Association between CYP2D6 genotype and vortioxetine exposure and therapeutic failure - a retrospective, cohort study

Trine Frederiksen[1], Robert Smith[2], Marin Jukić[3], and Espen Molden[4]

[1]H. Lundbeck A/S
[2]Center for Psychopharmacology
[3]Karolinska Institutet
[4]University of Oslo

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Abstract

The antidepressant vortioxetine is primarily metabolised by the polymorphic enzyme CYP2D6. The objective of this study was to investigate the effect of CYP2D6 genotype on exposure and therapeutic failure of vortioxetine. The analysis included data from CYP2D6-genotyped patients (N=458) on vortioxetine treatment from a Norwegian therapeutic drug monitoring database. Compared with CYP2D6 normal metabolizers (NMs; N=242), vortioxetine exposure was 3.0-fold ($p<0.001$) increased in poor metabolizers (PMs; N=35), 1.5-fold ($p<0.001$) increased in intermediate metabolizers (IMs; N=173), and not significantly changed ($p=0.21$) in ultra-rapid metabolizers (UMs; N=8). Compared with NMs, treatment switch from vortioxetine to alternative antidepressants was 8.0-fold (95%CI: 2.0-32.3, $p=0.001$) more frequent among PMs and 12.7-fold (95%CI: 1.1-94.9, $p=0.02$) more frequent among the CYP2D6 UMs. In conclusion, CYP2D6 genotype was associated with significant changes in vortioxetine exposure and may also be associated with risk of therapeutic failure.

INTRODUCTION

Numerous psychotropic medications are metabolized by the polymorphic CYP2D6 enzyme. The *CYP2D6* gene encoding the enzyme is highly polymorphic, which in turn causes substantial interindividual variability in enzyme activity. Based on their *CYP2D6* genotype, patients are commonly categorized into four phenotype groups: (1) poor metabolizer (PM) exhibit complete absence of active CYP2D6 enzyme, (2) intermediate metabolizer (IM) exhibit reduced CYP2D6 metabolic capacity, (3) normal metabolizer (NM) exhibit normal CYP2D6 metabolic and (4) ultra-rapid metabolizer (UM) exhibit increased CYP2D6 metabolic capacity. The frequency of phenotypes in the population varies across ethnicities with 3-10% being categorized as PMs, 15-40% as IMs, 1-9% as UMs and the remaining as NMs (40-85%) [1].

Vortioxetine is a novel antidepressant, indicated for the treatment of major depressive disorder (MDD). Clinical studies have demonstrated antidepressant efficacy and a favourable tolerability profile of vortioxetine in the dose range 5-20 mg/day. However, as for other antidepressants, there is substantial interindividual variability in clinical response [2]. Vortioxetine is metabolized by several CYP isoforms, with CYP2D6 accounting for approximately half of the total clearance [3]. The objective of this study was to investigate the effect of *CYP2D6* genotype on systemic vortioxetine exposure and therapeutic failure of vortioxetine in a naturalistic setting using data from therapeutic drug monitoring (TDM).

METHODS

Patients' data were included retrospectively from the TDM database at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, which is a service analysing both serum concentrations of

psychotropic drugs and offering *CYP* genotyping on request from clinicians.*CYP2D6* -genotyped patients were included in the study if they had been on vortioxetine treatment during the period January 2013 to June 2020. Exclusion criteria comprised concomitant use of potent CYP2D6 and/or CYP2C19 enzyme inhibitors (bupropion, fluoxetine, levomepromazine, or paroxetine), or CYP3A4 inducers (carbamazepine, phenobarbital, or phenytoin), detected by reviews of the TDM requisitions form, and serum concentrations of vortioxetine below the analytical assay's lower limit of quantification. Furthermore, patients with missing information on the prescribed vortioxetine daily dose were excluded.

