Pharmacogenetic profile and major depressive and/or bipolar disorder treatment: a retrospective, cross-sectional study

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Aim: To compare pharmacogenetic test predictions with self-reported treatment experience and side effect tolerability among patients with depression taking psychotherapeutic medications. **Methods:** Subjects completed a survey recalling medication effectiveness and side effects and then underwent pharmacogenetic testing. **Results:** Our 15 gene pharmacogenetic panel predicted efficacy ($p < 0.001$) but did not predict side effect tolerability ($p = 0.70$) in a group of 352 patients. The pharmacogenetic panel and reported efficacy corresponded 60% of the time and medication tolerability agreed 71% of the time. **Conclusion:** Pharmacogenetic testing may be a useful adjunct to predict efficacy of medications used to treat depression.

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One in ten Americans report taking an antidepressant which makes this drug class the third most commonly prescribed group of medications [1]. Providers often use clinical factors such as character of depressive symptoms, duration of the illness, family history and comorbid anxiety to guide treatment [2,3], and the standard of care for issuing a therapeutic regimen can be a prolonged ‘trial and error’ process [2]. Unfortunately, many patients with major depressive disorder (MDD) and other related mood disorders do not respond to the available psychiatric medications, and the rate of remission (absence of symptoms) to a first-line antidepressant is estimated at only 28–47% [4,5]. The need remains to identify strategies to improve these outcomes and better personalize psychiatric treatment [2].

Pharmacogenetic testing is increasingly solicited as a tool to improve treatment outcomes by providing clinicians with a better understanding of how a patient metabolizes psychiatric medications and how the patient may be predisposed to toxicity. An investigation from the Genome-Wide Complex Trait Analysis found that genetic variants explain 42% of individual differences in antidepressant response [6]. Many antidepressants are metabolized through the CYP450 enzyme system in the liver. Some variants reduce enzyme function resulting in poor or decreased metabolism of the drug, which can cause toxic drug concentrations in the plasma leading to greater intolerability. Other variants can induce enzyme function, which increases the rate of metabolism leading to lower than expected active drug levels and decreased effectiveness. Recommended guidelines for antidepressant use and treating patients with allelic variants have been put forth [7–9]. Several studies have reported improved treatment effectiveness in patient groups whose antidepressant selection and dosing were guided by pharmacogenetic testing compared with those with usual care [10–13]. A retrospective analysis showed that the patients with genetic variation resulting in a poor metabolizer status, but who were prescribed a medication metabolized by the affected pathway, were more likely to use healthcare resources or file a disability claim during the 1-year observation period [14]. Thus, using

a patient's genetic code to predict metabolism may shorten the time to find optimal medication management, improve treatment outcomes and prevent drug-toxicity-related illness and death [15].

This is a retrospective observational study examining the patient's prior experience with commonly used psychiatric medications among the patients with MDD and bipolar disorder (BPD). Potential genetic associations with treatment response and medication tolerability were explored.

Methods

Study design & participant recruitment

This study was conducted through a collaboration between PatientsLikeMe (PLM; Cambridge, MA, USA) and Pathway Genomics (CA, USA). PLM is a free online data-sharing platform that connects individuals to a community of others who are living with the same disease or condition. PLM has over 600,000 members of which more than 80,000 members report MDD or BPD as a condition. The research protocol was approved by the New England Institutional Review Board (IRB Number 20160581). The study included a treatment experience survey to capture recent medication use with effectiveness and side effect experiences and a pharmacogenomic test (Mental Health DNA Insight, Pathway Genomics). Participant recruitment and survey deployment was completed by PLM. Genotyping and data analysis were performed by Pathway Genomics. The study aimed to collect survey and genotype data for 300 subjects.

