum samples analyzed by HPLC-UV. Dosing frequency not stated	N = 283, various psychiatric diagnoses N = 164 (of the above 283) diagnosed with schizophrenia 109 male, 55 female Age 33.8 ± 10.8 (19–66) y 73% comedicated with various drugs 54% received additional antipsychotics	Not reported; other medication permitted	19.8 ± 8.2 (7.5–60)[b]	214 ± 140 (0–869)[b]	78 ± 59 (5–326)[b]	292 (174–375)[b]	Serum level to dose correlation: $r = 0.419$; $P < .01$[c]	Serum level to dose correlation: $r = 0.355$; $P < .01$[c]	Serum level to dose correlation: $r = 0.482$; $P < .01$[c]	13
Routine TDM study, analyzed by liquid chromatographic and tandem mass spectrometric detection. Serum samples were not confirmed as at steady state, Samples collected 10–26 h postdose	N = 118 with 155 samples Psychiatric diagnoses 62 male 56 female Age 32.8 (15–63) y	Not reported; subjects could take other medication	Low-dose range, 10–15; n = 98	101–233 (230–530 nmol/L)[d]	Not reported	145–317 (330–720 nmol/L)[d]	Interindividual C/D ratio (nmol/L/mg/d) ranged 37-fold	Interindividual C/D ratio (nmol/L/mg/d) ranged 78-fold (49-fold without 1 extreme outlier)	Interindividual C/D ratio (nmol/L/mg/d) ranged 27-fold	16
			High-dose range, 20–30; n = 57	233–423 (530–960 nmol/L)[d]	Not reported	339–533 (770–1210 nmol/L)[d]				
TDM study. Serum blood samples from patients already treated with aripiprazole. Steady-state, trough samples analyzed by HPLC-UV	N = 27 Diagnosed with schizophrenia 12 male 15 female Age 19–69 (mean not reported) y	Not reported	18.4 Median, 15 (range, 10–30)	Median: 219 ng/mL Range, 105–549 ng/mL 146–254 ng/mL[d]	Not reported	Not reported	Authors suggest that the interquartile range of 146–254 ng/mL (converted from µg/L) can be used as a preliminary target range for TDM of aripiprazole			17
TDM study of adolescents. Patients dosed according to clinical needs. Steady-state trough samples analyzed by HPLC	N = 33 with 117 samples 18 males 15 females Age 18.7 ± 1.7 (13.5–21.6) y	Not reported; other medication permitted	12.9 ± 6.4 (5–30)	142.0 ± 122.7 (40–648.3)	51.6 ± 22.3 (30.0–111.6)	Not reported	Correlation between daily dose and aripiprazole concentration: $r = 0.548$, $P = .001$ Correlation between daily dose and dehydroaripiprazole concentration: $r = 0.740$, $P < .0005$ No significant influence of effect of age, sex, BMI, or cigarette smoking on dose-related aripiprazole or dehydroaripiprazole concentration.			18

[a]All values are mean ± SD (range) unless otherwise stated. [b]Analysis of patients diagnosed with schizophrenia (n = 164). [c]Analysis from all samples (n = 283; 523 samples). [d]Interquartile range.
Abbreviations: C/D = concentration/dose, HPLC-UV = high-pressure liquid chromatography with UV detector, TDM = therapeutic drug monitoring.

