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Effect of *CYP2D6* genotype on duloxetine serum concentration

Kristine Hole[1,2] | **Sofie Gangsø**[1,2] | **Åsa Tonette Jensstuen**[1,2] | **Hanne Holte Ormøy**[1,2] | **Maren Paulsen**[1,2] | **Espen Molden**[1,3] | **Tore Haslemo**[1,2]

[1]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

[2]Department of Life Sciences and Health, Oslo Metropolitan University, Oslo, Norway

[3]Department of Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Oslo, Norway

Correspondence
Kristine Hole, Center for Psychopharmacology, Diakonhjemmet Hospital, PO Box 23 Vinderen, 0319 Oslo, Norway.
Email: kristine.hole@diakonsyk.no

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Abstract

Duloxetine is metabolized by cytochrome P450 (CYP)1A2 and CYP2D6. The aim of this study was to investigate the effect of the *CYP2D6* genotype on duloxetine serum concentration adjusting for age and sex. Patients were included retrospectively from a therapeutic drug monitoring service. Multiple linear regression analysis was used to investigate the effect of *CYP2D6* genotype, age and sex on the duloxetine concentration-to-dose (C/D) ratio. In total, 269 patients were included and assigned to the following genotype-predicted phenotype subgroups: CYP2D6 poor metabolizers (PMs, $n = 23$), intermediate metabolizers (IMs, $n = 121$), normal metabolizers (NMs, $n = 120$) and ultrarapid metabolizers (UMs, $n = 5$). Multiple linear regression analysis revealed a 95% higher duloxetine C/D ratio in PMs compared with NMs ($p = 0.009$). Patients ≥65 years had a 56% higher C/D ratio than younger patients ($p = 0.01$), while women had a 46% higher C/D ratio than men ($p = 0.04$). In conclusion, the CYP2D6 PM phenotype is associated with a twofold higher concentration at recommended dosing compared with the NM phenotype. CYP2D6 PM females above 65 years are at particular risk of high duloxetine levels as they may obtain a threefold higher C/D ratio compared with younger, male NMs.

KEYWORDS
age, CYP2D6, duloxetine, genotype, sex

1 | INTRODUCTION

Duloxetine is a combined serotonin and norepinephrine reuptake inhibitor. It was first approved by the FDA in 2004 for the treatment of depressive and anxiety disorders, as well as for neuropathic pain, with a dose interval of 30–120 mg per day.[1] Duloxetine is extensively metabolized by liver enzymes into several inactive metabolites, where two of the main metabolites are 4-hydroxy- and 5-hydroxy-duloxetine.[2] In vitro studies have identified cytochrome P450 (CYP)1A2 and CYP2D6 as the main enzymes involved in duloxetine biotransformation.[2,3] A number of nongenetic factors influence CYP1A2 activity, which is subject to induction and inhibition by many compounds. Cigarette smoke is one of the most described inducers of CYP1A2,

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while women are reported to have lower enzyme activity than men.[4]

Unlike CYP1A2, CYP2D6 exhibits considerable pharmacogenetic variation with implications for the dose requirements of several CYP2D6-metabolized drugs.[5] Based on the inheritance of *CYP2D6* diplotypes, patients are divided into the following genotype-predicted phenotype subgroups: CYP2D6 poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs) and ultrarapid metabolizers (UMs). CYP2D6 PMs and IMs have been reported to experience severe effects of duloxetine, and one case report described elevated exposure to duloxetine in a CYP2D6 PM.[6–9] In addition to these case reports, smaller studies have reported a 15%–80% elevated duloxetine exposure in IMs compared with NMs.[10,11] Duloxetine has a quite wide therapeutic reference range of 30–120 ng/mL,[12] and the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline currently concludes that the existing data do not support a clinically meaningful impact of *CYP2D6* genotype on duloxetine metabolism.[5] Due to very limited evidence of the *CYP2D6*-duloxetine gene-drug interaction, further studies are warranted to establish clinical relevance and obtain more conclusive data for recommendations on precision dosing of duloxetine.

The aim of this study was to investigate the effect of the *CYP2D6* genotype on duloxetine serum concentration in a large naturalistic patient population while adjusting for patient age and sex.

