Association between *CYP2D6* and *CYP2C19* genotypes and venlafaxine treatment failure: a retrospective study on two cohorts from Norway and the UK

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See Comment page 815

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Summary

Background Venlafaxine shows superior efficacy over SSRIs in treating major depression. Metabolism of venlafaxine is mediated by CYP2D6 with a secondary role of CYP2C19. The activity of both enzymes is determined by pharmacogenetic variability, which might affect therapeutic response to venlafaxine. We aimed to investigate associations between *CYP2D6* and *CYP2C19* genotypes and venlafaxine treatment failure.

Methods This retrospective, observational study included two independent, naturalistic cohorts of individuals treated with venlafaxine from the Center for Psychopharmacology (Oslo, Norway) and the UK Biobank. Participants were excluded if they were comedicated with strong CYP2D6 or CYP2C19 inhibitors (ie, bupropion, fluoxetine, paroxetine, fluvoxamine, or levomepromazine) or CYP inducers (ie, carbamazepine, phenobarbital, or phenytoin) at their last venlafaxine therapeutic drug monitoring measurement. Participants were stratified into genotype-predicted poor metabolisers (PMs), intermediate metabolisers (IMs), normal metabolisers (NMs), and ultra-rapid metabolisers (UMs). The primary outcome was treatment failure defined as switching away from venlafaxine to another antidepressant within 1 year after last exposure. People with lived experience did not contribute to the design and writing of this study.

Findings Between Jan 1, 2005, and Dec 15, 2025, 5443 participants genotyped for *CYP2D6* and *CYP2C19* (3315 [60·9%] women, 2128 [39·1%] men; mean age 48·9 years [SD 18·6]) were identified from the Center for Psychopharmacology. 3624 participants (2401 [66·3%] women, 1223 [33·7%] men; mean age 56·5 years [SD 9·8]) with prescription data were identified from the UK Biobank between 2006 and 2010. In the Norwegian cohort, odds of switching were 2·05 times higher in CYP2D6 PMs (95% CI 1·53–2·71, p<0·0001), 1·25 times higher in IMs (1·05–1·50, p=0·014), and 1·78 times higher in UMs (1·06–2·83, p=0·021) compared with NMs. Increased odds of switching in CYP2D6 PMs were also shown in the UK Biobank cohort (odds ratio 1·58 [95% CI 1·14–2·19], p=0·0060). CYP2C19 PM status amplified risk of failure in the Norwegian cohort with 6·11 times higher odds of switching in dual PMs versus NMs (95% CI 1·81–18·77, p=0·0019).

Interpretation CYP2D6 PM status was consistently associated with increased risk of venlafaxine treatment failure in two large, real-life cohorts, suggesting that pre-emptive genotyping could facilitate personalised venlafaxine therapy.

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Introduction

Venlafaxine is a serotonin-noradrenaline reuptake inhibitor (SNRI) widely used in the treatment of major depressive disorder, anxiety, and panic disorders.[1] Although SSRIs are the standard first-line therapy for depression, approximately half of patients do not have an adequate clinical response,[2] prompting the use of venlafaxine as a common second-line option. Despite its established efficacy,[3] venlafaxine treatment failure remains frequent, due to adverse effects[4] or insufficient clinical response.[5] One of the important reasons for heterogeneous clinical outcomes with venlafaxine treatment is inter-individual differences in venlafaxine metabolism.[6] Variability in venlafaxine metabolism can lead to widely differing drug exposure in patients using the same dose, which could increase the likelihood of toxicity in patients with slow clearance and insufficient efficacy in patients with a rapid metabolism.

Venlafaxine is predominantly metabolised by CYP2D6 to *O*-desmethylvenlafaxine, an active metabolite, with a secondary contribution from CYP2C19.[7,8] Polymorphisms in the genes encoding these enzymes are substantial, with specific diplotypes translating individual phenotypes into subgroups of poor metabolisers (PMs), intermediate metabolisers (IMs), normal metabolisers (NMs), rapid metabolisers (RMs, defined for CYP2C19) or ultra-rapid metabolisers (UMs), providing the mechanistic underpinning as to why *CYP2D6* and *CYP2C19* genotypes are important determinants of venlafaxine metabolism.[9,10] Previous studies have reported significant associations

Research in context

Evidence before this study

We searched PubMed for original articles in English, published until March 31, 2026, using the terms "venlafaxine", "CYP2D6", "CYP2C19", "antidepressant response", "drug switching", and "treatment failure". Previous studies with limited numbers of participants show that *CYP2D6* and *CYP2C19* genotypes determine venlafaxine metabolism and exposure, while the impact on therapeutic response is unclear. Thus, sufficiently powered studies investigating the associations between *CYP2D6*/*CYP2C19* genotypes and treatment outcomes of venlafaxine are scarce.

Added value of this study

The large number of included patients (n=9067) across two independent cohorts enabled robust estimation of the effect of *CYP2D6* and *CYP2C19* genotypes on venlafaxine treatment failure, measured as a switch from venlafaxine to other antidepressants, in real-world settings. The study confirmed a consistent increase in treatment failure among genotype-predicted poor metabolisers of CYP2D6 compared with normal metabolisers in a Norwegian therapeutic drug monitoring (TDM) cohort (n=5443) with replication in an independent population-based cohort from the UK Biobank (n=3624). It further showed that, in the TDM cohort, including *CYP2C19* genotypes alongside *CYP2D6* genotypes improved accuracy of predicting venlafaxine treatment failure, with significantly higher switch rates to other antidepressants in individuals with reduced (poor or intermediate metabolisers) versus normal (normal metabolisers) activity of both enzymes. In addition, dose and pharmacokinetic analyses in the TDM cohort showed genotype-dependent differences in venlafaxine exposure that were not compensated by clinical dose adjustments. These findings establish a clinically relevant link between *CYP2D6* and *CYP2C19* variability and venlafaxine treatment failure, supporting use of genotype-guided therapy.

