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ORIGINAL INVESTIGATION

The influences of *CYP2D6* genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment outcomes

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Abstract
Rationale Two biomarkers: concentration ratio of *O*-desmethylvenlafaxine/venlafaxine and concentration sum of venlafaxine+*O*-desmethylvenlafaxine were adopted to indicate venlafaxine responses, but neither is validated.
Objectives To evaluate the ability of two biomarkers in reflecting venlafaxine pharmacokinetic variations, and to further examine their relationship with venlafaxine treatment outcomes.
Methods Two well-defined influencing factors: *CYP2D6* genotypes and drug interactions were enriched into a three-period crossover study to produce venlafaxine pharmacokinetic variations: In each period, healthy CYP2D6 extensive metabolizers (EM group; $n=12$) and CYP2D6*10/*10 intermediate metabolizers (IM group; $n=12$) were pretreated with clarithromycin (CYP3A4 inhibitor), or nothing (control), or clarithromycin+paroxetine (CYP3A4+CYP2D6 inhibitors), before administration of a single-dose of 75 mg venlafaxine. Both biomarkers were evaluated (1) for their relationship with the influencing factors in healthy volunteers and (2) for their relationships with the venlafaxine responses/adverse events reported in two patient studies.
Results Significant venlafaxine pharmacokinetic variations were observed between the EM and IM groups (geometric mean ratio [95 % CI] of area under the curve, 3.0 [1.8–5.1] in the control period), and between the control and clarithromycin+paroxetine periods (4.1 [3.5–4.7] and 2.0 [1.7–2.4] in the EM and IM group, respectively). *O*-Desmethylvenlafaxine/venlafaxine was superior to venlafaxine+*O*-desmethylvenlafaxine to reflect the influencing factors. In the patient studies, *O*-desmethylvenlafaxine/venlafaxine >4 showed high precision in predicting venlafaxine responders/partial-responders (92 %) and patients without venlafaxine-related adverse events (88 %); the *O*-desmethylvenlafaxine/venlafaxine <4 and venlafaxine+*O*-desmethylvenlafaxine >400 ng/ml combination showed higher precision (100 %) than *O*-desmethylvenlafaxine/venlafaxine < 4 alone (65 %) in predicting venlafaxine non-responders.
Conclusion We propose using *O*-desmethylvenlafaxine/venlafaxine for CYP2D6 phenotyping, and *O*-desmethylvenlafaxine/venlafaxine with venlafaxine+*O*-desmethylvenlafaxine for predicting venlafaxine treatment outcomes in future prospective studies.

Keywords Venlafaxine · *O*-Desmethylvenlafaxine · CYP2D6 · Genetic polymorphism · Drug interaction · Pharmacokinetics · Pharmacodynamics · Dose response relation · Major depressive disorder

Hae-Deun Kim and Fen Jiang have contributed equally to this article.

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Introduction

Venlafaxine was the first serotonin norepinephrine reuptake inhibitor introduced to the market and is one of the most popularly prescribed antidepressants in many countries. However, over 30 % of patients prescribed venlafaxine do not respond to the treatment at all, and over 50 % fail to

achieve a remission (Entsuah et al. 2001). Adverse effects are another important consideration for venlafaxine treatment failure (de Silva and Hanwella 2012). It is believed that treatment outcomes (e.g., drug responses, adverse effects, etc.) of a drug are influenced by various intrinsic and extrinsic factors such as genotype, concomitant drugs, etc. Ideally, if we can discover all the factors and accurately measure their influence on treatment outcomes, we can make an early prediction of treatment failure or success as well as properly adjust dosage. Due to the difficulty in identifying all the different influencing factors, a unified biomarker (e.g., drug concentration) may be used instead to indicate treatment outcomes, but only when the biomarker is validated—which means (1) the biomarker truly represents the influences of different factors and (2) a good correlation exists between the biomarker and treatment outcomes.

So far, there is no such unified biomarker for venlafaxine; however, the US Food and Drug Administration (FDA) and the pharmacogenomics knowledge base (PharmGKB) have proposed using *CYP2D6* genotype as a biomarker for venlafaxine treatment. *CYP2D6* is the gene which encodes the cytochrome P450 enzyme CYP2D6—a drug-metabolizing enzyme whose activity is considered a major intrinsic influencing factor of venlafaxine pharmacokinetics. After a single oral dose of the drug, more than half of the dose converts to *O*-desmethylvenlafaxine (ODV, venlafaxine's major active metabolite), predominantly by CYP2D6; other enzymes such as CYP3A4 play a minor role in venlafaxine metabolism (Ereshefsky and Dugan 2000) (Fig. 1). CYP2D6 activity is largely (but not exclusively) influenced by over 100 alleles identified in *CYP2D6* gene (http://www.cypalleles.ki.se/cyp2d6.htm); individuals with different *CYP2D6* genotypes are roughly classified as *ultra*, *extensive*, *intermediate*, and *poor metabolizers* (*UM*, *EM*, *IM*, and *PM*; note that the abbreviations in italic font refer to *CYP2D6* genotypes; otherwise, refer to CYP2D6 phenotypes). The FDA added *CYP2D6* as the genetic biomarker onto venlafaxine labeling, but has not made any dose recommendation for different *CYP2D6* genotypes; the PharmGKB also published a *CYP2D6* genotype-based dosing guideline for venlafaxine (PharmGKB 2011), which currently only applies to *UM*, but not to *IM* or *PM*, due to "insufficient data to allow calculation of dose adjustment." In fact, there is no clinical evidence supporting the use of *CYP2D6* genotype testing for venlafaxine treatment. An important reason is that *CYP2D6* genotype does not always predict CYP2D6 enzyme activity (and hence venlafaxine treatment outcomes); the latter is often influenced by other extrinsic factors such as drug interactions, i.e., patients who are treated with venlafaxine are also prescribed other drugs, some of which may inhibit CYP2D6 (Flockhart 2007).

