JAMA Psychiatry | Original Investigation

Association of CYP2C19 and CYP2D6 Poor and Intermediate Metabolizer Status With Antidepressant and Antipsychotic Exposure
A Systematic Review and Meta-analysis

Filip Milosavljević, PharmM; Nikola Bukvić, PharmM; Zorana Pavlović, MD, PhD; Čedo Miljević, MD, PhD; Vesna Pešić, PharmD, PhD; Espen Molden, PharmD, PhD; Magnus Ingelman-Sundberg, PhD; Stefan Leucht, MD, PhD; Marin M. Jukić, PharmD, PhD

IMPORTANCE Precise estimation of the drug metabolism capacity for individual patients is crucial for adequate dose personalization.

OBJECTIVE To quantify the difference in the antipsychotic and antidepressant exposure among patients with genetically associated *CYP2C19* and *CYP2D6* poor (PM), intermediate (IM), and normal (NM) metabolizers.

DATA SOURCES PubMed, Clinicaltrialsregister.eu, ClinicalTrials.gov, International Clinical Trials Registry Platform, and CENTRAL databases were screened for studies from January 1, 1990, to June 30, 2020, with no language restrictions.

STUDY SELECTION Two independent reviewers performed study screening and assessed the following inclusion criteria: (1) appropriate *CYP2C19* or *CYP2D6* genotyping was performed, (2) genotype-based classification into *CYP2C19* or *CYP2D6* NM, IM, and PM categories was possible, and (3) 3 patients per metabolizer category were available.

DATA EXTRACTION AND SYNTHESIS The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for extracting data and quality, validity, and risk of bias assessments. A fixed-effects model was used for pooling the effect sizes of the included studies.

MAIN OUTCOMES AND MEASURES Drug exposure was measured as (1) dose-normalized area under the plasma level (time) curve, (2) dose-normalized steady-state plasma level, or (3) reciprocal apparent total drug clearance. The ratio of means (RoM) was calculated by dividing the mean drug exposure for PM, IM, or pooled PM plus IM categories by the mean drug exposure for the NM category.

RESULTS Based on the data derived from 94 unique studies and 8379 unique individuals, the most profound differences were observed in the patients treated with aripiprazole (*CYP2D6* PM plus IM vs NM RoM, 1.48; 95% CI, 1.41-1.57; 12 studies; 1038 patients), haloperidol lactate (*CYP2D6* PM vs NM RoM, 1.68; 95% CI, 1.40-2.02; 9 studies; 423 patients), risperidone (*CYP2D6* PM plus IM vs NM RoM, 1.36; 95% CI, 1.28-1.44; 23 studies; 1492 patients), escitalopram oxalate (*CYP2C19* PM vs NM, RoM, 2.63; 95% CI, 2.40-2.89; 4 studies; 1262 patients), and sertraline hydrochloride (*CYP2C19* IM vs NM RoM, 1.38; 95% CI, 1.27-1.51; 3 studies; 917 patients). Exposure differences were also observed for clozapine, quetiapine fumarate, amitriptyline hydrochloride, mirtazapine, nortriptyline hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and venlafaxine hydrochloride; however, these differences were marginal, ambiguous, or based on less than 3 independent studies.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, the association between *CYP2C19*/*CYP2D6* genotype and drug levels of several psychiatric drugs was quantified with sufficient precision as to be useful as a scientific foundation for *CYP2D6*/*CYP2C19* genotype-based dosing recommendations.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2020.3643
Published online November 25, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Marin M. Jukić, PharmD, PhD, Pharmacogenetics Section, Department of Physiology and Pharmacology, Karolinska Institute, Solnavägen 9, 17165 Solna, Sweden (marin.jukic@ki.se).

The efficacy of psychiatric drugs is suboptimal; however, because the development of new antipsychotics and antidepressants is slow, it is of paramount importance to use the currently available drugs as effectively as possible. An important aspect of effective use is dose personalization because, owing to interindividual differences in drug metabolism, the dose required to achieve optimal blood levels of antidepressants and antipsychotics varies substantially between patients.[1] Recently published meta-analyses[2,3] focused on dose-response curves for antipsychotics and antidepressants supported the claim that the appropriate dosing is important for maximizing the efficacy and tolerability of these drugs. In addition, according to recently published data on more than 5000 patients,[4-6] when treated with escitalopram oxalate, 10 mg/d, sertraline hydrochloride, 100 mg/d, risperidone, 4 mg/d, or aripiprazole, 20 mg/d, more than one-third of the patients exhibit blood drug levels outside the therapeutic concentration window defined for these drugs.[1] Therefore, although these daily doses fit an average patient well, there is an apparent need to personalize the dose and maximize the treatment response beyond population-based dosing.

Most antipsychotics and antidepressants are metabolized by the polymorphic CYP2C19 and CYP2D6 enzymes,[1] and their capacity is genetically determined.[7,8] First, normal metabolizers (NM category) have normal enzymatic capacity and carry homozygous wild-type (*Wt*) alleles; they may also carry other genotypes if the enzymatic capacity is not significantly different compared with *Wt*/*Wt* carriers. Second, *CYP2C19*/*CYP2D6* genotype-determined poor metabolizers (PM category) carry homozygous loss-of-function alleles and do not possess the active enzyme. Third, *CYP2C19*/*CYP2D6* genotype-determined intermediate metabolizers (IM category) carry genotypes connected with substantially reduced but not abolished enzymatic capacity. Finally, *CYP2C19*/*CYP2D6* genotype-determined ultrarapid metabolizers (UM category) carry genotypes connected with higher-than-normal enzymatic capacity. All these phenotypes are present in substantial proportion worldwide (**Table 1**).[9]

Key Points

Question What is the difference in the expected antipsychotic and antidepressant exposure between genetically associated *CYP2C19* and *CYP2D6* poor (PM), intermediate (IM), and normal (NM) metabolism?

Findings A systematic review and meta-analysis of 94 unique studies and 8379 unique patients quantified the increases of risperidone, aripiprazole, and haloperidol exposure in patients with *CYP2D6* PM and IM status and increases of escitalopram and sertraline exposure in patients with CYP2C19 PM and IM status as compared with patients with the NM group.

Meaning The obtained results represent a scientific foundation for *CYP2D6*/*CYP2C19* genotype-based dosing recommendations that could potentially lead to improved clinical outcome in drug treatment for patients with psychiatric disorders.

Well-replicated clinical findings indicate that the patients in the PM and IM categories exhibit a substantial increase in the exposure and adverse drug reactions of certain psychotropic drugs,[4-6,10,11] whereas those in the UM category most often have lower levels of response, owing to faster drug metabolism.[4,5,12,13] In addition, recent studies[4,5] found that those in the PM and UM categories are more prone to risperidone and escitalopram treatment failure, which was quantified as an increase in the incidence of switching to an alternative antipsychotic/antidepressant within 1 year. The recommended and maximum daily doses are originally designed to fit the mean genotype-weighted population. Thus, the official dosing recommendations for psychiatric drugs usually do not acknowledge the clinical relevance of *CYP2C19*/*CYP2D6* metabolizer categories and do not distinguish between them. Investigators[4-6] observed, however, that the daily doses of escitalopram, sertraline, risperidone, and aripiprazole, prescribed in naturalistic settings based on clinical observations alone, were lower in individuals in the PM compared with NM categories and that the observed dose

Table 1. Allele Frequencies of Variant *CYP2C19* and *CYP2D6* Genes Among Different Populations Worldwide[a]

Genotype-based phenotype by metabolism category	Population, %				
	European	African	East Asian	South Asian	Admixed American
CYP2C19					
PM	3.3	3.3	14.2	11.8	1.1
IM	21.7	21.2	45.8	35.8	16.0
PM plus IM	25.0	24.6	60.1	47.6	17.1
NM	43.4	42.5	38.1	36.4	62.8
UM	31.6	32.9	1.8	16.0	20.1
CYP2D6					
PM	6.2	2.8	0.7	2.1	3.8
IM	2.6	24.5	48.6	10.0	2.6
PM plus IM	8.8	27.3	49.3	12.2	6.4
NM	88.1	64.7	49.6	85.9	91.4
UM	3.2	8.0	1.2	1.9	2.2

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

[a] Data are based on Zhou et al.[9] Notable variations also exist within the global regions.

reductions were insufficient to fully compensate for the increased drug exposure. In rare cases, as with aripiprazole treatment, relevant sources such as the US Food and Drug Administration, European Medicines Agency, CPIC (Clinical Pharmacogenetics Implementation Consortium), and DPWG (Dutch Pharmacogenetics Working Group) recommend dose reduction for patients in the CYP2D6 PM category; however, these sources offer conflicting information related to the magnitude of dose adjustment. In fact, most of the recommendations are based on underpowered studies, and insufficient data are available to allow the estimation of the difference in drug exposure between metabolizer categories with sufficient precision.[14]

Many previous studies, often of limited sample size, have investigated the effects of *CYP2C19* and *CYP2D6* genotype on the exposure of antipsychotic and antidepressant drugs, and recently published reports substantially increased the number of participants undergoing genotyping.[4-6] Thus, the aim of this systematic review and meta-analysis of prospective and retrospective cohort studies was to quantify, with the best attainable precision, the increase of antidepressant and antipsychotic exposure in individuals in *CYP2C19/CYP2D6* PM and IM categories compared with those in the NM category. Individuals in the UM category were not included in the analysis owing to the limited number of studies considering this phenotypic group.

