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Pharmacokinetic-Pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder with history of citalopram / escitalopram treatment failure

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Abstract

Background: The purpose of this study was to identify specific pharmacokinetic (PK) and pharmacodynamics (PD) factors that affect the likelihood of treatment remission with a serotonin norepinephrine reuptake inhibitor (SNRI) in depressed patients whose initial selective serotonin reuptake inhibitor (SSRI) failed.

Methods: Multiple logistic regression modeling of PK and PD variation hypothesized to contribute to SNRI (i.e. duloxetine or venlafaxine) treatment remission in prior SSRI (i.e.

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Contributors

Dr Ahmed, Dr. Frye conceptualized the hypothesis, created the analytic plan, supervised the data analysis, interpreted the results, and drafted the manuscript. Dr Ahmed and Dr. Frye also had access to all data and take responsibility for the accuracy of the data analysis. Dr Ahmed preformed the literature search. Dr. Biernacka and Mr. Jenkins and Dr Ahmed performed the data analysis and interpreted the results. All authors contributed to and approve of the final manuscript.

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Supplementary materials

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citalopram or escitalopram) failure was conducted on 139 subjects from the Pharmacogenomics Research Network (PGRN) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) studies. Depressive symptoms were assessed with the Quick Inventory of Depressive Symptomatology Clinician-rated (QIDS-C_{16}).

Results: Venlafaxine-XR remission was associated with a significant interaction between *CYP2D6* ultra-rapid metabolizer (*URM*) phenotype *and SLC6A4 5-HTTLPR L/L* genotype. A similar significant interaction effect was observed between *CYP2D6 URM and SLC6A2 G1287A GA genotype*. Stratifying by transporter genotypes, venlafaxine-XR remission was associated with *CYP2D6 URM* in patients with *SLC6A4 L/L* ($p = 0.001$) and *SLC6A2 G1287A GA* genotypes.

Limitations: The primary limitation of this post hoc study was small sample size.

Conclusion: Our results suggest that *CYP2D6* ultra-rapid metabolizer status contributes to venlafaxine-XR treatment remission in MDD patients; in particular, there is a PK-PD interaction with treatment remission associated with *CYP2D6 URM* phenotype and *SLC6A4 5-HTTLPR* L/L or *SLC6A2 G1287A G/A* genotype, respectively. These preliminary data are encouraging and support larger pharmacogenomics studies differentiating treatment response to mechanistically different antidepressants in addition to further PK-PD interactive analyses.

Keywords

Venlafaxine-XR; Remission; CYP2D6; SLC6A4; SLC6A2; Pharmacodynamic-pharmacokinetic; interaction

1. Introduction

The World Health Organization (WHO) has ranked depression as the leading cause of medical disability worldwide with an estimated 300 million people living with depression (World Health Organization). In the US, major depressive disorder (MDD) is the leading cause of disability in young people age 15–44 (National Institute Mental Health). While selective serotonin reuptake inhibitors (SSRIs) are considered first line treatment for MDD (Nassan et al., 2016). Only 50% of these patients will respond to initial treatment with SSRIs, and even fewer (~ 30%) patients achieve remission (Sinyor et al., 2010; Connolly and Thase, 2011). Step-wise treatment trials after SSRI non-remission have shown variable response rates when switching to a second SSRI (Joffe et al., 1996; Thase et al., 1997; Thase et al., 2001), to any non-SSRI antidepressant (Fava et al., 2001; Fava et al., 2003a; 2003b), or to a serotonin noradrenergic reuptake inhibitor (SNRI) (de Montigny et al., 1999; Nierenberg et al., 1994; Saiz-Ruiz et al., 2002). A clinical strategy often employed in the setting of SSRI nonresponse is to shift to a second antidepressant with a different mechanism of action. For example, in a study of depressed patients, for whom the majority (65%) failed initial treatment with an SSRI, response and remission rates were significantly higher when patients were subsequently randomized to the SNRI venlafaxine vs a 2nd SSRI paroxetine (Poirier and Boyer, 1999), though other studies do not agree (Rush et al., 2006).