Several publications have used a validated CYP2D6 phenotype (EM and PM) biomarker—the concentration ratio of ODV/venlafaxine (Preskorn 2010) instead of *CYP2D6* genotype to indicate venlafaxine responses (Lobello et al. 2010; Shams et al. 2006; Veefkind et al. 2000). They reported that, although ODV/venlafaxine was significantly associated with venlafaxine response, its predictive precision (i.e., the observed responders/the predicted responders) was fairly low. In addition, the FDA uses another biomarker—the

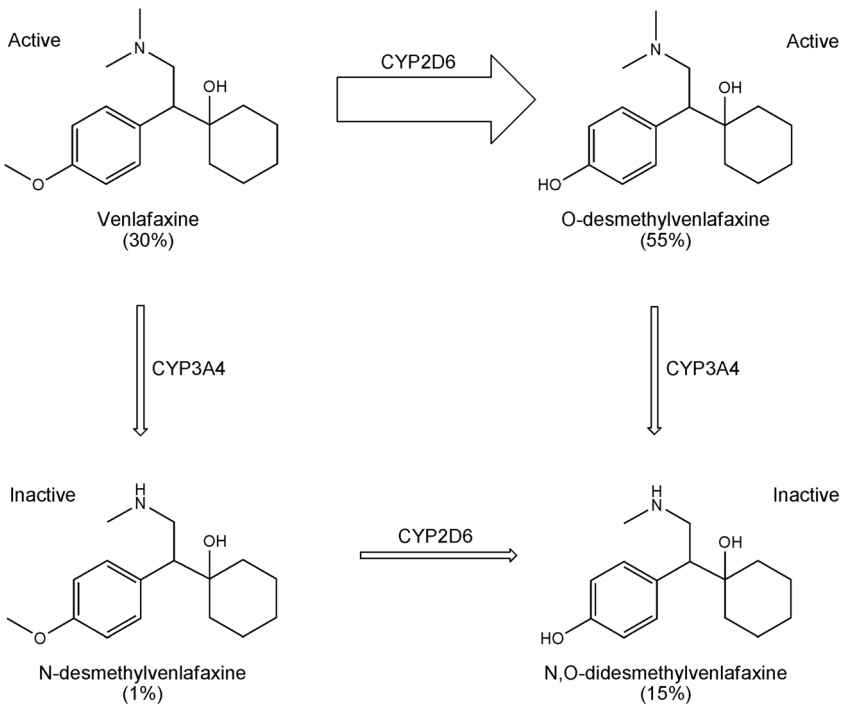

Fig. 1 Proposed pathway for venlafaxine phase I metabolism in humans. *Arrow thickness* represents estimated relative contribution of each pathway to overall venlafaxine metabolism; *numbers in parentheses* represent estimated percentage remained in circulation after a single oral dose of venlafaxine. The data were adopted from a previous study (Ereshefsky and Dugan 2000)

concentration sum of venlafaxine+ODV to guide venlafaxine dose adjustment for patients who are co-administered other CYP2D6 inhibitors, but no dose adjustment is recommended as "the total concentration of active compounds (venlafaxine+ODV) was not affected" (Effexor XR label, FDA). However, previous studies have failed to reach a consensus on the relationship between venlafaxine+ODV and venlafaxine treatment outcomes, using venlafaxine+ODV to justify venlafaxine dose recommendation seems inappropriate (Gex-Fabry et al. 2004; Lobello et al. 2010; Sakolsky et al. 2011).

As mentioned above, the two biomarkers—ODV/venlafaxine and venlafaxine+ODV which were adopted to indicate venlafaxine treatment outcomes on various occasions—have not been validated; the relationship between these two biomarkers is not yet clearly understood. The current guidelines and drug labeling for dose adjustment based on these biomarkers may need further improvement and revision. Driven by these challenges, we designed a clinical trial which introduced two major influencing factors of venlafaxine pharmacokinetics, *CYP2D6* genotype (*CYP2D6*10/*10 IM* and *EM*) and drug interaction (a CYP3A4 inhibitor clarithromycin or CYP2D6 + CYP3A4 inhibitors clarithromycin+paroxetine), into a single-dose venlafaxine pharmacokinetic study in healthy volunteers. The primary objective was to assess the ability of the two biomarkers, ODV/venlafaxine and venlafaxine+ODV, in reflecting venlafaxine pharmacokinetic variations produced by the two well-defined influencing factors. The *CYP2D6*10/*10 IM* were included because they are the most common mutant homozygotes in Korea. The single-inhibitor (clarithromycin) period was used to compare our results with previous CYP3A4 inhibition studies. The double-inhibitor (clarithromycin+paroxetine) period was used to ensure a maximum drug interaction effect. In addition, as the secondary objective, we further evaluated the relationship between the two biomarkers and venlafaxine treatment outcomes (venlafaxine responses and adverse events), based on data from previous prospective patient studies.

Methods

Subjects

It was calculated that a minimum of ten individuals would be required to demonstrate a 30 % difference in venlafaxine area under the curve (AUC) at a level of significance of $p=0.05$ and power of 80 %. In this study, 12 individuals each for the *CYP2D6 extensive* and *intermediate metabolizers* (*EM* and *IM*) groups were enrolled after a screening of *CYP2D6* genotype (for alleles **1*, **2*, **5*, **10*, and **XN*) and a physical and laboratory examination. The *CYP2D6* genotype was *CYP2D6*1/*1* or **1/*2* in the *EM* group, and *CYP2D6*10/*10* in the *IM* group. The individuals' median age is 23 (range, 21–27) years; mean body mass index (BMI) is 22.5 (standard deviation, 2.2); the demographic parameters were not different between the two groups. From 2 weeks before the trial commencement, until the end of the entire clinical trial, all individuals were required to abstain from other drugs and nutritional supplements, and from tobacco, alcohol, caffeine, and grapefruit juice. The study was approved by the Institutional Review Board of National Institute of Food and Drug Safety Evaluation, Republic of Korea. A written informed consent was signed by each volunteer. The clinical trial was conducted in the Clinical Trial Center in Metro Hospital, Anyang, Republic of Korea. The Clinical Research Information Service (CRiS), Republic of Korea (a primary registry in the WHO Registry Network) identifier is KCT0000960.

Clinical trial

The study was a three-period, fixed-sequence, crossover clinical trial. All three periods had identical procedures except that the pretreatments were different. In the first period, the pretreatment was 250 mg clarithromycin (Abbott, Seoul, Republic of Korea) twice per day for 7 days; in the second (control) period, the pretreatment was omitted; in the third period, the pretreatment was 250 mg clarithromycin twice per day plus 10 mg paroxetine once a day (Handok, Seoul, Republic of Korea) for 7 days. In each period, on the sixth day of pretreatment (on first day in the control period), after an overnight fast, all individuals were administered a pretreatment drug at 7:00 AM and 1 h later, a single 75-mg dose of venlafaxine XR (Pfizer, Seoul, Republic of Korea) was administered with 240 ml water. Blood samples (10 ml) were collected in tubes containing sodium heparin before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h after venlafaxine administration. Plasma samples were stored at −80 °C until analysis. There was a 2-week washout after the first and the second periods. Vital signs and electrocardiograph were observed before, during, and after the sampling time, all adverse reactions were recorded.