Table 4. Aripiprazole PET Studies

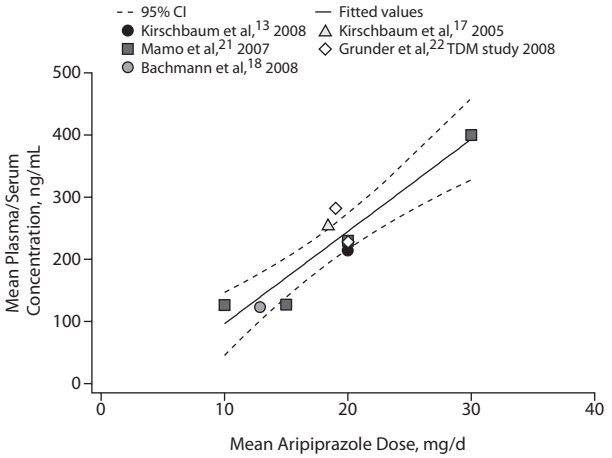
Design	Subjects[a]	Exclusion Criteria	Mean Dose, mg/d[b]	Plasma Aripiprazole Concentration, ng/mL[b]	Plasma Dehydroaripiprazole Concentration, ng/mL[b]	Receptor Occupancy, %	Ref
Dose response PET ([^{11}C]raclopride) scans with various doses of aripiprazole taken for 14 days. Trough samples analyzed by HPLC with UV detection	N = 15 Healthy volunteers Age 32 ± 9 (range not reported) All male	Not reported	0.5 1 2 10 30	Individual concentrations not reported	Not reported	33.7 ± 10.5 57.2 ± 5.6 71.6 ± 9.8 85.3 ± 7.4 86.4 ± 6.9[c]	19
PET study ([^{18}F]fallypride), to assess $D_{2/3}$ occupancy. Various aripiprazole doses at steady state. Plasma samples analyzed by HPLC with UV detection. Samples drawn at the time of scan and 2 hours after. Time from dose to scan not reported	N = 19 Diagnosis of schizophrenia/ schizoaffective disorder Age 29 ± 10 (range not reported) 15 male, 4 female	Medical illness, other *DSM-IV* Axis I disorder, substance misuse, any psychotropic medication in prior 21 days	2 40	Individual concentrations not reported	Not reported	71.6 ± 5.5 96.8 ± 5.3[d]	20
PET study. Patients randomly assigned to doses of aripiprazole for at least 14 days (at steady state) Peak plasma levels measured 3–5 hours postdose, at time of scan. Analyzed by LC-API-MS/MS assay. [^{11}C]raclopride, [^{18}F]setoperone, and [^{11}C]WAY100635—results are a mean of all scans	N = 12 Schizophrenia/ schizoaffective disorder Age 31 ± 7 (range not reported) 9 male, 3 female	Other antipsychotic medication, change in other psychotropic medication, active substance misuse, depot antipsychotic in previous 6 months	10 15 20 20	126 ± 78 127 ± 46 230 ± 193 400 ± 236	35 ± 4 48 ± 14 46 ± 37 83 ± 18	Mean striatal dopamine occupancy, across all dose ranges Putamen 86.6 ± 3.7 Caudate 92.9 ± 5.7 Ventral striatum 91 ± 4.0	21
PET scan ([^{18}F]fallypride.study) of 16 patients doses 5–30 mg/d according to clinical need for at least 4 weeks	PET study: N = 16 Diagnosis of schizophrenia/ schizoaffective disorder Age 30 ± 10 (19–50) 15 male, 1 female	PET study Not reported Did receive other medication	18.8 ± 7.2 (5–30)	282 ± 267 (50–862)	76 ± 84 (0–261)	Putamen 83 ± 11 Caudate nucleus 84 ± 11 Thalamus 85 ± 7 Amygdala 85 ± 6 Inferior temporal cortex 83 ± 9	22
Trough serum concentration data from 128 patients monitored in a routine TDM program Analyzed by HPLC with UV detection	TDM sample: N = 128 and 203 samples Age 33.8 ± 10.7 (range not given) 84 males, 44 females Comedication not reported	TDM study: not reported	20 ± 9 (10–60)	228 ± 142 (median, 196, 25th to 75th percentile; range, 134–294)	Not reported	Not measured	

[a]All schizophrenia/schizoaffective diagnoses unless stated; age presented as mean ± SD (range), y. [b]All values are mean ± SD (range) unless otherwise stated. [c]All mean putamen values. [d]Not all values published, mean of all subjects, all brain regions.