Between July and December 2016, recently active PLM members who reported MDD or BPD as a condition were invited to participate in the study by private email message. The email invitation contained an explanation of the study and survey link. Members were first asked screening questions to determine eligibility. Potential participants must have been ≥ 18 years of age, US residents and must have taken at least one prescription medication to treat their MDD or BPD in the last 2 years. Members who were pregnant or had not been diagnosed with either MDD or BPD by a healthcare provider were excluded. Those unwilling to provide contact information were also excluded from the study. Members meeting the eligibility criteria were then invited to complete the online informed consent and electronic treatment experience survey. Subjects who do not complete the survey within 3 days were sent one email reminder to encourage survey completion.

Treatment experience survey

The survey was developed by PLM and Pathway Genomics researchers. Demographic, healthcare diagnosis and medication satisfaction information were included. Out of the 53 medications included in the pharmacogenetic panel, 26 medications were identified by the research team as the most common prescription medications used in the target population before the start of the study and were only included in the survey (Supplementary Materials). Treatment effectiveness questions and presence and tolerability of side effects questions were asked to capture treatment experience for each of the 26 medications (Supplementary Materials).

Once consent was provided and the treatment experience survey was completed by the participant, a saliva-based DNA kit was mailed to the study participant. Genetic reports were provided to the patients by email within 4 weeks.

Genotyping procedure

Saliva samples were collected using the Oragene-Dx DNA saliva collection kit (ON, Canada) and analyzed in the Mental Health DNA Insight® (Pathway Genomics). Isolation of genomic DNA was conducted using Chemagic Magnetic Separation Module I instrument (PerkinElmer, MA, USA) and subsequently quantified using PicoGreen assay (Thermo Fisher Scientific, MA, USA). Library preparation was performed using a polymerase chain reaction-based amplification using the Juno Targeted DNA Sequencing Library Preparation System (Fluidigm, CA, USA). Last, next-generation sequencing (NGS) was performed using Illumina NextSeq500 (Illumina, CA, USA). Files generated after NGS were then analyzed by an internal bioinformatics pipeline. Some genotypes were determined with a real-time qPCR assay (Fluidigm). Validation of the saliva-Oragene tubes and the molecular analysis systems was completed in accordance to Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) requirement.

Variations in alleles were measured for 15 genes including some associated with drug metabolism (*CYP2B6*, *CYP3A4*, *CYP2C9*, *CYP2D6*, *CYP2C19*, *CYP1A2*, *CYP3A5* and *UGT1A4*), drug action (*DRD2*, *HTR2C*), and safety (*POLG*, *HTR2A*, *HLA-A*, *HLA-B* and *SLC6A4*). Using separate algorithms, genotype results were converted to a phenotypic drug response, categorized as: use as directed, preferential use, may have significant limitations

Table 1. Participant demographic characteristics.

Characteristic	Participant number n = 352	%
Age		
Years	50.6 (20–78)	100
20–29	18	5.1
30–39	39	11.1
40–49	81	23.0
50–59	144	40.9
60–69	61	17.3
70+	9	2.3
Sex		
Males	84	23.9
Females	268	76.2
Ethnicity		
African-American	8	2.3
Asian	2	0.3
Caucasian	311	88.4
Hispanic	9	2.6
Other/mixed race/not reported	22	6.3
Education		
Some high school	6	1.7
High school diploma	34	9.7
Some college	157	44.6
College diploma	85	24.1
Postgraduate degree	65	18.5
Other	5	1.4
Employment status		
Employed, full-time	57	16.2
Employed, part-time	41	11.6
Student	12	3.4
Retired	39	11.1
Unemployed	24	6.8
Disabled/unable to work due to MDD or bipolar disorder	105	29.8
Disabled/unable to work due to other condition	61	17.2
Other/preferred not to answer	13	3.7
Medication satisfaction		
Very dissatisfied	37	10.5
Moderately dissatisfied	76	21.6
Neither satisfied nor dissatisfied	49	13.9
Moderately satisfied	125	35.5
Very satisfied	52	14.8
I am not currently taking medication to treat my condition(s)	13	3.7

and may cause serious adverse events, for 53 medications in the pharmacogenetics report. Not all medications have all four phenotype outcomes based on valid genotype–phenotype associations used in the curation of the pharmacogenetic panel. The table in Supplementary Materials contains the detailed markers (rs#) tested for each gene.