Implications of all the available evidence

Non-functional CYP2D6 metabolism is associated with treatment outcome of venlafaxine in naturalistic settings, while reduced CYP2C19 activity could potentiate its importance. *CYP2D6* and *CYP2C19* genotyping could guide decision strategies on type and dose of antidepressants, particularly in patients requiring second-line therapy after SSRI failure.

between *CYP2D6* and *CYP2C19* genotypes and venlafaxine plasma concentrations and metabolic ratios,[11–15] but the potential effect on treatment response remains unclear. As a result, there is no consensus on the clinical implications of *CYP2D6* and *CYP2C19* genetic variation for venlafaxine treatment across existing guidelines,[1] including those from regulatory agencies and pharmacogenetic working groups (eg, The Dutch Pharmacogenetics Working Group or Clinical Pharmacogenetics Implementation Consortium).

In this study, we evaluated the association between *CYP2D6* and *CYP2C19* genotypes and venlafaxine treatment failure (defined as a switch to other antidepressants) using two large, independent, naturalistic cohorts. First, we analysed 5443 patients from a therapeutic drug monitoring (TDM) service in Norway to determine whether *CYP2D6* and *CYP2C19* genotypes were associated with switching from venlafaxine to other antidepressants. We then replicated the identified associations in an independent population-based cohort of 3624 venlafaxine-treated patients from the UK Biobank. Together, these retrospective analyses indicate the clinical relevance of genotype-predicted variability in CYP2D6 and CYP2C19 metaboliser status for venlafaxine treatment outcomes in real-world settings.

Methods

Study design and participants

This study was reported in accordance with STROBE guidelines (appendix pp 13–14).[16] The study comprised two independent populations: 1) participants from the TDM/pharmacogenetics service at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, and 2) from the UK Biobank. The Norwegian TDM cohort included participants who had been treated with venlafaxine in the period between Jan 1, 2005, and Dec 15, 2025. Based on the ethnic composition of the Norwegian population, participants were predominantly White, although individual-level ethnicity data were not available. UK Biobank data were derived from a population-based cohort of 502 629 individuals recruited across 22 assessment centres in the UK between 2006 and 2010.[17] In the UK Biobank, self-reported ethnicity was categorised as White, Black, Asian, Mixed, other ethnic group, or missing or unknown. In Norway, *CYP* genotyping and TDM analyses are reimbursed and used in psychiatric practice to personalise pharmacological treatment and optimise dosing to reach therapeutic levels. Laboratory reports were provided only to the treating physicians, not to the participants, and included recommendations on dose adjustment but not antidepressant switching. Unlike the Norwegian setting of personalised dosing using TDM and pharmacogenetics, the UK Biobank represents routine clinical prescribing without access to TDM or genotypes, but with biological samples available for retrospective, non-therapeutic genotyping.

Adult participants genotyped for both *CYP2D6* and *CYP2C19* and treated with venlafaxine were assessed for inclusion. In the TDM cohort, inclusion required detectable serum concentrations of venlafaxine and/or its metabolites (*O*-desmethylvenlafaxine and

See Online for appendix

N-desmethylvenlafaxine). Participants were excluded if they were comedicated with strong CYP2D6 or CYP2C19 inhibitors (ie, bupropion, fluoxetine, paroxetine, fluvoxamine, or levomepromazine) or CYP inducers (ie, carbamazepine, phenobarbital, or phenytoin) at their last venlafaxine TDM measurement. In the UK Biobank cohort, venlafaxine exposure was identified using general practitioner prescription records. The same comedication exclusions were applied for the UK Biobank cohort using a 30-day window before and after the last venlafaxine prescription to account for monthly resolution and limited temporal precision of prescription records. Antidepressant polypharmacy was defined as the concurrent use of at least two different antidepressants. For both cohorts, information on age, biological sex, and antidepressant polypharmacy was included in the treatment failure analyses (table 1). Separate information about participants' gender was not available. In the TDM cohort, information on age, sex, prescribed daily dosage, and time between last dose intake and blood sampling (withdrawal time) was obtained from the TDM requisition forms of venlafaxine.

Inclusion of participants from the Norwegian TDM database was approved before study initiation by the regional ethical committee (number 482562) and the hospital's investigational research board, in line with national legal requirements. As only retrospective data were included from the database without any burden or risk for the participants, the study was approved without need for informed consent. For the UK Biobank cohort, specific ethical approval and participant informed consent for use of registry data was not required, but the project was approved by the Swedish Ethical Review Board (Etikprövningsmyndigheten) under permit number 2024–05822–01. A person with lived experience meets regularly with the research group at the Center for Psychopharmacology and provides input on research methodology, ethical aspects, relevant outcome measures, and dissemination of findings, but was not specifically involved in the planning or writing of the present study. No lived experience contributor was involved from the UK Biobank cohort.

