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Pharmacogenetic testing in psychiatric inpatients with polypharmacy is associated with decreased medication side effects but not via medication changes

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Abstract

In psychiatric patients, medication adverse effects are regularly attributed to psychosomatic causes. However, many psychotropic medications are metabolized by cytochrome P450 (CYP450) enzymes. In the setting of polypharmacy, the activity of these enzymes may produce unfavorable drug-drug interactions (DDI) and drug-genotype interactions (DGI) that contribute to morbidity and mortality. This study sought to estimate the risk of adverse DDI and DGI in psychiatric inpatients with polypharmacy. We assessed whether medication changes made after pharmacogenetics (PGx) testing correlated with changes in side effects and overall improvement. Adult psychiatry inpatients with polypharmacy, defined as 5 or more scheduled prescription medications, completed the 24-item Antidepressant Side Effect Checklist (ASEC) questionnaire on enrollment and underwent PGx testing. Analysis of PGx results focused on whether the CYP2D6 and CYP2C19 phenotypes were “extreme,” defined as poor, poor to intermediate, or ultrarapid. Approximately 30 days after PGx results were sent to outpatient providers, patients were contacted to obtain their current medication list and ASEC and Clinical Global Impression

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Improvement (CGI-I) scores. A total of 80 patients were enrolled, and 52 (65%) completed follow-up. ASEC scores improved from 11.5 (±8.1) to 7.2 (±6.0) (p=0.0009). Mean CGI-I score was 2.7 (±1.4), between “minimal” to “much improved.” However, linear regression revealed that these improvements were not correlated with whether medications were changed. We concluded that the impact of drug-genotype interactions in this small sample of inpatients with polypharmacy was low, and that patient improvement was related not to PGx-guided medication changes but to other treatments during hospitalization.

Keywords

Polypharmacy; pharmacogenetics; cytochrome P450; polymorphism; drug-drug interaction; drug-genotype interaction

Introduction

The prevalence of polypharmacy is increasing in the United States, where an estimated 10% of the population and 30% of older adults are taking five or more drugs concurrently (Gu et al., 2010; Sutherland et al., 2015; Bushardt et al., 2008; Quinn and Shah, 2017). This is partly a result of high rates of medical comorbidities (Ward et al., 2014), and it is worsened by over-prescribing and poor monitoring (Shehab et al., 2016; Kessler et al., 2016). Patients 60 years of age and older on antidepressants were shown to have the highest incidence of polypharmacy in a study conducted by Veterans Administration Healthcare System (Preskorn, 2006). Indirect consequences of polypharmacy may include exacerbation of drug-drug interactions, adverse drug reactions (ADRs), prescribing cascades, chronic dependence, and hospitalization (Sharp et al., 2019). ADRs account for four hospitalizations per 1000 people per year (Shehab et al., 2016). A meta-analysis found that ADRs were the fourth to sixth most common causes of death in the United States (Lazarou et al., 1998).

It is believed that pharmacogenetic (PGx) testing has the potential to reduce unnecessary polypharmacy and improve outcomes by guiding the selection of appropriate medications (Sharp et al., 2019). Over 85% of patients demonstrate significant genetic variation in the CYP450 genes that metabolize the majority of the most commonly prescribed medications (Evans and Relling, 1999; Zanger and Schwab, 2013; Elliott et al., 2017). Abnormal metabolism increases the risk for adverse drug reactions and often leads to decreased medication effectiveness (Wilkinson, 2005; Cardelli et al., 2012). Interactions involving genes cause approximately 47% of significant interaction warnings (Verbeurgt et al., 2014; Hocum et al., 2016). However, factors including age, gender, inflammation and comorbidities may also contribute to altered CYP450 activity (Zanger and Schwab, 2013).

One mechanism by which PGx testing may reduce polypharmacy is through identification of interactions that prompt prescribing cascades (Sharp et al., 2019). The authors noted that clinical support tools which integrate PGx data with other medication information may not reduce the total number of medications prescribed to a patient. Rather, such tools could reduce unnecessary or inappropriate prescribing, thus abating risks associated with polypharmacy.

There is evidence that reducing drug-genotype interactions could improve other outcomes. A prospective 2017 study randomized patients age 50 and older with polypharmacy to receive PGx testing (n=57) or control (n=53) (Elliott et al., 2017). The PGx group received medication recommendations to decrease drug-drug, drug-genotype and cumulative drug-drug-gene interactions. At 60 days follow-up, the PGx group had fewer re-hospitalizations and emergency department visits.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was established in 2009 to facilitate the translation of genetic test results into actionable prescribing decisions for drugs (Caudle et al., 2014). CPIC guidelines for CYP2D6 and CYP2C19 with respect to the serotonin selective reuptake inhibitors (SSRIs) citalopram, escitalopram, sertraline, paroxetine, and fluvoxamine include a 25 to 50% dose reduction if the medication's metabolizing enzyme is poor, as higher plasma concentrations may increase the probability of side effects. If a medication's metabolizing enzyme is ultrarapid, then an alternative medication is recommended, as lower or undetectable plasma concentrations may increase the probability of pharmacotherapy failure. No adjustments are needed if the enzyme is normal or intermediate.

Despite existing guidelines, routine use of pharmacogenetic data in clinical practice remains controversial. It is challenging to demonstrate clinical utility of a PGx test, and stakeholders disagree on how best to define that utility and the level of evidence to support recommendations (Gillis and Innocenti, 2014). Further, evidence for implementing pharmacogenetics testing in psychiatry in particular is mixed. A review of evidence for multiple combinatorial PGx decision support tools concluded that there is insufficient data to support the widespread use of combinatorial PGx testing in clinical practice (Zeier et al., 2018). However, it is noted that in certain clinical situations, particularly prediction of side effects, PGx testing may be beneficial. Several ethical issues are raised, including publication bias, as some products receive more investment than others, and scientific integrity, as authors may have financial interests in the outcome. A viewpoint article emphasized that comedication and environmental factors such as age, sex, diet, alcohol use, hormonal status, and general health tend to be more important than heritable determinants of drug metabolism (Zubenko et al., 2018). The authors note that extremely rapid or slow metabolism is relatively rare, and thus dosing should be guided by careful drug choice and monitoring rather than PGx data.