Table 2. Participant diagnosis by total number of reported diagnoses.

	Number of psychological disorders diagnosed†					
Previous diagnosis	1 Diagnosis (n = 89)	2 Diagnoses (n = 156)	3 Diagnoses (n = 72)	4 Diagnoses (n = 27)	5 Diagnoses (n = 8)	Total (n = 352)
Major depressive disorder						
Yes	58 (65.2%)	132 (84.6%)	66 (91.7%)	26 (96.3%)	7 (87.5%)	289 (82.1%)
No	31 (34.8%)	24 (15.4%)	6 (8.3%)	1 (3.7%)	1 (14.3%)	63 (17.9%)
Bipolar disorder						
Yes	31 (34.8%)	40 (25.6%)	44 (61.1%)	24 (88.9%)	8 (100%)	147 (41.8%)
No	58 (65.2%)	116 (74.4%)	28 (38.9%)	3 (11.1%)	0 (-)	205 (58.2%)
General anxiety disorder						
Yes	0 (-)	121 (77.6%)	68 (94.4%)	25 (92.6%)	8 (100%)	222 (63.1%)
No	89 (100%)	35 (22.4%)	4 (5.6%)	2 (7.4%)	0 (-)	130 (36.9%)
Schizophrenia						
Yes	0 (-)	2 (1.2%)	2 (2.8%)	1 (3.7%)	4 (50.0%)	9 (2.6%)
No	89 (100%)	154 (98.7%)	70 (97.2%)	26 (96.3%)	4 (50.0%)	343 (97.4%)
Obsessive compulsive disorder						
Yes	0 (-)	7 (4.5%)	19 (26.4%)	13 (48.1%)	6 (75.0%)	45 (12.8%)
No	89 (100%)	149 (95.5%)	53 (73.6%)	14 (51.9%)	2 (25.0%)	307 (87.2%)
Borderline personality disorder						
Yes	0 (-)	10 (6.4%)	17 (23.6%)	19 (70.3%)	7 (87.5%)	53 (15.1%)
No	89 (100%)	146 (93.6%)	55 (76.4%)	8 (29.6%)	1 (14.3%)	299 (84.9%)
†Diagnoses include major depressive disorder, bipolar disorder, general anxiety disorder, schizophrenia, obsessive compulsive disorder and borderline personality disorder.						

[†]Diagnoses include major depressive disorder, bipolar disorder, general anxiety disorder, schizophrenia, obsessive compulsive disorder and borderline personality disorder.

Statistical analysis

The primary outcome measure was to establish the proportion of agreement between self-reported efficacy and side effects and the phenotype outcome for each of the 26 survey medications that a participant reported taking within the last 2 years. Subjects were asked, “In the last 2 years, at its peak, how effective was Product X?” for each medication taken within the last 2 years and taken for ≥ 6 weeks. Efficacy categories included: not effective, slightly effective, moderately effective and very effective. Subjects who reported taking a medication for ≤ 6 weeks were not asked effectiveness constructs in the survey. Presence and tolerability of side effect categories included: no side effects, not bothersome, mild, moderate and severe.

The phenotype outcome may cause serious adverse events is only applicable for 15 out of the 26 drugs in the study. For the side effect analysis, these 15 drugs were included and the phenotype may have significant limitations was removed to delineate safety only. Therefore, ‘use as directed and preferential use’ were combined into one category and may cause serious adverse events was the other category. Side effect responses were concatenated into the two groups ‘no side effects/not bothersome/mildly bothersome/moderately bothersome (kept taking medication)’ and ‘moderately bothersome (stopped taking medication due to side effects)/severely bothersome’.