	Overall	Non-switchers	Switchers	p value
Norwegian TDM cohort				
Number of participants	5443 (100%)	4803 (88·2%)	640 (11·8%)	ND
Age, years	48·9 (18·6)	48·6 (18·5)	51·8 (19·5)	0·0001
Sex	..	..	..	0·019
Female	3315 (60·9%)	2898 (60·3%)	417 (65·1%)	..
Male	2128 (39·1%)	1905 (39·7%)	226 (35·3%)	..
Antidepressant polypharmacy	770 (14·1%)	636 (13·2%)	134 (20·9%)	<0·0001
Venlafaxine dose, mg/day	168·2 (123·9)	167·2 (81·1)	175·6 (286·8)	0·49
UK Biobank cohort				
Number of participants	3624 (100%)	2477 (68·3%)	1147 (31·7%)	ND
Age, years	56·5 (9·8)	57·7 (10·0)	53·8 (8·9)	<0·0001
Sex	..	..	..	0·57
Female	2401 (66·3%)	1633 (65·9%)	768 (67·0%)	..
Male	1223 (33·7%)	844 (34·1%)	379 (33·0%)	..
Ethnicity				
White	3495 (96·4%)	2390 (96·5%)	1105 (96·3%)	0·38
Black	25 (0·7%)	14 (0·6%)	11 (1·0%)	..
Mixed	16 (0·4%)	13 (0·5%)	3 (0·3%)	..
Asian	49 (1·4%)	30 (1·2%)	19 (1·7%)	..
Other	23 (0·6%)	18 (0·7%)	5 (0·4%)	..
Missing or unknown	16 (0·4%)	12 (0·5%)	4 (0·3%)	..
Antidepressant polypharmacy	545 (15·0%)	358 (14·5%)	187 (16·3%)	0·15
Venlafaxine dose, mg/day*	134·1 (89·8); n=1856	132·7 (89·8); n=1430	138·9 (90·0); n=426	0·21

Data are n (%) or mean (SD). Percentages might not sum due to rounding. ND=not determined. TDM=therapeutic drug monitoring. *In the UK Biobank, average daily venlafaxine dose was calculated only for individuals with at least three venlafaxine prescriptions.

Table 1: **Baseline characteristics of participants treated with venlafaxine in the Norwegian TDM and UK Biobank cohorts at last venlafaxine exposure**

Procedures

Detailed procedures for determination of *CYP2C19* and *CYP2D6* genotypes are provided in the appendix (p 3). Genotype to phenotype (metaboliser status) translations were conducted according to the Clinical Pharmacogenetics Implementation Consortium guideline (appendix p 9).[18] The analytical methods used at the Center for Psychopharmacology to measure serum concentrations of venlafaxine and its metabolites (*O*-desmethylvenlafaxine and *N*-desmethylvenlafaxine) are described in the appendix (p 2).

Outcomes

The main outcome measure was switch from venlafaxine to another antidepressant within 1 year after last venlafaxine exposure in relation to genotype-predicted CYP2D6 and CYP2C19 metaboliser phenotypes. Switch of venlafaxine was assessed as a proxy measure for either intolerable side-effects or insufficient clinical response, together merged into a definition of treatment failure, in line with previous studies using similar designs.[19,20] Last exposure was defined as the last detectable venlafaxine (or metabolite) serum concentration measurement in the TDM cohort and the last recorded venlafaxine prescription date in the UK Biobank. Switch within 1 year was assumed to occur in the same depressive episode reflecting treatment failure due to either insufficient efficacy or adverse effects. In the UK Biobank, where prescription timing is less precise than serum measurements of the TDM cohort, additional criteria were applied to reduce outcome misclassification, including exclusion of cases with limited venlafaxine exposure (≤90 days between the first and last prescription or a total of ≤2 venlafaxine prescriptions, to avoid early discontinuation) and cases with a prolonged treatment gap between antidepressants (≥180 days); requirement of a minimum 5-day interval after the final venlafaxine prescription before initiation of a subsequent antidepressant to define a switch; exclusion of cases in which

the post-venlafaxine antidepressant had also been prescribed within 30 days before the final venlafaxine exposure to avoid cross-tapering or augmentation; and a requirement of at least three venlafaxine prescriptions among non-switchers to ensure sustained exposure.

Maintenance dose, defined as the mean daily dose across the three most recent eligible prescription or measurement intervals, was a predefined secondary outcome. For the TDM cohort, the venlafaxine daily dose was indicated by the physician on the requisition form. For the UK Biobank, venlafaxine maintenance doses were derived from linked primary care prescribing records. Drug names were standardised by harmonising generic and brand names. Prescriptions corresponding to combination products or that did not have complete information on dosage or quantity were excluded. The average daily dose was estimated as the prescribed dose multiplied by the dispensed quantity and divided by the number of days until the subsequent prescription.[21] To approximate continuous treatment, refill intervals were restricted to more than 7 days to minimise duplicate or acute entries and 6 months or less to exclude irregular or discontinued therapy.

Although concentration measurements are not available in the UK Biobank, such information is stored in the TDM database. Dose-adjusted serum concentration (nmol/L per mg per day), a pharmacokinetic measure reflecting the rate of overall venlafaxine clearance and calculated as a ratio of absolute concentration (nmol/L) and total daily dose of venlafaxine (mg/day), was another predefined secondary outcome. Dose-adjusted serum concentrations were calculated for venlafaxine, *O*-desmethylvenlafaxine, venlafaxine active moiety (sum of venlafaxine and *O*-desmethylvenlafaxine serum levels), and *N*-desmethylvenlafaxine.