Drug analysis

The plasma concentration of the active moieties: venlafaxine and its metabolites, and ODV were determined, by an ACQUITY UPLC/Xevo TQ MS/MS system (Waters Corp., USA). Briefly, 0.5 ml of plasma was spiked with 0.02 ml of verapamil (20 ng/ml) as an internal standard, alkalinized with 0.2 ml of 0.1 M NaOH and extracted with 3 ml of diethylether. After centrifugation (3,500×*g*, 4 °C, 10 min), the organic phase was evaporated to dryness at ambient temperature. The resulting residue was reconstituted in 0.1 ml of 85 % MeOH, and 10 μL was for injection. Chromatographic separation of the compounds was accomplished by an ACQUITY

UPLC BEH C18 Column (1.7 μm, 2.1×50 mm, Waters Corp., USA) and a mobile phase consisting of MeOH and 10 mM ammonium acetate (85:15, *v*/*v*) delivered at a flow rate of 0.2 ml/min. The MS positive mode was chosen. For venlafaxine, ODV, and verapamil, the precursor-to-product ion reactions were monitored; their mass to charge ratios were 278/58, 264/58, and 455/165, respectively. The lower limit of quantification for venlafaxine and ODV was 1 ng/ml. The inter-assay variation for all of the samples was less than 20 %. Each sample was analyzed in duplicate.

Pharmacokinetic analysis

The maximum plasma concentration (C_{max}) was derived directly from the plasma concentration versus time data. The area under the concentration time curve from time zero to infinity (AUC) and half-life ($t_{1/2}$) were estimated using the noncompartmental method of Phoenix WinNonlin 6.3 (Pharsight Corp., CA, USA).

Statistical analysis

All pharmacokinetic data were analyzed after log-transformation. Pharmacokinetic parameters were compared between the two genotypes from the same pretreatment period using an independent samples *t* test, or compared between two pretreatment periods in the same genotype group using paired samples *t* test. Mean and 95 % confidence interval (95 % CI) were used to describe the mean difference between two pretreatments. SPSS software 21.0 (SPSS Inc., IL, USA) was used for the statistical analysis. Differences were considered statistically significant at $p<0.05$.

Patients' data from two previous studies

Patients' data, including steady state venlafaxine and ODV concentrations, venlafaxine treatment outcomes (drug responses and adverse events), from two previous prospective studies were used for analysis. Data in the first patient study were directly cited from the publication (Veefkind et al. 2000). It was a cohort study of 33 adults with major depressive disorder who were under venlafaxine monotherapy for 7 weeks. Trough serum concentrations of venlafaxine and ODV were determined at steady state. Patients' responses were evaluated based on the Hamilton Depression rating scale (HAM-D 17-item): patients with a reduction of >50 %, ≤50 %, and ≥30; and <30 % from the baseline HAM-D score were classified as responder, partial-responder, and non-responder, respectively. The actual sample size we analyzed is 29; two (out of three) drop-outs with no concentration data and two patients with inconsistent ODV/venlafaxine were excluded. The other study was from the "Treatment of SSRI (selective serotonin reuptake inhibitor)-Resistant Depression in Adolescents" (TORDIA, the study was supported by NIMH Contract # MH61835 to the Western Psychiatric Institute and Clinic. The ClinicalTrials.gov identifier is NCT00018902). It is a multisite clinical trial in adolescents with depression, comparing the effectiveness of four randomly assigned different medication treatments, including one arm of 83 patients who were under venlafaxine monotherapy for at least 12 weeks. Plasma concentrations (not at same time points) of venlafaxine and ODV were determined at steady state. Patients' responses were based on the Clinical Global Improvement and Children's Depression Rating Scale-Revised. Venlafaxine-related (or possibly related) moderate to severe adverse events were counted. The predictive value or precision of the two biomarkers (venlafaxine+ODV and ODV/venlafaxine) for treatment outcomes (response or adverse event) is presented as the percentage (95 % CI) of true positive or negative tests, and calculated with the DAG STAT (Mackinnon 2000).

Results

Effects of *CYP2D6* genotype

The venlafaxine concentration time curves of the *CYP2D6 extensive metabolizers* (*IM*) and *intermediate metabolizers* (*IM*) were shown in Fig. 2, and the pharmacokinetic parameters of venlafaxine and *O*-desmethylvenlafaxine (ODV) were shown in Table 1; the mean (95 % CI) differences of those parameters between the *EM* and *IM* were shown in Table 2. After a single dose of 75 mg venlafaxine, the pharmacokinetics of venlafaxine were significantly different between the *EM* and *IM* in the control period; this difference became greater after the pretreatment of clarithromycin but diminished after the pretreatment of clarithromycin+paroxetine.

Effects of the clarithromycin and clarithromycin+paroxetine pretreatment

The geometric mean (95 % CI) differences of venlafaxine and ODV pharmacokinetic parameters between different pretreatment periods were shown in Table 2. Compared with the control pretreatment, the clarithromycin pretreatment moderately (by 30 %) increased venlafaxine exposure (AUC and C_{max}) in the *IM* group ($p<0.01$) but not in the *EM* group; however, the clarithromycin+paroxetine pretreatment greatly increased the venlafaxine exposure and decreased the ODV exposure in all individuals (all with $p<0.01$), especially in the *EM* group.

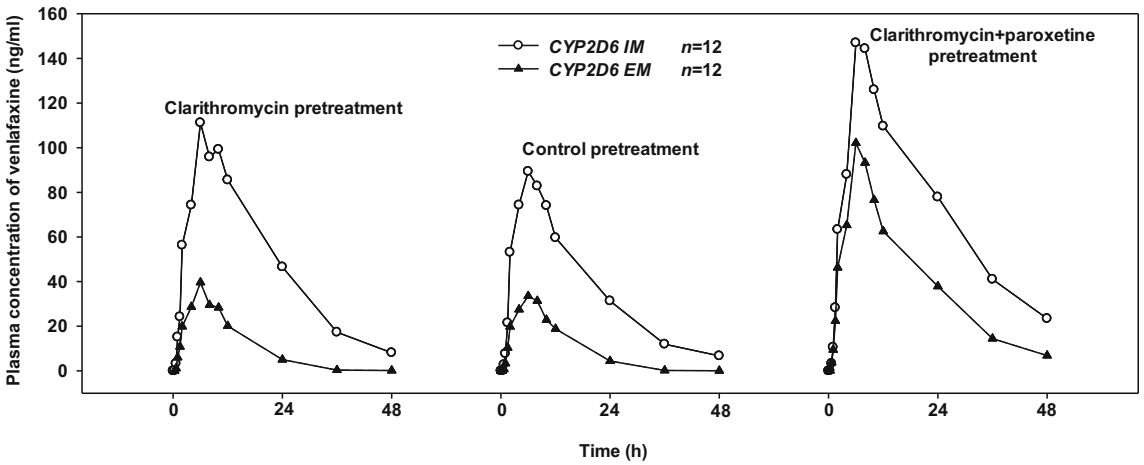

Fig. 2 Mean plasma concentration time curves of venlafaxine, following oral administration of a single dose of 75 mg venlafaxine after a pretreatment of control, or clarithromycin, or clarithromycin+paroxetine to 12 *CYP2D6 extensive metabolizers* (*EM*) and 12 *CYP2D6*10/*10 intermediate metabolizers* (*IM*)