Analyses were performed in R version 3.4.0 (Vienna, Austria). Pearson’s χ^2 test or Fisher’s exact test were used to compare proportions and two-sided independent t-tests were used to evaluate differences in means. A $p \leq 0.05$ value was considered significant.

Results

At the time of data collection, there were 5392 PLM members who self-identified as being diagnosed with MDD and/or BPD with PLM website activity within 90 days. Invitations were sent to 4756 recently active PLM members of which 1331 unique members accepted the invitation. Out of these, 670 individuals completed the survey and 656 study participants agreed to have an at-home DNA kit mailed for genotyping. A total of 375 kits were returned (response rate: 375/656, 57.2%). Participants who submitted a sample but did not receive a report either did not complete the necessary contact information and could not be reached, or the sample failed in genotyping and a second sample was not received. Subjects who completed the survey and had genotyping results were included in this analysis (n = 352). Figure 1 illustrates the inclusion of participants for the analysis.

Table 1A summarizes participant demographic characteristics and overall medication satisfaction. Table 2B shows diagnosis history. The mean age of the study participants was 51 years with the majority being females (76%) and

Table 3. Medications included in the survey and frequency study participants reported taking each medication in the last 2 years.

Medication class	Medication name	Gene(s)	Number of patients reported taking medication in last 2 years (%) [†]
Atypical antipsychotic	Aripiprazole	<i>HTR2C, CYP2D6</i>	72 (20.5)
	Olanzapine	<i>HTR2C, CYP1A2</i>	6 (1.7)
	Quetiapine	<i>HTR2C</i>	64 (18.2)
	Risperidone	<i>CYP2D6, HTR2C, DRD2</i>	24 (6.8)
	Ziprasidone	<i>HTR2C</i>	16 (4.5)
Benzodiazepine	Diazepam	<i>CYP2C19</i>	42 (11.9)
Other antidepressants	Bupropion	<i>CYP2B6</i>	122 (34.7)
	Buspirone	<i>CYP3A4</i>	49 (13.9)
	Duloxetine	<i>CYP2D6</i>	90 (26.6)
	Mirtazapine	<i>CYP2D6</i>	33 (9.4)
	Trazodone	<i>CYP3A4</i>	87 (24.7)
	Venlafaxine	<i>CYP2D6, SLC6A4</i>	83 (23.6)
	Valproic acid	<i>PLOG</i>	1 (0.3)
Mood stabilizer	Divalproex	<i>POLG</i>	19 (5.4)
	Carbamazepine	<i>HLAA, HLAB</i>	12 (3.4)
	Lamotrigine	<i>HLAB, UGT1A4</i>	84 (23.9)
	Oxcarbazepine	<i>HLAB</i>	13 (3.4)
	Phenytoin	<i>CYP2C9, HLAB</i>	5 (1.4)
	Valproic acid	<i>PLOG</i>	1 (0.3)
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	<i>SLC6A4, CYP2C19, HTR2A.CIT</i>	40 (11.4)
	Escitalopram	<i>CYP2C19</i>	57 (16.7)
	Fluoxetine	<i>SLC6A4, CYP2D6</i>	64 (18.2)
	Paroxetine	<i>SLC6A4, CYP2D6, HTR2A.ADV</i>	28 (8.0)
	Sertraline	<i>CYP2C19</i>	71 (20.2)
TCAs	Amitriptyline	<i>CYP2C19, CYP2D6</i>	34 (9.7)
	Nortriptyline	<i>CYP2D6</i>	18 (5.1)
Other	Modafinil	<i>CYP2D6</i>	20 (5.7)
Total			1154

[†] Counts exceed 352 subjects because most participants reported taking two or more medications within the last 2 years.
TCA: Tricyclic antidepressant.