This study investigated the risk of DDI and DGI in psychiatric inpatients with polypharmacy, whether PGx testing might lead to medication changes which reduce that risk, and whether medication changes made after PGx testing correlated with changes in patient-reported side effect burden and overall improvement.

Materials and Methods

Subjects

Adult inpatients with polypharmacy were recruited from the mood disorders unit (consisting primarily of patients with unipolar or bipolar depressive disorders), the acute psychiatry unit (patients with depressive, psychotic, and/or substance use disorders) and the

medical/geriatric unit (patients with psychiatric but also co-morbid medical illness and/or neurocognitive disorders). Patients were usually in acute distress and most with suicidal ideation, as expected as part of the admission criteria for a psychiatric inpatient unit. They were approached within 3 weekdays of admission and enrolled if appropriate. There were no exclusion criteria for diagnosis, and anxiety and personality disorders were frequent co-morbidities. However, patients were carefully assessed for the capacity to consent, and most patients with psychotic disorders or dementias were excluded. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. Patients were excluded if they had PGx testing within the previous 5 years. The study was carried out in accordance with the latest version of the Declaration of Helsinki. Our Institutional Review Board (IRB) approved this project.

Polypharmacy

Polypharmacy was defined as 5 or more scheduled prescription oral medications. Proton pump inhibitors such as omeprazole were counted as prescription medications given their previous recent prescription status, and as these are metabolized by CYP2C19. Antihistamines such as cetirizine were also counted as prescription medications which was their previous status. If an as-needed medication, such as clonazepam, was used consistently and daily, it would effectively be a scheduled medication and counted as such.

Drug-Drug Interactions (DDI)

The relative risk of DDI for the medications on admission was assessed. Medications were entered into the drug interaction checker on Micromedex, which is used by our institution. A systematic review of drug-drug interaction software found that Micromedex was the most commonly used among publications studied, with users reporting high sensitivity and reliability (Roblek et al., 2015).

The total number of drug-drug interactions was recorded for each patient, regardless of severity. The severity could range from unknown to minor, moderate, major or contraindicated, with a fair, moderate or excellent level of documentation. Although some interaction warnings were less useful than others, all were included for consistency. As an example, the combination of lisinopril and hydrochlorothiazide generated the warning that “concurrent use of ACE inhibitors and thiazide diuretics may result in reduction of blood pressure.” While important, this alert requires contextualization with the patient’s clinical history and goals of treatment. At the same time, aggressively lowered blood pressure may result in blurred vision and light-headedness on standing. Thus, we felt that it was reasonable to include each potential drug-drug interaction in our analysis. Other interactions, such as drug-food or drug-tobacco, were not considered. We arbitrarily defined the mean number of Micromedex-determined DDI across all patients in our cohort as medium risk. One standard deviation above was defined as high risk, and one standard deviation below was defined as low risk.

Pharmacogenetic Testing

PGx testing was performed from buccal samples using the OneOme (Minneapolis, MN) RightMed test. Genes of interest included those encoding pharmacokinetic enzymes

CYP2D6, CYP2C19, CYP1A2, CYP2B6, CYP2C9, CYP3A4, and CYP3A5 as well as the serotonin transporter gene. There were other genes as part of the test panel, such as that encoding the Opioid Receptor Mu 1 (OPRM1), but not used in this analysis. The phenotypes designated by the laboratory included poor, intermediate, normal, rapid, and ultrarapid, with in-between categories possible such as "poor to intermediate."

Drug-Genotype Interactions (DGI)

DGI analysis focused on whether the CYP2D6 and CYP2C19 phenotypes were "actionable" (using CPIC guidelines) and the medications prescribed to the patient. If the CYP2D6 and/or CYP2C19 phenotypes were poor, poor to intermediate, or ultrarapid, then the result was defined as in the "extreme" category. The risk for DGI was classified as low, medium, or high. Low risk comprised non-extreme CYP2D6 or CYP2C19, medium risk comprised CYP2D6 or CYP2C19 extreme but no medications metabolized by the corresponding enzyme, and high risk comprised an extreme result and a medication metabolized by the corresponding enzyme. For example, if a patient were a poor metabolizer of CYP2D6 and prescribed escitalopram (mainly metabolized by CYP2C19), the risk would be medium. Typically, medications are metabolized by more than one pathway, and only the major pathway was considered. For example, nortriptyline is metabolized by CYP2D6 and CYP2C19, but since CYP2C19 is a minor pathway, it was considered a CYP2D6-metabolized medication.

Furthermore, we introduced the term "compatible," defined as the use of medications metabolized by CYP2D6 or CYP2C19 when the corresponding gene did not have extreme results (that is, the phenotype would be intermediate or normal). For example, if a patient were prescribed escitalopram and the CYP2C19 phenotype was intermediate, then that would be compatible. If that patient's CYP2C19 phenotype were ultrarapid, then the medication and genotype would be not compatible. By our definition, DGI high risk is equivalent to "not compatible." Note that our definition of "compatible" is different from the concept of "congruent," defined as whether a prescribed medication was in the "use as directed" column of some laboratory test panels (Winner et al., 2015).