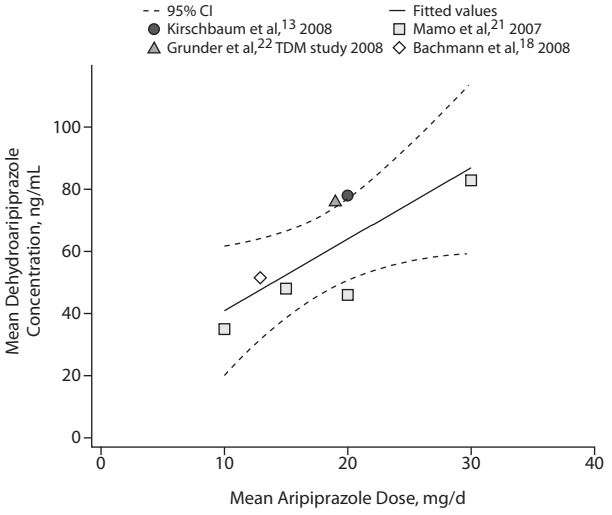
Abbreviations: HPLC = high-pressure liquid chromatography, LC-API-MS/MS = liquid chromatography with atmospheric pressure ionization tandem mass spectography, PET = proton emission tomography, TDM = therapeutic drug monitoring.

Figure 1. Comparison of Drug Dose or Plasma/Serum Concentration to Drug or Metabolite Concentration

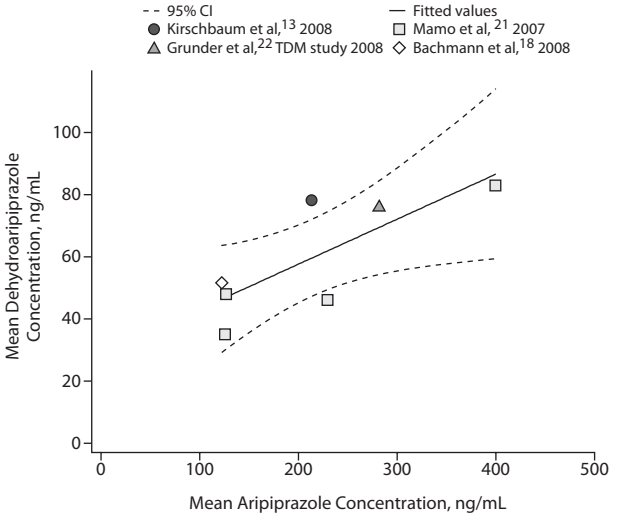
A. Mean Aripiprazole Dose Versus Mean Plasma/Serum Aripiprazole Concentration[a]



B. Mean Aripiprazole Dose Versus Mean Plasma/Serum Dehydroaripiprazole Concentration[b]



C. Mean Plasma/Serum Aripiprazole Concentration Versus Mean Plasma/Serum Dehydroaripiprazole Concentration[c]



[a]β Coefficient = 14.8 (95% CI, 9.7–20.0), $r^2 = 0.8707$, $P < .0001$.
[b]β Coefficient = 2.3 (95% CI, 0.3–4.4), $r^2 = 0.6211$, $P = .035$.
[c]β Coefficient = 0.15 (95% CI, 0.01–0.28), $r^2 = 0.6193$, $P = .035$.
Abbreviation: TDM = therapeutic drug monitoring.

in a set of 523 serum samples collected from TDM data of 283 patients diagnosed with various psychiatric conditions.[13] Serum concentrations correlated with dose for each of the compounds individually and their total moiety (Table 3; demographic and mean serum concentration information for this data set were not reported). Mean concentration of dehydroaripiprazole was calculated to represent 40% of the parent compound, with a coefficient of variation (CV) of 93% between patients. (Coefficient of variation is an indicator of the degree of variability in relation to the mean value: CV = 100 × [SD/mean value].) A subset of patients had their blood collected on multiple occasions, allowing intraindividual CVs of the parent/metabolite ratio to be calculated at 26% (n = 73; range, 2–9 serum samples).