Methods

Search Strategy and Selection Criteria

The list of antipsychotic and antidepressant drugs was based on the list of frequently used antidepressants[15] and antipsychotics.[16] The investigated antidepressants included escitalopram, sertraline, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, venlafaxine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, mianserin, and mirtazapine; the antipsychotics included clozapine, quetiapine fumarate, olanzapine, risperidone, aripiprazole, and haloperidol lactate. Racemic citalopram hydrobromide was not investigated owing to stereoselective metabolism. The information on which CYP450 isoforms are involved in the metabolism of each drug were retrieved from the recent consensus guidelines.[1] The search was performed in PubMed, ClinicalTrials.gov, Clinicaltrialsregister.eu, International Clinical Trials Registry Platform, and CENTRAL databases for reports published from January 1, 1990, to June 30, 2020. An independent literature survey was performed for each drug and the search terms **NameOfTheDrug** AND *CYP2C19* OR *CYP2D6* were used. During the initial screening step, all studies that did not deal with drug exposure were excluded, and the remaining studies were considered for inclusion based on the following criteria: (1) participants were genotyped for all known common functional *CYP2C19* or *CYP2D6* variant alleles with minor allele frequency of greater than 1% according to Zhou et al[9]; (2) adequate classification of participants into CYP2C19 and/or CYP2D6 NM, IM, and PM categories was possible based on genotyping; (3) the study included at least 3 participants per experimental group; and (4) drug exposure was measured in a representative way by (a) dose-normalized steady-state plasma levels, (b) dose-normalized area under the plasma level (time) curve, or (c) apparent total clearance of the drug (reciprocal value). The screening and scanning for eligibility were performed manually by 2 independent investigators (F.M. and N.B.). The decision on study inclusion was made by consensus with a third investigator (M.M.J.), with the final checkup made by consensus among 3 (E.M., M.I.-S., and M.M.J.). Six domains were assessed by using the standardized risk of bias in nonrandomized studies of interventions tool,[17] and studies with the critical risk of bias were excluded. No restrictions were made regarding the study design, participant characteristics (race, ethnicity, sex, age, smoking status, and patient vs healthy cohort), treatment duration, drug interactions, and language.

Data Extraction

The procedures of data acquisition and extraction, as well as the situations when the authors were contacted to provide the data that were inaccessible, are described in full detail in eMethods 1 in the Supplement. If a drug possesses an active metabolite, the drug exposure was calculated by pooling the parent compound and active metabolite (active moiety) exposure.[1] Participants were classified into PM, IM, and NM categories for CYP2C19 and CYP2D6 by using the previously described classification criteria (Table 1).[18] Participants in the PM category were homozygous carriers of the 2 loss-of-function (null) alleles for both CYP2C19 and CYP2D6. For CYP2C19, participants in the IM category carried 1 null and 1 *Wt* allele, whereas those in the NM category carried the *CYP2C19 Wt*/*Wt* genotype. The *CYP2D6* gene possesses alleles that reduce but do not abolish the enzymatic capacity (*Red*), and the CYP2D6 IM category consisted of participants carrying either *CYP2D6* Red/Null or *CYP2D6 Red*/*Red* genotype, whereas the subpopulation in the CYP2D6 NM category carries 1 or 2 *CYP2D6 Wt* alleles. For the purpose of this study, only the individuals carrying the *CYP2D6 Wt*/*Wt* genotype represented the NM reference group, as suggested by the consensus guidelines.[18]

Statistical Analyses

Meta-analyses were performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[19] and the checklist is available in eMethods 2 in the Supplement. Meta-analyses for specific phenotypes/drugs were performed and represented graphically if 3 or more studies met the inclusion criteria. The effect size was the mean exposure of the PM, IM, or PM plus IM groups divided by the mean exposure of the NM group, that is, the ratio of means (RoM).[20] For example, an IM:NM group RoM of 1.5 means a 1.5 times higher exposure (ie, a 50% higher exposure in the IM compared with the NM group). Standard mean differences (Hedges *g*) were also calculated and presented in eFigure 3 in the Supplement. Weighted RoM between subgroups was used in calculation of pooling effect between studies by fixed-effects meta-analysis model. Heterogeneity across the studies was assessed

Table 2. Overview of Search Process and Studies Incorporated Into Meta-analyses

Analyzed drug	Enzyme	No. of studies	No. of excluded studies			No. of included studies	No. of individuals by metabolism category[a]		
			Not dealing with exposure	Incorrect genotyping	No usable data		NM[b]	IM	PM
Antipsychotics									
Aripiprazole	CYP2D6	84	58	4	10	12	814	134	90
Clozapine	CYP2D6	86	78	3	0	5	33	15	4
	CYP2C19						127	65	8
Haloperidol	CYP2D6	109	83	10	3	13	532	158	46
Quetiapine	CYP2D6	45	44	0	0	1	171	0	20
Risperidone	CYP2D6	221	163	9	26	23	1134	186	172
Antidepressants									
Amitriptyline	CYP2D6	103	94	1	4	4	43	9	4
	CYP2C19						34	18	6
Escitalopram	CYP2C19	147	135	4	4	4	1110	760	152
Fluoxetine	CYP2D6	313	305	4	1	3	8	0	3
	CYP2C19						71	27	6
Fluvoxamine	CYP2D6	224	212	3	2	7	74	72	0
	CYP2C19						6	6	6
Mirtazapine	CYP2D6	70	59	2	4	5	142	14	19
Nortriptyline	CYP2D6	97	87	3	3	4	28	14	4
Paroxetine	CYP2D6	335	318	8	4	5	89	14	11
Sertraline	CYP2C19	74	68	1	2	3	565	352	40
Venlafaxine	CYP2D6	195	170	5	12	8	509	87	120
	CYP2C19						422	198	21
Total		2103	1874	57	75	94	8379[b]		

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer.

[a] The total number of patients is less than the sum of patients for all phenotypes/drugs owing to the fact that *CYP2C19* and *CYP2D6* genotyping was performed in certain studies.

[b] Indicates reference category.

using the Cochran *Q* test at a given significance level; the percentage of total variability attributable to heterogeneity was quantified by the I^2 value. A fixed-effects model was used because all the pooled studies represent the same genetic/biological construct; however, owing to considerable heterogeneity in certain analyses, a post hoc sensitivity analysis was performed by using the random-effects model, and the comparison between the fixed- and random-effects model analyses is presented in eTable 1 in the Supplement. Differences between the effect sizes of PM vs NM and IM vs NM groups were examined by using the subgroup test, and when no difference was observed, a post hoc comparison between the pooled PM plus IM and NM experimental groups was performed. For each individual study, the PM plus IM experimental group exposure was calculated by combining the PM and IM subgroups according to the Cochrane handbook formula (section 6.5.2.10 on combining groups).[21]

Small trial or publication bias was evaluated using the Egger test for funnel plot asymmetry,[22] and funnel plots are presented in the eFigure 5 in the Supplement. Statistical analyses were performed with RevMan, version 5.4, software (Cochrane). Ratios of means for the individual studies were calculated using Excel, version 2013 (Microsoft Corporation), according to the previously published formula,[20] and subsequently entered into RevMan with the generic inverse variance option. Two-sided $\alpha < .05$ indicated statistical significance.

Interpretation of Changes in Drug Exposure

If a lower boundary of the 95% CI for the drug exposure increase of the PM, IM, or PM plus IM groups compared with the NM group was greater than 1.25-fold, such an effect was considered clinically relevant. If this was not the case for a statistically significant effect, such an effect was considered preliminary or marginal. This quantitative cutoff was based on (1) the US Food and Drug Administration limits for bioequivalence (RoM, 0.80-1.25), which are based on the general consideration that the intraindividual variability in drug exposure from oral drug intake to intake is 20%,[23] and (2) the previous finding that changes of this magnitude are associated with an increased risk of therapeutic failure, measured by the drug switch rates in 2 recent studies[4,5] on patient cohorts treated with escitalopram (n = 2087) and risperidone (n = 890).