Rating Scales

Medication side effects were assessed with the Antidepressant Side Effect Checklist (ASEC), a 24-item questionnaire (Uher et al., 2009). The ASEC was developed as a self-report instrument to measure 21 potential adverse reactions to antidepressants, including dry mouth, nausea or vomiting, and drowsiness. For each item, participants rate the severity of the symptom on a four-point scale with 0=absent, 1=mild, 2=moderate, and 3=severe. Participants may also specify whether they believe a symptom is likely to be a medication side effect. Three free-text questions assess whether any other symptoms have been present, whether the patient has had treatment for a side effect, and whether any side effects have led to discontinuation of a drug. Patients were asked to include all of their medications, not just antidepressants, when answering the questionnaire. Total ASEC scores were calculated by summing the severity ratings for each item. Thus, scores could range from 0 to 63.

Overall improvement at follow-up was assessed with the one-item Clinical Global Impression Improvement (CGI-I) tool, which is rated on a 0 to 7 scale with 0 = “not assessed,” 1= “very much improved,” and 7= “very much worse.” The CGI was developed for use in National Institute of Mental Health (NIMH)-sponsored clinical trials to provide a brief assessment in the clinician’s view of the patient’s global functioning (Guy, 1976; Busner and Targum, 2007). In this study, patients rated global functioning themselves.

Procedures

On enrollment, the study coordinator interviewed the patient to confirm the medication list and to complete the ASEC. A clinical member of the patient’s care team, typically a nurse practitioner, physician assistant, or physician, obtained the buccal swab for PGx testing. PGx results were reviewed by the principal investigator, and a pharmacist consultation was also obtained. The principal investigator communicated the results to the clinical team taking care of the patient, noting whether medication changes were recommended to minimize DDI and DGI. If the patient was no longer in the hospital, the results were communicated to the patient’s outpatient providers.

Approximately 30 days after the PGx results and recommendations were sent to the patient’s prescriber, the study coordinator telephoned each patient and obtained an updated medication list, the follow-up ASEC score, and the CGI-I. For patients who were lost to follow-up, the hospital discharge medications were taken as the 30-day follow-up medications, so they could still be included in the assessment of compatibility of medications at follow-up. As per our hospital practice for ensuring accuracy, the medications on the hospital discharge summary were cross-referenced by a pharmacist against medications taken in the hospital.

Outcomes

The primary outcome was improvement in medication side effects as measured by the ASEC. Other variables were collected, including whether medication changes were made by the time of follow-up; whether medications on admission and at follow-up were compatible; and whether electroconvulsive therapy (ECT) was part of the treatment. Short-term memory loss and cognitive impairments lasting up to a few months can be experienced with ECT, and thus the ECT variable was collected in order to control for its potential influence on the follow-up questionnaires.

Statistical Analysis

Means and standard deviations were presented for continuous variables, including the number of medications metabolized byCYP450 enzymes; ASEC scores on enrollment and follow-up; and CGI-I scores on follow-up. Change in ASEC score from enrollment to follow-up was compared using the paired t-test. Oneway analysis was performed to detect relationships between the change in ASEC score or the CGI-I score and the following three categorical variables: the presence of medication change, drug-genotype compatibility on admission and drug-genotype compatibility on follow-up. Linear regression analysis was performed to assess the relationship between side effect change and the presence of a medication change, adjusted for age, gender and ECT treatment. The level of statistical

significance was set to $p < 0.05$ (two-sided). Statistical analysis was performed using JMP Pro 14.1.0 (Cary, NC).

Results

Subjects

Eighty patients were enrolled, but 5 were withdrawn prior to PGx testing: three had technical or logistical issues such that the buccal swab was not collected, one had insufficient DNA per the laboratory, and one was found to have had PGx testing within 5 years (an exclusion criterion). A total of 75 patients (mean age 48.4 years, 72% female) successfully underwent PGx testing, and 52 (69%) completed follow-up. There were no statistically significant differences between those patients who completed versus those who were lost to follow-up in terms of age (46.9 years vs 49.0 years on average, p=0.56) or gender (71.2% female vs 73.9% female, p=0.65). Of the 80 enrolled patients, 74 (92.5%) carried a diagnosis of major depressive disorder, bipolar disorder, persistent depressive disorder, or an unspecified mood disorder. Only 6 patients (7.5%) did not have a mood disorder diagnosis. Of the 80 patients, 20 (25.0%) received ECT, and 12 (23.1%) of the 52 completers received ECT.

Medications

Approximately 150 unique medications were used at hospital enrollment, and the 25 most common ones are listed in Table 1. In reviewing the top 13 medications, only three (bupropion, duloxetine, pantoprazole) were metabolized by pathways which were not CYP3A4 (which is most commonly normal) or metabolized at all. Of the remaining 12, only five had involvement of CYP2D6 or CYP2C19, suggesting fewer risks of drug-gene interactions as the other seven were not metabolized or metabolized by pathways which did not have wide variability (such as CYP3A4). These observations suggest that the most commonly used medications were at lower risk of posing drug-gene interactions.

A total of 17 antidepressants were prescribed at enrollment: amitriptyline (n=1), bupropion (20), citalopram (3), clomipramine (1), desvenlafaxine (1), doxepin (1), duloxetine (21), escitalopram (3), fluoxetine (6), mirtazapine (8), nortriptyline (3), paroxetine (6), sertraline (4), trazodone (34) (used mostly for insomnia), venlafaxine (11), vilazodone (1), and vortioxetine (5). Of these 17, only three (desvenlafaxine, vilazodone, trazodone) are metabolized by CYP3A4, indicating that the majority of antidepressants used were subjected to the variability of CYP450 polymorphisms.