Subjects with a diagnosis of schizophrenia (n = 164) were selected for further analysis; demographic and serum level information is shown in Table 3. Aripiprazole was the sole antipsychotic prescribed for 74 of these subjects. Clinical response of the aripiprazole monotherapy patients was measured by change in Clinical Global Impressions (CGI) (item 1 for evaluation of severity of illness and item 2 for global improvement) score.[14] Sixty percent of subjects within the aripiprazole monotherapy group were classed as *very much improved* or *much improved*. These patients were classed as responders to aripiprazole treatment. The serum aripiprazole concentration of the responders ranged from 124 to 286 ng/mL (25th to 75th percentile range). The interquartile range of the active moiety was 173 to 367 ng/mL. The authors therefore suggest a target aripiprazole concentration range of 150–300 ng/mL. A response rate of 68% was found within this proposed concentration range. In patients whose serum levels were above and below the target range, mean response rates were 50% and 57% respectively. Adverse effects (measured on a modified 4-point version of the Utvalg for Kliniske Undersogelser Side Effect Scale[15]) were absent or mild in those with concentrations in the ranges of 110 to 249 ng/mL for aripiprazole and 166 to 353 ng/mL for the total moiety (25th to 75th percentile ranges). Moderate to severe adverse effects were reported within the ranges 210 to 335 ng/mL for aripiprazole and 245–375 ng/mL for the total moiety (25th to 75th percentile range).

Several of the subjects in this study were comedicated with drugs suspected to affect the metabolism of aripiprazole. The effect of each drug (fluoxetine, fluvoxamine, metoprolol, paroxetine, and carbamazepine) was measured by comparison of the mean dose-corrected aripiprazole and dehydroaripiprazole concentrations (concentration/dose [C/D] ratio, ng/mL/mg). Although all of these drugs altered the C/D ratio to an extent that may be clinically significant, only those patients taking metoprolol had significantly altered C/D aripiprazole ratios (40% increase, n = 11, $P < .05$). The number of subjects taking any additional comedication (other than metoprolol) was less than 6 in each case.

A smaller study[16] collected information from routine hospital TDM data in order to investigate the pharmacokinetic variability of aripiprazole and dehydroaripiprazole and the effect of sex and comedication. Concentration of

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both aripiprazole and the active moiety (data not available) were significantly but weakly correlated with dose. Interquartile ranges are shown in Table 3. Pharmacokinetic variability was expressed as the range in dose-adjusted serum concentrations (C/D ratio; nmol/L/mg/d). As shown in Table 3, greatest interindividual variability was measured for dehydroaripiprazole. No significant difference was found between the median dose-adjusted concentration ratio of men and women (median difference less than 15%, $P > .14$).

Intraindividual variation was measured by the range in C/D ratio of the 24 subjects who had given multiple samples. Within this group, the majority of subjects had less than a 2-fold intraindividual difference between samples for aripiprazole, dehydroaripiprazole, and the active moiety (n = 19, 15, and 18, respectively). Those who had more than 3 samples were described individually (n = 9). The highest variability measured was a 9-fold range in aripiprazole C/D ratio, with a corresponding 3-fold range in the metabolite ratio.

Patients taking additional medication were included in the sample. The authors identified 3 patients with a coprescription of known potent cytochrome P450 (CYP) CYP2D6 inhibitors (fluoxetine and paroxetine). Although C/D ratios varied widely within the 3 patients also taking fluoxetine or paroxetine, a difference was not seen when compared with the whole sample. This study suggests that pharmacokinetic variability is extensive and unlikely to be related to dose or sex.

A smaller TDM study by Kirschbaum and colleagues[17] analyzed trough aripiprazole serum samples with the aim of establishing the utility of TDM for aripiprazole. Pure aripiprazole was not available for the assay, so it was obtained from incubation of 15 mg Abilify tablets. The authors stressed that the accuracy of the method was uncertain and urged caution when reviewing the results. The 27 subjects took aripiprazole across the dose range of 10–30 mg. The mean dose was 18.4 mg/d (median, 15 mg/d); the corresponding median serum concentration was 219 ng/mL, with an interquartile range of 146–254 ng/mL. In the absence of any established range for efficacy or adverse effects, the authors suggested this range as a preliminary target range for TDM of aripiprazole.