It is increasingly recognized that genetic factors may contribute to inter-individual differences in the overall risk (i.e. side effects) / benefit (i.e. response / remission rate) ratio of antidepressant treatment (Ahmed et al., 2018). Relevant genetic factors include both

pharmacokinetic (PK) variation that impacts drug metabolism (i.e. active metabolite) and pharmacodynamic (PD) variation that impacts drug action at the cellular level (Nassan et al., 2016). Several previously published reports have shown that PK (i.e. cytochrome (*CYP*) *2D6* and *2C19*) genetic variation is associated with variation in clinical response to SSRI's (Mrazek et al., 2011; Tsai et al., 2010; Gressier et al., 2015). While there is a suggestion that PD genetic variation in the gene encoding the serotonin transporter (*SLC6A4*) *5-HTTLPR* is associated with MDD (Caspi et al., 2003), there is a larger evidence base that the *S/S* genotype genetic variation is associated with greater antidepressant side effect burden, including antidepressant-induced mania (Frye et al., 2015) and lower treatment response rate than *S/L* and *L/L* genotype (Caspi et al., 2003; Murphy et al., 2004; Yu et al., 2002; Mrazek et al., 2009). Similarly, polymorphisms in the gene encoding for the norepinephrine transporter (*NET*) (*SLC6A2*) *T-182C* and *G1287A* have been associated with major depression (Inoue et al., 2004; Hahn et al., 2008), but also with decreased SNRI treatment response (*T-182C allele*) and slower onset of treatment response (*G1287A A/A* genotype) (Yoshida et al., 2004).

Interaction between pharmacokinetic (PK) and pharmacodynamics (PD) genetic factors (i.e. *CYP2D6* and serotonin transporter *5-HTTLPR*) and their relationship to treatment response have not been well studied, but they may be of greater value in predicting symptom burden and/or treatment outcome than either genetic factor alone (Suzuki et al., 2006). PK genetic variation contributes to a variable concentration of drug at the site of action, whereas PD genetic variation contributes to a variable quantity or ability of transporter protein to interact with these drugs; therefore, a PK-PD genetic variation interaction may be a meaningful analysis to apply when investigating clinical outcomes.

This study investigated the association between genetic polymorphisms in pharmacokinetic (*CYP2D6, CYP2C19*), and pharmacodynamic [*SLC6A4, SLC6A2* (*NET*)] genes and treatment remission with SNRIs (duloxetine and venlafaxine-XR) in patients with MDD. This study utilized data from two clinical trials (Mrazek et al., 2014; Rush et al., 2006) of SNRIs in patients with MDD who had previously failed prospective treatment with an SSRI. The questions addressed were: (1) does PK genetic variation in *CYP2D6 and CYP2C19* predict SNRI remission, (2) does PD genetic variation in serotonin and norepinephrine transporters (i.e. *SLC6A4* and *SLC6A2*) predict SNRI remission, (3) and does a PK (i.e. *CYP2D6* and *CYP2C19* metabolizer status) PD (i.e.*SLC6A4* and *SLC6A2* genetic variation) interaction predict SNRI remission?

2. Methods

2.1. Patient identification and recruitment

Data sources for these analyses include two clinical trials: the Pharmacogenomic Research Network (PGRN) Antidepressant Medication Pharmacogenomics Study (AMPS) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2006). The PGRN study was an 8-week open label clinical trial which enrolled 800 patients over 4 years who were treated with either citalopram or escitalopram. Patients who did not achieve remission over the course of 8 weeks of treatment were offered subsequent treatment with the SNRI duloxetine (n = 145, mean dose=53.3 mg/day) with enrollment over 2 years.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Level 1 was a 12-week open label randomized clinical trial which enrolled 1475 patients to receive citalopram over 3 years. Patients who did not achieve remission at 12 weeks entered Level 2 and were subsequently offered a number of augmentation and switch strategies including the SNRI venlafaxine-XR. The enrollment (N=250) for venlafaxine-XR (mean dose=193.6 mg/day) treatment occurred over 3 years. Both study designs and timelines are depicted in Fig. 1. Given known genetic variation by race and ethnicity, this analysis was conducted on Caucasian patients only [PGRN (N=79) and STAR*D (N=92)].