Results

Of the 2103 initially screened references, 94 unique studies[4-6,24-114] on 8379 unique individuals met the inclusion

criteria. Reasons for exclusion are presented in **Table 2** and eTable 2 in the Supplement. eFigure 1 in the Supplement gives the PRISMA[115] flow diagram. A list of included and excluded studies are presented in eMethods 3 in the Supplement.

Association Between CYP2D6 Metabolizer Status and Drug Exposure

The *CYP2D6* genotype was associated with significant exposure increases for aripiprazole[5,25-33,115,116] (eFigure 2 in the Supplement) (PM plus IM vs NM RoM, 1.48; 95% CI, 1.41-1.57; 12 studies; 1038 patients), haloperidol[26,34-36] (eFigure 2 in the Supplement) (PM vs NM RoM, 1.68; 95% CI, 1.40-2.02; 9 studies; 423 patients), and risperidone[5,26,35,37-41,43-57] (eFigure 2 in the Supplement) (PM plus IM vs NM RoM, 1.36; 95% CI, 1.28-1.44; 23 studies; 1492 patients). Nortriptyline exposure[58-60] (RoM, 2.36; 95% CI, 2.10-2.65; 3 studies; 37 patients) (eFigure 2 in the Supplement) and paroxetine exposure[61-63] (RoM, 3.50; 95% CI, 2.52-4.85; 3 studies; 41 patients) (eFigure 2 in the Supplement) were significantly increased in the CYP2D6 IM compared with the NM groups; however, after removing the studies associated with serious risk of bias (eResults in the Supplement), these differences were based on fewer than 3 independent studies. It is uncertain whether the exposure increases observed in the fluvoxamine IM group[64-69] and mirtazapine PM group[70-73] (eFigure 2 in the Supplement) compared with the NM groups are outside the bioequivalence (1.25) limit. Compared with the CYP2D6 NM group, marginal exposure increases were observed in the haloperidol IM group[74-82] (RoM, 1.14; 95% CI, 105-125; 9 studies; 423 patients) (eFigure 2 in the Supplement) and venlafaxine IM plus PM group (RoM, 1.19; 95% CI, 1.09-1.29; 8 studies; 716 patients)[83-90] (eFigure 2 in the Supplement). Statistically significant exposure increases based on less than 3 independent studies compared with the CYP2D6 NM group were observed in the quetiapine-treated PM (RoM, 1.32; 95% CI, 1.10-1.58; 1 study; 191 patients), amitriptyline-treated IM (RoM, 1.50; 95% CI, 1.23-1.84; 2 studies; 35 patients), mirtazapine-treated IM (RoM, 1.39; 95% CI, 1.23-1.57; 4 studies; 144 patients), paroxetine-treated PM (RoM, 5.13; 95% CI, 3.82-6.87; 2 studies; 73 patients), nortriptyline-treated PM (RoM, 3.32; 95% CI, 2.08-5.29; 1 study; 9 patients), and fluoxetine-treated PM (RoM, 2.26; 95% CI, 1.68-2.83; 1 study; 11 patients) groups (**Table 3**).

Association Between CYP2D6 Metabolizer Status and Drug Exposure

The *CYP2C19* genotype was associated with significant exposure increases for escitalopram (eFigure 2 in the Supplement) (PM vs NM RoM, 2.63; 95% CI, 2.40-2.89; 4 studies; 1262 patients)[4,91-93] and sertraline (eFigure 2 in the Supplement) (IM vs NM RoM, 1.38; 95% CI, 1.27-1.51; 3 studies; 917 patients).[6,94,95] Considerable heterogeneity was observed in the escitalopram meta-analyses, and the elevation in escitalopram exposure in the CYP2C19 IM group was not observed if the random-effect model was used (eFigure 4 in the Supplement). The CYP2C19 IM and NM groups did not exhibit statistically significant difference in clozapine exposure.[96-99] Statistically significant exposure increases based on less than 3 independent studies compared with the CYP2C19 NM group were observed in the clozapine-treated PM (RoM, 1.92; 95% CI, 1.32-2.79; 2 studies; 78 patients), fluoxetine-treated IM (RoM, 1.48; 95% CI, 1.24-1.76; 2 studies; 98 patients) and PM (RoM, 2.94; 95% CI, 2.36-3.67; 1 study; 10 patients), sertraline-treated PM (RoM, 2.70; 95% CI, 2.15-3.39; 2 studies; 577 patients), and venlafaxine-treated IM (RoM, 1.19; 95% CI, 1.11-1.31; 1 study; 669 patients) and PM (RoM, 2.13; 95% CI, 1.54-2.93; 1 study; 443 patients) groups (Table 3).

Heterogeneity, Small Trial or Publication Bias, and Risk of Bias Assessment

Significant heterogeneity was observed in the aripiprazole IM and IM plus PM, escitalopram PM and IM, mirtazapine PM, nortriptyline IM, and venlafaxine IM group meta-analyses. No small trial or publication bias was observed in the meta-analyses related to risperidone and aripiprazole (eResults in the Supplement), whereas asymmetry could not be assessed in other meta-analyses owing to the insufficient number of included studies ($n < 10$).

According to the standardized risk of bias in nonrandomized studies of interventions tool, 23 studies were associated with a serious risk of bias,[24,32,36,38,41,44,46,49,56,58,59,61,62,70,74,79,81,82,86,103,105,107,112] and 71 studies[4-6,25-31,33-35,37,39,40,42,43,45,47,48,50-55,57,60,63-69,71-73,75-78,80,83-85,87-102,104,106,108-111,113,114] were associated with moderate risk of bias (ie, the analysis is comparable with a well-performed nonrandomized study). The sensitivity analysis results performed for the studies with moderate risk of bias is presented in eTable 3 and eFigure 6 in the Supplement.

Discussion

The results obtained in this systematic review and meta-analysis provide precise quantifications of the differences in antipsychotic and antidepressant drug exposure between patients with PM or IM vs NM CYP2C19/CYP2D6 phenotypes. These results represent scientific foundations for *CYP2D6/CYP2C19* genotype-based dosing recommendations, which could lead to improved clinical outcomes in drug treatment of patients with psychiatric disorders.

Although many studies show that CYP2C19 and CYP2D6 PM and IM groups exhibit a significant increase in drug exposure compared with NM groups, the power of these studies was insufficient to quantify these exposure increases with sufficient precision and to evaluate their prospective clinical relevance. The present set of meta-analyses, which incorporates 8379 *CYP2C19* and *CYP2D6* genotyped individuals with exposure measurements for 16 frequently used psychiatric drugs, allowed (1) validation of whether CYP2C19 and CYP2D6 PM or IM phenotypes significantly increase the drug exposure compared with the NM phenotype, (2) differentiation between marginal changes and clinically relevant drug exposure increases caused by specific phenotypes, and (3) precise estimation of the magnitude of increase in drug exposure for the clinically relevant exposure changes. High precision of clinically relevant estimates is important for the clinical implementation

Table 3. Detailed Statistical Report of the Association of Metabolism Status With Antipsychotic and Antidepressant Exposure