Statistical analysis

The study population was stratified according to genotype-predicted metaboliser phenotypes for CYP2D6 and CYP2C19. The risk of treatment failure across metaboliser categories was evaluated using logistic regression for CYP2D6 and CYP2C19 separately, as well as 20 genotype-predicted phenotype subgroups defined by the combination of four CYP2D6 and five CYP2C19 phenotypes. All logistic regression models were adjusted for sex, age at the time of the last venlafaxine prescription, and antidepressant polypharmacy. In the logistic regression and maintenance dose analyses, the phenotype subgroups containing fewer than ten participants were excluded from the analyses, as the statistical power was too low to draw meaningful conclusions. For assessing venlafaxine dose-adjusted serum levels in relation to *CYP2D6* and *CYP2C19* genotypes in the TDM cohort, we used random intercept multivariate linear mixed model analysis with restricted maximum likelihood to use all eligible venlafaxine TDM measurements available during the study period. The models included age, sex, and withdrawal time as fixed effect covariates, and anonymised subject identification numbers as random effects. Dose-adjusted serum concentrations of venlafaxine and its metabolites were transformed to natural logarithmic scale before statistical analyses; however, results were presented in the linear scale for clarity. TDM measurements were considered for analysis if they included complete information on dose and serum levels of venlafaxine and its metabolites and withdrawal time between 10 h and 26 h. In all analyses, NMs served as the reference group (CYP2D6 NM in the main analyses and CYP2D6 NM × CYP2C19 NM in the secondary analyses). Baseline characteristics between groups were compared using *t* tests for continuous variables (age and daily dose of venlafaxine) and χ^2 tests for categorical variables (sex and antidepressant polypharmacy).

The statistical analyses were conducted using *R* (version 4.5.2). The forest plots were generated using the forestplot package (version 3.1.7). As analyses were hypothesis-driven based on published literature, no adjustment for multiple testing was applied. Statistical significance was defined as a two-sided p<0·05.

Role of the funding source

The funders had no role in study design, data collection, analysis, interpretation, manuscript preparation, or the decision to submit the manuscript.

Results

Baseline characteristics of participants treated with venlafaxine from the Norwegian TDM cohort and UK Biobank cohort are presented in table 1. The TDM cohort comprised 5443 participants with a history of venlafaxine treatment, of whom 3315 (60·3%) were female. Individual-level ethnicity data were not available. Overall, 640 (11·8%) participants switched from venlafaxine to another antidepressant. The participants who switched from venlafaxine were older (p=0·0001) and more likely to be female (p=0·019). Switchers were more frequently receiving antidepressant polypharmacy than non-switchers (134 [20·9%] of 640 *vs* 636 [13·2%] of 4803; p<0·0001). There were no differences observed in total daily dose of venlafaxine between switchers and non-switchers (p=0·49).

3624 individuals were identified from the UK Biobank cohort, of whom 2401 (66·3%) were female and the vast majority were White (3495 [96·4%]; table 1). 1147 participants (31·7%) met the definition of switching. In contrast to the TDM cohort, switchers in the UK Biobank cohort were significantly younger than non-switchers (p<0·0001) with no difference in sex distribution (p=0·57) or daily venlafaxine dose (p=0·21). There was no significant difference in antidepressant polypharmacy between switchers and non-switchers (187 [16·3%] of 1147 *vs* 358 [14·5%] of 2477; p=0·15). Venlafaxine and metabolite concentrations were not available in the UK Biobank.

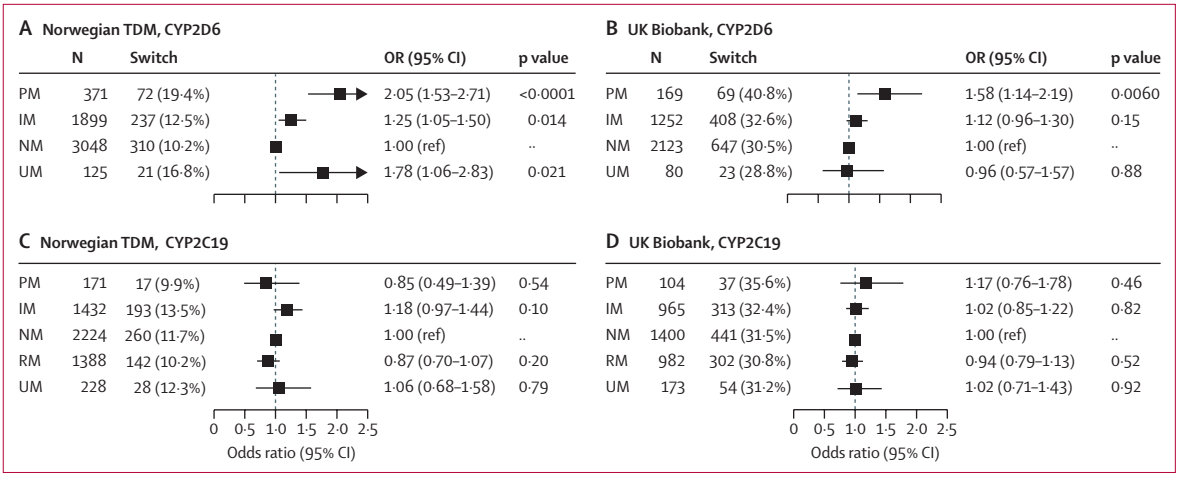


Figure 1: **Association between metaboliser phenotypes and risk of venlafaxine treatment failure for CYP2D6 and CYP2C19**
Panels show CYP2D6 results from the TDM cohort (A) and the UK Biobank cohort (B), and CYP2C19 results from the TDM cohort (C) and the UK Biobank cohort (D). ORs and 95% CIs comparing each metaboliser phenotype with normal metabolisers were estimated using logistic regression models adjusted for age at the last venlafaxine prescription, sex, and antidepressant polypharmacy. The x-axis is truncated at OR=2·5 for visualisation, and CIs extending beyond this range are truncated accordingly. IM=intermediate metaboliser. NM=normal metaboliser. OR=odds ratio. PM=poor metaboliser. RM=rapid metaboliser. TDM=therapeutic drug monitoring. UM=ultra-rapid metaboliser.