Antipsychotic medications prescribed at enrollment consisted of aripiprazole (n=12), lurasidone (7), olanzapine (3), risperidone (5), and quetiapine (16). Of these, aripiprazole and risperidone are metabolized by CYP2D6, olanzapine by CYP1A2 and CYP2D6, and lurasidone and quetiapine by CYP3A4.

Other medications used for psychiatric purposes included alprazolam, atomoxetine, buspirone, clonazepam, clorazepate, dextroamphetamine/amphetamine, disulfuram, gabapentin, lamotrigine, lisdexamfetamine, lithium, lorazepam, methadone, methylphenidate, naltrexone, prazosin, temazepam, valproic acid, and zolpidem. Most of

these medications are metabolized by CYP3A4, with exceptions such as atomoxetine and dextroamphetamine/amphetamine by CYP2D6, and lithium being renally excreted.

Table 2 shows the mean number of medications per patient on hospital admission by CYP450 pathway. Not surprisingly, the most common pathway was CYP3A4 (2.4 medications per patient), the second most common was CYP2D6 (1.2), and the third most common CYP2C19 (0.6).

Drug-Drug Interactions

For the 80 patients, the mean (±SD) number of medications on admission was 7.6 (± 2.3). The mean number of DDI reported by Micromedex was 4.5 (±3.4). Accordingly, 18 (22.5%) patients were identified as having relative low risk (DDI = 0–1), 45 (56.3%) as medium (DDI = 2–7), and 17 (21.3%) as high (DDI = 8–13). A total of 357 DDI were identified by Micromedex and distributed as follows: 1 (0.3%) “minor” severity interaction with a “fair” level of documentation (“minor, fair”); 2 (0.6%) “minor, excellent;” 31 (8.7%) “moderate, fair;” 38 (10.6%) “moderate, good;” 6 (1.7%) “moderate, excellent;” 231 (64.7%) “major, fair;” 35 (9.8%) “major, good;” 10 (2.8%) “major, excellent;” 3 (0.8%) “contraindicated, fair.” The majority (64.7%) fell in the “major, fair” category. As planned, all interactions were included regardless of severity, documentation, or clinical utility. For example, duloxetine and trazodone triggers a “major” interaction warning of “fair” documentation that concomitant use increases the risk of serotonin syndrome. In clinical practice, these medications are commonly used together without practical side effects. Thus, highlighting potential DDIs might be overreporting what is not clinically significant.

Pharmacogenetic Testing

The distribution of PGx results is shown in Table 2. Of the 75 patients who completed PGx testing, 21 (28.0%) had extreme CYP2D6 or CYP2C19 phenotypes. Normal was the most common phenotype for CYP2B6 (38.7%), CYP2C9 (74.7%), CYP2D6 (37.3%), CYP2C19 (30.7%), and CYP3A4 (90.7%). Rapid was the most common phenotype for CYP1A2 (88.0%) and poor was the most common phenotype for CYP3A5 (85.3%).

Drug-Genotype Interactions

Of 75 patients who successfully completed PGx testing, 54 (72.0%) were classified as low risk, 7 (9.3%) as medium risk, and 14 (18.7%) as high risk. Sixty-one patients (81.3%) were “compatible” with their admission medications. Only two patients did not retain their admission compatibility status: one patient went from incompatible to compatible at discharge, and one patient went from compatible to incompatible at 30 days follow-up.

Of the 52 patients who completed the study, 36 (69.2%) had their medications changed by the 30 days follow-up, and 43 (82.7%) were “compatible” with their follow-up medications. Of the 14 patients considered “high risk” of DGI on admission, 6 were lost to follow-up. The 8 who completed remained incompatible with their medications at follow-up. Five of the 8 underwent a medication change. In this high risk group, oneway analysis of change in ASEC score by whether medications were changed gives a non-significant result (p=0.29).

Outcomes

The mean (±SD) baseline ASEC score was 11.5 (±7.5) for the full 80 patients. When limiting the dataset to only the completers (n=52), the baseline ASEC score remained 11.5 (±8.1) compared to the follow-up of 7.2 (±6.0), p=0.0009. Oneway analysis of change in ASEC score by whether patients were compatible with their enrollment medications and follow-up medications revealed no significant relationships (p=0.63 and p=0.83, respectively). A linear regression model showed that the improvement in ASEC scores (n=52) from baseline to follow-up did not correlate with whether medications were changed (p=0.85), even after adjusting for age, gender and ECT treatment (p=0.97).

If we restrict analysis to the 21 patients who demonstrated poor, poor to intermediate, or ultrarapid activity at CYP2D6 and CYP2C19, eight were lost to follow-up. Of the 13 remaining, medication changes were still not significantly correlated with the change in ASEC score (p=0.41).

The mean CGI-I score was 2.7 (±1.4), falling between “minimally” (score=3) to “much improved” (score=2). Oneway analysis of CGI-I score by whether patients were compatible with their enrollment medications and follow-up medications revealed no significant relationships (p=0.89 and p=0.87, respectively). A linear regression model showed that the CGI-I score (n=52) did not correlate with whether medications were changed (p=0.73), even after adjusting for age, gender and ECT treatment (p=0.64).

Discussion

This study investigated whether PGx testing in psychiatric inpatients with polypharmacy could lead to medication changes resulting in decreased medication side effects. While there was a statistically significant improvement in medication side effects from baseline to 30 days following PGx results, the improvement was not correlated with whether medications were changed.