Drug	Enzyme	No. of studies	No. of patients by metabolism group		RoM (95% CI)	*P* value	I^2 value, %
			Reference	Comparator			
Antipsychotics							
Aripiprazole	CYP2D6	5	693 NM	90 PM	1.51 (1.38-1.65)	<.001	0
	CYP2D6	9	664 NM	134 IM	1.47 (1.38-1.57)	<.001	65
	CYP2D6	12	814 NM	224 PM plus IM	1.48 (1.41-1.56)	<.001	56
Clozapine	CYP2D6	1	22 NM	4 PM	1.00 (0.43-2.32)	>.99	NA
	CYP2D6	2	33 NM	15 IM	1.22 (0.79-1.88)	.51	0
	CYP2C19	2	70 NM	8 PM	1.92 (1.32-2.79)	.008	0
	CYP2C19	4	127 NM	65 IM	1.00 (0.84-1.19)	.84	10
Haloperidol	CYP2D6	4	267 NM	46 PM	1.68 (1.40-1.91)	<.001	21
	CYP2D6	9	265 NM	158 IM	1.14 (1.05-1.25)	.003	0
Quetiapine	CYP2D6	1	171 NM	20 PM	1.32 (1.10-1.58)	<.001	NA
Risperidone	CYP2D6	13	937 NM	172 PM	1.40 (1.30-1.50)	<.001	17
	CYP2D6	11	469 NM	186 IM	1.31 (1.20-1.43)	<.001	44
	CYP2D6	23	1134 NM	358 PM plus IM	1.36 (1.28-1.44)	<.001	34
Antidepressants							
Amitriptyline	CYP2D6	1	17 NM	4 PM	1.04 (0.65-1.68)	.86	NA
	CYP2D6	2	26 NM	9 IM	1.50 (1.23-1.84)	<.001	0
	CYP2C19	1	4 NM	6 PM	1.07 (0.81-1.41)	.58	NA
	CYP2C19	1	30 NM	18 IM	1.06 (0.89-1.25)	.50	NA
Escitalopram	CYP2C19	4	1110 NM	152 PM	2.63 (2.40-2.89)	<.001	84
	CYP2C19	4	1110 NM	760 IM	1.38 (1.28-1.48)	<.001	86
Fluvoxamine	CYP2D6	6	74 NM	72 IM	1.52 (1.23-1.89)	<.001	0
	CYP2C19	1	6 NM	6 IM	0.87 (0.31-2.45)	.77	NA
	CYP2C19	1	6 NM	6 PM	0.90 (0.31-2.65)	.84	NA
Fluoxetine	CYP2D6	1	8 NM	3 PM	2.26 (1.68-2.83)	<.001	NA
	CYP2C19	1	4 NM	6 PM	2.94 (2.36-3.67)	<.001	NA
	CYP2C19	2	71 NM	27 IM	1.48 (1.24-1.76)	<.001	13
Mirtazapine	CYP2D6	4	125 NM	19 PM	1.39 (1.23-1.57)	<.001	64
	CYP2D6	1	17 NM	14 IM	1.51 (1.20-1.91)	.010	NA
Nortriptyline	CYP2D6	1	5 NM	4 PM	3.32 (2.08-5.29)	<.001	NA
	CYP2D6	3	23 NM	14 IM	2.36 (2.10-2.65)	<.001	74
Paroxetine	CYP2D6	2	62 NM	11 PM	5.13 (3.82-6.87)	<.001	85
	CYP2D6	3	27 NM	14 IM	3.50 (2.52-4.85)	<.001	0
Sertraline	CYP2C19	3	565 NM	352 IM	1.38 (1.27-1.51)	<.001	0
	CYP2C19	2	537 NM	40 PM	2.70 (2.15-3.39)	<.001	0
Venlafaxine	CYP2D6	6	486 NM	120 PM	1.18 (1.04-1.33)	.01	50
	CYP2D6	3	436 NM	87 IM	1.14 (1.03-1.26)	.009	70
	CYP2D6	8	509 NM	207 PM plus IM	1.19 (1.09-1.29)	<.001	40
	CYP2C19	1	422 NM	21 PM	2.13 (1.54-2.93)	<.001	NA
	CYP2C19	1	422 NM	247 IM	1.19 (1.11-1.31)	<.001	NA

Abbreviations: IM, intermediate metabolizer; NA, not applicable; NM, normal metabolizer; PM, poor metabolizer; RoM, ratio of means.

of appropriate dose recommendations for subpopulations defined by *CYP2C19* or *CYP2D6* genotype.

There is a consensus in the field about the relevance of the *CYP2C19* and *CYP2D6* polymorphism for interindividual variability in drug metabolism and clinical response,[117,118] and *CYP2C19*/*CYP2D6* genotyping is already included in all currently commercially available pharmacogenetic tests.[119] Pharmacogenomic recommendations on drug labels offer a tool by which knowledge of the specific genotype can be translated to the clinical setting in a quantitative manner. However, the dosing recommendations are usually not uniform among the relevant sources,[14] and the dosing recommendations on the US Food and Drug Administration–approved drug labels[120-125] clearly do not comply on many points with the findings summarized herein. The results suggest that there is a need to distinguish between CYP2D6 metabolism categories when deciding on aripiprazole, haloperidol, and risperidone doses and to distinguish between CYP2C19 metabolism categories when deciding on escitalopram and sertraline dose. Furthermore, unlike the PM phenotype, the IM phenotype is seldom consid-

ered a relevant factor for drug dosing and treatment, which is noteworthy in relation to results and the fact that more than half of the East Asian population and a considerable amount of other populations have the CYP2C19 or CYP2D6 IM phenotype.[9]

To approach the question of whether preemptive *CYP2C19* and *CYP2D6* genotyping can improve the drug treatment outcome of patients with psychiatric disorders, one must (1) demonstrate the effect of serum concentration on adverse effects and efficacy and (2) quantify the effect of genotype on serum concentration. The former has been demonstrated by a series of pharmacokinetic, clinical, and positron emission tomography studies[1,126,127] and to an extent by 2 recent meta-analyses on dose-response curves for antidepressants and antipsychotics.[2,3] The present report addresses the latter, because it quantifies the effect of PM and IM CYP2C19/CYP2D6 phenotypes on blood levels. Therapeutic drug monitoring can be used as a tool in personalized dosing because it directly measures drug blood levels and encompasses all sources of variability in drug exposure, including *CYP2D6/CYP2C19* genotype. However, therapeutic drug monitoring becomes applicable only when the drug level reaches a steady state and is therefore not a suitable tool for preventing the suboptimal response or adverse effects during the initial weeks, or sometimes months, of psychiatric drug treatment. This period is critical for rapid symptom control, patients' treatment belief, and adherence; in a therapeutic field characterized by a substantial degree of trial and error, preemptive genotyping has a potential to improve dose personalization and subsequently the drug treatment outcome as well. Overall, the optimal dose stabilization would be obtained in an ideal clinical situation, in which a psychiatrist would know the patients' *CYP2D6/CYP2C19* genotype before the drug treatment initiation to make the best possible initial dosing decisions. These decisions can be checked by therapeutic drug monitoring after the steady state is achieved. However, although several industry-sponsored clinical trials[128-130] advocate the advantage of genotype-guided over usual treatment in psychiatry, a well-designed trial is still necessary to validate and quantify the clinical utility of preemptive *CYP2C19/CYP2D6* genotyping.

Limitations

The most important limitation of this report is the potential presence of confounding factors, which arise from the nature of the studies incorporated into meta-analyses. Most of the studies were performed in naturalistic settings, and the factors that are known to affect drug metabolism are seldom completely controlled for. Next, the inclusion and exclusion criteria were designed in a way to eliminate the possibility of erroneous classification into metabolism categories, and this revealed the apparent scarcity of representative studies for many gene-drug interactions. In addition, approximately one-third of the studies that dealt with drug exposure did not measure exposure representatively, and the data were therefore not usable. Although CYP2C19/CYP2D6 UM status may also affect the exposure of certain drugs, and although the CYP2C19 and CYP2D6 PM and/or IM status significantly affect drug exposures of most of the analyzed drugs, more studies and larger cohorts are needed to ascertain the relevance of many gene-drug interactions (eFigure 8 in the Supplement). Also, in some cases, the number of usable studies was relatively low and heterogeneity was considerable; the most notable example is the analysis of CYP2C19-escitalopram interaction with 4 representative studies for each comparison[4,91-93] and $I^2 > 80\%$. Although the directionality of the effect is apparent, more representative studies on this interaction are needed to precisely quantify the effect size of the exposure increase. Next, it was possible to address the presence of small trial or publication bias only for several comparisons owing to the small number of studies ($n < 10$) for many gene-drug interactions. Although the test result was negative for the analyzed comparisons, we cannot exclude the possibility that the publication bias is present in some of the gene-drug interaction comparisons to a degree. Finally, we were able to compare the effect of ethnicity in several comparisons by the subgroup test only, and these post hoc tests are presented in the eFigure 7 in the Supplement. Although these test results were negative, we cannot completely exclude the possibility that the exposure increases of certain drugs may be ethnicity dependent to a degree.

Conclusions

In this systematic review and meta-analysis, the association between *CYP2C19/CYP2D6* genotype and drug levels of aripiprazole, haloperidol, risperidone, escitalopram, and sertraline was quantified with sufficient precision as to be useful as a scientific foundation for *CYP2D6/CYP2C19* genotype-based dosing recommendations. In addition, there was an indication that the *CYP2C19/CYP2D6* genotype is associated with changes in drug levels of clozapine, quetiapine, amitriptyline, fluvoxamine, fluoxetine, mirtazapine, nortriptyline, paroxetine, and venlafaxine. However, more representative studies focused on these specific gene-drug associations are necessary for an adequate quantification of the magnitude of drug level changes and for representative evaluation of the relevance of these changes.

ARTICLE INFORMATION

Accepted for Publication: September 21, 2020.

