Psychiatry Research 279 (2019) 111–115

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication

Lucas M. Walden[a,b], Eva J. Brandl[a,c,d], Arun K. Tiwari[a], Sheraz Cheema[a], Natalie Freeman[a], Nicole Braganza[a], James L. Kennedy[a,e], Daniel J. Müller[a,e,f,*]

[a] Pharmacogenetic Research Clinic, Campbell Family Mental Health Research Institute, Center for Addiction and Mental Health, Toronto, Ontario, Canada
[b] National University of Ireland, Galway, Ireland
[c] Department of Psychiatry and Psychotherapy, Campus Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany
[d] Berlin Institute of Health, Berlin, Germany
[e] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[f] Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Keywords:
Pharmacogenetics
Psychiatric medication
Personalized medicine
Clinical
Genetics

ABSTRACT

Individuals carrying genetic variants that result in non-extensive CYP2D6 and CYP2C19 enzyme activity seem to be more prone to non-response and side-effects of psychotropic medications. Therefore, tailoring prescriptions using genetic information may improve patient outcomes. This study examined treatment outcome in psychiatric care after CYP2D6 and CYP2C19 genetic information was provided to patients and physicians. CYP2D6 and CYP2C19 genotyping, assessment of side effects and medical histories were obtained from 80 subjects who were prescribed either antidepressant or antipsychotic medications. Our measure of outcome was mainly physicians' opinions however UKU side effects scores were also used. For CYP2D6, we calculated an activity score based on genotype and psychiatric medications. Correlation analysis was performed for CYP2D6 activity scores and UKU scores. Overall, we received supportive responses from physicians who enrolled patients in our study. Notably, while almost every fourth physician reported improvement in patient outcome, not a single physician indicated that their patient's symptoms worsened after they had used a pharmacogenetic report to guide treatment. We did not observe statistically significant differences in side effects. Overall, our results suggest improved patient outcome following pharmacogenetic testing; nonetheless, more research is required to assess the exact benefit of pharmacogenetics in clinical practice.

1. Introduction

With accumulating evidence to support the use of pharmacogenetic testing for drug metabolizing enzymes, drug manufacturers and regulators have responded to an increasing demand for genetic information. Currently, 24 psychotropic medications such as amitriptyline, clozapine, and fluoxetine have been labelled by the FDA to include dose recommendations based on polymorphisms in CYP450 enzymes (U.S. Food and Drug Administration, 2015). These recommendations are largely based upon CYP2D6 polymorphisms but also include CYP2C19 variants.

CYP2D6 and CYP2C19 belong to the CYP450 superfamily and are among the most important enzymes in the metabolism of psychotropic medication (Hicks et al., 2013). CYP2D6 is significantly involved in the metabolism of most antidepressants and approximately 40% of antipsychotics (Clinical Pharmacogenetics Implementation Consortium, 2015). CYP2C19 plays a key role in the metabolism of clozapine as well as many antidepressants such as citalopram, amitriptyline, and sertraline (Pouget et al., 2014). Furthermore, a systematic literature review examining CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, HTR2C, HTR2A, and SLC6A4 found that the strongest gene-outcome associations for psychiatric pharmacotherapy were for CYP2D6 and CYP2C19 genes (Altar et al., 2013).

Polymorphisms in the genes coding for CYP2D6 and CYP2C19 result in altered metabolism of most psychotropic medication and hence increase odds for non-response or adverse drug reactions (ADR). Using genetic information, a predicted clinical metabolizer status can be assigned to each enzyme. The most common classification assigns an individual to a normal metabolizer (NM), intermediate metabolizer (IM), ultra-rapid metabolizer (UM), or a poor metabolizer (PM) phenotype

* Corresponding author at: Pharmacogenetics Research Clinic, Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute, Department of Psychiatry, University of Toronto, 250 College Street, Toronto, ON Canada M5T1R8.
E-mail address: daniel.mueller@camh.ca (D.J. Müller).

https://doi.org/10.1016/j.psychres.2018.02.055
Received 7 August 2017; Received in revised form 22 January 2018; Accepted 27 February 2018
Available online 09 March 2018
0165-1781/

(Hicks et al., 2013).

First practice guidelines recommending dose changes based on CYP450 phenotypes have been published by experts and large expert consortiums (Hicks et al., 2015; Stingl and Viviani, 2015, Hicks et al., 2013). Such recommendations are based on reports suggesting for example that CYP2D6 PMs taking haloperidol should have their dose reduced by 50% or choose an alternative medication (Ravyn et al., 2013) or that CYP2C19 UMs should avoid amitriptyline all together (Spina and de Leon, 2015). In addition, certain side effects have been associated with CYP450 phenotypes and certain medications; for example, CYP2D6 PMs taking haloperidol are at an increased risk for extrapyramidal symptoms and CYP2D6 PMs taking risperidone are at increased risk for lengthening of QT interval and/or parkinsonism (Ravyn et al., 2013). Spina and de Leon (2015) outlined the clinical utility of CYP450 genotyping in psychiatry and stressed the importance of psychiatrists having expertise in CYP2D6 and CYP2C19 genotyping, especially for clinicians prescribing tricyclic antidepressants (TCAs). Our own previous data indicated a positive opinion of psychiatrists on pharmacogenetics testing and a high level of satisfaction with pharmacogenetic test reports (Walden et al., 2015).

Notably, only few studies examined patient outcome in psychiatric practice *after* physicians and patients have been given information on patients' CYP2D6 and CYP2C19 genotypes (Hoop et al., 2010). Therefore, we conducted a study assessing the implementation of pharmacogenetic testing in clinical practice, determining the clinical utility of pharmacogenetic testing by following patients before and after their physician received the genetic report, and evaluating physicians' and patients' opinions of pharmacogenetic testing.

2. Methods

All subjects were participants of a pharmacogenetic study project at the Centre for Addiction and Mental Health, Toronto (Canada). Patients were enrolled in the study by referral from their treating physician and followed up prospectively over three months at baseline, week 6 and week 12 (for details, see also Walden et al., 2015; Muller et al., 2013). Although drug-naïve patients were also included, patients were mostly chronically ill and had already been taking psychiatric medication but were frequently described as treatment resistant, and therefore might also tend to not respond well to other medications. DNA was extracted and for the first 45 patients six alleles (*3, *4, *5, *10, *17, *41) and copy number variation in the CYP2D6 gene were determined while three alleles were determined in CYP2C19 (*2, *3 and *17) using TaqMan® assays (Kalman et al., 2016). For the remaining portion of patients (n = 35), genotyping was expanded to assess nine alleles and copy number variants in CYP2D6 (*2, *3, *4, *5, *6, *10, *17, *29, *41; gene copy number). Data regarding patients' past and present medications, medical history, current medical condition, and family ancestry were also collected. After genetic analysis, the patients' physicians were provided with a concise, two-page report that places commonly prescribed psychiatric medication (18 antidepressants and 10 antipsychotics) into one of three color coded bins: red, yellow, and green. Medications in the red bin would indicate that one of the drugs is primarily metabolized by either CYP2D6 or CYP2C19 and should be avoided due to the patient´s genotype, medications in the green bin can be taken in standard dosages, and medications in the yellow bin should be taken with more caution and frequent monitoring. A sample report can be found at in the Supplementary materials.

In contrast to most other studies, we were able to ask most treating physicians about their patient's outcome following pharmacogenetic testing, which represents a unique asset of our study. Physician assessment was the key outcome variable. Physicians' opinions regarding their patients' clinical status once they were given genetic information for CYP2D6 and CYP2C19 was assessed using the Pharmacogenetics in Psychiatry Follow-Up Questionnaire (PIP-FQ) (Walden et al., 2015). In the survey, physicians were asked about satisfaction with the pharmacogenetic report, improvement in their patient's clinical status, and the future of pharmacogenetics in psychiatry; some of these results are detailed in Walden et al., 2015. The PIP-FQ was sent to physicians via fax or email 6–8 weeks after they had received the pharmacogenetic report. This allowed physicians adequate time to determine if changes in medication were appropriate.

As our secondary outcome measure, at study entry, all patients were assessed for side effects using a modified UKU side effects scale (Lingjaerde et al., 1987). The rationale being that non-normal metabolizers might develop more side effects than normal metabolizers. Furthermore, we decided to use side effects as a secondary measure of outcome because if patients have fewer side effects, adherence to treatment will be improved. The modified UKU scale included sections 1.2, 1.3, 1.7, 1.8, 3.2, 3.4, 3.5, 3.6, 3.8, 3.9, and 3.10 from the full UKU scale. The minimum score for our scale was 0 and the highest score was 33. A copy of the modified UKU scale is included in the Supplementary information. Statistical analysis was performed using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

In addition, we assigned a CYP2D6 activity score based on genotype as proposed by Gaedigk et al. (2008). Each allele was given a value between 0 and 2 based on its activity level and the sum of the two alleles equaled the patients' CYP2D6 activity score. Next, we made adjustments to the activity score based on CYP2D6 inhibition from psychiatric medication. To do this, we established which medications were inhibitors of CYP2D6 (Black et al., 2007) and then used several publications (Borges et al., 2010; Cronin-Fenton and Lash, 2011; Shin et al., 2001; Skinner et al., 2003) to assess the degree of inhibition. Using the inhibition factor model proposed in Borges et al., we multiplied the CYP2D6 activity score by 0.5 for weak inhibition and 0 for strong inhibition. The activity score multiplied by the inhibitory factor provided us with the overall activity score. Individuals taking no CYP2D6 inhibitory medication kept the activity score based solely on their alleles. Since there are no comparable guidelines for CYP2C19, no similar methodology was applied for CYP2C19 analysis.

Given that our data were not normally distributed, nonparametric tests were used to assess differences between metabolizer groups. Kruskal-Wallis tests were applied to determine any difference in number of previous treatments between NMs and non-NMs. Kruskal-Wallis tests were also used to compare UKU side effect scores between NMs and non-NMs. Correlation analysis was performed using Spearman's correlation.

3. Results

Our sample consisted of 80 patients with a mean age of 43 ($\bar{8}$ 13) years who had been diagnosed with schizophrenia or schizoaffective disorder (n = 43), depression or anxiety (n = 32), or other psychiatric disorders (n = 5). Demographic data is presented in Table 1. Participants were treated with a variety of medications and, in most cases, patients took more than one psychiatric drug. Medication data is also presented in Table 1. For both CYP2D6 and CYP2C19, a predicted metabolic status was determined for each patient; these results can be found in Table 1. The majority of our sample had NM status for both CYP2D6 (n = 66, 82%) and CYP2C19 (n = 54, 67.5%). Overall activity scores for CYP2D6 are presented in Table 2.

As for our main outcome variable, data from PIP-FQ indicated that physicians reported their patients either improved or did not change after treatment changes based on their CYP2D6 and CYP2C19 genotype. Of the physicians who completed our survey and had assessed their patients prior to receiving the questionnaire, 23% (n = 14) of doctors reported that their patient had an improved outcome following pharmacogenetic testing. 41% (n = 25) of physicians reported no change in patient outcome. Importantly, there was not a single physician who indicated that their patient had a worse outcome following pharmacogenetic testing. These results are presented in Fig. 1.

Table 1
Demographics and medication.

Characteristic	responses	# (%) of participants
Sex	Male	45 (56.3)
	Female	35 (43.8)
Ethnicity	European Caucasian	55 (68.8)
	African	3 (3.8)
	Asian	3 (3.8)
	Others	10 (12.5)
	Mixed	9 (11.3)
Diagnosis	Schizophrenia/Schizoaffective	43 (53.8)
	Anxiety/Depression	32 (40.0)
	Other Mood Disorders	5 6.3)
Medication	Antipsychotics	38 (47.5)
	Antidepressants	19 (23.8)
	Anxiolytics	6 (7.5)
	Antipsychotics and Antidepressants	9 (11.3)
	Antipsychotics, Antidepressants, and Anxiolytics	5 (6.3)
	No Medication	3 (3.8)
CYP2D6	EM	66 (82.5)
	IM	10 (12.5)
	UM	2 (2.5)
	PM	2 (2.5)
CYP2C19	EM	58 (72.5)
	IM	17 (21.3)
	UM	2 (2.5)
	PM	3 (3.8)

Table 2
CYP2D6 activity score and UKU side effects scores from modified UKU Scale.

Activity Score (no inhibitor)	# of Participants (%)	Overall Activity Score	# of Participants (%)
0	2 (2.5)	0	13 (16.3)
0.50	8 (10)	0.50	15 (18.8)
1	23 (29)	0.75	1 (1.3)
1.5	11 (14)	1.0	18 (22.5)
2	34 (43)	1.5	9 (11.3)
Missing	2 (2.5)	2.0	20 (25.0)
		2.5	1 (1.3)
		Missing	3 (3.8)

	UKU Side Effects		
	Median	Minimum	Maximum
Total UKU Score (n = 77)	4.0	0	16
Psychic UKU Score (n = 77)	2.0	0	8
Autonomic UKU Score (n = 77)	2.0	0	10

Note. The modified UKU scale ranges from 0 to 33 in total, 0–12 for psychic side effects, and 0–21 for autonomic side effects.

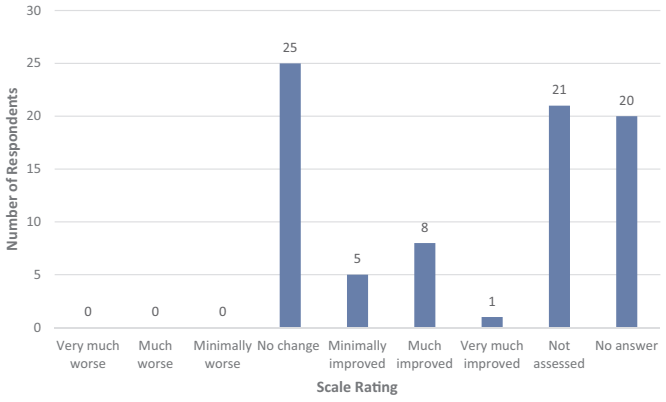

Fig. 1. Results of the question "If you were given treatment recommendations, and have taken these into consideration, would you say that compared to baseline, your patient has benefited from the treatment changes?"

As for our secondary analyses, we used a single measure of UKU side effects scores. Our modified UKU scale was completed by 77 participants and had a median score of 4.0 (range: 0–16). Our total sample consisted of 80 patients however 3 patients did not complete the modified UKU scale. The results from UKU side effect assessments are presented in Table 2. There was no statistically significant difference between UKU scores between NMs, IMs, UMs, and PMs for both CYP2D6 and CYP2C19.

We then compared the number of previous treatments between patients with NM status and patients with non-NM status for both CYP2D6 and CYP2C19. No statistically significant difference in number of previous treatments was found between CYP2D6 metabolic groups. For CYP2C19, we found a nominally significant result; patients with NM status had on average tried 3.45 different medications compared to 2.46 medications for individuals with non-NM status ($p = 0.041$). However, when we removed the 4 outliers with greater than 8 previous treatments, the difference was not significant ($p = 0.122$). Furthermore, the initial result did not withstand correction for multiple testing.

Correlation analysis between CYP2D6 overall activity score, total UKU score, psychic UKU score, and autonomic UKU score was completed using Spearman's rho for all patients taking a drug metabolized primarily or secondarily by CYP2D6. Analysis was carried out for the entire sample and only in participants with Caucasian ethnicity. No statistically significant correlation was observed. The results of the Spearman's correlation matrix for the entire sample and only the participants of European ancestry are presented in Table 3.

Because no comparable CYP2C19 activity score is available, differences in UKU side effect scores were assessed comparing NMs and Non-NMs. Kruskal-Wallis tests were used to calculate p-values and the analysis was completed for participants taking a drug metabolized primarily or secondarily by CYP2C19 and repeated for patients of all ethnicities and only individuals of Caucasian ethnicity. For the purpose of comparison, this process was repeated for CYP2D6. There were no statistically significant results (all $p > 0.050$).

4. Discussion

The aim of this study was to assess patient outcome after both patient and physician had been provided patient genotype for CYP2D6 and CYP2C19. This was primarily measured in terms of clinical judgement by physician. Notably, almost every fourth physicians reported to believe their patient improved after treatment recommendations were taken into consideration. More specifically, of the 39 patients that were prospectively assessed by their physician, 14 patients were found to have benefited from pharmacogenetic testing and not a single patient had a worse outcome after treatment changes based on the pharmacogenetics test. This is consistent with the results of our first study report which showed that 80% of participating physicians believed that pharmacogenetic testing would become common standard in psychiatric drug treatment (Walden et al., 2015).

In terms of our secondary measure, we did not find any statistically significant differences between CYP2D6 and CYP2C19 metabolic status and UKU scores. We observed one nominally significant trend in the number of previous treatments and CYP2C19 metabolizer status. However, when corrected for multiple testing and outliers, this result was non-significant. It is important to note that this secondary analysis only included a single measure of UKU side effects. For this reason, the results should be interpreted with caution.

Pharmacogenetics is a rapidly growing field and healthcare providers need to know its use it has in clinical practice. Several articles have shown that pharmacogenetic testing may reduce healthcare costs in a clinical setting, which is appealing from an economic perspective (Berm et al., 2016; Plothner et al., 2016). One study found that individuals taking a psychiatric drug not recommended based on their genetic information (i.e. CYP2D6, CYP2C19, CYP2C9, CYP1A2, serotonin

Table 3
Correlation Matrix for CYP2D6 Activity Score and UKU Scores.

All ethnicities		**UKU Total Score (n = 61)**	**UKU Psychic Score (n =;61)**	**UKU Autonomic Score (n = 61)**
CYP2D6 Overall Activity Score (n = 61)	Correlation Coefficient	0.019	− 0.065	0.138
	p-value	.885	0.618	0.287
Only Caucasians		**UKU Total Score (n = 38)**	**UKU Psychic Score (n = 38)**	**UKU Autonomic Score (n = 38)**
CYP2D6 Overall Activity Score (n = 38)	Correlation Coefficient	− 0.073	− 0.187	0.110
	p-value	.663	0.260	0.510

Note. Correlation coefficients calculated using Spearman's correlation.

transporter gene (SLC6A4), or serotonin 2 A receptor gene (5HTR2A)) had 69% more total health care visits, 67% more general medical visits, over three times as many medical absence days, and more than four times as many disability claims in comparison to individuals taking drugs recommended based on their genotypes (Winner et al., 2013).

Regarding association of CYP2D6 non-NM status and side effects, several studies have indicated a significant role of CYP2D6 activity (Hicks et al., 2013, Brandl et al., 2014). For example, in a retrospective matched case-control study examining side effects in patients diagnosed with schizophrenia, extrapyramidal side effects were significantly more common in PMs compared to NMs or IMs (Kobylecki et al., 2009). In addition, Shams et al. (2006) studied 100 patients with depression taking venlafaxine and found that PMs were at an increased risk for side effects. In their sample, they found PMs were particularly more at risk for gastrointestinal side effects.

In contrast, Hodgson et al. examined 868 patients diagnosed with depression taking either escitalopram or nortriptyline and found that CYP450 genotyping did not predict the total number of ADRs or any specific ADR (Hodgson et al., 2014). In the STAR*D study, subjects taking citalopram found that CYP2D6 and CYP2C19 metabolizer status was not associated with drug response or side effects (Peters et al., 2008). In summary, additional studies are required using large and well characterized samples to understand the effects of CYP2D6 variation and occurrence of side effects on a larger scale.

Nonetheless, based on comprehensive literature reviews followed by expert consensus practice, first dose recommendations based on CYP450 phenotypes are being used in clinical practice particularly for antidepressants (Hicks et al., 2016, 2015; Spina and de Leon, 2015; Hicks et al., 2013; Ravyn et al. (2013). Furthermore, specific side effects have been associated with CYP2D6 and CYP2C19 phenotype-drug combinations (Ravyn et al., 2013; Spina and de Leon, 2015). The FDA has acknowledged these recommendations and there is a growing number psychiatric drugs being relabelled to include dose recommendations based on CYP450 genotyping.

Our study has several important limitations. Firstly, UKU assessments only included a single measurement and therefore this section of our analysis has limited statistical power. Also, the modified UKU scale we used to assess patients' side effects included only 11 of the 48 questions in the complete UKU assessment, although we felt these 11 questions assessed the most common side effects. Because of these factors, the UKU data should be interpreted with caution. In addition, our sample was composed of patients with various diagnoses and all participants were taking different medications. Consequently, UKU scores may vary significantly between participants due to the presence or severity of side effects associated with certain medications or diseases. In the analysis, we did not take into account drug interactions or CYP450 inhibition from non-psychiatric medication that could potentially alter metabolic status. Our sample size was modest (n = 80) and contained only two CYP2D6 PMs and three CYP2C19 PMs resulting in low statistical power. As a result, it is likely that the reason we did not see differences in UKU scores between different metabolizer groups is lack of statistical power. Larger samples are needed to fully assess the influence of CYP2D6 and CYP2C19 on UKU scores in future studies. Furthermore, our sample was composed of a heterogeneous population of treatment resistant patients, drug-naive patients, and patients with a variety of diagnoses including schizophrenia, bipolar disorder, and/or depression. Therefore, this high level of heterogeneity may have influenced our results as we did not account for these variables. Additionally, medication data collected did not include compliance or dosage and the medication selected after the report was provided was not assessed. In some cases, physicians might have chosen medications which were not recommended as part of the 'green bin'. Also, we only genotyped CYP2D6 and CYP2C19. Thus, analysis was made difficult for the patients taking medications that were metabolized in pathways that involved additional enzymes.

Another major limitation of our study is the fact that for the vast majority of patients (n = 61), follow-up data were not available. In Fig. 1, it is important to note that most patients did not change (n = 25), were not assessed (n = 21), or no answer was provided (n = 20). For the group of patients who did not change, this may reflect their treatment resistant nature or may be explained by other confounding variables such as medication non-adherence. The groups that "were not assessed" and had "no answer" study may be explained by the fact that many physicians did not return their questionnaires and an equally large group were lost to follow up or refused to be re-contacted. "Not assessed" and "no answer" can be distinguished by the fact that some physicians did not have a follow up appointment with their patients by the time they received our survey and therefore were unable to assess their patient. And for the no answer group, these physicians neglected to answer the question.

Further limitations are that physicians might have been biased in their perception based on positive expectation using genetics. However, this patient population was referred to us because they failed on previous treatments and were frequently described as treatment resistant. Therefore, it is remarkable that improvement was observed in this population following delivery of genetic information. It remains unclear at this point of time, at which stage of treatment pharmacogenetic testing might be most beneficial for patients and for this reason, many large pharmacogenetic studies such as The IMACT Study recruit patients at various stages of their treatment to determine to whom pharmacogenetic testing may benefit the most.

Similarly, a viable explanation for why physicians noted patient improvements could be attributed to the patients feeling more comfortable with their medication and report subjective improvement comparable to a 'placebo' effect. On the other hand, it is also possible that patients who are informed they have an abnormal metabolizer status may perceive themselves to have a worse outcome because they metabolize medication abnormally. Lineweaver et al. (2014) found that informing older adults that they carry the APOE genotype associated with a higher risk of developing Alzheimer's disease had an adverse effect on their perception of their memory abilities and it is possible for patients receiving unfavorable CYP450 genotyping results could influence their expectations and subsequently affect symptom improvement. Such potential 'placebo/nocebo' effects were not assessed in our study and should be addressed in future studies. Nonetheless, it remains remarkable that none of the patients were reported as having deteriorated, suggesting clinical benefits of the genetic evaluation. In summary, while such effects could have influenced the results, future randomized clinical trials are needed which will include a 'treatment as usual' arm for comparison.

5. Conclusion

The positive feedback from physicians indicates a beneficial effect of genetic testing in psychiatry. While pharmacogenetics remains a promising field, large-scale studies are required to compare guided and unguided trials to evaluate superiority of guided treatment and to assess the clinical utility in terms of time to remission, health care costs and patient satisfaction.

Acknowledgements

DJM is supported by the Canadian Institutes of Health Research (CIHR Operating Grant MOP 142192), the National Institutes of Health (R01MH085801), the Centre for Addiction and Mental Health Foundation (Joanne Murphy Professorship); in addition he received a Brain & Behaviour Research (NARSAD) Independent Investigator Award, the Michael Smith New Investigator Salary Prize for Research in Schizophrenia (CIHR), an Early Researcher Award by the Ministry of Research and Innovation of Ontario and was supported by the Dean's Funds of the University of Toronto, Ontario. JLK has been a consultant to GSK, Sanofi-Aventis, and Dainippon-Sumitomo. AKT was a recipient of NARSAD 2010 Young Investigator Award. EJB is participant in the BIH Charité Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health.

We would like to thank Jessica Sturgess, Alexander Soibel and Janna Fe Notario for collection of data and are greatly indebted to physicians and patients who supported our study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2018.02.055.

References

Altar, C.A., Hornberger, J., Shewade, A., Cruz, V., Garrison, J., Mrazek, D., 2013. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. Int. Rev. Psychiatry 25 (5), 509–533.

Berm, E.J., Looff, M., Wilffert, B., Boersma, C., Annemans, L., Vegter, S., Boven, J.F., Postma, M.J., 2016. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. second update of the literature. PLoS One 11 (1), e0146262.

Black 3rd, J.L., O'Kane, D.J., Mrazek, D.A., 2007. The impact of CYP allelic variation on antidepressant metabolism: a review. Expert Opin. Drug Metab. