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Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists

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ABSTRACT

Failed medication trials are common in the treatment of major depressive disorder (MDD); however, the use of combinatorial pharmacogenomics to guide medication selection has been previously associated with improved outcomes in the psychiatric care setting. The utility of combinatorial pharmacogenomics in patients with MDD in primary care and psychiatric care settings was evaluated here. Patients enrolled in a naturalistic, open-label, prospective study [Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT)] with MDD were evaluated (N = 1871). Pharmacogenomic testing was performed for all patients and medications were categorized based on gene-drug interactions. Beck's Depression Inventory (BDI) was evaluated at baseline and follow-up (weeks 8–12). Symptom improvement (percent decrease in BDI), response (≥50% decrease in BDI), and remission (BDI≤10) at follow-up were evaluated according to provider type and whether medications were genetically congruent (little/no gene-drug interactions). There was a 27.9% reduction in depression symptoms at follow-up, as well as response and remission rates of 25.7% and 15.2%, respectively. Outcomes were significantly better among patients treated by primary care providers versus psychiatrists (symptom improvement 31.7% versus 24.9%, $p < 0.01$; response rate 30.1% versus 22.3%, $p < 0.01$; remission rate 19.5% versus 12.0%, $p < 0.01$). There was a 31% relative improvement in response rate among patients taking congruent versus incongruent medications, with slightly higher congruence among primary care providers (87.6%) versus psychiatrists (85.2%). Following combinatorial pharmacogenomic testing, outcomes were significantly improved among patients treated by primary care providers compared to psychiatrists, which supports the use of pharmacogenomics in broader treatment settings.

1. Introduction

Major depressive disorder (MDD) is a significant health burden, with a prevalence of 8.7% in the United States (U.S.) and 8.2% in Canada (Vasiliadis et al., 2007). The World Health Organization has ranked depressive disorders as the largest contributor to non-fatal health loss globally (World Health Organization, 2017). Depression is also a risk factor for multiple chronic illnesses, with increased incidences of heart disease, arthritis, asthma, back pain, chronic bronchitis, hypertension, migraines, and diabetes among patients with MDD (Patten et al., 2008; Rotella and Mannucci, 2013). Accordingly, the economic burden of MDD in the U.S. increased by more than 20% from 2005 ($173.2 billion) to 2010 ($210.5 billion), resulting from increased workplace ($102.0 billion), direct ($98.9 billion), and suicide-related costs ($9.7 billion) (Greenberg et al., 2015).

In the U.S. and Canada, primary care physicians (i.e. family doctors and general practitioners) are often the main physician point of contact for patients with MDD. One study of patients with depression in the U.S. and Canada showed that 24–38% of patients saw a family doctor or general practitioner compared to only 10–14% who saw a psychiatrist (Vasiliadis et al., 2007). This higher usage of primary care providers likely reflects the shortage of psychiatrists in both countries. Overall, the number of practicing psychiatrists in the U.S. and Canada is decreasing while the unmet need for psychiatric services is increasing (Bishop et al., 2016; Canadian Collaborative Centre for Physician Resources, 2012; National Council Medical Director Institute, 2017; Thomas et al., 2009).

Regardless of healthcare provider type, more than half of patients with MDD do not respond to their first medication trial (Rush et al., 2006). The resultant prolonged disease duration is associated with a

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decreased probability of achieving remission (Warden et al., 2007) along with an increased side-effect burden and medical costs (Mrazek et al., 2014). Pharmacogenomics can be utilized to improve medication selection by identifying significant gene-drug interactions for an individual patient. While multiple approaches to testing have been developed, pharmacogenomics generally involves the evaluation of one or more pharmacokinetic (drug metabolism) and/or pharmacodynamic (mechanism of action) genes. The degree of gene-drug interactions are then evaluated based on individual genotypes of a single gene (single-gene testing), individual genotypes of multiple genes (multi-gene testing), or a combined phenotype compiled from multiple genotypes (combinatorial pharmacogenomic testing) to identify medications unlikely to be safe and/or effective. Studies evaluating the validity and utility of pharmacogenomics have been mixed (Rosenblat et al., 2017); however, each testing approach is unique and must be evaluated separately (Bousman and Dunlop, 2018). To this end, a combinatorial pharmacogenomic test has been shown to improve patient outcomes (Greden et al., 2018; Hall-Flavin et al., 2012, 2013; Winner et al., 2013b) while decreasing polypharmacy and healthcare costs (Winner et al., 2013a, 2015).

Although the validity and utility of this combinatorial pharmacogenomic test has been well established for patients with MDD, the majority of these studies were conducted among patients in psychiatric care. Findings from the STAR*D trial suggest that mental health outcomes are similar among patients treated by psychiatrists and primary care providers (Gaynes et al., 2005, 2007, 2008). There is also evidence that adherence to test results and polypharmacy are similar in the primary care and psychiatric care settings for patients with MDD following combinatorial pharmacogenomic testing (Brown et al., 2017). In addition, adherence to combinatorial pharmacogenomic results resulted in medical cost savings regardless of provider type, with improved savings among those treated by primary care providers (Brown et al., 2017).

Given the large proportion of patients with depression who are treated by primary care providers, it is important to determine the utility of combinatorial pharmacogenomic testing in this setting. The present study evaluated symptom improvement, response, and remission rates following treatment guided by combinatorial pharmacogenomic testing among patients with MDD enrolled in a large, prospective study: Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT). Patient outcomes were evaluated separately for those treated by primary care providers and psychiatrists.

2. Materials and methods

2.1. Study design

This analysis was conducted as part of the IMPACT study, which has been previously described in detail (Herbert et al., 2018). Briefly, IMPACT was a seven-year, naturalistic, un-blinded, prospective study examining the effect of a combinatorial pharmacogenomic test (GeneSight® Psychotropic) in guiding prescription decisions for psychiatric medications. Patients were referred for inclusion in the study by their clinician. Patient consent and enrollment was obtained online or at the baseline visit. At baseline, pharmacogenomic testing was performed and test results were made available to providers within one week of testing. Clinicians made medication decisions with the aid of the combinatorial pharmacogenomic test report anytime between the baseline and follow-up visits. Assessments were performed at baseline and at a follow-up visit after 8–12 weeks. The primary assessment for depression was the Beck's Depression Inventory (BDI; patient reported). Ethical approval for study procedures was obtained from the Centre for Addiction and Mental Health (CAMH) Research Ethics Board. All participants provided informed consent.

2.2. Study participants

Patients enrolled in the IMPACT study who had moderate-to-severe depression and were treated by primary care providers or psychiatrists were evaluated here. Participants were selected for using the following inclusion criteria: baseline BDI score ≥ 20 (corresponds to moderate depression) irrespective of referral diagnosis, BDI scores available from baseline and follow-up, patient had prospective combinatorial pharmacogenomic testing, referral by a primary care provider or psychiatrist. Primary care providers included general practitioners, family doctors, internists, obstetricians/gynecologists, and pediatricians. In addition, patients were only included if the referring physician viewed the electronic test report prior to patient follow-up, which indicated that the physician was aware of the combinatorial pharmacogenomic test report. A total of 1871 participants met these criteria.

2.3. Combinatorial pharmacogenomic testing

Combinatorial pharmacogenomic testing was performed by Assurex Health, Ltd. (Toronto, ON). Select polymorphisms were measured within 8 genes (*CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *HTR2A*, and *SLC6A4*). Genomic DNA was isolated from buccal samples, and the relevant genomic regions were amplified by polymerase chain reaction (PCR). Specific mutations for *CYP2B6* (*A*785G, *G*516T) and *SLC6A4* were detected by gel electrophoresis of PCR products. Analysis of *CYP1A2*, *CYP2C19*, *CYP2C9*, *CYP3A4* and *HTR2A* was completed by using a custom xTAG® assay (Luminex Molecular Diagnostics). Analysis of *CYP2D6* was completed using xTAG® kits (Luminex Molecular Diagnostics). The following genetic variants may be detected in the assay: *CYP1A2* -3860G > *A*, -2467T > *delT*, -739T > *G*, -729C > *T*, -163C > *A*, 125C > *G*, 558C > *A*, 2116G > *A*, 2473G > *A*, 2499A > *T*, 3497G > *A*, 3533G > *A*, 5090C > *T*, 5166G > *A*, 5347C > *T*; *CYP2B6 *1, *4, *6, *9; CYP2C19 *1, *2, *3, *4, *5, *6, *7, *8, *17; CYP2C9 *1, *2, *3, *4, *5, *6; CYP2D6 *1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41*, gene duplication; *CYP3A4 *1, *13, *15A, *22; HTR2A* -1438G > *A; SLC6A4 L, S*.

For each patient, genotyping results and the known pharmacological profile for the 33 medications included in the panel were integrated into the interpretive test report using a validated combinatorial pharmacogenomic algorithm (Hall-Flavin et al., 2013). This involved weighting the measured genotypes for each variant or allele to determine the level of gene-drug interaction for an individual patient for each medication included in the test report. Based on the level of gene-drug interactions, medications were placed into one of three report categories: 'use as directed' (green), 'use with caution' (yellow), or 'use with increased caution and more frequent monitoring' (red). Medications in the green bin were predicted to be effective without any clinical modifications and those in the yellow bin were predicted to be effective with dose modification. Medications in the red bin were predicted to have severe-drug interactions that may significantly impact their safety and/or efficacy.

2.4. Statistical analyses

Demographics and descriptive statistics were determined for the full cohort and according to treating physician type (primary care provider, psychiatrist). The primary outcome was symptom improvement, defined as the percent change in BDI at follow-up relative to baseline. The rate of response ($\geq 50\%$ decrease in BDI from baseline) and remission (BDI score ≤ 10) at follow-up was also assessed. Patient outcomes were evaluated for the overall cohort, according to provider type, and according to patient age at testing (< 65, ≥ 65 years).

Medications were considered congruent with the combinatorial pharmacogenomic test results if they were classified in the green ('use as directed') or yellow ('use with caution') report categories (Altar

et al., 2015). Incongruent medications were classified as those in the red ('use with increased caution and more frequent monitoring') report category. The proportion of patients taking only congruent medications at baseline and follow-up was assessed for the overall cohort and according to provider type. Prescribing was considered incongruent if a patient was prescribed one or more incongruent medications. Patient outcomes were evaluated according to whether medications prescribed at follow-up were congruent with combinatorial pharmacogenomic testing for the overall cohort. Patients were excluded from this analysis if they were not taking any medications included on the combinatorial pharmacogenomic test report.

The severity of patients' depression symptoms (BDI scores) were compared between baseline and follow-up using a paired T-test. Symptom improvement was compared according to provider type using analysis of covariance (ANCOVA), and adjusting for baseline BDI score and the number of psychiatric medications reported by the patient at baseline. Rates of response and remission were compared according to provider type (primary care provider, psychiatrist) and medication congruence (congruent, incongruent) using Chi-squared tests. The odds ratios (OR) and 95% confidence intervals (CI) for achieving response and remission were calculated for patients treated by primary care providers using logistic regression modeling, with the psychiatrist-treated group as the reference. Baseline BDI score and the number of reported medications at baseline were used as surrogates for patient complexity in all analysis. Logistic regression modeling was performed while adjusting for baseline BDI score and psychiatric medications. All analyses were conducted using SPSS Statistics software (version 25), and p-values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Patient demographics

A total of 1871 patients with moderate-to-severe depression were included in this analysis. In the full cohort, 29.9% of patients were male and the mean age at testing was 41.2 years, with 94.3% of patients being younger than 65 years old (Table 1). There were no significant differences in these demographics according to provider type. More than half of patients were under the care of a psychiatrist, regardless of age (Fig. 1). The mean BDI score at baseline was significantly higher among patients treated by psychiatrists compared to primary care providers (35.0 versus 33.5; $p < 0.01$), along with the mean number of psychotropic medications reported by patients at baseline (1.7 versus 1.4, $p < 0.01$ Table 1).

About three-quarters of the cohort had a clinical diagnosis of depression with or without co-occurring psychiatric conditions (Table 1). A significantly larger proportion of patients being seen by primary care providers had co-occurring conditions compared to those being seen by a psychiatrist ($p < 0.01$). The remaining patients did not have a clinical diagnosis of depression, but had moderate-to-severe depression according to their BDI score at baseline.