Published Online: November 25, 2020. doi:10.1001/jamapsychiatry.2020.3643

Author Affiliations: Department of Physiology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia (Milosavljević, Bukvić, Pešić, Jukić); Department of Psychiatry, Faculty of Medicine, University of Belgrade, Belgrade, Serbia (Pavlović, Miljević); Psychiatry Clinic, Clinical Centre of Serbia, Belgrade (Pavlović); Institute for Mental Health, Belgrade, Belgrade, Serbia (Miljević); Department of Pharmacokinetics, University of Oslo Pharmacy School, Oslo, Norway (Molden); Pharmacogenetics Section, Department of Physiology and Pharmacology, Karolinska Institutet, Solna, Sweden (Ingelman-Sundberg, Jukić); Department of Psychiatry and Psychotherapy, Technische Universität München School of Medicine, Munich, Germany (Leucht).

Author Contributions: Dr Jukić had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Milosavljević, Pavlović, Miljević, Pešić, Molden, Ingelman-Sundberg, Jukić.

Acquisition, analysis, or interpretation of data: Milosavljević, Bukvić, Molden, Ingelman-Sundberg, Leucht, Jukić.
Drafting of the manuscript: Milosavljević, Bukvić, Molden, Ingelman-Sundberg, Jukić.
Critical revision of the manuscript for important intellectual content: Milosavljević, Pavlović, Miljević, Pešić, Molden, Ingelman-Sundberg, Leucht, Jukić.
Statistical analysis: Milosavljević, Bukvić, Jukić.
Obtained funding: Pavlović, Pešić, Jukić.
Administrative, technical, or material support: Pavlović, Pešić, Molden, Ingelman-Sundberg, Jukić.
Supervision: Pavlović, Miljević, Leucht, Jukić.

Conflict of Interest Disclosures: Dr Miljević reported receiving personal fees from Actavis Generics, Alkaloid AD Skopje, Gedeon Richter, Janssen Pharmaceutica, Krka, and Pfizer, Inc. Dr Ingelman-Sundberg reported being a cofounder and co-owner of the company HepaPredict AB. Dr Leucht reported receiving personal fees from Angelini, Boehringer Ingelheim, Gedeon Richter, Janssen Pharmaceutica, Johnson & Johnson, LB Pharmaceuticals, LTS Lohmann, H Lundbeck A/S, Merck Sharp & Dohme, Otsuka Pharmaceutical Co Ltd, Recordati Rare Diseases, Sandoz, Inc, Sanofi Aventis, Sunovian Pharmaceuticals, Inc, and Teva Pharmaceutical Industries Ltd outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by grant 6066800/PsyCise from the Science Fund of the Republic of Serbia PROMIS program (Dr Jukić), grant 2015-02760 from the Swedish Research Council (Dr Ingelman-Sundberg), grant 668353/U-PGx the European Union's Horizon 2020 research and innovation program (Dr Ingelman-Sundberg), and grant FO2019-0260 the Swedish Brain foundation (Drs Ingelman-Sundberg and Jukić).

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

2. Furukawa TA, Cipriani A, Cowen PJ, Leucht S, Egger M, Salanti G. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. *Lancet Psychiatry*. 2019;6(7):601-609. doi:10.1016/S2215-0366(19)30217-2

3. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. *Am J Psychiatry*. 2020;177(4):342-353. doi:10.1176/appi.ajp.2019.19010034

4. Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of *CYP2C19* genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. *Am J Psychiatry*. 2018;175(5):463-470. doi:10.1176/appi.ajp.2017.17050550

5. Jukic MM, Smith RL, Haslemo T, Molden E, Ingelman-Sundberg M. Effect of *CYP2D6* genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *Lancet Psychiatry*. 2019;6(5):418-426. doi:10.1016/S2215-0366(19)30088-4

6. Bråten LS, Haslemo T, Jukic MM, Ingelman-Sundberg M, Molden E, Kringen MK. Impact of *CYP2C19* genotype on sertraline exposure in 1200 Scandinavian patients. *Neuropsychopharmacology*. 2020;45(3):570-576. doi:10.1038/s41386-019-0554-x

7. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of *CYP2D6* phenotype from genotype across world populations. *Genet Med*. 2017;19(1):69-76. doi:10.1038/gim.2016.80

8. Fricke-Galindo I, Céspedes-Garro C, Rodrigues-Soares F, et al. Interethnic variation of *CYP2C19* alleles, "predicted" phenotypes and "measured" metabolic phenotypes across world populations. *Pharmacogenomics J*. 2016;16(2):113-123. doi:10.1038/tpj.2015.70

9. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome *P450* alleles: a meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther*. 2017;102(4):688-700. doi:10.1002/cpt.690

10. Fabbri C, Tansey KE, Perlis RH, et al. Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: Meta-analysis of data from genome-wide association studies. *Eur Neuropsychopharmacol*. 2018;28(8):945-954. doi:10.1016/j.euroneuro.2018.05.009

11. de Leon J, Susce MT, Pan RM, Fairchild M, Koch WH, Wedlund PJ. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. *J Clin Psychiatry*. 2005;66(1):15-27. doi:10.4088/JCP.v66n0103

12. Jukić MM, Opel N, Ström J, et al. Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment. *Mol Psychiatry*. 2017;22(8):1155-1163. doi:10.1038/mp.2016.204

13. Rahikainen AL, Vauhkonen P, Pett H, et al. Completed suicides of citalopram users-the role of *CYP* genotypes and adverse drug interactions. *Int J Legal Med*. 2019;133(2):353-363. doi:10.1007/s00414-018-1927-0

14. Ingelman-Sundberg M. Translation of pharmacogenomic drug labels into the clinic: current problems. *Pharmacol Res*. 2020;153:104620. doi:10.1016/j.phrs.2019.104620

15. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018;391(10128):1357-1366. doi:10.1016/S0140-6736(17)32802-7

16. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3

17. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi:10.1136/bmj.i4919

18. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing *CYP2D6* genotype to phenotype translation: consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020;13(1):116-124. doi:10.1111/cts.12692

19. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

20. Friedrich JO, Adhikari NKJ, Beyene J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. *BMC Med Res Methodol*. 2008;8(1):32. doi:10.1186/1471-2288-8-32

21. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions, version 6.1 (updated September 2020)*. Cochrane; 2020.

22. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002. doi:10.1136/bmj.d4002

23. US Food and Drug Administration. Guidance for Industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. Center for Drug Evaluation and Research; 2003.

24. Lisbeth P, Vincent H, Kristof M, Bernard S, Manuel M, Hugo N. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. *Eur J Clin Pharmacol*. 2016;72(2):175-184. doi:10.1007/s00228-015-1965-1

25. Belmonte C, Ochoa D, Román M, et al. Influence of *CYP2D6*, *CYP3A4*, *CYP3A5* and *ABCB1* polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. *Basic Clin Pharmacol Toxicol*. 2018;122(6):596-605. doi:10.1111/bcpt.12960

26. van der Weide K, van der Weide J. The influence of the *CYP3A4*22* polymorphism and *CYP2D6* polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. *J Clin Psychopharmacol*. 2015;35(3):228-236. doi:10.1097/JCP.0000000000000319

27. Tveito M, Molden E, Høiseth G, Correll CU, Smith RL. Impact of age and CYP2D6 genetics on exposure of aripiprazole and dehydroaripiprazole in patients using long-acting injectable versus oral formulation: relevance of poor and intermediate metabolizer status. *Eur J Clin Pharmacol*. 2020;76(1):41-49. doi:10.1007/s00228-019-02768-0

28. Suzuki T, Mihara K, Nakamura A, et al. Effects of the *CYP2D6*10* allele on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. *Ther Drug Monit*. 2011;33(1):21-24. doi:10.1097/FTD.0b013e3182031021

29. Suzuki T, Mihara K, Nakamura A, et al. Effects of genetic polymorphisms of *CYP2D6*, *CYP3A5*, and *ABCB1* on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. *Ther Drug Monit*. 2014;36(5):651-655. doi:10.1097/FTD.0000000000000070

30. Nagai G, Mihara K, Nakamura A, et al. Prolactin concentrations during aripiprazole treatment in relation to sex, plasma drugs concentrations and genetic polymorphisms of dopamine D2 receptor and cytochrome P450 2D6 in Japanese patients with schizophrenia. *Psychiatry Clin Neurosci*. 2012; 66(6):518-524. doi:10.1111/j.1440-1819.2012.02391.x

31. Azuma J, Hasunuma T, Kubo M, et al. The relationship between clinical pharmacokinetics of aripiprazole and *CYP2D6* genetic polymorphism: effects of CYP enzyme inhibition by coadministration of paroxetine or fluvoxamine. *Eur J Clin Pharmacol*. 2012;68(1):29-37. doi:10.1007/s00228-011-1094-4