2.2. Gene selection

We first focused on metabolizer phenotypes for *CYP2D6* and *CYP2C19* which included: poor metabolizer (*PM*), intermediate metabolizer (*IM*), extensive metabolizer (*EM*) and ultra-rapid metabolizer (*URM*). Duloxetine is mainly metabolized to active metabolites (i.e. 4-OH, 5-OH and 6-OH duloxetine) by *CYP2D6* and *CYP1A2*, while venlafaxine-XR is predominately metabolized by *CYP2D6* and partially by *CYP2C19* to an active metabolite O-desmethylvenlafaxine (ODV) (Gaedigk, 2013). Pharmacodynamically, the initial mechanism of action (MOA) of an SSRI or an SNRI is to block serotonin and norepinephrine reuptake transporters. Therefore, we also investigated allelic variation for *SLC6A4, 5-HTTLPR* (*S/S*, *L/S* and *L/L* genotypes), *SLC6A4 5-HTVNTR (12/12, [9/12, 9/10, 10/12]* and 10/10), *SIC6A2 G1287A* (*A/A, G/A* and *G/G* genotypes), and *SIC6A2 T182C* (*C/C*, *T/C* and *T/T* genotypes) (Caspi et al., 2003; Inoue et al., 2004; Hahn et al., 2008; Lesch, 2001). For the PK investigation, 47/79 (PGRN) and 90/92 (STAR*D) samples were genotyped. For the PD investigation, 77/79 (PGRN) and 90/92 (STAR*D) samples were available for genotyped.

2.3. Statistical analysis

Fig. 1 shows that 57 Caucasian patients completed the entire study duration of 8 weeks with duloxetine (PGRN) and 82 Caucasian patients completed 8 weeks of the 12 week study duration with venlafaxine-XR (STAR*D). There were participants who were genotyped but never started medication (PGRN $n = 1$, STAR*D $n = 6$) and participants who were genotyped, but dropped out after starting the medication for either inefficacy or side effects (PGRN $n = 21$, STAR D $n = 4$);a secondary intent to treat analysis was attempted by adding the 4 subjects from STAR*D trial to completers analysis.

Remission, defined as QIDS-$C_{16} \leq 5$ at week 8, was the primary outcome measure for both the STAR*D and PGRN clinical trials (Rush et al., 2006; Mrazek et al., 2014) and was used as the primary outcome measure for this pharmacogenomic analysis. Using Chi-square test or Fisher's exact test (if expected frequencies were small), the metabolizer status of *CYP2D6* and *CYP2C19*, as well as the genetic variants *SLC6A4 5-HTTLPR*, *SLC6A4 5-HTVNTR*, *SLC6A2 G1287A*, and *SLC6A2 T182C* were compared between patients who achieved remission vs patients who did not. Multiple genetic variants and metabolizer status factors were tested concurrently for their association with remission in multiple logistic regression models. To evaluate the effects of metabolizer status of *CYP2D6* or *CYP2C19*, separate models were constructed treating metabolizer status as ordinal (tested via a 1df test) and not ordinal (tested via a 2df test). Separate logistic regression models were used to test pairwise

interactions between the effects of metabolizer status and SNPs in PD genes with respect to remission.

A fixed effects model of meta-analysis was performed using the estimates/SE of estimates from both studies for SNPs/metabolizer status modeled univariately versus remission. Pooled odds ratios and 95% confidence intervals are presented for each predictor. To assess heterogeneity across the two studies, we used the I^2 statistic (Higgins et al., 2003). Statistical analysis was performed using IBM SPSS Statistics version 22.0 (Armonk, NY: IBM Corp.) or STATA version 14 (StataCorp LP, College Station, Texas).

3. Results

As presented in Table 1, the only significant demographic difference between the two study groups was rate of employment (PGRN=81% vs. STAR*D=60%, p-value=0.009).

3.1. CYP2D6 / CYP2C19 metabolizers and SLC6A4 / SLC6A2 genotypes

Venlafaxine-XR remission was associated with *CYP2D6* metabolism phenotype ($p = 0.027$). Specifically, remission rates were higher among *URM* ($n = 5$, 71.4%) in comparison to *CYP2D6 PM* ($n = 1$, 10%). Assuming a linear effect of *CYP2D6* metabolizer status on venlafaxine-XR remission, (i.e., increasing level of metabolism: *PM*, *IM/EM* and *URM*), higher metabolism was associated with greater odds of remission (OR = 4.72, $p = 0.018$) (Table 2 and Fig. 2). An intent to treat analysis did not change the significance of phenotype and remission. We found no significant difference in duloxetine remission rates by *CYP2D6* metabolism phenotype. Moreover, we found no significant differences in venlafaxine-XR or duloxetine remission rates by *CYP2C19*, *SLC6A4 5-HTTLPR*, *SLC6A4 5-HTTVNTR, and* by *SLC6A2 G1287A* genotypes (Table 2)