We inferred metaboliser phenotypes from genotype data according to the criteria shown in the appendix (p 9). Figure 1 presents the logistic regression results for the association between CYP2D6 and CYP2C19 phenotypes and venlafaxine treatment failure, with predicted probabilities of switching from venlafaxine by metaboliser phenotype (appendix p 3). Sex-stratified results for single gene analyses are also provided in the appendix (pp 4–5).

In the TDM cohort, the risk of switching was significantly higher in CYP2D6 PMs, IMs, and UMs compared with CYP2D6 NMs, with the highest odds observed in PMs (odds ratio [OR] 2·05 [95% CI 1·53–2·71], p<0·0001), followed by UMs (1·78 [1·06–2·83], p=0·021) and IMs (1·25 [1·05–1·50], p=0·014; figure 1A). In the UK Biobank cohort, a statistically significant increase in the risk of switching was found only among CYP2D6 PMs (1·58 [1·14–2·19], p=0·0060; figure 1B).

When considered individually, CYP2C19 phenotypes were not significantly associated with treatment failure in either cohort (figure 1C, D). However, CYP2C19 phenotypes interacted significantly with CYP2D6 phenotypes. In the TDM cohort, the strongest effect was observed in CYP2D6 PM×CYP2C19 PM, with 6·11 times higher odds of switching compared with dual NMs (95% CI 1·81–18·77, p=0·0019; figure 2A). These effects were observed for other phenotype groups in which both CYP2D6 and CYP2C19 activity were reduced (CYP2D6 PM×CYP2C19 IM, OR 1·79 [95% CI 0·98–3·10], p=0·046; CYP2D6 IM×CYP2C19 IM, 1·77 [1·29–2·40], p=0·0003). In the UK Biobank cohort, the PM×PM subgroup was too small (n=8) for a sufficiently powered assessment of switch rates, but increased switching was observed for CYP2D6 PM×CYP2C19 IM (2·14 [1·08–4·23], p=0·028), CYP2D6 PM×CYP2C19 NM (2·69 [1·75–4·07]; p<0·0001), and CYP2D6 IM×CYP2C19 UM (1·75 [1·02–2·95]; p=0·04; figure 2B) compared with NM×NM participants. Sex-stratified associations between combined metaboliser phenotypes and risk of venlafaxine treatment failure are shown in the appendix (pp 6–7).

In the TDM cohort, venlafaxine maintenance dose differed across metaboliser phenotypes (table 2). A graded increase in dose was observed across CYP2D6 phenotypes—with lower doses among PMs (mean 135·7 mg/day [95% CI 128·8–142·9], times-change 0·91, p=0·0005) and higher doses among UMs (161·0 mg/day [147·3–175·9], 1·07, p=0·12) compared with NMs (149·7 mg/day [147·0–152·5]). When CYP2C19 phenotypes were considered, this gradient became more pronounced. Compared to participants with combined NMs, PM phenotypes had the largest effect on maintenance doses in the TDM cohort, with substantially lower prescribed maintenance doses in participants who were PMs for both enzymes (112·8 mg/day [85·9–148·2], 0·73, p=0·026). In contrast, participants with combined rapid metaboliser status (ie, CYP2D6 UM×CYP2C19 RM) were prescribed the highest doses with 187·5 mg/day ([158·8–221·3], 1·22, p=0·023). When CYP2C19 phenotypes were considered together with CYP2D6, only the CYP2D6 UM×CYP2C19 RM showed a significantly higher mean daily dose than the reference group in the UK Biobank cohort (167·6 mg/day [112·2–250·4], 1·56, p=0·033). No association was observed between daily dose and CYP2C19 metabolic activity when considered alone (appendix p 8).

For the TDM cohort, serum concentration data with required dose information and withdrawal time were

available for 3385 patients. Estimated means and relative changes of dose-adjusted serum concentration of venlafaxine and its metabolites in relation to CYP2D6 and CYP2D6×CYP2C19 combined phenotypes are presented in the appendix (pp 10–11). The results confirm that *CYP2D6* genotype has a large and significant effect on levels of venlafaxine (4·46-times higher in PMs *vs* NMs; p<0·0001), *O*-desmethylvenlafaxine (70% reduced in PMs *vs* NMs; p<0·0001), and *N*-desmethylvenlafaxine (20-times higher in PMs *vs* NMs; p<0·0001), but with limited influence on the active moiety (1·1-times higher in PMs *vs* NMs; p=0·0005), as venlafaxine and *O*-desmethylvenlafaxine levels change in opposite directions (appendix p 10). When considering both *CYP2D6* and *CYP2C19* genotypes, venlafaxine levels increase 17-times accompanied by a 20-times reduction in *O*-desmethylvenlafaxine levels; together, this results in a three-times increase of the active moiety in dual CYP2D6/CYP2C19 PMs versus dual NMs (p<0·0001; appendix p 11).

Discussion

In this large two-cohort study, genotype-predicted CYP2D6 PM status was significantly associated with treatment failure of venlafaxine across independent real-life clinical settings. These findings provide evidence that pharmacogenetic variability in CYP2D6 metabolism influences the clinical outcomes of venlafaxine treatment. *CYP2C19* genotype significantly amplified the switching risk observed for the CYP2D6 PM phenotype alone. These results support a possible benefit of pre-emptive genotyping of *CYP2D6* and *CYP2C19* to guide precision dosing of venlafaxine, but this needs to be considered in the context of cost-effectiveness.