ODV/venlafaxine and venlafaxine+ODV in relation to *CYP2D6* genotypes and drug interactions

The AUC and C_{max} of ODV/venlafaxine and venlafaxine+ODV were shown in Table 1, and their geometric mean (95 % CI) differences between the *EM* and *IM* groups, and between different pretreatment periods were shown in Table 2. (Because the biomarkers calculated using AUC and C_{max} showed similar differences, for simplicity, in the following text, we do not specify whether the venlafaxine+ODV and ODV/venlafaxine were calculated from AUC or C_{max}). The venlafaxine+ODV and ODV/venlafaxine from all individuals were displayed in Fig. 3, a and b, respectively. This shows that, in the control and clarithromycin period, ODV/venlafaxine well differentiated *IM* and *EM*, with a cutting-line crossing ODV/venlafaxine=1, but venlafaxine+ODV of *IM* and *EM* largely overlapped; ODV/venlafaxine changed more consistently in all individuals over different periods, in comparison with venlafaxine+ODV.

The 0–48-h plasma concentration of ODV/venlafaxine

Plasma concentration ratio of ODV/venlafaxine at each sampling time point within the first 12 h was calculated. Figure 4

Table 1 Pharmacokinetic parameters (presented as mean±SD) of venlafaxine and *O*-desmethylvenlafaxine

CYP2D6 genotype	Control pretreatment		Clarithromycin pretreatment		Clarithromycin+paroxetine pretreatment	
	EM (*n*=12)	*IM* (*n*=12)	*EM* (*n*=12)	*IM* (*n*=12)	*EM* (*n*=12)	*IM* (*n*=12)
Venlafaxine						
$AUC_{0-\infty}$ (ng h/ml)	463.7±216.4	1,837.8±1,011.1‡‡	500.1±248.9	2,417.3**±1,342.2‡‡	1,985.9**±1,156.9	4,113.0**±3,070.9
C_{max} (ng/ml)	34.4±11.5	91.3±30.0‡‡	39.7±12.3	117.9**±39.8‡‡	104.3**±33.7	151.8**±67.9
$t_{1/2}$ (h)	5.3±1.8	10.8±3.1‡‡	5.5±1.7	10.6±2.5‡‡	9.8**±3.3	14.4**±5.9
ODV						
$AUC_{0-\infty}$ (ng h/ml)	1,750.6±279.5	1,479.8±585.9	1,653.5±363.3	1,486.4±587.2	1,247.3**±287.2	1,162.6**±335.2
C_{max} (ng/ml)	70.8±12.7	46.5±12.1‡‡	66.7±12.1	44.1±9.5‡‡	36.0**±10.1	28.7**±8.4
$t_{1/2}$ (h)	12.2±1.9	15.7±4.8‡	12.5±3.1	16.1±5.1	15.1*±3.1	17.9±4.3
Venlafaxine+ODV						
$AUC_{0-\infty}$ (ng h/ml)	2,184.9±361.0	3,277.5±1427.4‡	2,129.6±465.8	3,852.3*±1785.1‡‡	3,248.3**±1054.5	5,288.5**±3215.8
C_{max} (ng/ml)	99.4±17.8	131.9±35.2‡‡	104.2±15.7	159.3**±41.5‡‡	132.5**±26.0	172.1**±67.9
ODV/venlafaxine						
$AUC_{0-\infty}$ (fold)	4.5±1.8	0.9±0.3‡‡	3.9*±1.7	0.7**±0.2‡‡	0.9**±0.5	0.4**±0.2‡
C_{max} (fold)	2.3±0.8	0.6±0.2‡‡	1.8**±0.6	0.4**±0.1‡‡	0.4**±0.2	0.2**±0.1‡

ODV O-desmethylvenlafaxine, *EM CYP2D6*1/*1* or **1/*2 extensive metabolizers*, *IM CYP2D6**10/*10 *intermediate metabolizers*

‡ $p<0.05$, ‡‡ $p<0.01$; statistically significant, detected by independent-samples *t* test; *$p<0.05$, **$p<0.01$; statistically significant, detected by paired-samples *t* test

Table 2 The geometric mean ratio (95 % CI) of venlafaxine and *O*-desmethylvenlafaxine pharmacokinetic parameters, when comparing between two *CYP2D6* genotype groups, or comparing between two different pretreatment periods

	IM (n=12) vs. *EM* (n=12)			Clarithromycin vs. control pretreatment		Clarithromycin+paroxetine vs. control pretreatment	
	Control pretreatment	Clarithromycin pretreatment	Clarithromycin+paroxetine control pretreatment	*EM* (n=12)	*IM* (n=12)	*EM* (n=12)	*IM* (n=12)
Venlafaxine							
$AUC_{0-\infty}$ (ng h/ml)	3.0 (1.8–5.1)	3.7 (2.1–6.6)	1.5 (0.8–2.7)	1.1 (0.9–1.3)	1.3 (1.2–1.5)	4.1 (3.5–4.7)	2.0 (1.7–2.4)
C_{max} (ng/ml)	2.3 (1.6–3.4)	2.5 (1.7–3.6)	1.3 (0.9–1.8)	1.2 (1.0–1.3)	1.3 (1.1–1.5)	3.1 (2.7–3.5)	1.6 (1.4–1.8)
$t_{1/2}$ (h)	1.8 (1.3–2.5)	1.8 (1.3–2.4)	1.3 (0.9–1.7)	1.1 (0.8–1.4)	1.0 (0.9–1.2)	1.9 (1.4–2.4)	1.3 (1.2–1.5)
ODV							
$AUC_{0-\infty}$ (ng h/ml)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.8 (0.6–1.1)	1.0 (0.9–1.1)	0.7 (0.6–0.8)	0.8 (0.7–0.9)
C_{max} (ng/ml)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.9 (0.7–1.3)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.5 (0.4–0.6)	0.6 (0.5–0.7)
$t_{1/2}$ (h)	1.3 (1.1–1.6)	1.2 (0.9–1.5)	1.2 (0.9–1.4)	0.9 (0.7–1.3)	1.0 (0.8–1.3)	1.2 (1.0–1.5)	1.2 (1.0–1.4)
Venlafaxine+ODV							
$AUC_{0-\infty}$ (ng h/ml)	1.4 (1.1–1.8)	1.7 (1.3–2.3)	1.5 (1.0–2.2)	1.0 (0.8–1.1)	1.2 (1.0–1.3)	1.4 (1.2–1.7)	1.5 (1.3–1.7)
C_{max} (ng/ml)	1.3 (1.1–1.6)	1.5 (1.2–1.8)	1.2 (1.0–1.6)	1.1 (0.9–1.2)	1.2 (1.1–1.4)	1.3 (1.2–1.5)	1.3 (1.1–1.4)
ODV/venlafaxine							
$AUC_{0-\infty}$ (fold)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.5 (0.3–0.9)	0.9 (0.8–1.0)	0.8 (0.7–0.8)	0.2 (0.1–0.2)	0.4 (0.3–0.5)
C_{max} (fold)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.6 (0.3–0.9)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.2 (0.1–0.2)	0.4 (0.3–0.5)