Caucasians (88%). Most subjects reported having some college as the highest level of education attained (45%) and many (105/352, 30%) reported being unable to work due to their MDD or BPD condition. There were no significant differences between those who did not return a DNA sample and those that did: mean age ($p = 0.57$) and ethnicity ($p = 0.37$), employment status ($p = 0.24$), education ($p = 0.13$), diagnosis and total number of reported diagnoses ($p = 0.32$), and medication satisfaction ($p = 0.52$).

Subjects were asked if a healthcare professional had ever diagnosed them with MDD, BPD, generalized anxiety disorder, schizophrenia, obsessive compulsive disorder and/or borderline personality disorder. Most of the study participants had a previous diagnosis of MDD (289/352, 82%) followed by generalized anxiety disorder (222/352, 63%) and BPD (147/352, 42%). Many subjects had been diagnosed with two of these psychiatric conditions (156/352, 44%) (Table 2B). Out of the 26 medications included in the survey, most subjects reported taking between two and five medications within the last 2 years and reported moderate satisfaction (125/352, 36%) or moderate dissatisfaction (76/352, 22%) with the current medication treatment (Table 1A). There were 33 subjects who reported taking only one medication within the last 2 years. There was no significant difference in reported medication satisfaction between those taking one medication and those taking two or more medications ($\chi^2 [5, N = 352] = 4.5, p = 0.47$). Out of the 26 medications in the survey, bupropion, duloxetine, trazodone, venlafaxine and lamotrigine were the most commonly prescribed medications in the study cohort (Table 3).

Tables 4A and 5 shows efficacy results for each drug with phenotype outcomes. A total of 985 subject–medication encounters for reported effectiveness responses and phenotype outcomes were included since most subjects were

Table 4. Reported efficacy and composite phenotype outcome stratified by medication.

Medication	Not effective/slightly effective/moderately effective (stopped taking medication due to ineffectiveness)		Moderately effective (kept taking)/very effective		Total [†]
	Use as directed/preferential use	May have significant limitations/may cause serious adverse events	Use as directed/preferential use	May have significant limitations/may cause serious adverse events	
Aripiprazole	18	4	33	4	59
Olanzapine	0	1	1	3	5
Quetiapine	15	0	38	0	53
Risperidone	7	3	3	6	19
Ziprasidone	6	0	9	0	15
Diazepam	5	0	26	1	32
Bupropion	24	23	33	27	107
Buspirone	18	0	25	0	43
Duloxetine	31	3	39	7	80
Mirtazapine	9	3	12	2	26
Trazodone	22	0	50	0	72
Venlafaxine	14	14	34	14	76
Divalproex	4	0	12	0	16
Carbamazepine	3	1	5	1	10
Lamotrigine	9	2	53	9	73
Oxcarbazepine	1	0	8	1	10
Phenytoin	1	0	3	1	5
Valproic acid	0	0	1	0	1
Citalopram	3	20	1	15	39
Escitalopram	6	18	14	13	51
Fluoxetine	18	10	18	9	55
Paroxetine	4	31	3	4	42
Sertraline	9	16	16	21	62
Amitriptyline	7	6	6	5	24
Nortriptyline	4	2	6	1	13
Modafinil	5	0	9	1	15
Total	246	139	455	145	985

[†]Totals shown represent the number of subjects who reported taking each medication in the survey within the last 2 years. Most efficacy counts are less than side effect counts because subjects who reported taking a medication for ≤ 6 weeks were asked to skip the effectiveness questionnaire section.

Table 5. Total efficacy counts of subject-medication encounters and phenotype outcomes 2x2 cross tabulation.