3.2. Pharmacokinetic-pharmacodynamic interaction and SNRI remission

Venlafaxine-XR remission was associated with an interaction between *SLC6A4 5-HTTLPR* and *CYP2D6*, when *URM* were compared with *IM/EMs* ($p = 0.021$). A similar interaction effect on remission was observed between *CYP2D6 URM* and *SIC6A2 G1287A* ($p = 0.021$). Post-hoc analysis of venlafaxine-XR remission stratified by *SLC6A4 5-HTTLPR* genotypes showed that remission was associated with *CYP2D6* metabolizer status in *L/L* genotype carriers ($p = 0.001$), while, analysis stratified by *SLC6A2 G1287A* also revealed an association between *CYP2D6* and remission in patients with the *GA* genotype at *SLC6A2 G1287A* ($p = 0.015$) (Fig. 3a, b). These stratified analyses suggested that *CYP2D6 URM* (i.e. those metabolizing more venlafaxine-XR to the active metabolite O-desmethylvenlafaxine) had a higher rate of remission, especially in patients with *SLC6A4 5-HTTLPR L/L* or *SLC6A2 G1287A G/A* genotype.

3.3. Meta-analysis

In the meta-analysis across the two studies, *CYP2D6 URM* was significantly associated ($p = 0.023$) with greater odds of SNRIs remis-sion (OR = 3.9; $I^2 = 0.0$). None of the other genetic variations were associated with SNRI remission in meta-analyses combining the two studies.

4. Discussion

This is one of the first studies to investigate the association between prospectively confirmed SNRI treatment remission and genetic polymorphisms in *CYP2D6, CYP2C19, SLC6A4*, and *SLC6A2* in MDD patients with prospectively confirmed prior SSRI treatment failure. In this study, venlafaxine-XR remission rate was significantly higher in patients with the *CYP2D6 URM* phenotype. Among patients with the *SLC6A4 5-HTTLPR L/L* or *SLC6A2 G1287A G/A* genotypes, those with the *CYP2D6 URM* phenotype were more likely to achieve remission with venlafaxine-XR in comparison with those with *IM/EM* phenotypes or *PM* phenotypes.

We found that the *CYP2D6 URM* phenotype was associated with greater odds of venlafaxine-XR remission (i.e. increasing level of metabolism from *PM* to *IM/EM* to *URM*). Patients with the URM phenotype were more likely to achieve remission with venlafaxine-XR than those with the *IM/EM* or *PM* phenotype. Similarly, Lobello and colleagues showed that patients with the *EM* phenotype (i.e. "normal" metabolism), in comparison to the *PM* phenotype, had significantly higher response and remission rates when treated with venlafaxine-XR (Lobello et al., 2010). Unlike our study, Lobello and colleagues did not test *URM* phenotype in comparison to *EM phenotype*.

To our knowledge, this is the first PK-PD interaction associated with venlafaxine-XR treatment remission. Among patients with the *SLC6A4 5-HTTLPR* L/L genotype, those with the *CYP2D6 URM* phenotype were more likely to achieve remission with venlafaxine-XR in comparison to those with *IM/EM* or *PM* phenotypes. Secondly, patients with the combination of the *CYP2D6 URM* phenotype and *SLC6A2 G1287A G/A* genotype were more likely to achieve remission with venlafaxine-XR in comparison to the *IM/EM* or *PM* phenotype. There is less systematic research on the *SLC6A2 G1287A* and *T182C* polymorphisms and pharmacogenomic treatment response in comparison to the well-studied serotonin transporter. Ueda and colleagues, however, found a relationship between the volume of the dorsolateral prefrontal cortex and the *SLC6A2 G1287A* polymorphism in MDD patients, suggesting an area for future research on disease risk (Ueda et al., 2016). Minn and colleagues (2009) investigated the PD-PD interaction between *SLC6A2-T182C* and the serotonin transporter in patients with major depression ($n = 579$) and reported that patients with the combination of *SLC6A2-T182C C/C* and *5-HTTLPR S/S* genotypes ($n = 16$) had a significantly lower symptom burden of depression in comparison with patients who were *T*-allele carriers and L-allele carriers respectively ($n = 247$). In contrast, patients with the *5-HTTLPR L/L* and *VNTR 12/12* genotypes ($n = 21$) had a better clinical response to SSRIs treatment in comparison to *S*-carriers and *10*-repeat allele carriers respectively ($n = 31$) (Min et al., 2009).