32. Kubo M, Koue T, Inaba A, et al. Influence of itraconazole co-administration and *CYP2D6* genotype on the pharmacokinetics of the new antipsychotic aripiprazole. *Drug Metab Pharmacokinet*. 2005;20(1):55-64. doi:10.2133/dmpk.20.55

33. Kubo M, Koue T, Maune H, Fukuda T, Azuma J. Pharmacokinetics of aripiprazole, a new antipsychotic, following oral dosing in healthy adult Japanese volunteers: influence of *CYP2D6* polymorphism. *Drug Metab Pharmacokinet*. 2007; 22(5):358-366. doi:10.2133/dmpk.22.358

34. Desai M, Tanus-Santos JE, Li L, et al. Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6. *Pharmacogenomics J*. 2003;3(2):105-113. doi:10.1038/sj.tpj.6500160

35. Gassó P, Papagianni K, Mas S, et al. Relationship between *CYP2D6* genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. *Pharmacogenomics*. 2013;14 (13):1551-1563. doi:10.2217/pgs.13.150

36. Brockmöller J, Kirchheiner J, Schmider J, et al. The impact of the *CYP2D6* polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. *Clin Pharmacol Ther*. 2002;72(4):438-452. doi:10.1067/mcp.2002.127494

37. Troost PW, Lahuis BE, Hermans MH, et al. Prolactin release in children treated with risperidone: impact and role of CYP2D6 metabolism. *J Clin Psychopharmacol*. 2007;27(1): 52-57. doi:10.1097/JCP.0b013e31802e68d5

38. Jovanović N, Božina N, Lovrić M, Medved V, Jakovljević M, Peleš AM. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naïve patients with first-episode schizophrenia treated with risperidone. *Eur J Clin Pharmacol*. 2010;66(11):1109-1117. doi:10.1007/s00228-010-0850-1

39. Hendset M, Molden E, Refsum H, Hermann M. Impact of *CYP2D6* genotype on steady-state serum concentrations of risperidone and 9-hydroxyrisperidone in patients using long-acting injectable risperidone. *J Clin Psychopharmacol*. 2009;29(6):537-541. doi:10.1097/JCP.0b013e3181c17df0

40. Mas S, Gassó P, Torra M, et al; PEPs Group. Intuitive pharmacogenetic dosing of risperidone according to CYP2D6 phenotype extrapolated from genotype in a cohort of first episode psychosis patients. *Eur Neuropsychopharmacol*. 2017;27(7): 647-656. doi:10.1016/j.euroneuro.2017.03.012

41. Mannheimer B, Holm J, Koukel L, Bertilsson L, Osby U, Eliasson E. Risperidone metabolic ratio as a biomarker of individual *CYP2D6* genotype in schizophrenic patients. *Eur J Clin Pharmacol*. 2014; 70(6):695-699. doi:10.1007/s00228-014-1664-3

42. Gassó P, Mas S, Papagianni K, et al. Effect of CYP2D6 on risperidone pharmacokinetics and extrapyramidal symptoms in healthy volunteers: results from a pharmacogenetic clinical trial. *Pharmacogenomics*. 2014;15(1):17-28. doi:10.2217/pgs.13.204

43. Scordo MG, Spina E, Facciolà G, Avenoso A, Johansson I, Dahl ML. Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. *Psychopharmacology (Berl)*. 1999;147(3):300-305. doi:10.1007/s002130051171

44. De Leon J, Susce MT, Pan RM, Wedlund PJ, Orrego ML, Diaz FJ. A study of genetic (*CYP2D6* and *ABCB1*) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. *Pharmacopsychiatry*. 2007;40 (3):93-102. doi:10.1055/s-2007-973836

45. Novalbos J, López-Rodríguez R, Román M, Gallego-Sandín S, Ochoa D, Abad-Santos F. Effects of *CYP2D6* genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. *J Clin Psychopharmacol*. 2010; 30(5):504-511. doi:10.1097/JCP.0b013e3181ee84c7

46. Cabaleiro T, Ochoa D, López-Rodríguez R, et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. *Hum Psychopharmacol*. 2014; 29(5):459-469. doi:10.1002/hup.2420

47. Bondolfi G, Eap CB, Bertschy G, Zullino D, Vermeulen A, Baumann P. The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychotic patients. *Pharmacopsychiatry*. 2002; 35(2):50-56. doi:10.1055/s-2002-25026

48. Xiang Q, Zhao X, Zhou Y, Duan JL, Cui YM. Effect of *CYP2D6*, *CYP3A5*, and *MDR1* genetic polymorphisms on the pharmacokinetics of risperidone and its active moiety. *J Clin Pharmacol*. 2010;50(6):659-666. doi:10.1177/0091270009347867

49. Jung SM, Kim KA, Cho HK, et al. Cytochrome P450 3A inhibitor itraconazole affects plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenic patients. *Clin Pharmacol Ther*. 2005;78(5):520-528. doi:10.1016/j.clpt.2005.07.007

50. Yagihashi T, Mizuno M, Chino B, et al. Effects of the *CYP2D6*10* alleles and co-medication with CYP2D6-dependent drugs on risperidone metabolism in patients with schizophrenia. *Hum Psychopharmacol*. 2009;24(4):301-308. doi:10.1002/hup.1025

51. Yasui-Furukori N, Mihara K, Kondo T, et al. Effects of *CYP2D6* genotypes on plasma concentrations of risperidone and enantiomers of 9-hydroxyrisperidone in Japanese patients with schizophrenia. *J Clin Pharmacol*. 2003;43(2):122-127. doi:10.1177/0091270002239819

52. Kang RH, Jung SM, Kim KA, et al. Effects of *CYP2D6* and *CYP3A5* genotypes on the plasma concentrations of risperidone and 9-hydroxyrisperidone in Korean schizophrenic patients. *J Clin Psychopharmacol*. 2009;29(3):272-277. doi:10.1097/JCP.0b013e3181a289e0

53. Roh HK, Kim CE, Chung WG, Park CS, Svensson JO, Bertilsson L. Risperidone metabolism in relation to *CYP2D6*10* allele in Korean schizophrenic patients. *Eur J Clin Pharmacol*. 2001;57(9):671-675. doi:10.1007/s002280100372

54. Suzuki Y, Fukui N, Tsuneyama N, et al. Effect of the cytochrome P450 *2D6*10* allele on risperidone metabolism in Japanese psychiatric patients. *Hum Psychopharmacol*. 2012;27(1):43-46. doi:10.1002/hup.1260

55. Yoo HD, Lee SN, Kang HA, Cho HY, Lee IK, Lee YB. Influence of *ABCB1* genetic polymorphisms on the pharmacokinetics of risperidone in healthy subjects with *CYP2D6*10/*10*. *Br J Pharmacol*. 2011; 164(2b):433-443. doi:10.1111/j.1476-5381.2011.01385.x

56. Mihara K, Kondo T, Yasui-Furukori N, et al. Effects of various *CYP2D6* genotypes on the steady-state plasma concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, in Japanese patients with schizophrenia. *Ther Drug Monit*. 2003;25(3):287-293. doi:10.1097/00007691-200306000-00006

57. Cho HY, Lee YB. Pharmacokinetics and bioequivalence evaluation of risperidone in healthy male subjects with different *CYP2D6* genotypes. *Arch Pharm Res*. 2006;29(6):525-533. doi:10.1007/BF02969428

58. Morita S, Shimoda K, Someya T, Yoshimura Y, Kamijima K, Kato N. Steady-state plasma levels of nortriptyline and its hydroxylated metabolites in Japanese patients: impact of *CYP2D6* genotype on the hydroxylation of nortriptyline. *J Clin Psychopharmacol*. 2000;20(2):141-149. doi:10.1097/00004714-200004000-00005

59. 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(3): 382-387. doi:10.1097/01.ftd.0000211823.80854.db

60. Yue QY, Zhong ZH, Tybring G, et al. Pharmacokinetics of nortriptyline and its 10-hydroxy metabolite in Chinese subjects of different *CYP2D6* genotypes. *Clin Pharmacol Ther*. 1998;64(4):384-390. doi:10.1016/S0009-9236(98)90069-8

61. Chen R, Wang H, Shi J, Shen K, Hu P. Cytochrome P450 *2D6* genotype affects the pharmacokinetics of controlled-release paroxetine in healthy Chinese subjects: comparison of traditional phenotype and activity score systems. *Eur J Clin Pharmacol*. 2015;71(7):835-841. doi:10.1007/s00228-015-1855-6

62. Sawamura K, Suzuki Y, Someya T. Effects of dosage and *CYP2D6*-mutated allele on plasma concentration of paroxetine. *Eur J Clin Pharmacol*. 2004;60(8):553-557. doi:10.1007/s00228-004-0792-6

63. Yoon YR, Cha IJ, Shon JH, et al. Relationship of paroxetine disposition to metoprolol metabolic ratio and *CYP2D6*10* genotype of Korean subjects. *Clin Pharmacol Ther*. 2000;67(5):567-576. doi:10.1067/mcp.2000.106128

64. Ohara K, Tanabu S, Ishibashi K, Ikemoto K, Yoshida K, Shibuya H. *CYP2D6*10* alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. *Eur J Clin Pharmacol*.