At baseline, a total of 1302 patients were taking at least one medication that was included on the combinatorial pharmacogenomic test report. Of these patients, 1047 (80.4%) patients were incidentally prescribed congruent medication(s) prior to combinatorial pharmacogenomic testing. At follow-up, 1360 patients were taking at least one medication that was included on the combinatorial pharmacogenomic test report. Of these patients, 1173 (86.3%) were prescribed medications that were congruent with their combinatorial pharmacogenomic test report (Table 1). A slightly higher proportion of primary care providers made congruent prescription decisions (87.6%) compared to psychiatrists (85.2%); however, this difference was not significant ($p = 0.21$).

3.2. Symptom improvement, response, and remission

In the full cohort, patients exhibited a 27.9% decrease in depression symptoms at follow-up compared to baseline ($p < 0.01$; Fig. 2). In addition, the rate of response at follow-up was 25.7% and the rate of remission was 15.2% (Fig. 2). Outcomes at follow-up among patients < 65 years of age were similar to the overall cohort: 27.4% symptom improvement relative to baseline ($p < 0.01$), a response rate of 25.2%, and a remission rate of 14.6% (Supplemental Fig. 1). Among patients ≥65 years of age, symptoms improved 36.7% from baseline to follow-up ($p < 0.01$), and response and remission rates were 34.0%, and 26.4%, respectively (Supplemental Fig. 1).

Patients experienced symptom improvement between their baseline visit and follow-up regardless of provider type; however, symptom improvement was significantly higher among patients treated by primary care providers (31.7%) compared to those treated by psychiatrists (24.9%, $p < 0.01$; Fig. 3). All analyses were adjusted for patient complexity (BDI, number of medications). When age and gender were added as covariates, symptom improvement remained significantly higher among patients treated by primary care providers compared to those treated by psychiatrists ($p < 0.01$).

The rate of response among patients treated by primary care providers (30.1%) was also significantly higher at follow-up compared to those treated by psychiatrists (22.3%, $p < 0.01$; Fig. 3). The corresponding odds of responding to treatment were 1.5 times greater for patients treated by primary care providers than those treated by psychiatrists (OR 1.5, 95% CI 1.2–1.8, $p < 0.01$). For patients treated by primary care providers, the rate of remission at follow-up was

Table 1
Demographics of patient sample, based on healthcare provider subgroup.

	Full Cohort	Primary Care Providers	Psychiatrists	p-value
Baseline Demographics				
Total, N (% of total)	1871 (100)	810 (43.3)	1061 (56.7)	–
Male, N (%)	560 (29.9)	232 (30.9)	362 (28.6)	0.29
Age at testing, Mean (SD)	41.2 (14.7)	41.0 (14.4)	41.1 (14.9)	0.85
Age < 65 years, N (%)	1765 (94.3)	768 (94.3)	997 (94.0)	0.43
Baseline BDI score, Mean (SD)	34.3 (9.2)	33.5 (8.9)	35.0 (9.4)	< 0.01
Number of psychiatric medications at baseline, Mean (SD)[a]	1.6 (1.2)	1.4 (1.1)	1.7 (1.3)	< 0.01
Referral Diagnosis				
Depression Only, N (%)	459 (24.5)	196 (24.2)	263 (24.8)	0.77
Depression and ≥1 additional psychiatric condition, N (%)	953 (50.9)	447 (55.2)	506 (47.7)	< 0.01
Psychiatric condition(s) other than depression, N (%)	459 (24.5)	167 (20.6)	292 (27.5)	< 0.01
Medication Congruence at Follow-Up				
Prescribed ≥1 medication on test report at follow-up, N (%)	1360 (72.7)	581 (71.7)	779 (73.4)	0.21
Prescribed only congruent medications at follow-up, N (%)[b]	1173 (86.3)	509 (87.6)	664 (85.2)	0.21

[a] Self-reported by patient.
[b] Percentages were calculated for patients who were on ≥1 medication from the combinatorial pharmacogenomic test report.