2 | METHODS

2.1 | Patient inclusion

Duloxetine serum concentration measurements and *CYP2D6* genotype were retrieved from a routine therapeutic drug monitoring (TDM) database at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, during the period 2010–2022. Inclusion criteria were (a) that patients had both duloxetine measurements and *CYP2D6* genotype available from the database; (b) TDM requisition forms provided information about duloxetine dose; and (c) last dose intake was 12–26 h before blood sampling. For patients with multiple serum concentration measurements, only the last measurement was included in the study. Exclusion criteria were (a) serum measurements of duloxetine outside the analytical limits of quantification; (b) inconclusive *CYP2D6* genotype, that is, allele multiplication combined with decreased- or loss-of-function variant alleles, due to uncertainties related to the number of gene copies and allele being duplicated; and (c) if TDM requisition forms mentioned use of drugs interacting with CYP1A2 or CYP2D6 according to a compilation of inhibitors and inducers which are listed in Table S1.[12]

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[13] The study was approved by the Regional Committee for Medical and Health Research Ethics (#482562) and the Hospital Investigational Review Board. Ethical approval was given without the requirement of patient consent since the study was based on existing data retrospectively retrieved from a routine TDM service.

2.2 | Duloxetine serum concentration measurement

Serum concentration analysis of duloxetine was performed by a validated analytical method developed for routine TDM analyses at the Center for Psychopharmacology. The method did not provide quantification of duloxetine metabolites. The method was based on ultrahigh-performance liquid chromatography (UPLC) high-resolution mass spectrometry (HRMS). Serum samples were prepared by protein precipitation with a mix of 9:1 acetonitrile:methanol and duloxetine-D_3 as internal standard. Purified samples were injected into a Vanquish-UPLC system (Thermo Fisher Scientific, Waltham, MA) with an XBridge BEH C18 column (2.6 μm, 2.1 × 75 mm; Waters, Milford, MA). The mobile phase consisted of a gradient mixture of ammonium acetate (pH = 4.8) and acetonitrile (20%–52%), and the retention time of duloxetine was 2.07 min. Detection was achieved with QExactive Orbitrap HRMS (Thermo Fisher Scientific) operated in positive ionization mode. The m/z values were 298.12601 for duloxetine and 301.14484 for duloxetine-D_3. Lower and upper limits of quantification were 3–298 ng/mL (10–1000 nmol/L), and intra- and inter-day imprecision and inaccuracy were <15%.

2.3 | Genotyping

The *CYP2D6* pharmacogenetic routine panel included the loss-of-function variant alleles *CYP2D6*3* (*rs35742686*), *CYP2D6*4* (*rs3892097*), *CYP2D6*5* (gene deletion) and *CYP2D6*6* (*rs5030655*); the decreased-function alleles *CYP2D6*9* (*rs5030656*), *CYP2D6*10* (*rs1065852*) and *CYP2D6*41* (*rs28371725*); as well as allele multiplication. The absence of variant alleles was interpreted as the presence of the wild-type allele

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(**1*). Analysis of *CYP2D6* variant alleles was performed using TaqMan-based real-time PCR assays implemented for routine pharmacogenetic analyses at the Center for Psychopharmacology. Analysis of *CYP2D6* copy number was performed using TaqMan Copy number assay targeting exon 9 with RNase P as endogenous control.

2.4 | Genotype to phenotype translation

Patients were divided into genotype-predicted phenotype subgroups according to guidelines from the CPIC.[5] Carriers of two loss-of-function alleles were defined as PMs. Patients carrying one loss-of-function allele combined with either **1* or a decreased-function allele were defined as IMs, as were patients with two decreased-function alleles. Patients carrying more than two *CYP2D6*1* alleles were defined as UMs. The remaining patients were defined as NMs.

2.5 | Data analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 29.0.0 (IBM Corp, Armonk, NY), and GraphPad Prism version 10.0.0 for Windows (GraphPad Software, Boston, MA, USA) was used for graphical presentations. Comparison of sex distribution across CYP2D6 genotype-predicted phenotype groups was performed with a chi-square test. Comparison of age, dose, sampling time, serum concentration and serum concentration-to-dose (C/D) ratio across phenotype groups was performed with the ANOVA test, followed by post-hoc Dunnett's test with NMs as a control group. Finally, multiple linear regression analysis was performed to investigate the combined effect of multiple variables on the duloxetine C/D ratio. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

Initially, a search in the database identified 305 patients who were eligible for inclusion in the study. After review of the requisition forms of the last TDM measurements, 10 patients were excluded due to duloxetine serum concentrations outside the limits of quantification, 10 patients had inconclusive *CYP2D6*-genotype, 13 patients used CYP2D6-inhibitors, while 2 patients used CYP1A2-inducers. During the review of the requisition forms, it was discovered that one patient had undergone gastric bypass surgery, which may affect drug metabolism. Therefore, this patient was also excluded. In total, 269 patients were included in the study.