Our findings if replicated will have important practical implications. Reliable and valid biological markers that could inform clinical practice with regard to when one should bypass first line treatment with SSRIs for SNRIs as a treatment intervention would have clinical value. This potential biomarker would be an additional factor for inclusion in clinical decision support guidelines, in addition to subtypes of depression (i.e. pain conditions such as fibromyalgia, neuropathy, and musculoskeletal) known to respond to SNRIs.

The primary limitation of this post hoc study was small sample size. That is the main reason that we did not pursue a genome wide association study. Moreover, our multiple stratified analyses were not corrected for multiple testing. While the intent to treat analyses did not differ from the completer analysis, the small sample size, again, may limit the conclusions from these statistical analyses. Additional limitations focus on trial design. While the rating scales and scheduled research visits were the same, the longer 12-week STAR*D trial allowed for a slower titration of study drug in comparison to the shorter 8-week PGRN trial; the maximum dose of venlafaxine-XR was reached at week 8 while the maximum dose for duloxetine was reached by week 4. Moreover, the STAR*D study subjects immediately received SNRI treatment after SSRI treatment failure, whereas the time of receiving SNRIs treatment in the PGRN study subjects varied.

Providing greater precision for antidepressant recommendations for individual patients beyond the large-scale, clinical trials evidence base can potentially reduce side effect toxicity profiles and increase response rates and overall effectiveness. These results underscore the multidimensional aspects of precision medicine as an approach to optimize drug treatment of MDD.

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Dr. Rush is named as co-inventor on two patents: (1) U.S. Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson

AS. (2) U.S. Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S.

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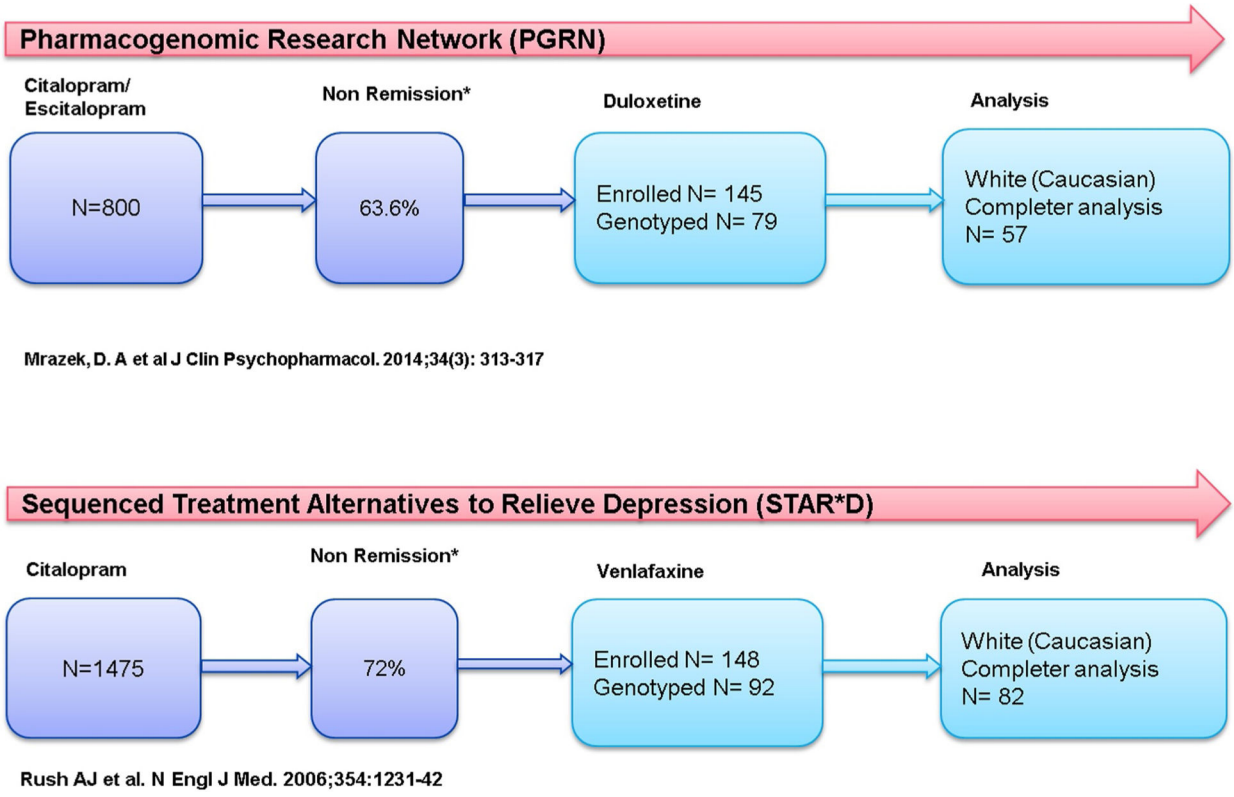

Fig. 1.
Study and patient enrollment timeline.