The serum concentration of aripiprazole in adolescents was studied by Bachmann and coworkers.[18] Thirty-three patients diagnosed with schizophrenia spectrum disorders and having a mean ± SD age of 18.7 ± 1.7 (range, 13.5–21.6) years were dosed and treated according to clinical needs. Mean ± SD aripiprazole dose was 12.9 ± 6.4 (range, 5–30) mg/d Mean ± SD serum concentration of aripiprazole was 142.0 ± 122.7 (range, 40–648.3) ng/mL, and of dehydroaripiprazole was 51.6 ± 22.3 (range, 30.0–111.6) ng/mL. There was a significant correlation between daily dose and aripiprazole concentration ($r = 0.548$, $P = .001$), which was stronger for dehydroaripiprazole ($r = 0.740$, $P < .0005$). Patients who provided more than 1 sample at a stable dose of aripiprazole were assessed for intrapatient variability. Aripiprazole C/D ratio between the lowest and highest concentration varied 9.3-fold. There was a maximum interpatient variability of 6.4 times. By calculation of variance components, it was found that the percentage of total variability in serum concentration caused by intraindividual variability was 30.5% for aripiprazole and 87.5% for dehydroaripiprazole.

The majority of patients (32 of 33) were also treated concomitantly with other medication. Serum C/D ratio was compared between patients; grouped according to the class of any concomitantly prescribed drug (eg, antipsychotic, SSRI, and anti-Parkinson medication) No significant serum concentration differences were found to be associated with comedication. There were no drugs prescribed with the potential to induce or inhibit CYP2D6 or CYP3A4 enzymes. A multiple regression analysis found no significant influence of effect of age, sex, body mass index, or cigarette smoking on dose-corrected aripiprazole or dehydroaripiprazole concentration.

Positron Emission Tomography Studies

Four PET studies were identified during which human in vivo dopamine occupancy of aripiprazole was investigated (Table 4).[19–22] The earliest of these studies was a dose-response study carried out during the drug development stage.[19] Plasma levels were not reported, but a highly significant positive correlation was found between daily aripiprazole dose and peak plasma concentration at steady state ($r = 0.97$, $P < .01$). A hyperbolic relationship was found between both aripiprazole dose and plasma levels with striatal dopamine D_2/D_3 receptor occupancy. Almost complete saturation was found at peak plasma levels above 100–200 ng/mL. Similarly, there appeared to be no important increase in striatal dopamine D_2/D_3 receptor occupancy in doses above 10 mg/d.

Kegeles and colleagues[20] reported a further dose-occupancy study that compared aripiprazole D_2 receptor occupancy in striatal and extrastriatal areas. A strong correlation was found between plasma concentration and daily dose ($r = 0.814$, $P = .0002$; actual concentrations not reported). Because of the high correlation found, authors deemed it unnecessary to continue plasma-level investigation, and subsequent analyses of occupancy were performed in relation to dose rather than plasma level. Occupancy was not reported for all doses, but it ranged from 71.6 ± 5.5% at 2 mg/d to 96.8 ± 5.3% at 40 mg/d (mean of all subjects at all regions). Changes in PANSS positive symptom subscale correlated positively with striatal subregional occupancy (n = 7). No such relationship was found for extrastriatal regions or for the negative symptom subscale in any region. Extrastriatal occupancy was consistently higher than in the striatal regions for any given dose.

Two PET studies were identified that directly investigated the relationship between plasma aripiprazole concentration and dopamine D_2 receptor occupancy.[21,22] Study methods and results are shown in Table 4. Mamo and colleagues[21] reported the PET scans of 12 subjects diagnosed with schizophrenia or schizoaffective disorder, randomly assigned to 1 of 4 fixed doses of aripiprazole.[21] High striatal dopamine D_2 occupancy was found at all doses. At the lowest dose of 10 mg, mean occupancy was 85% (putamen range, 81%–88%),

and it increased with dose. At a 30-mg dose, a mean occupancy of 91% was recorded (range, 90%–94%). Dopamine D_2 occupancy in the putamen was consistently lower than in the caudate ($P<.001$) and ventral striatum ($P=.01$). D_2 receptor occupancy in all 3 areas was significantly correlated with aripiprazole dose and plasma concentration. As dose increased, aripiprazole and dehydroaripiprazole plasma concentration also increased, displaying a modest linear correlation ($r=0.67$, $P=.02$ and $r=0.63$, $P=.03$, respectively).