Several factors possibly contribute to this negative finding. First is the low baseline incidence of poor and ultrarapid metabolizers of CYP2D6 and CYP2C19, which was only 21 patients (28.0%) in our study. While 28% is not an insignificant amount, what makes a drug-gene combination “actionable” (implying increased side effects or non-response) is that a medication metabolized by that pathway is prescribed. PGx testing was conducted reactively rather than preemptively in this study, and it was by chance that the majority of medication regimens (81.3%) on enrollment were already “compatible” with the patient’s phenotype. Changes made by follow-up did not substantially impact compatibility. Thus, the drug-gene combinations used at admission and follow-up serendipitously conferred a lower risk of side effects, even without specific awareness of PGx. Future studies focusing on greater numbers of patients with extreme phenotypes using case-control or cohort methodologies may reveal significant results.

Another factor relates to the controversy of whether drug-gene interactions are truly associated with side effects. While there is evidence to support that CYP450 phenotype affects serum levels (Hicks et al., 2015; Scordo et al., 2005; Guzey and Spigset, 2006;

Charlier et al., 2003; Rudberg et al., 2008), the link to side effects is unclear. Some smaller studies do report this association (Zourková and Hadasová, 2003; Grasmäder et al., 2004; Suzuki et al., 2006), but larger studies are generally negative or inconclusive (Hodgson et al., 2015; Peters et al., 2008). In a meta-analysis, CYP2C19 poor metabolizers had a higher risk of gastrointestinal, neurologic, and sexual side effects at weeks 2–4 during treatment with citalopram/escitalopram, but by week 9, no difference in total side effect burden was observed among differing phenotypes (Fabbri et al., 2018).

However, several PGx panel studies have reported improvement in side effects or medication tolerability after PGx testing. In a naturalistic study, significant decreases in medication side effects were found at 3 months (Brennan et al., 2015). As in our study, there was no treatment-as-usual comparison group, so the contribution of PGx testing to these improvements could not be evaluated. In a prospective randomized trial, tolerability was better in the PGx-guided group than in controls at 6 weeks and maintained at 12 weeks (Pérez et al., 2017). Given the consistently higher side effect burden in the control group, this result may challenge the general trend that antidepressant side effects are more frequent early in treatment and then decrease (Uher et al., 2009; Fabbri et al., 2018). In another 12-week prospective randomized study, the PGx-guided group had significantly fewer medication tolerability problems, lower risk of taking sick leave (4% versus 15%, p=0.0272) and reduced duration of sick leave compared to controls (4.3 days versus 7.7 days, p=0.014) (Singh, 2015).

The relationship between phenotype and side effects has also been evaluated using the concept of congruence. The Genomics Used to Improve DEpression Decisions (GUIDED) trial found that patients taking “incongruent” medications prior to baseline who switched to “congruent” medications experienced greater symptom improvement, response and remission compared to those remaining incongruent (Greden et al., 2019). There were no statistically significant differences between the guided-care arm and the treatment-as-usual arm regarding the mean number of side effects at week 8, or the proportion of patients experiencing side effects. However, patients who switched from incongruent to congruent medications by week 8 had a significantly lower mean number of side effects compared to those who remained incongruent. In our study, given that only one patient switched from “incompatible” to “compatible” at discharge, and was eventually lost to follow-up, it was not possible to conduct a similar assessment of the impact of improved compatibility on side effect burden.

Other factors contributing to our negative findings could relate to the patient population and study duration. Psychiatric inpatients are hospitalized due to acute stressors, conferring less stability than outpatients, possibly affecting the patient’s report of side effects, even at follow-up. During hospitalization, patients improve not only because of biological treatments, but also psychological interventions, which decrease the necessity of medication changes. Also, the study duration of about 45 days (typically one week to obtain PGx test results, another week for the investigators to review the results and send the letter to the clinical team, and then the 30 day follow-up) was not as lengthy as comparable outpatient studies showing positive results which stretch towards 12 weeks. A longer study duration would ensure that the patient had a post-hospitalization visit with the outpatient provider

and a chance to change medications if indicated, then waiting the appropriate time to assess whether side effects diminished.

Of course, another possibility to explain our negative findings is that the null hypothesis that PGx does not impact side effects is true. At least in our real-world scenario of acute psychiatric inpatients with polypharmacy and a relatively short follow-up duration, that seems to be the case.

There were several limitations of this study including a small sample size, a large number of patients lost to follow-up, a lack of a comparison group, and no direct guidance for outpatient prescribers for changing medications toward more drug-genotype compatibility. In general for PGx studies, one variable is the decision-making of the clinicians. Despite a growing number of laboratories available to perform testing, there is a lack of guidelines and training for implementation into clinical practice. This can be attributed to lack of formal recommendations regarding the utility of these tests, and to lack of tools for interpreting and utilizing PGx information (Sharp et al., 2019). In our study, while the PGx results were communicated to the patient's clinical team, there was no obligation for the team to review, understand, or implement any changes. We did not survey the treating clinicians as to their knowledge or reasoning for changing or not changing medications.

Our analysis focused on CYP2D6 and CYP2C19, as CPIC recommendations regarding antidepressants have been established for these enzymes. Because a range of metabolic activity is likely present in the setting of polypharmacy, this focus presents a limitation. However, the 75 patients who underwent PGx testing demonstrated normal (12.0%) or rapid (88.0%) metabolism at CYP1A2 and intermediate to normal (9.3%) or normal (90.7%) metabolism at CYP3A4. These phenotypes are effectively normal. One patient (1.3%) demonstrated poor to intermediate metabolism at CYP2C9, yet was not prescribed a CYP2C9-metabolized medication, suggesting drug-genotype compatibility across enrolled patients at this enzyme. Eight patients (10.7%) demonstrated poor to intermediate metabolism at CYP2B6. Of these, one patient was prescribed buproprion, a CYP2B6 substrate. Although certain CYP2B6 polymorphisms have been shown to affect bupropion levels, the impact of CYP2B6 polymorphisms on bupropion efficacy in depression is unclear (Høiseth et al., 2015). Further, analysis of CYP2C9 and CYP2B6 is made difficult by the small sample size of extreme phenotypes and incompatible interactions in our study. Finally, 64 patients (85.3%) demonstrated poor metabolic activity at CYP3A5. Because most medications were developed in patients with poor CYP3A5 activity, dose changes are usually not required. However, there are important exceptions with respect to ethnicity, gender and specific CYP3A5-metabolized medications, including tacrolimus and saquinavir (Zanger and Schwab, 2013).