Among the included patients, there were 23 CYP2D6 PMs (8.6%), 121 IMs (45.0%), 120 NMs (44.6%), and 5 UMs (1.9%). Patient characteristics according to CYP2D6 genotype-predicted phenotype groups are presented in Table 1. There were no differences in the distribution of patient sex or age between CYP2D6 phenotype groups ($p \geq 0.3$) nor in duloxetine sampling time ($p = 0.8$). The mean daily duloxetine dose was 51 mg for PMs compared with 69 mg for NMs (Dunnett's $p = 0.01$), that is, PMs used 26% lower doses than NMs.

3.2 | Effect of *CYP2D6* genotype on duloxetine serum concentration

The absolute serum concentration of duloxetine was not different between CYP2D6 phenotype groups ($p = 0.7$, Table 2). The duloxetine C/D ratio ranged 41-fold in the included population, from 0.11 to 4.47 (ng/mL)/mg, with a mean of 0.74 (ng/mL)/mg. As presented in Table 2, the duloxetine C/D ratio was significantly different across CYP2D6 phenotype groups (ANOVA $p = 0.03$, Figure 1).

TABLE 1 Clinical characteristics according to CYP2D6 genotype-predicted phenotype.

	Poor metabolizers ($n = 23$)	Intermediate metabolizers ($n = 121$)	Normal metabolizers ($n = 120$)	Ultrarapid metabolizers ($n = 5$)	p
Female sex, *n*	19 (83%)	92 (76%)	81 (68%)	4 (80%)	0.3
Age, y	47 (39–55)	52 (48–55)	51 (48–54)	52 (29–75)	0.7
Duloxetine daily dose, mg	51 (40–62)	63 (59–67)	69 (64–75)	78 (36–120)	0.01
Sampling time, h	20 (18–22)	20 (20–21)	20 (19–21)	19 (13–25)	0.8

Note: Values are presented as mean (95% confidence interval). *p*-values are derived from chi-square and ANOVA tests.

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TABLE 2 Duloxetine serum concentration and concentration-to-dose (C/D) ratio according to CYP2D6 genotype-predicted phenotype.

	Poor metabolizers ($n = 23$)	Intermediate metabolizers ($n = 121$)	Normal metabolizers ($n = 120$)	Ultrarapid metabolizers ($n = 5$)	p
Duloxetine serum concentration, ng/mL	47 (34–60)	45 (39–52)	41 (34–47)	37 (−0.6–74)	0.7
Duloxetine C/D ratio, (ng/mL)/mg	1.02 (0.70–1.34)	0.80 (0.68–0.91)	0.65 (0.54–0.76)	0.40 (0.07–0.74)	0.03

Note: Values are presented as mean (95% confidence interval). p-values are derived from ANOVA test.

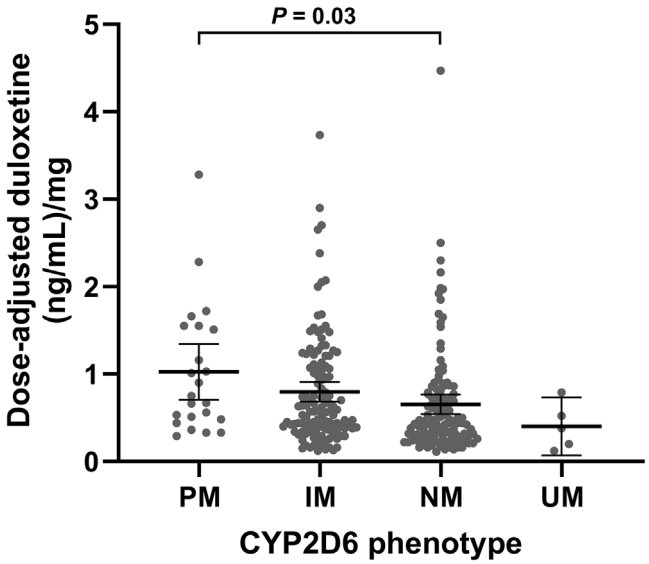

FIGURE 1 Scatterplot of duloxetine concentration-to-dose (C/D) ratio in CYP2D6 genotype-predicted poor metabolizers (PM, $n = 23$), intermediate metabolizers (IM, $n = 121$), normal metabolizers (NM, $n = 120$) and ultrarapid metabolizers (UM, $n = 5$). p-values are derived from Dunnett's tests with NMs as the control group. Means with 95% confidence intervals are presented as solid lines with error bars.