CYP2D6 genotyping was performed using TaqMan®-based real-time PCR assays (Life Technologies, USA) including the following allele variants:*CYP2D6*3* (*rs35742686*), *CYP2D6*4* (*rs3892097*),*CYP2D6*5* (whole gene deletion), *CYP2D6*6*(*rs5030655*), *CYP2D6*9* (*rs5030656*), *CYP2D6*10*(*rs1065852*), *CYP2D6*41* (*rs28371725*), and copy number variation. Based on the *CYP2D6* genotype, patients were categorized into CYP2D6 PM, IM, NM or UM categories according to the consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) [4].

Serum concentration of vortioxetine was determined by an ultra-high-performance LC (UHPLC)-high resolution mass spectrometry (HRMS) method validated for use in clinical practice. The same analytical method was used to detect presence of other antidepressants in serum including amitryptyline, nortryptyline, bupropion, citalopram, escitalopram, fluoxetine, duloxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, clomipramine, trimipramine, mianzerin and mirtazapine.

Longitudinal reviews of serum-detected drugs in the included patients' TDM profiles were performed to identify cases of treatment switch from vortioxetine treatment to another antidepressant within three months after their last vortioxetine TDM measurement, in line with procedures from recent publications on escitalopram [5] and risperidone [6]. As the timeframe of three months represents a major depressive episode, an event of treatment switch was interpreted as therapeutic failure of vortioxetine, regardless of cause.

When comparing vortioxetine exposure between CYP2D6 phenotype groups, serum concentration measurements of vortioxetine were dose-harmonized and ln-transformed to restore normal distribution. The dose-harmonized, ln-transformed concentrations in each CYP2D6 phenotype group were compared using the one-way analysis of variance (ANOVA) followed by the Tukey*post-hoc* tests. Treatment failure rates were compared between CYP2D6 phenotype groups using Fisher's exact test.

The study was approved by the Regional Ethical Committee of the South-Eastern Health Authority in Norway and the Hospital Investigational Review board.

RESULTS

516 *CYP2D6* -genotyped patients on vortioxetine treatment were identified in the TDM database. Among these, 29 were excluded due to concomitant use of CYP inhibitors/inducers, 8 due to serum concentration measurements of vortioxetine being below the lower limit of quantification, and 21 patients lacking information about the prescribed vortioxetine dose. Thus, a total of 458 patients were included in the analysis.

The frequencies of *CYP2D6* genotype-predicted PMs, IMs, NMs and UMs in the population were 7.6%, 37.8%, 52.8% and 1.7%, respectively, and all the *CYP2D6* variant alleles were in Hardy-Weinberg equilibrium. There were no significant differences in patient demographics or time intervals between the last vortioxetine dose and TDM blood sampling between the CYP2D6 phenotype groups (see**Table 1**). The median vortioxetine dose administered in the PM and IM groups were lower than those in the NM and UM groups, but the differences were not statistically significant.

The median vortioxetine exposure, measured by dose-harmonized concentration, was highest among the CYP2D6 PMs (23.9 ng/mL), followed by the IMs (12.5 ng/mL), NMs (8.1 ng/mL), and lowest for the UMs (5.9 ng/mL) (see **Figure 1**). The CYP2D6 PMs and IMs exhibited significantly higher vortioxetine exposures ($P<0.001$) compared to NMs with ratios of medians being 3.0 and 1.5, respectively. No significant difference in vortioxetine exposure was found between the CYP2D6 UMs and NMs ($P=0.21$).

In addition to the exposure differences, the frequency of patients switching from vortioxetine to an alternative antidepressant during the course of three-month follow-up was significantly higher among PMs compared to NMs (P=0.001, odds ratio (OR) 8.0, 95% CI=2.0-32.2). CYP2D6 UMs also showed a significantly higher frequency of treatment switch compared to NMs (P=0.02, OR 12.7, 95% CI=1.1-94.9), while no significant difference was found between the IMs and NMs (P=0.28, OR 1.9, 95% CI=0.6-6.8).