2003;58(10):659-661. doi:10.1007/s00228-002-0529-3

65. Sugahara H, Maebara C, Ohtani H, et al. Effect of smoking and *CYP2D6* polymorphisms on the extent of fluvoxamine-alprazolam interaction in patients with psychosomatic disease. *Eur J Clin Pharmacol*. 2009;65(7):699-704. doi:10.1007/s00228-009-0629-4

66. Gerstenberg G, Aoshima T, Fukasawa T, et al. Effects of the *CYP 2D6* genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. *Ther Drug Monit*. 2003;25(4):463-468. doi:10.1097/00007691-200308000-00008

67. Watanabe J, Suzuki Y, Fukui N, et al. Dose-dependent effect of the *CYP2D6* genotype on the steady-state fluvoxamine concentration. *Ther Drug Monit*. 2008;30(6):705-708. doi:10.1097/FTD.0b013e31818d73b3

68. Katoh Y, Uchida S, Kawai M, et al. Effects of cigarette smoking and cytochrome P450 *2D6* genotype on fluvoxamine concentration in plasma of Japanese patients. *Biol Pharm Bull*. 2010;33(2):285-288. doi:10.1248/bpb.33.285

69. Suzuki Y, Sugai T, Fukui N, et al. *CYP2D6* genotype and smoking influence fluvoxamine steady-state concentration in Japanese psychiatric patients: lessons for genotype-phenotype association study design in translational pharmacogenetics. *J Psychopharmacol*. 2011;25(7):908-914. doi:10.1177/0269881110370504

70. Sirot EJ, Harenberg S, Vandel P, et al. Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression. *J Clin Psychopharmacol*. 2012;32(5):622-629. doi:10.1097/JCP.0b013e3182664d98

71. Lind AB, Reis M, Bengtsson F, et al. Steady-state concentrations of mirtazapine, *N*-desmethylmirtazapine, 8-hydroxymirtazapine and their enantiomers in relation to cytochrome P450 *2D6* genotype, age and smoking behaviour. *Clin Pharmacokinet*. 2009;48(1):63-70. doi:10.2165/0003088-200948010-00005

72. Kirchheiner J, Henckel HB, Meineke I, Roots I, Brockmöller J. Impact of the *CYP2D6* ultrarapid metabolizer genotype on mirtazapine pharmacokinetics and adverse events in healthy volunteers. *J Clin Psychopharmacol*. 2004;24(6):647-652. doi:10.1097/01.jcp.0000145341.30547.f0

73. González-Vacarezza N, Abad-Santos F, Carcas-Sansuan A, et al. Use of pharmacogenetics in bioequivalence studies to reduce sample size: an example with mirtazapine and CYP2D6. *Pharmacogenomics J*. 2013;13(5):452-455. doi:10.1038/tpj.2012.29

74. Park JY, Shon JH, Kim KA, et al. Combined effects of itraconazole and *CYP2D6*10* genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. *J Clin Psychopharmacol*. 2006;26(2):135-142. doi:10.1097/01.jcp.0000203199.88581.c3

75. Suzuki A, Otani K, Mihara K, et al. Effects of the *CYP2D6* genotype on the steady-state plasma concentrations of haloperidol and reduced haloperidol in Japanese schizophrenic patients. *Pharmacogenetics*. 1997;7(5):415-418. doi:10.1097/00008571-199710000-00013

76. Mihara K, Suzuki A, Kondo T, et al. Effects of the *CYP2D6*10* allele on the steady-state plasma concentrations of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. *Clin Pharmacol Ther*. 1999;65(3):291-294. doi:10.1016/S0009-9236(99)70108-6

77. Roh HK, Chung JY, Oh DY, et al. Plasma concentrations of haloperidol are related to *CYP2D6* genotype at low, but not high doses of haloperidol in Korean schizophrenic patients. *Br J Clin Pharmacol*. 2001;52(3):265-271. doi:10.1046/j.0306-5251.2001.01437.x

78. Someya T, Suzuki Y, Shimoda K, et al. The effect of cytochrome P450 *2D6* genotypes on haloperidol metabolism: a preliminary study in a psychiatric population. *Psychiatry Clin Neurosci*. 1999;53(5):593-597. doi:10.1046/j.1440-1819.1999.00611.x

79. Ohara K, Tanabu S, Yoshida K, Ishibashi K, Ikemoto K, Shibuya H. Effects of smoking and cytochrome P450 *2D6*10* allele on the plasma haloperidol concentration/dose ratio. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(6):945-949. doi:10.1016/S0278-5846(03)00154-4

80. Shimoda K, Morita S, Yokono A, et al. *CYP2D6*10* alleles are not the determinant of the plasma haloperidol concentrations in Asian patients. *Ther Drug Monit*. 2000;22(4):392-396. doi:10.1097/00007691-200008000-00005

81. Inada T, Senoo H, Iijima Y, Yamauchi T, Yagi G. Cytochrome P450 II *D6* gene polymorphisms and the neuroleptic-induced extrapyramidal symptoms in Japanese schizophrenic patients. *Psychiatr Genet*. 2003;13(3):163-168. doi:10.1097/00041444-200309000-00005

82. Someya T, Shimoda K, Suzuki Y, et al. Effect of *CYP2D6* genotypes on the metabolism of haloperidol in a Japanese psychiatric population. *Neuropsychopharmacology*. 2003;28(8):1501-1505. doi:10.1038/sj.npp.1300213

83. Hermann M, Hendset M, Fosaas K, Hjerpset M, Refsum H. Serum concentrations of venlafaxine and its metabolites *O*-desmethylvenlafaxine and *N*-desmethylvenlafaxine in heterozygous carriers of the *CYP2D6*3*, **4* or **5* allele. *Eur J Clin Pharmacol*. 2008;64(5):483-487. doi:10.1007/s00228-007-0453-7

84. Whyte EM, Romkes M, Mulsant BH, et al. *CYP2D6* genotype and venlafaxine-XR concentrations in depressed elderly. *Int J Geriatr Psychiatry*. 2006;21(6):542-549. doi:10.1002/gps.1522

85. Nichols AI, Focht K, Jiang Q, Preskorn SH, Kane CP. Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy CYP2D6 extensive and poor metabolizers: a randomized, open-label, two-period, parallel-group, crossover study. *Clin Drug Investig*. 2011;31(3):155-167. doi:10.2165/11586630-000000000-00000

86. Shams ME, Arneth B, Hiemke C, et al. *CYP2D6* polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther*. 2006;31(5):493-502. doi:10.1111/j.1365-2710.2006.00763.x

87. Preskorn S, Patroneva A, Silman H, et al. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *J Clin Psychopharmacol*. 2009;29(1):39-43. doi:10.1097/JCP.0b013e318192e4c1

88. Kringen MK, Bråten LS, Haslemo T, Molden E. The influence of combined *CYP2D6* and *CYP2C19* genotypes on venlafaxine and *O*-desmethylvenlafaxine concentrations in a large patient cohort. *J Clin Psychopharmacol*. 2020;40(2):137-144. doi:10.1097/JCP.0000000000001174

89. Fukuda T, Nishida Y, Zhou Q, Yamamoto I, Kondo S, Azuma J. The impact of the *CYP2D6* and *CYP2C19* genotypes on venlafaxine pharmacokinetics in a Japanese population. *Eur J Clin Pharmacol*. 2000;56(2):175-180. doi:10.1007/s002280050737

90. Jiang F, Kim HD, Na HS, et al. The influences of *CYP2D6* genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment outcomes. *Psychopharmacology (Berl)*. 2015;232(11):1899-1909. doi:10.1007/s00213-014-3825-6

91. Tsai MH, Lin KM, Hsiao MC, et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. *Pharmacogenomics*. 2010;11(4):537-546. doi:10.2217/pgs.09.168