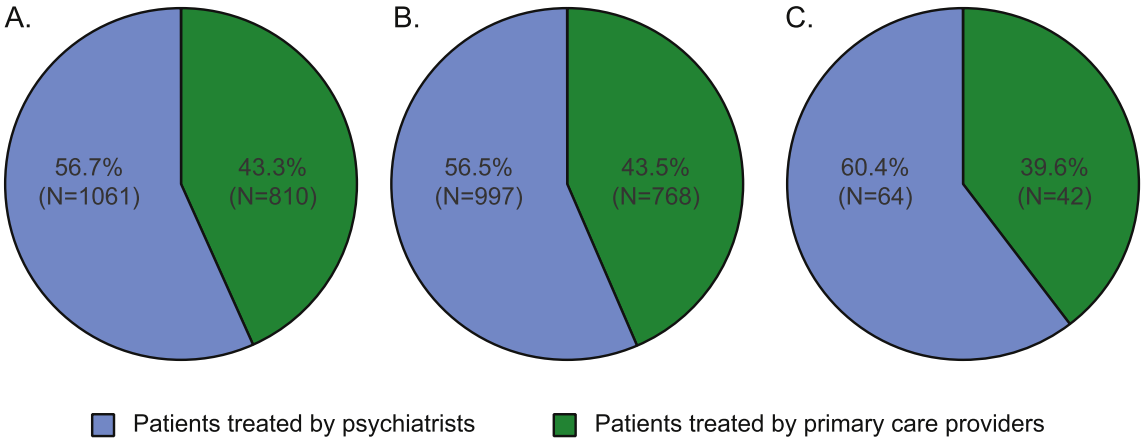

Fig. 1. Distribution of healthcare providers treating patients with moderate-to-severe depression (BDI ≥20) at baseline in (A) the overall sample, (B) patients younger than 65 years of age, and (C) patients 65 years of age and older.

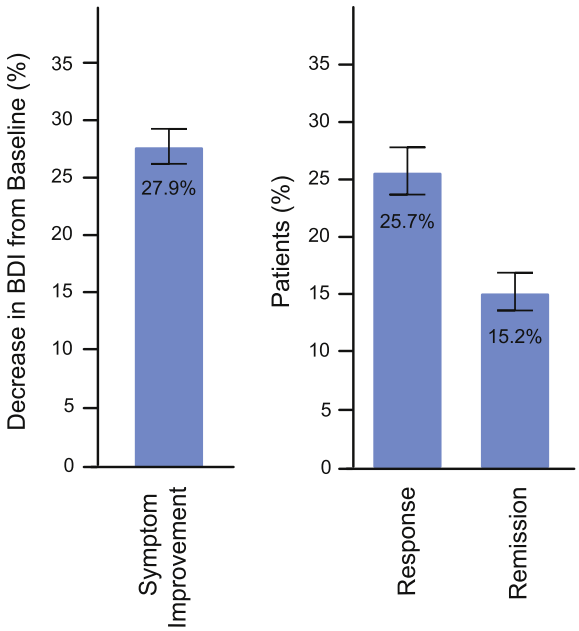

Fig. 2. Patients' symptom improvement, response rate, and remission rate from baseline to follow-up in the full cohort (N = 1871).

significantly higher compared to those treated by psychiatrists (19.5% versus 12.0%, p < 0.01; Fig. 3) and the odds of achieving remission were 1.8 times greater (OR 1.8; 95% CI 1.4–2.3; p < 0.01). Higher baseline BDI scores were associated with a lower likelihood of responding and remitting (data not shown).

The relationship between patient outcomes and healthcare provider type was similar in the overall cohort and in patients < 65 years of age, while patients ≥65 years of age had greater improvements (Supplemental Fig. 2). Patient outcomes were improved among those treated by primary care providers compared to psychiatrists when age and gender were included as additional covariates for patients < 65 years of age (p < 0.01) or patients ≥65 years of age (p = 0.29).

3.3. Congruence with the combinatorial pharmacogenomic test

Symptom improvement at follow-up was 29.5% for patients taking congruent medications compared to 27.0% for those taking one or more incongruent medications; however, this difference was not statistically significant (p = 0.33). Notably, 73.9% (867/1173) of patients who were taking congruent medications at follow-up were incidentally prescribed congruent medications prior to combinatorial pharmacogenomic testing at baseline. The response rate at follow-up was 28.0% among patients who were taking medications congruent with their combinatorial pharmacogenomic test report, compared to 21.4% of patients who were taking incongruent medications (p = 0.057). This