Although certain phenotypes are not currently "actionable" by CPIC guidelines for antidepressants, they may still have the potential to influence outcomes. One mechanism is through enzymatic interactions with other drugs and substances. For example, CYP1A2 activity is challenging to ascertain from a genetics perspective alone, as CYP1A2 can be induced by smoking tobacco and cruciferous vegetable intake (Gunez et al., 2009). In addition, combined polymorphisms across several enzymes may produce unfavorable

interactions. For example, five of seven patients with CYP3A4 intermediate to normal phenotypes demonstrated either CYP2D6 or CYP2C19 intermediate metabolizer phenotypes as well. In theory, patients with reduced function of both CYP2D6 and CYP3A4 may undergo reduced overall metabolism of dual metabolized drugs, such as aripiprazole. However, this situation is not considered actionable as guidelines do not exist for combined polymorphisms, with the exception of tricyclic antidepressants. At the same time, FDA prescribing information for aripiprazole includes the recommendation that a 75% dose decrease be applied in those with poor metabolic activity at CYP2D6 who are also taking a CYP3A4 inhibitor. Thus, an absence of guidelines likely represents a gap in available literature.

Another limitation of our study is the inherent difficulty in trying to classify medication regimens as “compatible” or “congruent” with the all-or-nothing categorization by medication without regard to dose. For example, patients who are poor 2D6 metabolizers and prescribed nortriptyline would be classified as not “compatible,” and recommended to avoid nortriptyline. However, that patient could be prescribed nortriptyline, as long as the dose is lower and drug levels are monitored. Additionally, some studies report that medications not “compatible” with genotype, such as citalopram in poor 2C19 metabolizers and venlafaxine XR in ultrarapid 2D6 metabolizers, were actually associated with better remission (Mrazek et al., 2011; Ahmed et al., 2019).

We concluded that the impact of drug-genotype interactions in this small sample of inpatients with polypharmacy was low. The improvement in side effects was not related to medication changes but possibly to other treatments during inpatient hospitalization, including psychological interventions. The placebo effect of making a medication change, or of receiving PGx testing, might also contribute to patient improvement. While our study found a statistically and clinically significant improvement in patient side effects from baseline to follow-up, further studies will be needed to assess the influence of pharmacogenetics testing and recommendations on such improvements.

References

Ahmed AT, Biernacka JM, Jenkins G, Rush AJ, Shinozaki G, Veldic M, Kung S, Bobo WV, Hall-Flavin DK, Weinshilboum RM, Wang L, Frye MA, 2019. Pharmacokinetic-Pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder with history of citalopram / escitalopram treatment failure. J Affect Disord. 246, 62–68. doi: 10.1016/j.jad.2018.12.021. [PubMed: 30578947]

Brennan FX, Gardner KR, Lombard J, Perlis RH, Fava M, Harris HW, Scott R, 2015. A Naturalistic Study of the Effectiveness of Pharmacogenetic Testing to Guide Treatment in Psychiatric Patients With Mood and Anxiety Disorders. Prim Care Companion CNS Disord.17(2). doi: 10.4088/PCC.14m01717.

Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN, 2008. Polypharmacy: misleading, but manageable. Clin Interv Aging. 3(2), 383–389. doi: 10.2147/cia.s2468. [PubMed: 18686760]

Busner J, Targum SD, 2007. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 4(7), 28–37.

Cardelli M, Marchegiani F, Corsonello A, Lattanzio F, Provinciali M, 2012. A review of pharmacogenetics of adverse drug reactions in elderly people. Drug Saf. 35 Suppl 1, 3–20. doi: 10.1007/BF03319099. [PubMed: 23446782]

Caudle KE, Klein TE, Hoffman JM, Muller DJ, Whirl-Carrillo M, Gong L, McDonagh EM, Sangkuhl K, Thorn CF, Schwab M, Agundez JA, Freimuth RR, Huser V, Lee MT, Iwuchukwu OF, Crews KR, Scott SA, Wadelius M, Swen JJ, Tyndale RF, Stein CM, Roden D, Relling MV, Williams MS, Johnson SG, 2014. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 15(2), 209–217. doi: 10.2174/1389200215666140130124910. [PubMed: 24479687]

Charlier C, Broly F, Lhermitte M, Pinto E, Ansseau M, Plomteux G, 2003. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Ther Drug Monit. 25(6), 738–742. doi: 10.1097/00007691-200312000-00014. [PubMed: 14639062]

Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK, 2017. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS One. 12(2):e0170905. doi: 10.1371/journal.pone.0170905.