92. Hodgson K, Tansey K, Dernovsek MZ, et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. *J Psychopharmacol*. 2014;28(2):133-141. doi:10.1177/0269881113512041

93. Tsuchimine S, Ochi S, Tajiri M, et al. Effects of cytochrome P450 (CYP) *2C19* genotypes on steady-state plasma concentrations of escitalopram and its desmethyl metabolite in Japanese patients with depression. *Ther Drug Monit*. 2018;40(3):356-361. doi:10.1097/FTD.0000000000000506

94. Rudberg I, Hermann M, Refsum H, Molden E. Serum concentrations of sertraline and *N*-desmethyl sertraline in relation to *CYP2C19* genotype in psychiatric patients. *Eur J Clin Pharmacol*. 2008;64(12):1181-1188. doi:10.1007/s00228-008-0533-3

95. Saiz-Rodríguez M, Belmonte C, Román M, et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. *Basic Clin Pharmacol Toxicol*. 2018;122(5):501-511. doi:10.1111/bcpt.12938

96. Lesche D, Mostafa S, Everall I, Pantelis C, Bousman CA. Impact of *CYP1A2*, *CYP2C19*, and *CYP2D6* genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. *Pharmacogenomics J*. 2020;20(2):192-201. doi:10.1038/s41397-019-0108-y

97. Sirot EJ, Knezevic B, Morena GP, et al. *ABCB1* and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. *J Clin Psychopharmacol*. 2009;29(4):319-326. doi:10.1097/JCP.0b013e3181acc372

98. Vasudev K, Choi YH, Norman R, Kim RB, Schwarz UI. Genetic determinants of clozapine-induced metabolic side effects. *Can J Psychiatry*. 2017;62(2):138-149. doi:10.1177/0706743716670128

99. Tóth K, Csukly G, Sirok D, et al. Potential role of patients' CYP3A-status in clozapine pharmacokinetics. *Int J Neuropsychopharmacol*. 2017;20(7):529-537. doi:10.1093/ijnp/pyx019

100. Koller D, Saiz-Rodríguez M, Zubiaur P, et al. The effects of aripiprazole and olanzapine on pupillary light reflex and its relationship with pharmacogenetics in a randomized multiple-dose trial. *Br J Clin Pharmacol*. 2020;86(10):2051-2062. Published online April 6, 2020. doi:10.1111/bcp.14300

101. Akamine Y, Sugawara-Kikuchi Y, Uno T, Shimizu T, Miura M. Quantification of the steady-state plasma concentrations of clozapine and *N*-desmethylclozapine in Japanese patients with schizophrenia using a novel HPLC method and the effects of CYPs and ABC transporters polymorphisms. *Ann Clin Biochem*. 2017;54(6):677-685. doi:10.1177/0004563216686377

102. Ryu S, Park S, Lee JH, et al. A Study on *CYP2C19* and *CYP2D6* polymorphic effects on pharmacokinetics and pharmacodynamics of amitriptyline in healthy Koreans. *Clin Transl Sci*. 2017;10(2):93-101. doi:10.1111/cts.12451

103. Halling J, Weihe P, Brosen K. The *CYP2D6* polymorphism in relation to the metabolism of amitriptyline and nortriptyline in the Faroese population. *Br J Clin Pharmacol*. 2008;65(1):134-138. doi:10.1111/j.1365-2125.2007.02969.x

104. Steimer W, Zöpf K, von Amelunxen S, et al. Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in *CYP2C19* and *CYP2D6* extensive and intermediate metabolizers. *Clin Chem*. 2004; 50(9):1623-1633. doi:10.1373/clinchem.2003.030825

105. Jiang ZP, Shu Y, Chen XP, et al. The role of *CYP2C19* in amitriptyline N-demethylation in Chinese subjects. *Eur J Clin Pharmacol*. 2002;58(2): 109-113. doi:10.1007/s00228-002-0445-6

106. Hayashi Y, Watanabe T, Aoki A, et al. Factors affecting steady-state plasma concentrations of enantiomeric mirtazapine and its desmethylated metabolites in Japanese psychiatric patients. *Pharmacopsychiatry*. 2015;48(7):279-285. doi:10.1055/s-0035-1565069

107. Charlier C, Broly F, Lhermitte M, Pinto E, Ansseau M, Plomteux G. Polymorphisms in the *CYP 2D6* gene: association with plasma concentrations of fluoxetine and paroxetine. *Ther Drug Monit*. 2003;25(6):738-742. doi:10.1097/00007691-200312000-00014

108. Ververs FF, Voorbij HA, Zwarts P, et al. Effect of cytochrome P450 *2D6* genotype on maternal paroxetine plasma concentrations during pregnancy. *Clin Pharmacokinet*. 2009;48(10):677-683. doi:10.2165/11318050-000000000-00000

109. Dalén P, Dahl ML, Bernal Ruiz ML, Nordin J, Bertilsson L. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther*. 1998;63(4): 444-452. doi:10.1016/S0009-9236(98)90040-6

110. Yasui-Furukori N, Takahata T, Nakagami T, et al. Different inhibitory effect of fluvoxamine on omeprazole metabolism between *CYP2C19* genotypes. *Br J Clin Pharmacol*. 2004;57(4):487-494. doi:10.1111/j.1365-2125.2003.02047.x

111. Scordo MG, Spina E, Dahl ML, Gatti G, Perucca E. Influence of *CYP2C9, 2C19* and *2D6* genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. *Basic Clin Pharmacol Toxicol*. 2005;97(5):296-301. doi:10.1111/j.1742-7843.2005.pto_194.x

112. Eap CB, Bondolfi G, Zullino D, et al. Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers. *J Clin Psychopharmacol*. 2001;21(3): 330-334. doi:10.1097/00004714-200106000-00013

113. Liu ZQ, Cheng ZN, Huang SL, et al. Effect of the *CYP2C19* oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol*. 2001;52(1):96-99. doi:10.1046/j.0306-5251.2001.01402.x

114. Bakken GV, Molden E, Hermann M. Impact of genetic variability in *CYP2D6, CYP3A5*, and *ABCB1* on serum concentrations of quetiapine and *N*-desalkylquetiapine in psychiatric patients. *Ther Drug Monit*. 2015;37(2):256-261. doi:10.1097/FTD.0000000000000135

115. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

116. Koller D, Belmonte C, Lubomirov R, et al. Effects of aripiprazole on pupillometric parameters related to pharmacokinetics and pharmacogenetics after single oral administration to healthy subjects. *J Psychopharmacol*. 2018;32(11):1212-1222. doi:10.1177/0269881118798605

117. Zeier Z, Carpenter LL, Kalin NH, et al. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. *Am J Psychiatry*. 2018;175(9):873-886. doi:10.1176/appi.ajp.2018.17111282

118. Stingl JC, Brockmöller J, Viviani R. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry*. 2013;18(3):273-287. doi:10.1038/mp.2012.42

119. Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry*. 2016;3(6):585-590. doi:10.1016/S2215-0366(16)00017-1

120. US Food and Drug Administration. Risperidal drug label. Published June 2009. Accessed June 20, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf

121. US Food and Drug Administration. Abilify drug label. Published August 2016. Accessed June 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021436s041,021713s032,021729s024,021866s026lbl.pdf

122. US Food and Drug Administration. Lexapro drug label. Published January 2017. Accessed June 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.pdf

123. US Food and Drug Administration. Zoloft drug label. Published December 2016. Accessed June 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839S74S86S87_20990S35S44S45lbl.pdf

124. US Food and Drug Administration. Paxil drug label. Published December 2012. Accessed June 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020031s067,020710s031.pdf

125. US Food and Drug Administration. Pamelor drug label. Published May 2007. Accessed June 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/018013s58lbl.pdf

126. McCutcheon R, Beck K, D'Ambrosio E, et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. *Acta Psychiatr Scand*. 2018;137(1):39-46. doi:10.1111/acps.12825

127. Veselinović T, Scharpenberg M, Heinze M, et al; NeSSy Study Group. Dopamine D2 receptor occupancy estimated from plasma concentrations of four different antipsychotics and the subjective experience of physical and mental well-being in schizophrenia: results from the randomized NeSSy Trial. *J Clin Psychopharmacol*. 2019;39(6):550-560. doi:10.1097/JCP.0000000000001131

128. Pérez V, Salavert A, Espadaler J, et al; AB-GEN Collaborative Group. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2017;17 (1):250. doi:10.1186/s12888-017-1412-1

129. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. *J Psychiatr Res*. 2018;96:100-107. doi:10.1016/j.jpsychires.2017.09.024

130. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*. 2019;111:59-67. doi:10.1016/j.jpsychires.2019.01.003