ODV O-desmethylvenlafaxine, *EM CYP2D6*1/*1* or **1/*2 extensive metabolizers*, *IM CYP2D6*10/*10 intermediate metabolizers*

shows that ODV/venlafaxine between 1.5 and 12 h remains relatively stable in all individuals. In both control and clarithromycin period, the *EM* and *IM* can be well differentiated by a cutting-line crossing ODV/venlafaxine=1, with only a few exceptions. But in the clarithromycin+paroxetine period, the ODV/venlafaxine decreased in all, especially in the *EM*; the *EM* and *IM* largely overlapped in the area of ODV/venlafaxine<1.

Concentration ratio of ODV/venlafaxine and concentration of venlafaxine+ODV

Two venlafaxine biomarkers: venlafaxine+ODV and ODV/venlafaxine, were defined as *Y* and *X* axes, respectively. Data from the 24 healthy volunteers were illustrated on a two-dimensional diagram in Fig. 5a. In addition, data from the 29 patients with major depressive disorder from the first

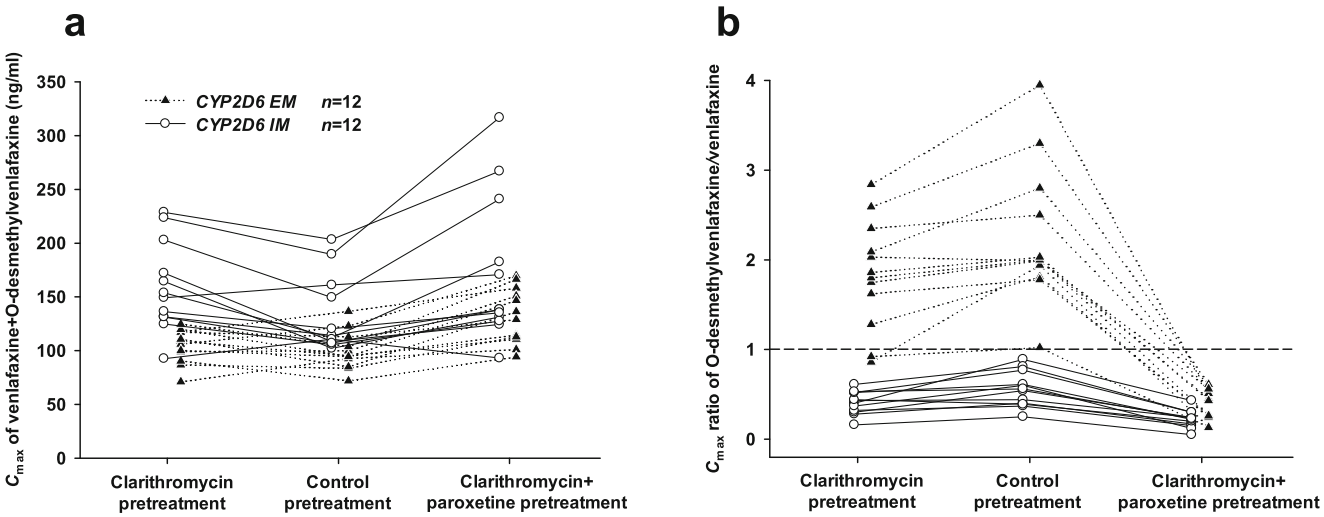

Fig. 3 **a** C_{max} of venlafaxine+*O*-desmethylvenlafaxine, **b** C_{max} ratio of *O*-desmethylvenlafaxine/venlafaxine, following oral administration of a single dose of 75 mg venlafaxine after a pretreatment of control, or clarithromycin, or clarithromycin+paroxetine to 12 *CYP2D6 extensive metabolizers* (*EM*) and 12 *CYP2D6*10/*10 intermediate metabolizers* (*IM*)

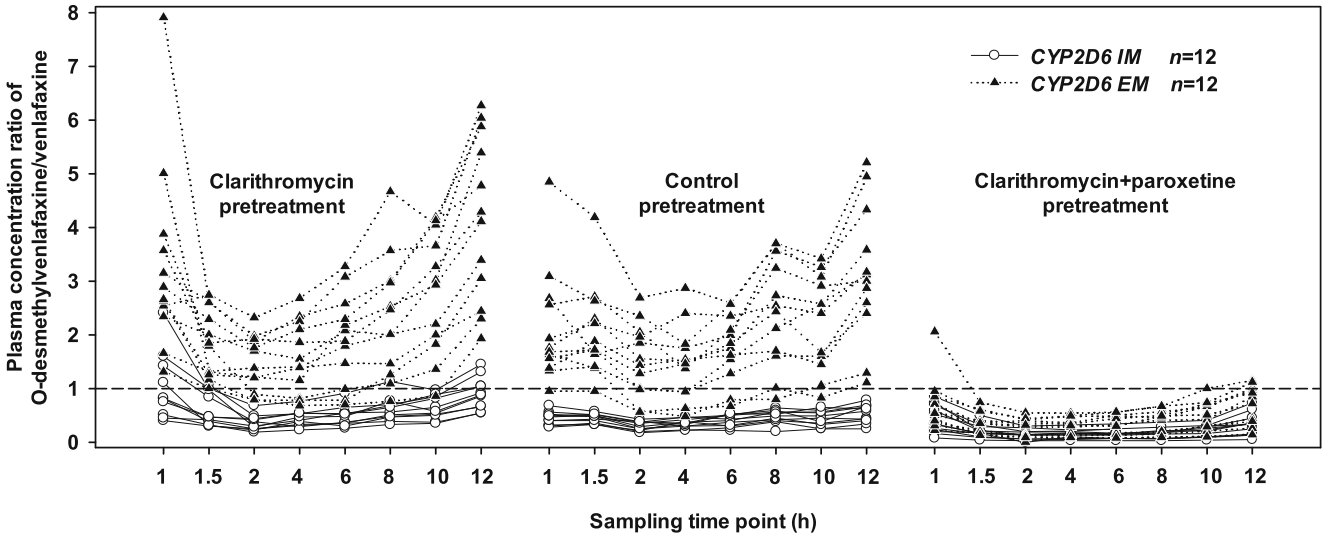

Fig. 4 Plasma concentration ratio of *O*-desmethylvenlafaxine/venlafaxine measured between 1 and 12 h, following oral administration of a single dose of 75 mg venlafaxine after a pretreatment of control, or clarithromycin, or clarithromycin+paroxetine to 12 *CYP2D6 extensive metabolizers* (*EM*) and 12 *CYP2D6*10/*10 intermediate metabolizers* (*IM*)

patient study were illustrated on another two-dimensional diagram in Fig. 5b. Data in both diagrams distribute in an L shape: Individuals with smaller ODV/venlafaxine showed wider range of venlafaxine+ODV; individuals with smaller venlafaxine+ODV showed wider range of ODV/venlafaxine. In the healthy volunteers, the *EM* and *IM* distributed in two separated areas in the control and clarithromycin periods, divided by a cutting-line crossing ODV/venlafaxine=1, but then all the *EM* shifted to the area of the *IM* in the clarithromycin+paroxetine period.