DISCUSSION

In this retrospective study, we found a significant effect of *CYP2D6* genotype on vortioxetine exposure measured in routine clinical practice. The systemic exposure of vortioxetine observed in the CYP2D6 PM group was 3-fold higher than that observed in the NM group, while the exposure in the IM group was increased 1.5-fold compared to the NM group. A population pharmacokinetic study of vortioxetine has previously shown a significant effect of CYP2D6 phenotype on oral clearance of vortioxetine with average estimated values being 53 L/h for UMs, 34 L/h for NMs, 27 L/h for IMs and 18 L/h for PM [7]. This is reflected in the vortioxetine drug label, where it is recommended that CYP2D6 PMs should be treated with a maximum dose of 10 mg vortioxetine per day [8]. The present study confirms this recommendation based on data from a naturalistic setting, which is important from a clinical point of view. Although the vortioxetine exposure for CYP2D6 UMs is expected to be reduced compared to NMs, clinical studies have shown a significant overlap in exposures between UMs and NMs and therefore dose adjustment for UMs is not recommended [3]. This is in line with the results from the current study where no significant difference in vortioxetine exposure was found between CYP2D6 UMs and NMs. However, it should be noted that this finding was based on a limited number of UM patients (N=8).

The current study showed that CYP2D6 PMs and UMs, as compared with NMs, had an increased frequency of switching to another antidepressant within the expected time frame of a depressive episode (three months). As PMs exhibited significantly higher exposures compared to the other CYP2D6 phenotype groups, the increased switch rate in PMs is likely to be driven by a higher frequency of adverse events caused by supratherapeutic drug concentrations. By decreasing the dose among the CYP2D6 PMs, patients could have achieved lower vortioxetine concentrations, which may have increased the probability of staying within the therapeutic window and reduced their risk of concentration-dependent adverse drug reactions. Although no significant difference in vortioxetine exposure was found between CYP2D6 UMs and NMs, the median concentration observed among the UMs was lower than 10 ng/mL, which has been reported as the lower limit for efficacy of vortioxetine [9]. As the UM patients generally had exposure levels close to the lower limit of the therapeutic window, the increased frequency of antidepressant switch may be related to insufficient clinical response. However, these findings are based on a very limited number of patients and larger studies would be needed to adequately address this hypothesis.

Overall, the findings from this study are in line with previous reports on the effect of *CYP2D6* and *CYP2C19* genotypes on risperidone and escitalopram treatment outcomes, respectively [5,6]. In a study of 725 patients treated with risperidone, CYP2D6 PMs and IMs were found to have a significant increase in serum levels of risperidone active moiety compared to NMs (P<0.0001). Furthermore, the incidence of treatment switch from risperidone to another antipsychotic was significantly increased in PMs (P=0.015) and UMs (P=0.003) compared to NMs[6]. Similarly, a study of more than 2,000 escitalopram-treated patients showed a 3.3-fold increase in escitalopram exposure among CYP2C19 PMs and a 10% reduction in exposure in CYP2C19 UMs compared to NMs. Paralleled by the differences in exposure, the CYP2C19 PMs and UMs showed significantly higher frequencies of switching from escitalopram to another antidepressant compared to CYP2C19 NMs (P<0.001) [5].

The main limitations of the current study were the limited number of UM patients and lack of clinical information retrieved from the patients' medical records due to privacy issues. Although switch of antidepressant treatment within three months may indicate therapeutic failure, exact information on treatment outcomes (including the reasons for treatment switch) was not obtainable from the TDM database. Furthermore, lack of knowledge on covariates that may affect drug exposure, such as comedications, renal function and body size represent additional limitations. However, the use of TDM data also represents several advantages, e.g.

exact information on drug use and replacement (switch), as the analytical method allows for the detection of serum concentration levels of multiple antidepressants simultaneously. Furthermore, the availability of serum concentration levels enables identification and exclusion of non-compliant patients, where the drug levels are undetectable.

In conclusion, this study confirms the significant effect of*CYP2D6* genotype on vortioxetine exposure and provides novel data on the association between *CYP2D6* genotype and therapeutic failure in a naturalistic, clinical setting. Together with previous studies, these results underline the importance of variability in CYP metabolism on treatment outcomes of psychiatric medications and support the value of routine TDM and *CYP* genotyping in personalised medicine in psychiatry.