Reported efficacy	Phenotype outcome		Total
	Use as directed/preferential use	May have significant limitations/may cause serious adverse events	
Not effective/slightly effective/moderately effective (stopped taking medication due to ineffectiveness)	246 (disagree)	139 (agree)	385
Moderately effective (kept taking)/very effective	455 (agree)	145 (disagree)	600
Total	701	284	985

Pearson's χ^2 (1, N = 985) = 16.28, $p < 0.001$.

taking two to five medications. The prevalence of self-reported efficacy and phenotype agreement among subjects with a phenotype of 'Use as Directed/Preferential Use' was 64% (455/701) and 49% (139/284) in agreement for those with a phenotype outcome of 'may cause serious adverse events', respectively. Overall efficacy status was significantly associated with phenotype outcome (χ^2 [1, n = 985] = 16.29, $p < 0.001$). Individual drugs also showed this trend; however, escitalopram was the only drug that was statistically significant, when broken down by

Figure 1. Inclusion of study participants.
BPD: Bipolar disorder; MDD: Major depressive disorder.

individual drug ($\chi^2 [1, n = 51] = 3.84, p = 0.049$). Efficacy status among subjects who reported taking only one drug ($n = 33$) was not significantly associated with phenotype outcome (Fisher's exact test: $p = 0.40$).

Table 6A and Table 7 shows side effect results for each drug with phenotype outcomes. Overall, 367 subject-medication encounters for reported side effects and phenotype outcomes were analyzed and 259 were in agreement (70.6%). The prevalence of side effect response and phenotype agreement among those with a phenotype outcome of 'use as directed/preferential use' was 72% (253/340) and 22% (6/27) agreement among those with a phenotype of 'May Cause Serious Adverse Events'. However, there was no significant association between reported medication tolerability and phenotype outcome for combined results ($\chi^2 [1, n = 367] = 0.15, p = 0.70$). Though reported side effects and phenotype outcome trended toward agreement for individual drugs, there was no significant association per medication or medication class for side effect results. There also was no significant association between side effect status and phenotype outcome among subjects who reported taking only one drug ($n = 15$, Fisher's exact test: $p = 0.48$), however, this analysis is limited by the small sample size.

Discussion

According to the most recent data available from the National Health and Nutrition Examination Survey, an estimated 7.6% Americans over the age of 12 had depression between 2009 and 2012 [16]. Physician office visits where a mood disorder was the primary diagnosis was estimated to be 65.9 million for 2014 alone [17]. Many of these patients only achieve partial response to psychiatric medication treatment and the odds of recovering from depression diminish with each subsequent treatment strategy needed [18]. Understanding contributors of psychiatric medication response and tolerability, such as genetic variation, is of public health and clinical interest [19]. Our study explored the patients' perception of efficacy and side effects from their treatment regimen within the last 2 years and

Table 6. Reported side effects response and composite phenotype outcome stratified by drug.

Medication	No side effects/not bothersome/mildly bothersome/moderate side effects (kept taking medication)		Moderate side effects (stopped taking medication)/severe side effects		Total [†]
	Use as directed/preferential use	May cause serious adverse events	Use as directed/preferential use	May cause serious adverse events	
Aripiprazole	44	1	18	2	65
Risperidone	7	2	5	1	15
Venlafaxine	43	8	10	0	61
Divalproex	12	0	7	0	19
Carbamazepine	4	3	5	0	12
Lamotrigine	60	0	9	0	69
Oxcarbazepine	8	1	4	0	13
Phenytoin	4	0	0	1	5
Valproic acid	1	0	0	0	1
Citalopram	2	0	2	0	4
Escitalopram	20	0	3	0	23
Paroxetine	4	1	7	0	12
Sertraline	21	3	8	1	33
Amitriptyline	14	2	4	1	21
Nortriptyline	9	0	5	0	14
Total	253	21	87	6	367

[†]Totals shown represent the number of subjects who reported taking each medication in the survey within the last 2 years. Most of the study subjects reported taking more than one medication.

Table 7. Total side effect counts of subject–medication encounters and phenotype outcomes 2x2 cross tabulation.