Evans WE, Relling MV, 1999. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 286(5439), 487–491. doi: 10.1126/science.286.5439.487. [PubMed: 10521338]

Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, Mors O, Placentino A, Rietschel M, Souery D, Breen G, Curtis C, Lee SH, Newhouse S, Patel H, O'Donovan M, Lewis G, Jenkins G, Weinshilboum RM, Farmer A, Aitchison KJ, Craig I, McGuffin P, Schruers K, Biernacka JM, Uher R, Lewis CM, 2018. Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: Meta-analysis of data from genome-wide association studies. Eur Neuropsychopharmacol. 28(8), 945–954. doi: 10.1016/j.euroneuro.2018.05.009. [PubMed: 30135031]

Gillis NK, Innocenti F, 2014. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. Clin Pharmacol Ther. 96(6), 655–657. doi: 10.1038/clpt.2014.185. [PubMed: 25399714]

Grasmäder K, Verwohlt PL, Rietschel M, Dragicevic A, Müller M, Hiemke C, Freymann N, Zobel A, Maier W, Rao ML, 2004. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol. 60(5), 329–336. doi: 10.1007/s00228-0040766-8. [PubMed: 15168101]

Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, DeBattista C, Conway CR, Forester BP, Mondimore FM, Shelton RC, Macaluso M, Li J, Brown K, Gilbert A, Burns L, Jablonski MR, Dechairo B, 2019. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 111, 59–67. doi: 10.1016/j.jpsychires.2019.01.003. [PubMed: 30677646]

Gu Q, Dillon CF, Burt VL, 2010. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. NCHS Data Brief. (42), 1–8.

Gunes A, Ozbey G, Vural EH, Uluoglu C, Scordo MG, Zengil H, Dahl ML, 2009. Influence of genetic polymorphisms, smoking, gender and age on CYP1A2 activity in a Turkish population. Pharmacogenomics. 10(5), 769–778. doi: 10.2217/pgs.09.22. [PubMed: 19450128]

Guy W, 1976. ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Güzey C, Spigset O, 2006. Low serum concentrations of paroxetine in CYP2D6 ultrarapid metabolizers. J Clin Psychopharmacol. 26(2), 211–212. doi: 10.1097/01.jcp.0000203225.79364.85. PubMed PMID: 16633156. [PubMed: 16633156]

Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, 2015. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 98(2), 127–134. doi: 10.1002/cpt.147. [PubMed: 25974703]

Hocum BT, White JR Jr., Heck JW, Thirumaran RK, Moyer N, Newman R, Ashcraft K, 2016. Cytochrome P-450 gene and drug interaction analysis in patients referred for pharmacogenetic testing. Am J Health Syst Pharm. 73(2), 61–7. doi: 10.2146/ajhp150273. [PubMed: 26721535]

Hodgson K, Tansey KE, Uher R, Dernovšek MZ, Mors O, Hauser J, Souery D, Maier W, Henigsberg N, Rietschel M, Placentino A, Craig IW, Aitchison KJ, Farmer AE, Dobson RJ, McGuffin P, 2015. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl). 232(14), 2609–2617. doi: 10.1007/s00213-015-3898-x. [PubMed: 25761838]

Høiseth G, Haslemo T, Uthus LH, Molden E, 2015. Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data. Ther Drug Monit. 37(5), 589–593. doi: 10.1097/FTD.0000000000000183. [PubMed: 25565674]

Kessler C, Ward MJ, McNaughton CD, 2016. Reducing Adverse Drug Events: The Need to Rethink Outpatient Prescribing. JAMA. 316(20), 2092–2093. doi: 10.1001/jama.2016.16392. [PubMed: 27893112]

Lazarou J, Pomeranz BH, Corey PN, 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279(15), 1200–1205. doi: 10.1001/jama.279.15.1200. [PubMed: 9555760]

Mrazek DA, Biernacka JM, O'Kane DJ, Black JL, Cunningham JM, Drews MS, Snyder KA, Stevens SR, Rush AJ, Weinshilboum RM, 2011. CYP2C19 variation and citalopram response. Pharmacogenet Genomics. 21(1), 1–9. doi: 10.1097/fpc.0b013e328340bc5a. [PubMed: 21192344]

Peters EJ, Slager SL, Kraft JB, Jenkins GD, Reinalda MS, McGrath PJ, Hamilton SP, 2008. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One. 3(4), e1872. doi: 10.1371/journal.pone.0001872. [PubMed: 18382661]

Preskorn SH, 2006. Pharmacogenomics, informatics, and individual drug therapy in psychiatry: past, present and future. J Psychopharmacol. 20(4 Suppl), 85–94. doi: 10.1177/1359786806066070. [PubMed: 16785276]

Pérez V, Salavert A, Espadaler J, Tuson M, Saiz-Ruiz J, Sáez-Navarro C, Bobes J, Baca-García E, Vieta E, Olivares JM, Rodriguez-Jimenez R, Villagrán JM, Gascón J, CañeteCrespillo J, Solé M, Saiz PA, Ibáñez Á, de Diego-Adeliño J, Menchón JM, 2017. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. 17(1), 250. doi: 10.1186/s12888-017-1412-1. [PubMed: 28705252]

Quinn KJ, Shah NH, 2017. A dataset quantifying polypharmacy in the United States. Sci Data. 4, 170167. doi: 10.1038/sdata.2017.167.

Roblek T, Vaupotic T, Mrhar A, Lainscak M, 2015. Drug-drug interaction software in clinical practice: a systematic review. Eur J Clin Pharmacol. 71(2), 131–142. doi: 10.1007/s00228-0141786-7. [PubMed: 25529225]

Rudberg I, Hermann M, Refsum H, Molden E, 2008. Serum concentrations of sertraline and Ndesmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol. 64(12), 1181–1188. doi: 10.1007/s00228-008-0533-3. [PubMed: 18677622]

Scordo MG, Spina E, Dahl ML, Gatti G, Perucca E, 2005. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol. 97(5), 296–301. doi: 10.1111/j.17427843.2005.pto_194.x. [PubMed: 16236141]

Sharp CN, Linder MW, Valdes R Jr., 2019. Polypharmacy: a healthcare conundrum with a pharmacogenetic solution. Crit Rev Clin Lab Sci. 1–20. doi: 10.1080/10408363.2019.1678568.

Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS, 2016. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013–2014. JAMA. 316(20), 21152125. doi: 10.1001/jama.2016.16201.