Our study design did not allow us to assess whether switching from venlafaxine was due to insufficient efficacy or side-effects. In CYP2D6 PMs, *N*-desmethylvenlafaxine and venlafaxine levels are greatly increased, while levels of *O*-desmethylvenlafaxine are decreased. Given that venlafaxine and its primary metabolite, *O*-desmethylvenlafaxine, are often considered as equipotent antidepressants, one might expect that altered CYP2D6 metabolism would not affect the overall therapeutic exposure to a clinically relevant extent. However, both selectivity towards reuptake inhibition of norepinephrine and serotonin, as well as higher brain penetration of venlafaxine compared with *O*-desmethylvenlafaxine, are important pharmacological differences between venlafaxine and *O*-desmethylvenlafaxine.[22] Thus, the shift in metabolic ratio potentially provides a higher brain availability of the parent drug compared with its metabolite, as well as an overall higher adrenergic effect.[23] Taken together, this could potentially cause reduced tolerability in CYP2D6 PMs, despite only a modest increase in total active moiety exposure in the circulation. For example, increased brain exposure to the parent drug and a shift towards formation of *N*-desmethylvenlafaxine over *O*-desmethylvenlafaxine might enhance noradrenergic effects, potentially

A Norwegian TDM

CYP2D6	CYP2C19	N	Switch	OR (95% CI)	p value
PM	PM	13	5 (38·5%)	6·11 (1·81–18·77)	0·0019
	IM	98	16 (16·3%)	1·79 (0·98–3·10)	0·046
	NM	159	36 (22·6%)	2·69 (1·75–4·07)	<0·0001
	RM	88	12 (13·6%)	1·57 (0·79–2·88)	0·17
	UM	13	3 (23·1%)	2·66 (0·59–8·90)	0·14
IM	PM	54	5 (9·3%)	1·02 (0·35–2·40)	0·96
	IM	504	78 (15·5%)	1·77 (1·29–2·40)	0·0003
	NM	781	97 (12·4%)	1·38 (1·04–1·84)	0·026
	RM	483	53 (11·0%)	1·18 (0·83–1·66)	0·34
	UM	77	4 (5·2%)	0·52 (0·16–1·29)	0·21
NM	PM	101	7 (6·9%)	0·73 (0·30–1·50)	0·43
	IM	800	96 (12·0%)	1·34 (1·00–1·78)	0·048
	NM	1232	116 (9·4%)	1·00 (ref)	..
	RM	782	70 (9·0%)	0·96 (0·70–1·31)	0·81
	UM	133	21 (15·8%)	1·83 (1·08–2·98)	0·019
UM	PM	3	0	NE	NE
	IM	30	3 (10·0%)	1·04 (0·24–3·03)	0·95
	NM	52	11 (21·2%)	2·71 (1·29–5·27)	0·0051
	RM	35	7 (20·0%)	2·29 (0·90–5·10)	0·058
	UM	5	0 (0·0%)	NE	NE

B UK Biobank

CYP2D6	CYP2C19	N	Switch	OR (95% CI)	p value
PM	PM	8	3 (37·5%)	NE	NE
	IM	37	19 (51·4%)	2·14 (1·08–4·23)	0·028
	NM	62	27 (43·5%)	1·86 (1·08–3·18)	0·023
	RM	52	17 (32·7%)	1·14 (0·61–2·07)	0·68
	UM	10	3 (30·0%)	1·21 (0·25–4·49)	0·79
IM	PM	30	13 (43·3%)	1·82 (0·84–3·87)	0·12
	IM	344	112 (32·6%)	1·11 (0·84–1·46)	0·46
	NM	483	155 (32·1%)	1·11 (0·86–1·42)	0·42
	RM	330	102 (30·9%)	1·02 (0·77–1·35)	0·90
	UM	65	26 (40·0%)	1·75 (1·02–2·95)	0·040
NM	PM	63	20 (31·7%)	1·06 (0·59–1·83)	0·85
	IM	562	177 (31·5%)	1·05 (0·83–1·34)	0·66
	NM	822	248 (30·2%)	1·00 (ref)	..
	RM	584	179 (30·7%)	1·00 (0·79–1·26)	1·0
	UM	92	23 (25·0%)	0·76 (0·45–1·23)	0·28
UM	PM	3	1 (33·3%)	NE	NE
	IM	22	5 (22·7%)	0·64 (0·21–1·68)	0·40
	NM	33	11 (33·3%)	1·25 (0·57–2·60)	0·56
	RM	16	4 (25·0%)	0·92 (0·25–2·69)	0·88
	UM	6	2 (33·3%)	NE	NE

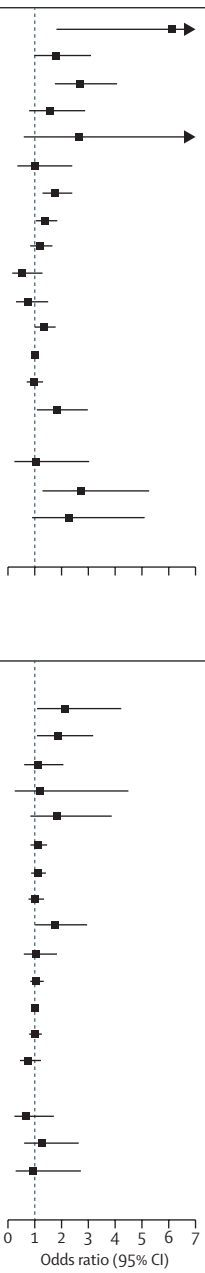


Figure 2: **Association between combined metaboliser phenotypes and risk of venlafaxine treatment failure in the TDM cohort (A) and in the UK Biobank cohort (B)**
ORs and 95% CIs were estimated relative to the CYP2D6 NM × CYP2C19 NM reference group using logistic regression models adjusted for age at the last venlafaxine prescription, sex, and antidepressant polypharmacy. ORs and corresponding p values for each combined metaboliser phenotype are shown. For visualisation, the x-axis is truncated at OR=7. CIs extending beyond this range are truncated. p<0·05 was considered statistically significant. IM=intermediate metaboliser. NE=not estimable. NM=normal metaboliser. OR=odds ratio. PM=poor metaboliser. RM=rapid metaboliser. TDM=therapeutic drug monitoring. UM=ultra-rapid metaboliser.