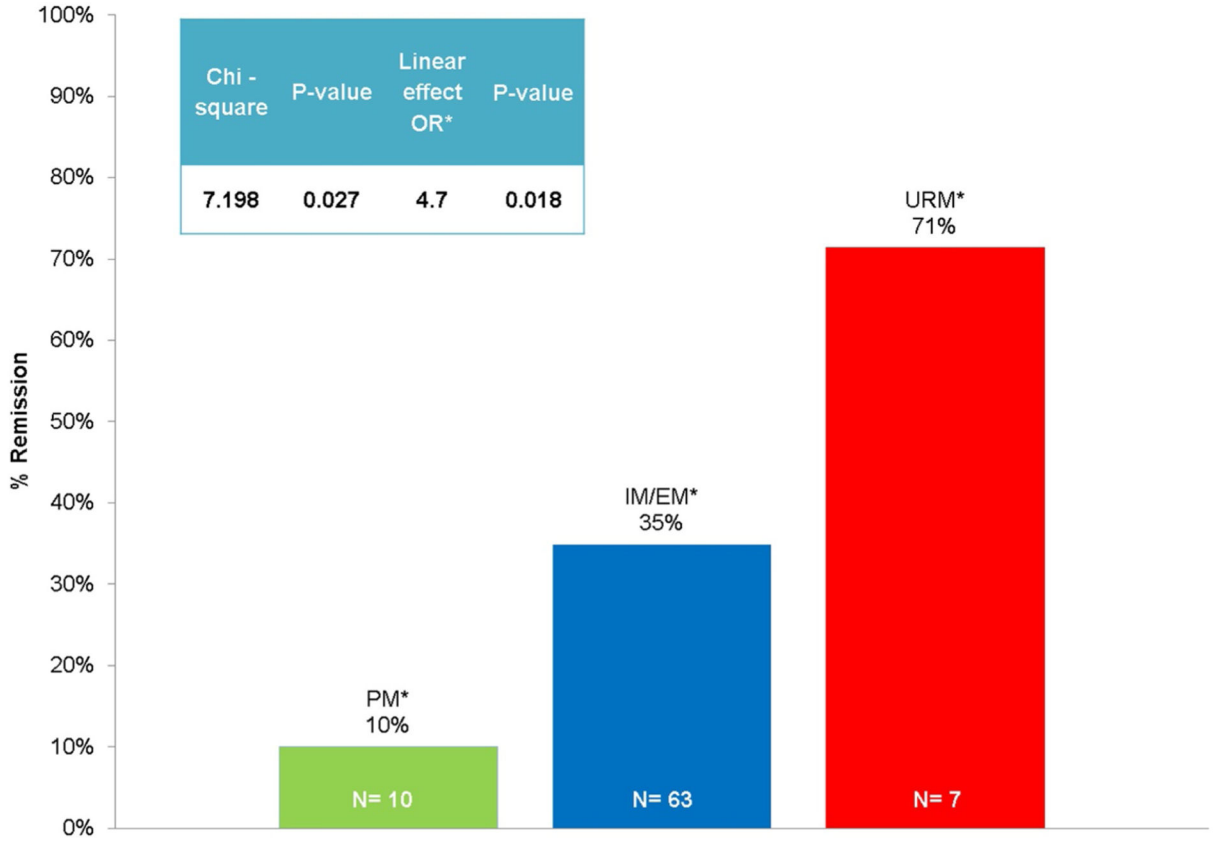

Fig. 2.

CYP2D6 ultra-rapid metabolizer (URM) phenotype associated with highest rate of remission with venlafaxine. PM=poor metabolizer; IM/EM=intermediate metabolizer/ extensive metabolizer; URM=ultra-rapid metabolizer; OR=odds ratio.