Singh AB, 2015. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. Clin Psychopharmacol Neurosci. 13(2), 150156. doi: 10.9758/cpn.2015.13.2.150.

Sutherland JJ, Daly TM, Liu X, Goldstein K, Johnston JA, Ryan TP, 2015. Co-prescription trends in a large cohort of subjects predict substantial drug-drug interactions. PLoS One. 10(3), e0118991. doi: 10.1371/journal.pone.0118991.

Suzuki Y, Sawamura K, Someya T, 2006. Polymorphisms in the 5-hydroxytryptamine 2A receptor and Cytochrome P450 2D6 genes synergistically predict fluvoxamine-induced side effects in japanese depressed patients. Neuropsychopharmacology. 31(4), 825–831. doi: 10.1038/sj.npp.1300919. [PubMed: 16205777]

Uher R, Farmer A, Henigsberg N, Rietschel M, Mors O, Maier W, Kozel D, Hauser J, Souery D, Placentino A, Strohmaier J, Perroud N, Zobel A, Rajewska-Rager A, Dernovsek MZ, Larsen ER, Kalember P, Giovannini C, Barreto M, McGuffin P, Aitchison KJ, 2009. Adverse reactions to antidepressants. Br J Psychiatry. 195(3), 202–210. doi: 10.1192/bjp.bp.108.061960. [PubMed: 19721108]

Verbeurgt P, Mamiya T, Oesterheld J, 2014. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. Pharmacogenomics. 15(5), 655–665. doi: 10.2217/pgs.14.6. [PubMed: 24798722]

Ward BW, Schiller JS, Goodman RA, 2014. Multiple chronic conditions among US adults: a 2012 update. Prev Chronic Dis. 11, E62. doi: 10.5888/pcd11.130389. [PubMed: 24742395]

Wilkinson GR, 2005. Drug metabolism and variability among patients in drug response. N Engl J Med. 352(21), 2211–2221. doi: 10.1056/NEJMra032424. [PubMed: 15917386]

Winner JG, Carhart JM, Altar CA, Goldfarb S, Allen JD, Lavezzari G, Parsons KK, Marshak AG, Garavaglia S, Dechairo BM, 2015. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr Med Res Opin. 31(9), 1633–1643. doi: 10.1185/03007995.2015.1063483. [PubMed: 26086890]

Zanger UM, Schwab M, 2013. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 138(1), 103141. doi: 10.1016/j.pharmthera.2012.12.007.

Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, Nemeroff CB, 2018. Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. Am J Psychiatry. 175(9), 873–886. doi: 10.1176/appi.ajp.2018.17111282. [PubMed: 29690793]

Zourková A, Hadasová E, 2003. Paroxetine-induced conversion of cytochrome P450 2D6 phenotype and occurence of adverse effects. Gen Physiol Biophys. 22(1), 103–113. [PubMed: 12870705]

Zubenko GS, Sommer BR, Cohen BM, 2018. On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment. JAMA Psychiatry. 75(8), 769–770. doi: 10.1001/jamapsychiatry.2018.0834. [PubMed: 29799933]

Table 1:

Twenty-Five Most Commonly Prescribed Medications on Hospital Admission

Medication	Occurrences	Metabolic Pathway(s)
Trazodone	34	CYP3A4
Gabapentin	33	Not metabolized
Levothyroxine	25	Not significant CYP450
Atorvastatin	22	CYP3A4
Duloxetine	21	CYP1A2, CYP2D6
Bupropion	20	CYP2B6, also inhibits CYP2D6
Clonazepam	17	CYP3A4
Pantoprazole	17	CYP2C19
Quetiapine	16	CYP3A4
Metformin	13	Not metabolized
Buspirone	13	CYP3A4
Prazosin	12	Not significant CYP450
Lisinopril	12	Not metabolized
Aripiprazole	12	CYP2D6, CYP3A4
Metoprolol	11	CYP2D6
Venlafaxine	11	CYP2D6
Montelukast	10	CYP2C8
Omeprazole	10	CYP2C19
Lorazepam	10	Not significant CYP450
Amlodipine	10	CYP3A4
Lamotrigine	9	Not significant CYP450
Losartan	8	CYP2C9, CYP3A4
Mirtazapine	8	Minor CYP2D6, CYP1A2, CYP3A4
Topiramate	7	Not CYP450
Lurasidone	7	CYP3A4

Table 2:

Distribution of Phenotypes and Mean Number of Medications on Admission by CYP450 pathways

	Mean number of enrollment medications metabolized by pathway (±SD)	Poor	Poorintermediate	Intermediate	Intermediatenormal	Normal	Rapid	Ultrarapid
CYP1A2	0.3 (±0.5)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (12.0%)	66 (88.0%)	0 (0%)
CYP2B6	0.3 (±0.4)	0 (0%)	8 (10.7%)	19 (25.3%)	16 (21.3%)	29 (38.7%)	3 (4.0%)	0 (0%)
CYP2C19	0.6 (±0.6)	1 (1.3%)	0 (0%)	16 (21.3%)	7 (9.3%)	23 (30.7%)	19 (25.3%)	9 (12.0%)
CYP2C9	0.2 (±0.4)	0 (0%)	1 (1.3%)	4 (5.3%)	14 (18.7%)	56 (74.7%)	0 (0%)	0 (0%)
CYP2D6	1.2 (±0.9)	3 (4%)	8 (10.7%)	20 (26.7%)	15 (20.0%)	28 (37.3%)	0 (0%)	1 (1.33%)
CYP3A4	2.4 (±1.3)	0 (0%)	0 (0%)	0 (0%)	7 (9.3%)	68 (90.7%)	0 (0%)	0 (0%)
CYP3A5	0.1 (±0.2)	64 (85.3%)	0 (0%)	10 (13.3%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)