	Norwegian TDM cohort				UK Biobank cohort			
	N	Mean (95% CI)	Times change	p value	N	Mean (95% CI)	Times change	p value
CYP2D6 PM	359	135·7 (128·8–142·9)	0·91	0·0005	88	98·1 (85·7–112·4)	0·89	0·11
PM × PM	13	112·8 (85·9–148·2)	0·73	0·026	4	66·4 (35·2–125·3)	0·62	NE
PM × IM	94	130·7 (118·1–144·7)	0·85	0·0022	23	103·5 (79·4–134·8)	0·96	0·77
PM × NM	153	131·5 (121·5–142·4)	0·85	0·0002	29	97·0 (76·7–122·8)	0·90	0·40
PM × RM	86	148·2 (133·3–164·8)	0·96	0·48	28	106·6 (83·9–135·5)	0·99	0·93
PM × UM	13	171·3 (130·4–225·0)	1·11	0·45	4	65·0 (34·5–122·6)	0·60	NE
CYP2D6 IM	1799	145·9 (142·5–149·3)	0·97	0·085	658	109·2 (103·9–114·7)	0·99	0·82
IM × PM	50	108·6 (94·5–124·8)	0·71	<0·0001	12	125·6 (87·1–181·2)	1·17	0·42
IM × IM	482	143·3 (137·0–149·8)	0·93	0·0069	198	106·5 (97·4–116·6)	0·99	0·84
IM × NM	739	145·4 (140·2–150·7)	0·94	0·013	246	115·7 (106·7–125·4)	1·07	0·17
IM × RM	456	151·7 (144·9–158·8)	0·98	0·56	169	102·8 (93·2–113·3)	0·95	0·42
IM × UM	72	163·9 (146·0–184·0)	1·06	0·31	33	106·5 (85·4–132·8)	0·99	0·92
CYP2D6 NM	2918	149·7 (147·0–152·5)	..	..	1077	110·0 (105·8–114·3)	..	..
NM × PM	96	130·9 (118·4–144·7)	0·85	0·0021	30	102·3 (81·1–129·0)	0·95	0·67
NM × IM	761	142·7 (137·7–147·8)	0·93	0·0009	276	112·5 (104·2–121·4)	1·04	0·39
NM × NM	1179	154·1 (149·8–158·6)	..	..	424	107·8 (101·3–114·6)	..	..
NM × RM	757	151·1 (145·8–156·6)	0·98	0·39	295	111·4 (103·5–120·0)	1·03	0·50
NM × UM	125	161·1 (147·4–175·7)	1·04	0·36	52	111·9 (98·8–133·4)	1·04	0·69
CYP2D6 UM	124	161·0 (147·3–175·9)	1·07	0·12	33	133·2 (106·8–166·2)	1·21	0·094
UM × PM	3	108·2 (61·3–190·8)	0·70	NE	0	..	..	..
UM × IM	29	143·5 (119·6–172·3)	0·93	0·45	5	104·0 (59·0–183·4)	0·97	NE
UM × NM	52	157·0 (137·0–180·0)	1·02	0·79	17	129·9 (95·5–176·7)	1·21	0·24
UM × RM	35	187·5 (158·8–221·3)	1·22	0·023	10	167·6 (112·2–250·4)	1·56	0·033
UM × UM	5	176·1 (113·7–273·8)	1·14	NE	1	71·5 (20·1–254·5)	0·66	NE

Daily dose is presented as geometric mean (95% CI), derived from linear regression models of log-transformed dose. Times-change represents the ratio of means compared with the reference group (NM for CYP2D6-only analyses; NM × NM for compound phenotype analyses), and p values reflect comparisons with the same reference group. IM=intermediate metaboliser. NE=not estimable. NM=normal metaboliser. PM=poor metaboliser. RM=rapid metaboliser. TDM=therapeutic drug monitoring. UM=ultra-rapid metaboliser.

Table 2: **Venlafaxine maintenance dose according to CYP2D6 phenotype and CYP2D6 × CYP2C19 compound phenotypes in the Norwegian TDM and UK Biobank cohorts**

contributing to increased risk of cardiotoxicity in CYP2D6 PMs.[24–26]

The lower doses prescribed in CYP2D6 PMs versus NMs (approximately 10% less in both study cohorts) support that reduced tolerability was a major cause underlying venlafaxine switch in CYP2D6 PMs. However, to prevent assumed side-effects, larger genotype-guided dose reductions are likely required in CYP2D6 PMs. In CYP2D6 UMs, where increased risk of venlafaxine switching was observed in the TDM cohort, higher doses than usually recommended might be required to prevent insufficient treatment response. As in the Norwegian TDM cohort, higher venlafaxine maintenance doses were observed in the CYP2D6 UM × CYP2C19 RM subgroup of the UK Biobank cohort, indicating that increased metabolic capacity could be partially managed through clinical dose titration in routine care, without access to the patient's genotype. However, altered enzyme activity might represent a pharmacokinetic liability that cannot be easily mitigated by dose adjustments of venlafaxine, as increasing the dose could result in higher parent drug exposure without restoring metabolite balance. These findings provide a rationale for further prospective evaluation of genotype-guided dosing of venlafaxine.