In the first patient study, venlafaxine responders/partial-responders and non-responders also distributed in two separated areas, divided by a cutting-line crossing ODV/venlafaxine =4. When using a value of ODV/venlafaxine >4 as a predictor for responders/partial-responders, the predictive value or precision (95 % CI) which is defined as true positive/negative to tested positive/negative was 92 % (65–99 %): Eleven out of 12 patients of ODV/venlafaxine >4 were responders/partial-responders; one was a drop-out. And when using a value of ODV/venlafaxine <4 as a predictor for non-

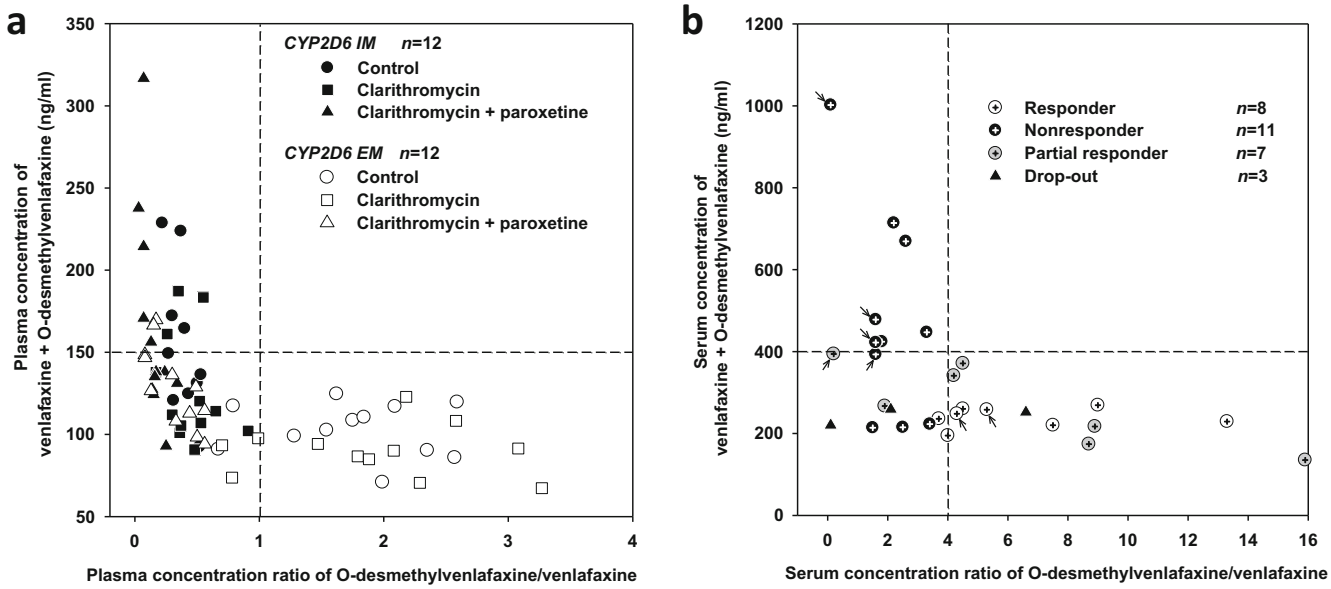

Fig. 5 The relationship between concentration of venlafaxine+*O*-desmethylvenlafaxine and concentration ratio of *O*-desmethylvenlafaxine/venlafaxine, **a** in 12 *CYP2D6 extensive metabolizers* (*EM*) and 12 *CYP2D6*10/*10 intermediate metabolizers* (*IM*), following oral administration of a single dose of 75 mg venlafaxine after a pretreatment of control, or clarithromycin, or clarithromycin+paroxetine, and **b** in 29 adult patients with major depressive disorder on steady state of 225 mg/day venlafaxine. *Arrows* are pointed at carriers of *CYP2D6*4* allele(s)

responders, the predictive precision (95 % CI) was 65 % (41–83 %): Eleven out of 17 patients of ODV/venlafaxine <4 were non-responder, but, when adding venlafaxine+ODV > 400 mg/ml as the second predictor, the predictive precision (95 % CI) increased to 100 % (65–100 %): All seven patients of ODV/venlafaxine <4 and venlafaxine+ODV >400 mg/ml were non-responders.

The plasma samples from the second patient study were not taken at the same time point after dosing, thus only the ODV/venlafaxine but not venlafaxine+ODV can be calculated. No relationship was found between ODV/venlafaxine and venlafaxine response (data were shown in supplementary Fig. 1). The relationship between ODV/venlafaxine and venlafaxine-related (or possibly related) moderate to severe adverse event was determined and shown in Fig. 6. Using a value of ODV/venlafaxine >4 as a predictor for patients free of such adverse events, the predictive precision (95 % CI) is 88 % (64–97 %): Fourteen out of 16 patients of ODV/venlafaxine >4 were free of these adverse events.

Discussion

Despite the ongoing prosperity of pharmacogenomic research, its implementation in clinical practice has been under debate and greatly inhibited by a lack of clinical evidence (Crews et al. 2012). Efforts must be made to bring pharmacogenomics research findings into clinical utility, and we hope this study will contributed in some small way to the clinical application of pharmacogenomics in patient care. In this study, we gained a few new insights: (1) In comparison with *CYP2D6 extensive metabolizers* (*EM*), *CYP2D6*10/*10 intermediate metabolizers* (*IM*) have significantly lower venlafaxine metabolism which may be comparable to *CYP2D6 poor metabolizers* (*PM*). (2) The concentration ratio of ODV/venlafaxine, measured in 1.5–12 h after a single oral dose of venlafaxine, may serve as a reliable assay for CYP2D6 phenotype. (3) The combination of the two biomarkers, the concentration ratio of ODV/venlafaxine, and the concentration sum of active moieties venlafaxine+SODV well predicts venlafaxine drug responses and adverse events retrospectively, warranting future clinical studies to verify their validity in guiding dose adjustment.