Multiple linear regression analysis was performed to investigate the combined effect of CYP2D6 phenotype, age, sex and sampling time on duloxetine C/D ratio (Table 3). The intercept of the regression model had an estimated mean C/D ratio of 0.39 (ng/mL)/mg, which refers to the reference population of CYP2D6 NMs, male patients <65 years at an estimated trough sampling time of 24 h. The model explained 9.2% of the variation in duloxetine C/D ratio ($R^2 = 0.092$). For male patients <65 years and sampling time 24 h, the duloxetine C/D ratio was 95% higher in CYP2D6 PMs compared with NMs (0.76 vs. 0.39 (ng/mL)/mg, $p = 0.009$). CYP2D6 IMs and UMs did not have significantly different C/D ratios from NMs ($p \geq 0.09$). However, the estimated mean C/D ratio was 56% higher in patients ≥65 years compared with younger patients (0.61 vs. 0.39 (ng/mL)/mg, $p = 0.01$). Furthermore, the regression model showed that female patients had a 46% higher mean C/D ratio compared with male patients (0.57 vs. 0.39 (ng/mL)/mg, $p = 0.04$). Subsequently, combining the effects of independent variables in the regression model, older female CYP2D6 PMs had on average 197% higher duloxetine C/D ratio compared with younger male CYP2D6 NMs (1.16 vs. 0.39 (ng/mL)/mg, $p < 0.05$).

4 | DISCUSSION

The present study, including a large number of genotyped patients from a TDM service, showed that CYP2D6 PMs on average had almost double the duloxetine C/D ratio compared with NMs. This indicates that CYP2D6 PMs may be at increased risk of dose-dependent side effects during treatment with duloxetine, and TDM may be a valuable tool to personalize the treatment to the individual patient.

Previous reports regarding the association between *CYP2D6* genotype and duloxetine exposure have not included enough PMs to perform sufficiently powered statistical analyses,[6,14] and international pharmacogenetic guidelines indicate that the existing data is too weak to support a clinically meaningful gene-drug interaction between *CYP2D6* and duloxetine.[5] However, one case report has described elevated duloxetine exposure and one case report described side effects in PMs.[6,7] The present study included 23 PMs and provided evidence that CYP2D6 metabolism is significantly associated with duloxetine exposure. Based on a multiple linear regression analysis, we report a 95% higher duloxetine C/D ratio in CYP2D6 PMs compared with NMs. This coincides well with a previous report of the potent CYP-inhibitor paroxetine leading to a 60% elevation in the duloxetine area under the concentration-time curve (AUC).[15] It is not surprising that having PM phenotype would be of more consequence than use of an inhibitor, as several studies have reported a slightly higher CYP2D6 activity in patients using potent CYP2D6 inhibitors compared with patients who have genotype-assigned PM phenotype.[16,17] Furthermore, a pharmacokinetic model developed by Stingl et al. estimated that duloxetine oral clearance in CYP2D6 PMs was 69% of the average

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TABLE 3 Multiple linear regression analysis estimating the effects of included variables on duloxetine concentration-to-dose (C/D) ratio.

Variable	Beta[b]	95% confidence interval		*p*
		Lower bound	Upper bound	
Intercept[a]	0.39	0.21	0.57	<0.001
CYP2D6 phenotype:				
Poor metabolizers	+0.37	+0.09	+0.65	0.009
Intermediate metabolizers	+0.14	−0.02	+0.29	0.09
Ultrarapid metabolizers	−0.27	−0.82	+0.28	0.3
Age, ≥65 years	+0.22	+0.05	+0.39	0.01
Sex, female	+0.18	+0.01	+0.34	0.04
Blood sampling time, h	−0.02	−0.03	−0.01	0.009

[a]The intercept is the estimated mean duloxetine C/D ratio ((ng/mL)/mg) in the reference population, which consists of patients with CYP2D6 genotype-predicted normal metabolizer phenotype, who are <65 years, male, and with trough sampling time 24 h after dose intake.
[b]The +/− signs express the estimated increase/decrease in C/D ratio associated with a tested variable.