CONFLICT OF INTEREST: TF is an employed PhD student at H. Lundbeck A/S marketing vortioxetine. The other authors declare no potential conflict of interest.

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Table 1 Summary of patient characteristics and information related to the TDM analyses of vortioxetine and antidepressant switch frequencies according to CYP2D6 metabolizer phenotype

Patient characteristics (N = 516)

Patient characteristics (N = 516)
Males/Females (N)
Age (years) (median (IQR))
Time from last dose to blood sample (h) (median (IQR))
Vortioxetine dose (mg) (median (IQR))
Vortioxetine exposure
Concentration (ng/mL) (median (95% CI))
Ratio of medians
Vortioxetine exposure (dose-harmonized to 10 mg/day)
Concentration (ng/mL) (median (95% CI))
Ratio of medians
Ln-transformed concentration (mean (95%CI))
P value[b]
95% confidence interval
Patients switching to alternative antidepressant treatment within 3 months
Switch / No switch (N)
P value[c]
Odds-ratio (95% CI)
[a] CYP2D6 phenotype was assigned based on *CYP2D6* genotype according to recommendation from the Clinical Pharmacog

Figure 1 Frequency of patients switching to an alternative antidepressant within three months (red bars indicate percentage) and vortioxetine exposure (dose-harmonized concentration) (blue points represent medians and error bars represent 95% confidence intervals) by CYP2D6 phenotype group

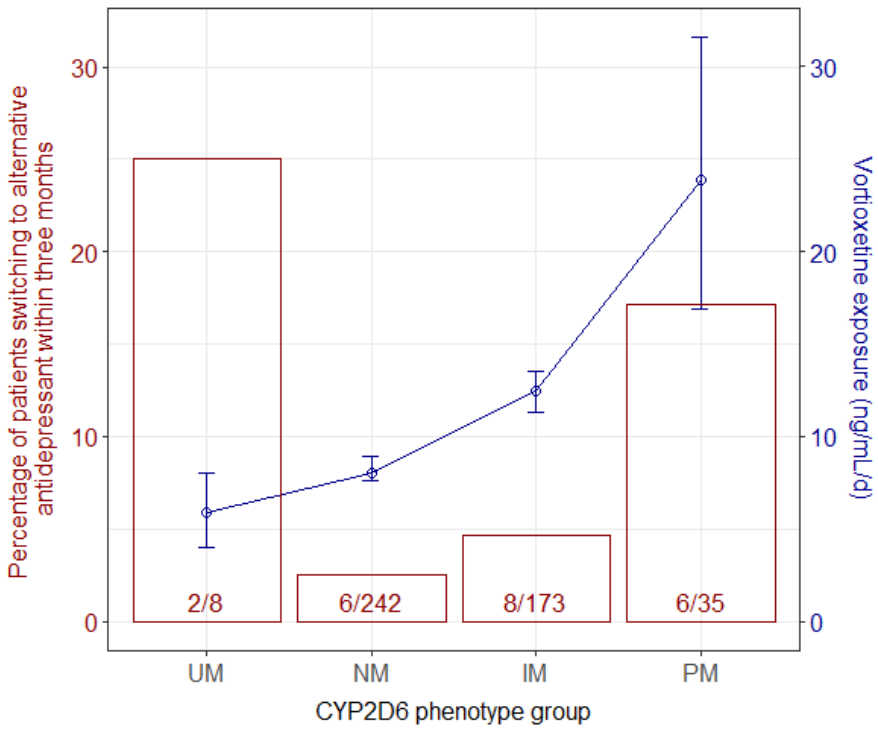

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Table 1.pdf available at https://authorea.com/users/378366/articles/494905-association-between-cyp2d6-genotype-and-vortioxetine-exposure-and-therapeutic-failure-a-retrospective-cohort-study