The associations between *CYP2D6* genotype and venlafaxine treatment failure parallel the associations established between *CYP2C19* genotype and treatment failure of the SSRI escitalopram.[19] Specifically, as for escitalopram,[19] for venlafaxine the likelihood of treatment failure had a U-shaped association with metabolic activity where both PMs and UMs had a higher rate of switching in TDM populations (appendix p 3). Thus the pharmacogenetics of CYP metabolism are an important contributor to variation in clinical response of two of the most commonly prescribed antidepressant drugs.

Inclusion of two distinct clinical populations strengthens the confidence and robustness of our findings on venlafaxine treatment failure, with CYP2D6 PM status being consistently associated with treatment failure in both the TDM and UK Biobank cohorts. The TDM cohort represents a specialised clinical setting that includes cases of both pre-emptive and reactive

pharmacogenetic analyses; moreover, exposure is actively surveilled and prescribed doses might be adjusted based on the patient's serum concentrations. The TDM cohort is probably also enriched by cases where the therapeutic response is unfavourable and therefore more sensitive towards detecting differences in switch frequencies in relation to *CYP2D6* genotype than the UK Biobank cohort. This enrichment of patients with unfavourable treatment response could be a factor of importance for the significantly increased switch frequency in CYP2D6 UMs versus NMs within the TDM cohort, which was not observed in the UK Biobank cohort (reflecting routine primary care prescribing without access to TDM or genotype information). The replication of genetic signals between CYP2D6 PM status and treatment failure across these complementary real-life settings reduces the likelihood that the observed associations are driven by expectation bias or treatment modifications influenced by previous knowledge of genotype, as discussed for open-label pharmacogenomics trials such as PREPARE.[27] The replication of this association across both clinical settings and health-care systems, therefore, supports the generalisability and clinical validity of the CYP2D6 PM finding, extending its relevance beyond specialised pharmacogenetic services into routine psychiatric care.

Our findings have broader implications for pharmacogenetic-guided antidepressant therapies. Previous studies have shown that patients for whom first-line SSRI therapy is unsuccessful have a higher proportion of non-normal CYP2C19 and CYP2D6 metaboliser phenotypes, suggesting that variability in drug metabolism contributes to treatment failure.[11,19,20,28] In stepped-care models for major depressive disorder, venlafaxine is frequently used as second-line therapy if individuals do not respond to SSRI treatment.[5] The present results show that pharmacogenetic variation in *CYP2D6* remains clinically relevant beyond first-line antidepressant therapy. Given that venlafaxine is commonly introduced after SSRI non-response, *CYP2D6* genotypes could help to identify patients at increased risk of successive treatment failure, supporting closer monitoring or consideration of alternative antidepressants less dependent on CYP2D6-mediated metabolism.

Several study limitations should be acknowledged. First, treatment failure of antidepressants is a multifactorial and complex clinical outcome. Switching to another antidepressant is a surrogate (indirect) measure of treatment failure and does not identify the reasons behind the unsuccessful treatment. Second, data on indication, comorbidity, individual-level ethnicity, or concomitant medication use were not consistently available in either cohort. Consequently, residual confounding from these factors cannot be fully excluded. Third, some combined phenotype categories were infrequent, which could limit the precision of effect size estimates. Differences in absolute switching frequencies between cohorts likely reflect structural differences in exposure definition and health-care context rather than true differences in severity. In particular, the use of the last venlafaxine prescription date in the UK Biobank cohort might create a new 1-year risk window beginning at switching that captures relapse-related prescriptions or transitional prescribing patterns such as trial-and-stop patterns or temporary bridging. Nevertheless, drug switching represents a clinically meaningful treatment decision regardless of causality, hence is a relevant outcome measure showing consistency of key findings across two large and distinct study populations. Fourth, the study populations had limited diversity, with most participants being White, which might limit the generalisability of our findings to other populations. Finally, no lived experience contributor was involved from the UK Biobank cohort, which limited the incorporation of patient perspectives into the interpretation of findings from this population.

Taken together, our findings identify CYP2D6 metaboliser status as a clinically important determinant of venlafaxine metabolism that can contribute to the risk of treatment failure. Integration with genetic variability in *CYP2C19* might improve the accuracy of risk predictions, particularly for patients with combined CYP2D6 PM×CYP2C19 PM/IM phenotypes. These findings provide incentives for pre-emptive *CYP2D6* and *CYP2C19* genotyping to facilitate personalised venlafaxine treatment strategies. Future prospective studies are warranted to evaluate whether implementation of *CYP2D6*-guided venlafaxine dosing or antidepressant selection can reduce treatment failure in a cost-effective manner.

Contributors

All authors participated in the conceptualisation of the study. YP processed and analysed the data from the purchased UK Biobank file. VML also had access to the UK Biobank file and verified the data analyses from this cohort. HÇL extracted data on patients from the Norwegian TDM database and processed and analysed data from this cohort. EM had access to the data file from the Norwegian TDM cohort and verified analyses of these data. YP and HÇL drafted the manuscript with input from YZ. VML and EM supervised the writing and were responsible for reviewing and editing. All authors approved the final manuscript before submission.

Declaration of interests

VML is CEO and shareholder of HepaPredict, as well as co-founder and shareholder of Shanghai Hepo Biotechnology. All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the corresponding author, EM, upon reasonable request.

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