patient.[18] The results from our study are close to this estimation, with a C/D ratio that was almost doubled in PMs compared with NMs. In fact, the included PM patients were on average prescribed 26% lower doses than NMs, suggesting that their doses already had been somewhat adjusted according to TDM measurements. Although we consider information about the *CYP2D6* genotype to be useful for estimating duloxetine dose requirement, one should keep in mind that duloxetine concentration is reported to increase by 140% when using a potent CYP1A2 inhibitor, proposing that the impact of CYP1A2 phenotype is of greater relevance for duloxetine than CYP2D6 phenotype.[2] In the present study, we excluded patients if TDM requisition forms mentioned the use of CYP1A2- or CYP2D6-interacting drugs. However, it is possible that some patients used interacting drugs that were not listed on the TDM requisition forms, which could have impacted duloxetine levels. Furthermore, smoking is known to induce CYP1A2 and has been reported to be associated with 30% lower duloxetine clearance.[19] Unfortunately, due to the naturalistic nature of the present study, smoking status and *CYP1A2* genotype were not available for the included patients. These factors could possibly have explained more of the variation in duloxetine exposure in the cohort. Hoffmann et al. reported that a drug-drug-gene interaction of duloxetine occurring in a CYP2D6 PM patient comedicated with ciprofloxacin—a CYP1A2 inhibitor—led to severe CNS depression.[7] This suggests that using a CYP1A2 inhibitor will be of great clinical relevance in CYP2D6 PMs, where CYP1A2 inhibitors should be avoided.

Patients with CYP2D6 IM or UM phenotype did not significantly differ in duloxetine C/D ratio from NMs. The patients in the CYP2D6 NM phenotype group had >40-fold variation in duloxetine C/D ratio, and the effect of having IM or UM phenotype may not be strong enough to be detected with our naturalistic study design. The study included only five UMs, and we cannot rule out that UM phenotype would be associated with decreased duloxetine C/D ratio in a larger population. Duloxetine is a mild to moderate inhibitor of CYP2D6 and is reported to increase the AUC of CYP2D6 substrates with 70%–190%.[15,20–22] Subsequently, duloxetine inhibits its own metabolism via CYP2D6, and this phenoconversion may make it harder to detect differences in duloxetine C/D ratio between genotype-predicted CYP2D6 phenotype groups.

In the present study, patients who were ≥65 years old had a 56% higher duloxetine C/D ratio than younger patients. Elderly healthy volunteers are reported to have a 30% lower elimination rate than younger people. The same study reported only an insignificant trend towards lower clearance in the elderly, perhaps due to the small sample size.[23] However, our laboratory has previously reported a 60% higher duloxetine C/D ratio in patients >65 years compared with patients <40 years, which concurs well with our present findings.[24] Decreased renal function may contribute to higher exposure in the elderly, as end-stage renal disease has been associated with a doubling in duloxetine exposure compared with healthy volunteers.[25] We also report almost 50% higher duloxetine C/D ratio in women compared with men, which coincides with a previous pharmacokinetic model predicting 64% higher duloxetine concentration in women.[19] The difference in exposure may be due to lower CYP1A2-activity in women, which can result in both higher oral bioavailability—due to lower presystemic metabolism—and reduced clearance of duloxetine.[19]

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Oestrogens are inhibitors of CYP1A2, and this may contribute to explaining the sex difference in duloxetine serum concentration.[26,27] When combining the effect of the different variables included in the regression model in the present study, elderly women who were CYP2D6 PMs had on average threefold higher C/D ratio compared with younger men who were NMs, indicating that they are at particular risk of high duloxetine levels.

In the present study population, the frequency of reduced genotype-predicted CYP2D6 phenotype was slightly higher than the European population average. Of the included patients, 9% were PMs and 45% were IMs, while the European average is 5% PMs and 35% IMs.[28] Since the indication for genotyping in patients with depression often is the occurrence of side effects, which is more likely to occur in patients with reduced CYP2D6 metabolism, a higher frequency of CYP2D6 IMs and PMs may be expected in our population. Since the study was based on TDM data, we lacked information such as comorbidity, organ function, duration of duloxetine treatment, concurrently used drugs not provided on the TDM requisition forms and smoking habits. The multiple linear regression analysis explained only 9% of the variation in duloxetine C/D ratio, and having information regarding these factors would probably have explained more of the variation. Furthermore, treatment nonadherence is an issue in naturalistic studies and may influence the assessment of duloxetine pharmacokinetic variability. We excluded duloxetine measurements that were nondetectable or below the lower limit of quantification, thus avoiding measurements probably reflecting poor adherence. The limitations of the study may be outweighed by the large real-world patient population which could be included by using existing TDM data.

In conclusion, the CYP2D6 PM phenotype is associated with a twofold higher concentration at recommended dosing compared with the NM phenotype. The study indicates that older, female CYP2D6 PM patients are at particular risk of high duloxetine levels, as they may obtain a threefold higher concentration at recommended dosing compared with younger, male CYP2D6 NM patients. Due to the great variation in duloxetine exposure caused by multiple factors, including the *CYP2D6* genotype, TDM may be a valuable tool to personalize the treatment to the individual patient.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Kristine Hole https://orcid.org/0000-0001-7300-5329

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