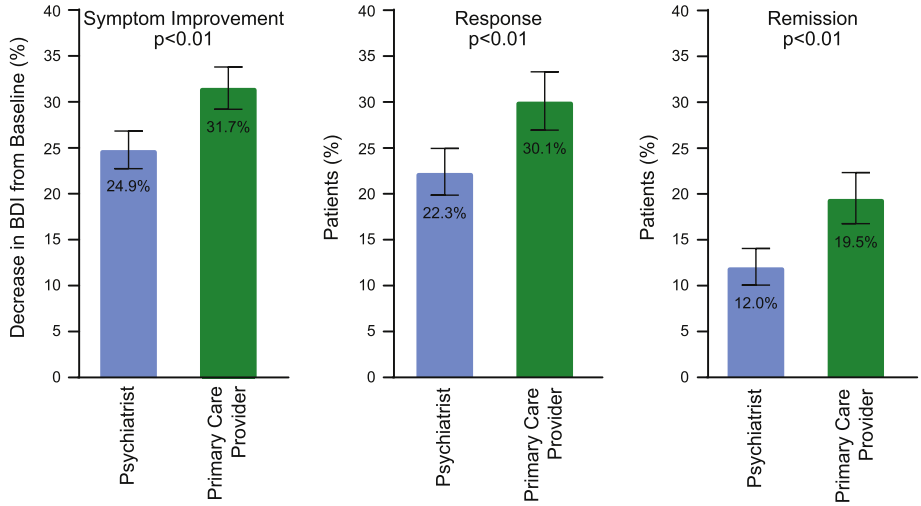

Fig. 3. Patients' symptom improvement, response rate, and remission rate from baseline to follow-up according to healthcare provider type in the overall sample (N = 1871).

represents a 31% relative improvement in the rate of response among patients taking congruent medications. Similarly, 16.4% of patients who were taking congruent medications achieved remission by follow-up, compared to 13.9% of patients who were taking incongruent medications (p = 0.39).

4. Discussion

In a large, prospective, open-label trial, the use of combinatorial pharmacogenomic testing to aid in medication selection for patients with moderate-to-severe MDD resulted in a significant reduction in depression symptoms after 8–12 weeks. The symptom reduction observed here (27.9%) was consistent with a recent double-blind randomized controlled trial reported by Greden et al. that utilized the same combinatorial pharmacogenomic test (N = 1167), wherein there was a 27.2% improvement in symptoms (Greden et al., 2018). Although the study presented here did not include a control arm, the rates of response and remission were also similar to the intervention arm of the randomized controlled trial (Greden et al., 2018). This adds to the body of evidence that use of combinatorial pharmacogenomic testing improves patient outcomes in MDD.

As access to specialized psychiatric services is decreasing in the U.S. and Canada (Bishop et al., 2016; Canadian Collaborative Centre for Physician Resources, 2012; National Council Medical Director Institute, 2017; Thomas et al., 2009), primary care providers are often the main point of contact for patients with depression (Vasiliadis et al., 2007). In this study, approximately 43% of patients were treated by a primary care provider; this is likely an underestimation relative to the general population, as a large proportion of patients recruited to the IMPACT study were patients of the tertiary care hospital, CAMH. The present study demonstrated that treatment guided by combinatorial pharmacogenomics was associated with significantly greater improvement in patient outcomes for those treated by a primary care provider compared to a psychiatrist. This suggests that the utility of combinatorial pharmacogenomic testing to guide psychotropic medication choice is not limited to the psychiatric care setting.

There are several potential explanations for observing better patient outcomes among those treated by primary care providers compared to psychiatrists. First, primary care providers had a slightly elevated degree of congruence with the combinatorial pharmacogenomic test result. Although this was not statistically significant, these findings were similar to those reported by Brown et al. (2017), where congruence was slightly higher among primary care providers compared to psychiatrists. This suggests that congruence may account for some of the differences in treatment response between patients treated by primary care providers and psychiatrists. In addition, patients may visit with their primary care providers more often than their psychiatrists. More frequent patient-doctor interaction may improve patient outcomes through additional opportunities for non-specific behavioral counselling or therapy. Further, primary care providers also treat the non-psychiatric health conditions of their mental health patients, which could result in an overall improvement in patient health.