Reported side effects	Phenotype outcome		Total
	Use as directed/preferential use	May cause serious adverse events	
No side effects/not bothersome/mildly bothersome/moderate side effects (kept taking medication)	253 (agree)	21 (disagree)	274
Moderate side effects (stopped taking medication)/severe side effects	87 (disagree)	6 (agree)	93
Total	340	27	367

Pearson's χ^2 (1, n = 367) = 0.15, p = 0.70.

compared their medication use to a pharmacogenetic panel. We found that the pharmacogenetic panel predicted efficacy ($p < 0.001$) but did not predict side effect tolerability ($p = 0.70$). Approximately 60.3% (594/985) of the self-reported efficacy and phenotype outcomes agreed. For side effect tolerability, 70.6% (259/367) of the reported side effect tolerability and phenotype outcome agreed (Tables 5B & 7).

Others have evaluated the clinical utility of pharmacogenetic testing-guided treatment among patients with MDD and measured effects of remission, response and tolerability [20]. A randomized control trial (RCT) in a population of 148 white adults reported a 2.5-fold increase in remission rates (72 vs 28%) in the group whose treatment was guided by a pharmacogenetics test compared with the nonguided group [12]. Another RCT using a different pharmacogenetic test reported a 20% remission achievement in the intervention group compared with 8.3% in the treatment-as-usual group, though the difference in improved remission or response was not significant [13]. Also, use of this test demonstrated improved efficacy over the treatment-as-usual approach to medication selection in two prospective, open label studies [10,21,22]. Last, a recent RCT using another pharmacogenetic test reported a 35% remission rate in the pharmacogenetic-guided group compared with 13% in the usual care group at 12 weeks of treatment, and the response rates were significantly higher for patients in the experimental group compared with the control group at the 12-week follow-up as well [11].

Our study took a different methodological approach in that the cohort of subjects were already in treatment for MDD or BPD condition and had been taking one or more medications for ≥ 6 weeks and notably, perception

of effectiveness and side effects were asked retrospectively. Though there are considerable differences in study design, outcome measures and important limitations to weigh, these studies show a trend toward improvement in treatment efficacy outcomes in the pharmacogenetic-guided treatment groups and in our case, corresponding phenotype outcomes and reported efficacy.

Similar to results reported here, Bradley *et al.* also did not find a significant difference between the experimental and control groups with regard to adverse drug events [11]. The authors remark that implementing a new treatment may increase the patient's awareness of new side effects associated with the new medication. This could also be true for subjects in our study who had only been taking a medication for <2 weeks and even <6 weeks. Furthermore, most subjects in our study reported taking multiple drugs and this could potentially limit the accuracy of reporting of which drug causes what side effect and how bothersome that side effect was. Additionally, research on the psychosocial context around treatment and side effects of medications have found that individuals report nonspecific side effects that are not a direct result of the specific pharmacological action of the drug [23].

Important limitations should be considered when interpreting this study's findings. First, the cohort of patients who participated in the study mostly represented Caucasian women between the ages of 50–59 (41%); therefore, we could not stratify the analysis by race or sex. Currently, the majority of genetics research is within this patient group and there is a need to study differences in genetic variations in broader populations [20]. Also, our response rate was low with approximately half of the subjects having completed the survey and submitting a DNA sample for testing. We could be missing patients on the extreme ends of treatment response. For instance, those who have responded well to their treatment or experienced a manageable level of side effects and those whose symptoms were severe may have elected not to participate (e.g., one patient indicated, “I could not get the energy to do this even though I really wanted to”). However, among those who did not return a DNA sample and those that did, mean age, ethnicity, employment status, education, diagnosis and total number of reported diagnoses, and medication satisfaction distributions were similar. Second, the survey that captured perception of efficacy and side effects was retrospective in nature and subject to recall bias. We are unable to measure the degree of under- or over-reporting of effectiveness and tolerability of side effects due to the survey being self-administered and reported past as well as present use. Also, self-reported data assumes patient medication adherence and it was not feasible to obtain adherence through additional interviews or serum drug levels.