Our study design successfully produced venlafaxine pharmacokinetic variations in healthy volunteers by including two well-defined influencing factors: *CYP2D6* genotype and drug interaction. First of all, a significantly higher plasma exposure to venlafaxine was observed in the *CYP2D6*10/*10 IM* than in the *EM* in the control period. This pharmacokinetic difference was similar to that found between Japanese *IM* and *EM* (Fukuda et al. 1999), and between American *PM* and *EM* (Preskorn et al. 2009)—the geometric mean differences between the genotypes for AUC and C_{max} were 3.0- and 2.3-fold in our study; 4.8- and 1.8-fold in the Japanese study; and 3.3- and 1.5-fold in the American study, respectively. Although the three studies were independent from each other, they all used a single oral dose of 75 mg venlafaxine in healthy volunteers, and the differences between two genotypes were noted as geometric mean ratios (rather than absolute values); therefore, we are able to compare the results among the three studies. In the Japanese study, both *CYP2D6*5/*10* and **10/*10* genotypes were included into the *IM* group; in East Asia (China, Japan, Korea, etc.), around 20 % people have *CYP2D6*10/*

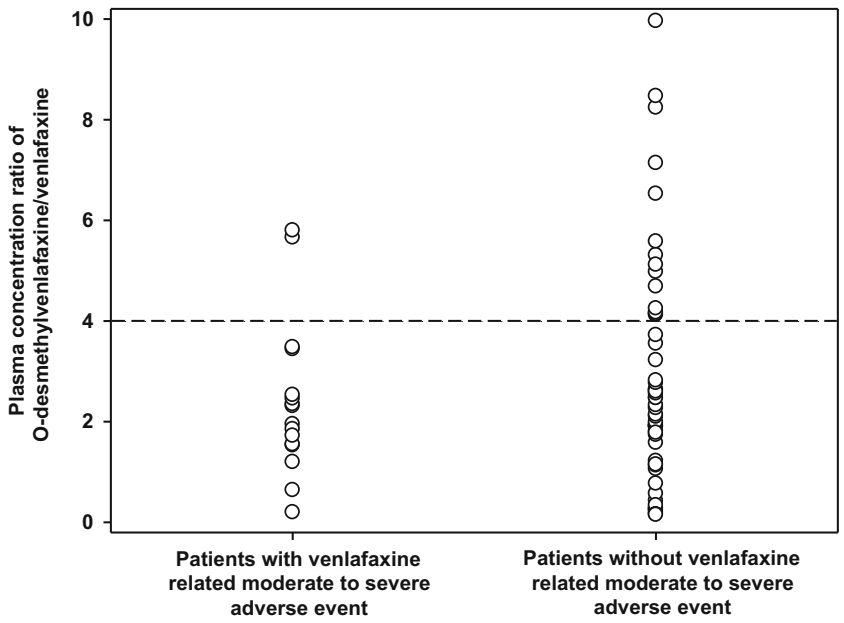

Fig. 6 The relationship between concentration ratio of *O*-desmethylvenlafaxine/venlafaxine and venlafaxine related (or possibly related) moderate to severe adverse events, in 68 adolescent patients with major depressive disorder on steady state of 150 or 225 mg/day venlafaxine

**10 IM* genotype, and 5 % people have *CYP2D6*5/*10 IM* genotype; only less than 1 % people have *PM* genotypes (Myrand et al. 2008); hence, *PM* were not included by our clinical trial. Second of all, a strong inhibition on CYP3A4 (by clarithromycin) did not cause any meaningful venlafaxine pharmacokinetic change in the *EM* but caused a moderate (around 30 %) increase of venlafaxine exposure (AUC and C_{max}) in the *IM*, which suggests that *IM*, compared with *EM*, may rely more on CYP3A4 for venlafaxine metabolism, due to their lower CYP2D6 activity. Our study was in agreement with two previous CYP3A4 inhibition studies on venlafaxine (Hynninen et al. 2008; Lindh et al. 2003). Third of all, a strong inhibition on both CYP2D6 and CYP3A4 (by clarithromycin + paroxetine) dramatically changed the pharmacokinetic profile of the *EM*, which then looked similar to that of the *IM* in the control period (Table 1 and Fig. 2). In a recent study among 900 patients with major depressive disorder treated with venlafaxine, 243 patients were classified as PM phenotype (ODV/venlafaxine <1), but only 34/243 of them turned out to be genetic *PM*. The fact that more individuals of PM were non-genetic *PM* was explained by two major reasons: (1) 60 % of the patients with *IM* genotypes manifested a PM phenotype; (2) those non-genetic *PM* patients who co-administered CYP2D6 substrates/inhibitors demonstrated decreased CYP2D6 activity which was close to PM (Preskorn et al. 2013). Both causes for the CYP2D6 genotype–phenotype discrepancies were confirmed by our study: The significantly lower venlafaxine metabolism observed in *CYP2D6*10/*10 IM* relative to *EM* were similar to that observed in *PM* relative to *EM*; and co-administration of CYP2D6 inhibitor (but not CYP3A4 inhibitor) can cause phenoconversion in *EM*.

Because *CYP2D6* genotype and drug interaction successfully produced venlafaxine pharmacokinetic variations, we assume a biomarker that can well indicate these two factors may also be useful to indicate other influencing factors for venlafaxine pharmacokinetics. Therefore, we examined the two biomarkers (venlafaxine+ODV and ODV/venlafaxine) in all individuals in relation to the two influencing factors. In this study, ODV/venlafaxine was more sensitive than venlafaxine+ODV in differentiating between the *EM* and *IM*—except in the clarithromycin+paroxetine period, when venlafaxine metabolism was severely inhibited in all individuals—and ODV/venlafaxine also showed more consistent change than venlafaxine+ODV following the two pretreatments in all individuals (Fig. 3). We compared our ODV/venlafaxine value with previous studies (Preskorn 2010; Preskorn et al. 2013), and while in our study, in the control period, all the *EM* had ODV/venlafaxine >1, and all the *IM* had ODV/venlafaxine <1; however, previously, ODV/venlafaxine <1 was defined as PM phenotype (Preskorn 2010). This finding once again suggests that it may be more appropriate to classify *CYP2D6*10/*10* individuals as PM—it should be noted that the current CYP2D6 phenotyping based on ODV/venlafaxine only differentiates between EM and PM, but does not differentiate other phenotypes such as IM and UM. Considering 3–4 % of the 1.5 billion people in East Asia are diagnosed with major depressive disorder (Andrade et al. 2003; Gu et al. 2013; Ohayon and Hong 2006), we estimate that around one million patients with major depressive disorder have *CYP2D6*10/*10* genotype (not including other *IM* genotypes such as *CYP2D6*5/*10*), which implies an enormous potential for individualized venlafaxine treatment. Notably, the concentration ratio of ODV/venlafaxine determined between 1.5 and 12 h after a single oral dose of venlafaxine may serve as a useful indicator for CYP2D6 activity (it differentiates CYP2D6 activity in a categorical manner, e.g., ODV/VEN >1 and ODV/VEN <1), because it remains relatively stable over time and well differentiated between *IM* and *EM* genotypes, and is also sensitive to CYP2D6 but not 3A4 inhibition.