In the Mamo and colleagues[21] study, 4 patients had D_2 occupancy exceeding 90%. Two of these patients suffered with extrapyramidal side effects (EPSE) during the study period, and both had parent and metabolite plasma levels considerably higher than the mean level recorded for the dose they were taking (aripiprazole levels: 442 ng/mL at 30 mg/d and 663 ng/mL at 20 mg/d). Reasons for the elevated plasma concentrations were not investigated.

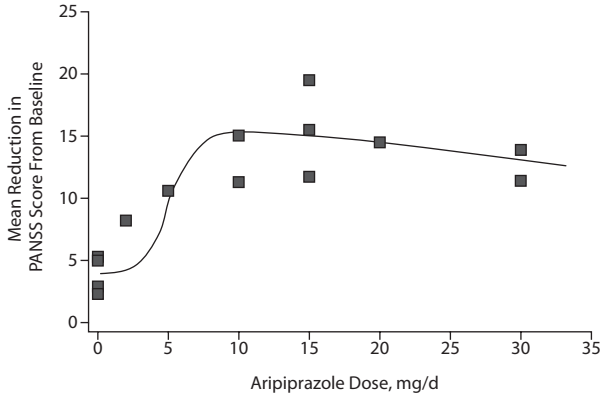
Grunder and colleagues[22] investigated the dopamine receptor binding of aripiprazole in relation to its serum concentration. Positron emission tomography scans were performed and serum levels were taken from 16 aripiprazole-treated patients. In addition, 203 routine TDM serum samples were also collected from 128 patients prescribed aripiprazole. Aripiprazole occupied both striatal and extrastriatal D_2/D_3 receptors at values close to saturation throughout the brain. There was no significant difference in receptor occupancy across the different regions, and no preferential extrastriatal binding was observed (see Table 4). The PET study revealed no correlation between the dose of aripiprazole and trough plasma concentration or between aripiprazole dose and receptor occupancy in any area of the brain. However, in the independent larger TDM study, there was a correlation between dose and plasma concentration ($r=0.510$, $P<.01$, Figure 1A, 1B, and 1C). There was a significant correlation between aripiprazole concentration and dopamine receptor occupancy in all brain regions ($r=0.51$ to 0.62 across regions, $P=.0001$ in each region). At plasma levels above the range 100–150 ng/mL, D_2 receptor occupancy approached 100% in all brain areas studied. The mean serum concentration in the clinical sample was in excess of 200 ng/mL.

CONCLUSIONS

A strong linear correlation exists between aripiprazole dose and plasma/serum aripiprazole concentration. There is also evidence that there is a similarly robust correlation between aripiprazole dose and concentration of both its active metabolite dehydroaripiprazole and the total moiety. In addition, there is a clear relationship between the concentration of aripiprazole and that of dehydroaripiprazole. Positron emission tomography scan analyses suggest that there are statistically significant relationships between dopamine D_2/D_3 receptor occupancy and both aripiprazole dose and blood concentration.

Therapeutic drug monitoring is a useful practice when plasma concentration is not predictable from dose alone and when a therapeutic range is established in which efficacy is enhanced and toxic effects are largely avoided. The available data for aripiprazole demonstrate a strong relationship between dose and concentration, making it possible to predict with some certainty an approximate plasma level for a given dose. All reports of this relationship have confirmed a correlation between dose and plasma level, with the single exception of the relatively small PET scan study by Grunder and colleagues.[22] In the larger TDM arm of this last study, a clear relationship was found between aripiprazole dose and serum concentration.