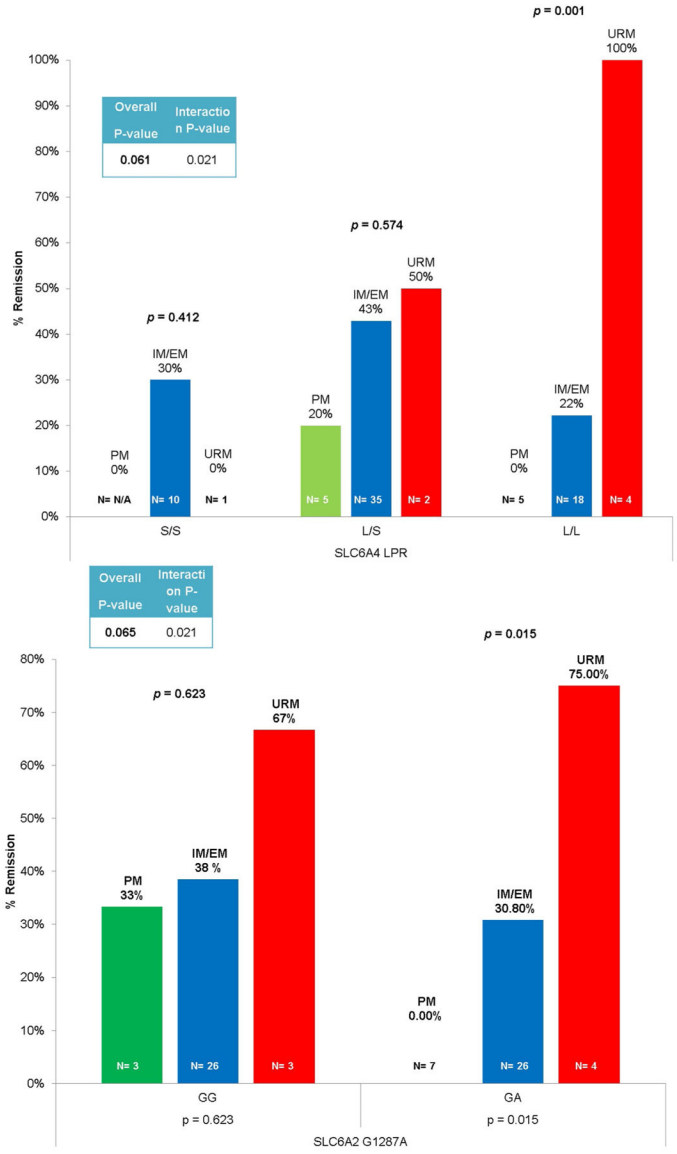

Fig. 3.

(a) *CYP2D6* URM phenotype & *SLC6A4* L/L genotype associated with highest rate of remission with venlafaxine. SLC6A4=serotonin transporter PM=poor metabolizer; IM/EM=intermediate/extensive metabolizer; URM=ultra-rapid metabolizer. (b) *CYP2D6* ultra-rapid metabolism phenotype & SLC6A2 G/A genotype associated with highest rate of remission with venlafaxine. SLC6A2=norepinephrine transporter; PM=poor metabolizer; IM/EM=intermediate/extensive metabolizer; URM=ultra-rapid metabolizer.

Table 1

Basic demographics, depression ratings, and genotyping outcomes.