As noted above, the majority of these patients were on multiple medications that may have had a confounding effect on their ability to ascribe a positive or negative response to a specific medication. The analysis matches a subject's reported efficacy and side effects with the phenotype outcome per medication, and we could not compare those taking one medication versus greater than or equal to two medications due to different denominators (number of subjects in one medication group and number of reported efficacy/side effect and phenotype matches for greater than or equal to two medications group). Furthermore, only a small portion of subjects (efficacy: $n = 33$; side effects: $n = 15$) reported taking one medication. This limits further analysis of drug–drug interaction in the study.

Third, small sample numbers for individual drugs limit our ability to see strong inferences between reported efficacy and side effects and phenotype. Though most individual medications showed more subjects reported efficacy and side effects that agreed with their phenotype, the association lacked significance at the single medication and medication class level. The pharmacogenetic panel used at the time of the study may not measure all genetic variants that are now known to affect metabolism and could partially explain the lack of association. The complete list of genes, variants and allelic frequencies included in the pharmacogenetic panel are listed in Supplementary Materials. Moreover, variants affecting medication transporters and receptors may play a role in decreased efficacy or increased side effects in our study population. Additionally, these patients were taking multiple medications, some of which may have induced or inhibited the CYP450 enzymes that metabolize the psychoactive medication of interest. Carbamazepine, for example, is a potent drug inducer of oxidative enzyme systems in the liver and can accelerate metabolism of concurrently prescribed medications [24]. Finally, dietary factors that affect medication metabolism were not evaluated and also may have masked the effect of genotype on the pharmacokinetics or pharmacodynamics of individual medications.

Conclusion

This retrospective, patient recall study provides support for the use of pharmacogenetic testing as a tool for helping to guide the choice of treatment for MDD and BPD as the predictions significantly correlate with efficacy. Prospective testing in a larger study cohort investigating response to single regimen medication will be helpful to address medication-specific efficacy and tolerability.

Future perspective

Our findings further support the use of pharmacogenetic testing in the context of psychiatric care. Combining genotyping with traditional clinical practice will continue to improve treatment outcomes, and will aid in the development of novel therapeutic approaches. The ability to estimate the metabolism rate and risk of side effects of individual medications prior to therapy is a valuable tool for prescribers and patients. As pharmacogenetic testing continues to be incorporated into routine clinical practice, we anticipate that this will lead to better predictive, preventive and personalized psychiatric medicine.

Summary points

Background

- The rate of successful treatment of patients with major depressive disorder (MDD) and other related mood disorders using psychotherapeutic medications is low. There remains a need to identify strategies to improve these outcomes and better personalize psychiatric treatment.
- Potential genetic associations with treatment response and medication tolerability were explored.

Patients & methods

- Volunteer subjects of the PatientsLikeMe network who had reported taking one or more psychiatric medications for their condition were asked to complete a survey recalling medication effectiveness and side effects. Participants were then sent a saliva kit for DNA processing and were provided a pharmacogenetic report.
- Self-reported medication effectiveness and side effects were correlated with the genotype-based phenotype outcome predictions.

Results

- Out of the 352 subjects who completed the survey and had genotyping results, most had a previous diagnosis of MDD (289/352, 82%) followed by generalized anxiety disorder (222/352, 63%), and bipolar disorder (147/352, 42%).
- The pharmacogenetic panel predicted efficacy ($p < 0.001$) with approximately 60.3% (594/985) of the self-reported efficacy and phenotype outcomes were in agreement.
- Despite 70.6% (259/367) of the reported side effect tolerability and phenotype outcomes having agreed, the pharmacogenetic panel did not predict side effect tolerability ($p = 0.70$) in this group.

Discussion

- This study further demonstrates support for clinical utility of pharmacogenetic testing as a tool for helping to guide effective treatment for MDD and BPD patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:

<https://www.futuremedicine.com/doi/suppl/10.2217/pgs-2018-0088>

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study was approved by the New England Institutional Review Board (IRB Number 20160581). Informed consent was obtained from all participating subjects.

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