Figure 2. Aripiprazole Daily Dose Versus Mean Reduction in PANSS Score From Baseline[a]



[a]Reproduced with permission from Mace and Taylor.[4]

Dose-response studies for aripiprazole suggest a threshold of approximately 10 mg/d for clinical response, with little clinical benefit found above this dose (Figure 2).[4] Dopamine occupancy PET scans studied here have shown that high dopamine receptor occupancy is found even at low aripiprazole doses, with little increase in occupancy and almost complete saturation measured above 10 mg/d. For D_2 antagonist antipsychotics it has been postulated that a striatal occupancy of 65% produces efficacy, and a striatal occupancy of 78% produces EPS.[23] Aripiprazole's partial agonist activity is indicated by the observations that D_2 occupancy of more than 65% (at 2 mg/d)[19,20] shows no therapeutic benefit[24] and that occupancies well above 78% seem not to give rise to EPS.[19,25] What is important, however, is that D_2 occupancy and clinical response appear to reach something of a plateau at doses above 10 mg, supporting the observation that 10 mg/d is the optimal dose for aripiprazole. This observation is somewhat supported by the evidence that, in clinical practice, dosage in patients treated with aripiprazole is not often increased above the recommended range, unlike patients treated with other atypical antipsychotics.[26]

Only 2[19,21] of the 4 PET studies reviewed were able to establish a significant correlation between dose and dopamine receptor occupancy, while a correlation between plasma level and occupancy was found by all 3 research groups that investigated the relationship. The small finite dose range of aripiprazole, along with the small numbers of participants in each study, may mean that a statistically significant correlation is less likely to be found between dose and occupancy than between plasma level and occupancy.

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Regardless of the lack of significant correlation, it is clear that occupancy and response increase up to a dose of 10 mg, after which no significant further increase is evident.[19,21]

Kirschbaum and colleagues[13,17] were the only study groups to suggest a serum target range for either efficacy or adverse effects. In their smaller study,[17] a serum target range of 146–254 ng/mL was suggested, based on the interquartile range measured in their whole study sample (without direct reference to efficacy). In a larger and later study[13] a wider efficacy range of 150–300 ng/mL was suggested, based on those patients who made a clinical response to aripiprazole. This study also found 2 ranges for adverse effects—one in which adverse effects were "absent to mild" (110–249 ng/mL) and the other in which they were "moderate to severe" (210–335 ng/mL). These 3 ranges found in the later study[13] might suggest that a plasma/serum level range for optimal efficacy and avoidance of adverse effects is between 150 and 210 ng/mL. Both studies used a method of finding a target range based on the interquartile ranges found in their population rather than on any statistical method to establish significance. Additionally, the authors of the earlier study advised caution when considering their results, as their standard aripiprazole assay sample was not pure and authentic. However, these are the only studies to investigate the relationship between blood concentration and response, and the later study is one of only 2 to comment on adverse effects in any way.

In the reviewed studies, a concentration range of 150–210 ng/mL corresponds to an approximate predicted dose range of 10–15 mg/d Dopamine receptor occupancy at these doses would be expected to be in excess of 80%. In all studies in which patients were dosed according to clinical need (rather than being randomly assigned to a dose), all mean doses were within the range of 15–20 mg/d, and the majority of serum levels were just greater than the upper end of the suggested 150–210 ng/mL range. All serum levels were within the efficacy range of 150–300 ng/mL suggested by the later Kirschbaum study group. As patients were dosed freely according to clinical decision, it may be assumed that doses were titrated for optimal efficacy and avoidance of adverse effects, which would provide some support for the efficacy and adverse effect range suggested by Kirschbaum and colleagues.