		PGRN[a] Duloxetine N=(57)	STAR*D[a] Venlafaxine N=(82)	P-value
Demographics				
Age, yrs (Mean, SD)		43.8(11.4)	43.7(11.9)	0.960
Gender (N, %)	**Female**	31(54.4%)	48(58.5%)	0.755
	Male	26(45.6%)	34(41.5%)	
Marital status (N, %)	**Married**	23(40.4%)	33(40.3%)	0.989
	Not Married	34(59.6%)	49(59.7%)	
Employment status (N, %)	**Employed**	46(80.7%)	49(59.8%)	**0.009**
	Unemployed	11(19.3%)	33(40.2%)	
Education, yrs (N, %)	**< 12**	5(8.8%)	10(12.2%)	0.379
	12-15	26(45.6%)	44(53.7%)	
	≥16	26(45.6%)	28(34.1%)	
Depression ratings &outcomes				
QIDS-C_{16}[b] score(Mean, SD)	**Baseline**	12.23(3.86)	13.27(4.56)	0.120
	Week 8	8.91(4.50)	8.95(5.81)	0.961
Remitters (QIDS-C_{16}*score ≥ 5) (N, %)	**Yes**	13(22.8%)	28(34.1%)	0.210
	No	44(77.2%)	54(65.9%)	
Genotyping		**N (%)**	**N (%)**	
CYP2D6	***PM***[C]	1(3.6%)	10(8.4%)	0.373
	IM/EM[C]	25(89.3%)	63(75.9%)	
	URM[C]	2(7.1%)	7(12%)	
CYP2C19	***PM***[C]	2(3.1%)	1(1.2%)	0.240
	IM/EM[C]	29(90.6%)	74(91.4%)	
	URM[C]	1(6.3%)	6(7.4%)	
SLC6A4 5-HTTLPR	***L/L***	6(21.4%)	27(32.9%)	0.499
	L/S	17(60.7%)	44(53.7%)	
	S/S	5(17.9%)	11(13.4%)	
SLC6A4 5-HTVNTR	***12/12***	N/A	33(41.3%)	N/A
	9/12–9/10–10/12	N/A	30(37.5%)	
	10/10	N/A	17(21.3%)	
SLC6A2 G1287A	***A/A***	4(7.1%)	10(12.3%)	0.613
	G/A	28(50%)	38(46.9%)	
	G/G	24(42.9%)	33(40.7%)	
SLC6A2 T182C	***C/C***	4(7%)	5(6.2%)	0.781
	T/C	24(42.1%)	39(48.1%)	
	T/T	29(50.9%)	37(45.7%)	

[a]PGRN, Pharmacogenomic Research Network, START*D, Sequenced Treatment Alternatives to Relieve Depression,

[b]QIDS-C16, Quick Inventory of Depressive Symptomatology Clinician-rated,

[c]PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; URM, ultra-rapid metabolizer;

[C]L, long; S, short allele variants

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Table 2

The association between metabolizer status, *SLC6A4* and *SLC6A2* allele variants, and SNRIs remission.

Gene	Drug	Remission rate by genotype			P-value[a]	Assuming linear effeet[b] OR[c]	P-value[d]
CYP2D6		***PM***[d]	***IM/EM***[d]	***URM***[d]			
	Duloxetine	0(0%)	6(24.0%)	0(0%)	0.462	1.559	0.762
	Venlafaxine	1(10.0%)	22(34.9%)	5(71.4%)	**0.027**	4.727	**0.018**
CYP2C19		***PM***[d]	***IM/EM***[d]	***URM***[d]			
	Duloxetine	1(50.0%)	7(24.1%)	0(0%)	0.559	0.266	0.332
	Venlafaxine	0(0%)	26(35.1%)	2(33.3%)	0.650	1.194	0.825
SLC6A4[e] ***5-HTTLPR***		***L/L***[d]	***S/L***[d]	***s/s***[d]			
	Duloxetine	1(16.7%)	6(35.3%)	0(0%)	0.135	0.692	0.603
	Venlafaxine	8(29.6%)	17(38.6%)	3(27.3%)	0.645	1.061	0.869
SLC6A4[e] ***5-HTVNTR***[f]		***12/12***	***9/12, 10/12, 9/10***	***10/10***			
	Venlafaxine	13(39.4%)	9(30.0%)	5(29.4%)	0.671	0.777	0.423
SLC6A2[e] ***G1287A***		***AA***	***GA***	***GG***			
	Duloxetine	0(0%)	8(28.6%)	5(20.8%)	0.270	0.908	0.853
	Venlafaxine	4(40.0%)	11(28.9%)	13(39.4%)	0.604	0.880	0.715
SLC6A2[e] ***T182C***		***C/C***	***T/C***	***T/T***			
	Duloxetine	1(25.0%)	9(37.5%)	3(10.3%)	**0.059**	2.525	0.07
	Venlafaxine	0(0%)	17(43.6%)	11(29.7%)	**0.05**	1.009	0.981

[a] Chi-square test.

[b] By coding different allele variants as continuous variable.

[c] OR, Odds Ratio.

[d] Linear regression model.

[d] PM, poor metabolizer; IM/EM, intermediate metabolizer/extensive metabolizer; URM, ultra-rapid metabolizer;

[d] L, long; S, short allele variants;

[e] SLC6A4, serotonin transporter; SLC6A2, norepinephrine transporter.

[f] VNTR, variable number of tandem repeats.