Another factor to consider is the complexity of the patient's illness. Compared to patients treated in a primary care setting, those treated by psychiatrists possess more psychiatric comorbidities (Gaynes et al., 2007), which has been associated with a lower probability of achieving remission (Trivedi et al., 2006). In this study, baseline BDI score and the number of self-reported psychiatric medications at baseline were used as surrogate measures of patient complexity. Patients treated by primary care providers had a lower average BDI score and lower number of medications at baseline compared to those treated by psychiatrists. However, after adjusting for these factors, improvement in patient outcomes remained significantly higher among patients treated by primary care providers compared to psychiatrists. Because we were unable to adjust for patient comorbidities directly, the complexity of patient illness may not have been fully accounted for as a significant factor in the differences in patient outcomes based on provider type.

The utility in combinatorial pharmacogenomics lies in identifying medications that are unlikely to be effective and/or safe in an individual patient based on gene-drug interactions. Previous studies have demonstrated that changing from genetically incongruent to congruent medications is associated with significant improvements in patient outcomes (Greden et al., 2018; Hall-Flavin et al., 2013; Winner et al., 2013a, 2015). While there was a 31% relative improvement in patient response at follow-up for patients on congruent versus incongruent medications here, this was not statistically significant. This is likely related to the small number of patients taking incongruent medications at follow-up (13.8% of patients taking a medication included on the test report). The relatively small sample size limited our power to detect a difference in patient outcomes between those who were taking congruent and incongruent medications.

The relatively large proportion of patients included in this study who were incidentally prescribed genetically congruent medications at baseline (80%) is consistent with previous studies (Greden et al., 2018). However, this does not detract from the clinical utility of combinatorial pharmacogenomic testing demonstrated here for both the primary care and psychiatry settings. While the greatest utility in pharmacogenomic testing is expected for patients taking incongruent medications at baseline, patients may not respond to medication for reasons unrelated to gene-drug interactions. Combinatorial pharmacogenomic testing enables patients who are not responding to a genetically congruent medication to change to another congruent medication or adjust the dose of their existing medication. In addition, there is no way to know whether a patient is taking a genetically congruent medication at baseline. Therefore, pharmacogenomic testing provides information about whether a patient is not responding to medication due to gene-drug interactions (i.e. taking an incongruent medication) or another reason.

There were several limitations to the current study. The overall proportion of patients who saw a primary care provider may be lower in this IMPACT cohort than expected for a general population due to the availability of psychiatric services within the tertiary care centre, CAMH. In addition, the study design was naturalistic. As such, healthcare providers were not required to make prescription decisions based on the combinatorial pharmacogenomic test result and there was no control arm of patients who did not receive combinatorial pharmacogenomic testing. However, the naturalistic design of the current study is representative of combinatorial pharmacogenomic testing in real-world practice. Finally, diagnosis of MDD was based on self-reported BDI scores at baseline rather than their healthcare provider's diagnosis at the time of referral. While this provides a consistent metric to apply to the cohort, patients with comorbidities were included. Variation in patients' psychiatric comorbidities between those treated by primary care providers and psychiatrists may account for differences in response from baseline to follow-up.

In summary, this study demonstrated that patients with moderate-to-severe depression who had combinatorial pharmacogenomic testing had substantial improvements in depression outcomes. In addition, patients treated by primary care providers exhibited greater symptom improvement, rates of response, and rates of remission than those treated by psychiatrists. The study data suggest that if the physician follows the combinatorial pharmacogenomic test recommendations (i.e. congruence), better patient outcomes may result, in particular higher response rates. Previous studies have demonstrated the utility of combinatorial pharmacogenomic testing in psychiatric treatment settings (Hall-Flavin et al., 2012, 2013; Winner et al., 2013a, 2013b). The current study further shows that the use of this treatment approach in the wider primary care setting would be advantageous for patients with depression. Considering the shortage of psychiatric resources and the substantial burden of mental health care on primary care providers, these findings are promising for mental health care in the U.S. and Canada, and likely across other nations.

Disclosures

JAT, PED, AG, and BMD were employed by Assurex Health at the time of this study. JLK is an unpaid member of the Assurex Health Scientific Advisory Board. All other authors declare no conflicts of interest.

JAT contributed to data interpretation, manuscript drafting, and manuscript revisions. PED contributed to data analysis and interpretation, manuscript drafting, and manuscript revisions. NCV contributed to study concept and design and manuscript revisions. AS, DH, NB, and AG contributed to study design, conduct, and data acquisition. BMD and JLK contributed to study concept and design, data interpretation, and manuscript revisions. All authors approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.07.012.

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