Subsequently, the relationship between the two biomarkers (venlafaxine+ODV and ODV/venlafaxine) was illustrated in both healthy volunteers and patients on a two-dimensional diagram with these two biomarkers as the *X* and *Y* axes, respectively (Fig. 5). The very similar L-shaped distribution seen in both healthy volunteers and patients suggests that the relationship between the two biomarkers remains stable and independent of venlafaxine dose regimens. The L shape can be divided into two parts, by a cutting-line crossing the ODV/venlafaxine axis: In the healthy volunteers, this method is efficient in dividing the different *CYP2D6* genotypes (except after the pretreatment of CYP2D6+CYP3A4 inhibitors); however, in the patients, this process is only efficient for dividing different venlafaxine responses but not for dividing the patients' *CYP2D6* genotypes—as mentioned previously, patients' CYP2D6 phenotypes can deviate greatly from their actual genotypes. In the patient studies, ODV/venlafaxine >4 showed high predictive precision (92 %) for responder/partial-responders (first patient study) and also for patients free of venlafaxine-related adverse events (second patient study), although all non-responders had ODV/venlafaxine <4, but a few responders/partial-responders also had ODV/venlafaxine <4; however, by further referring to their venlafaxine+ODV value, we devised improved predictive precision (100 %) for non-responders (first patient study). In the second patient study, we did not analyze venlafaxine+ODV due to the inconsistent dosing-sampling intervals; therefore, we were unable to discern if venlafaxine+ODV can also improve the prediction of venlafaxine adverse effects for those with ODV/venlafaxine <4. There are a few things to be noted: (1) in the second patient study, no relationship was found between ODV/venlafaxine and venlafaxine responses, probably because all patients in this study were SSRI-resistant adolescents and their responses to venlafaxine may have been controlled by other factors than pharmacokinetics. It has been reported

that polymorphisms in *FKBP5*, *SLC6A4* and *HTR2A* genes, etc., could alter patients' responses to venlafaxine (Kirchheiner et al. 2008; Lohoff et al. 2013), but, as yet, none have been confirmed in these patients (Brent et al. 2010); (2) other than the different venlafaxine+ODV range owing to differing doses used in our study and the first patient study, the ODV/venlafaxine range was also different: It was 0–4 in our study, but four times wider (0–16) in the first patient study. Since CYP2D6 is not inducible, this difference is likely caused by different dose regimens as well, which needs further study to prove; (3) not only the ODV/venlafaxine range differed but also the cutting-lines were four times different: which are ODV/venlafaxine =1 in our study and ODV/venlafaxine =4 in the first patient study; it seems that there exists a discrepancy between a theoretical and a clinically meaningful classification of CYP2D6 phenotype; in addition, although ODV/venlafaxine >4 alone could well indicate venlafaxine responders, when it was used together with venlafaxine+ODV, it showed higher predictive precision for non-responders. The above two reasons may partly explain why in the previous study ODV/venlafaxine >1 did not have enough power to predict venlafaxine responses (Lobello et al. 2010); maybe using the value of ODV/venlafaxine >4 instead of ODV/venlafaxine >1 and including venlafaxine+ODV information could improve the prediction; we wanted to review the data of the study but were unable to contact the authors.

Since both venlafaxine and ODV are active antidepressants, it seems logical to assume that a higher concentration of venlafaxine+ODV is likely lead to a better drug response, but this assumption has been proven false by previous studies (Lobello et al. 2010; Sakolsky et al. 2011). On the contrary, PM patients who tend to have a higher concentration of venlafaxine+ODV than EM patients are actually at higher risk of being non-responders (Lobello et al. 2010). Preskorn et al. mentioned: "CYP2D6 poor metabolizers, for as yet unknown reasons, are less responsive to antidepressants such as venlafaxine" (Macaluso and Preskorn 2011). Although there is no clear explanation, a few recent studies have suggested that both venlafaxine and ODV are P-glycoprotein substrates (Karlsson et al. 2010). But, only venlafaxine, not ODV, is able to induce P-glycoprotein on the blood–brain barrier, and the induction occurs several days after venlafaxine administration. These results could explain why earlier responders (those who responded within 14 days) had higher plasma concentration of venlafaxine+ODV (Bachmeier et al. 2011). We speculate that a higher venlafaxine concentration may induce more active moieties pumping out of the blood–brain barrier thus less of the drug remaining in the brain, which may eventually lead to a poorer venlafaxine response.

Our study has a few limitations: (1) It focused on factors that influence venlafaxine treatment outcomes through impacting its pharmacokinetics, and therefore, the biomarkers may not give good prediction if a factor (e.g., variation in drug receptors, receiving cognitive behavioral therapy, etc.) influences venlafaxine treatment outcomes without changing its pharmacokinetics; (2) the relationship between the two biomarkers with venlafaxine treatment outcomes was evaluated retrospectively only; we emphasize that our study was preliminary, and the actual utilization of the two biomarkers for predicting venlafaxine treatment outcomes should be considered only after further confirmation by fully powered prospective studies in patients with major depressive disorder; (3) our study in healthy volunteers only used a single dose of venlafaxine, but the biomarkers proposed for prediction were from multiple-dose studies; therefore, it would be interesting to find out the relationship of these biomarkers between a single-dose and a multiple-dose study, because making a prediction using a single dose venlafaxine will be more valuable than after taking multiple doses.

In general, our study provides experience in exploring biomarkers for drug treatment outcomes, first by using a small sample-size clinical trial in healthy volunteers, and further by evaluating biomarkers using previous studies. There is growing support that high level of evidence can also be obtained from prospective retrospective such as this current study (Patterson et al. 2011). Prior to adopting pharmacogenomics knowledge into clinical practice, it is very important to consider any discrepancy between a molecule's (e.g., CYP2D6) phenotype and genotype, and discrepancy between a molecule's theoretical and clinically meaningful classification (e.g., the current classification of CYP2D6 PM and EM does not well correlate with venlafaxine treatment outcomes, but our modified classification of CYP2D6 activity was more successful). Finally, we anticipate the rule we proposed—ODV/venlafaxine >4 predicts a favorable response and adverse events profile of venlafaxine, and ODV/venlafaxine <4 plus venlafaxine+ODV > 400 ng/ml predicts a poor response of venlafaxine—may serve as a reference in future prospective patient studies for individualized venlafaxine therapy.

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Conflicts of interest The authors declare no conflicts of interest.

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