Two study groups discussed adverse effects caused by aripiprazole.[13,21] Several pooled analyses of tolerability data from different studies of patients diagnosed with schizophrenia have shown that up to 12.5% of patients taking aripiprazole report extrapyramidal symptoms (EPS) and akathisia.[27–29] The studies discussed here report only patients diagnosed with schizophrenia or schizoaffective disorders, but aripiprazole-induced EPS may be more common in patients diagnosed with affective disorders. A large meta-analysis analyzing the frequency of EPS in patients taking 5 different antipsychotic drugs and diagnosed with affective disorders and schizophrenia found that patients being treated for bipolar affective disorder were more likely to suffer EPS than those diagnosed with schizophrenia. Patients prescribed aripiprazole were significantly more likely to suffer akathisia if diagnosed with bipolar mania or depression than schizophrenia.[30] In the PET study conducted by Mamo and colleagues, [21] EPSE were reported by 2 subjects in whom plasma levels were far above the mean for their dose. Possible explanations for these high levels were not investigated, but it may be that plasma level and not dose predicts likelihood of EPSE. To the best of our knowledge, there are no further available data concerning the relationship between plasma levels and EPS or akathisia for any group of patients. If plasma levels, more than dose, predict likelihood of EPSE or akathisia, TDM may be a particularly useful tool for use in treating patients diagnosed with an affective illness.

Interindividual variability in aripiprazole and metabolite plasma concentration, particularly in dehydroaripiprazole concentrations, was found to be extensive in 3 TDM studies.[13,16,18] Only 2 studies[16,18] investigated the effect of sex on plasma concentration, and they found no relationship between the two. Other possible reasons for variability, such as age and metabolic enzyme genotype, were not investigated by any of the research groups, although they were suggested as a likely cause of interindividual variability. The effect of comedication was investigated by 3 studies,[13,16,18] and they found that several drugs affect the metabolism and therefore the concentration of aripiprazole and its metabolite. These interactions were not investigated in detail and do not explain all the variability found. This interindividual variation within the same prescribed dose supports the argument for plasma level monitoring of aripiprazole.

Our review of the literature includes data from many different studies and from more than 600 subjects. The majority of the data are from naturalistic studies, which, although less controlled than a randomized controlled trial, may more accurately reflect prescribing in a clinical population, and they are therefore valuable when applying these findings to clinical practice. Although the majority of studies were in groups of patients diagnosed with schizophrenia or schizoaffective disorder, one PET study was carried out in healthy volunteers.[19] Many of the studies did not report exclusion criteria, and only 2 studies clearly excluded subjects who had a substance misuse diagnosis and who were taking other medication (Tables 3 and 4). None of the studies we have reported investigated the CYP2D6 metabolizing capability of the participants. The CYP2D6 genotype is known to have an extensive effect on the metabolism, and therefore on the plasma and serum concentration, of aripiprazole in individual patients.[31] In all the studies, despite a mixture of both males and females and an age range of 13 to 69 years, the majority of subjects were male, and all studies had a mean age near 30 years old. These limitations should be considered when applying the results to clinical practice.

The dose range for aripiprazole is well defined, and it reliably predicts plasma or serum aripiprazole level, dopamine receptor occupancy, and clinical response. Some variability in plasma/serum concentrations of parent and metabolite is evident between patients treated with the same doses of aripiprazole. This variation appears to have minimal impact on clinical response, but it may predict EPS and other

significant adverse effects. Doses between 10 and 20 mg/d have consistently been shown to be optimally clinically effective. A putative target plasma level range of between 150 and 210 ng/mL is suggested.

The use of TDM to monitor treatment adherence and the magnitude of a drug interaction is well established for many drugs and is sensible and justified in the case of aripiprazole. Therapeutic drug monitoring may also be helpful to optimize aripiprazole treatment in individuals showing little or no clinical response or intolerable EPS. For the most part, however, TDM should not be considered routine practice for aripiprazole.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), metoprolol (Toprol, Lopressor, and others), paroxetine (Paxil, Pexeva, and others).

Author affiliations: Pharmacy Department, South London and Maudsley National Health Service Foundation Trust (Ms Sparshatt and Dr Taylor); School of Biomedical & Health Sciences, King's College (Dr Taylor); Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, King's College (Dr Patel); and Institute of Psychiatry, King's College (Dr Kapur), London, United Kingdom.

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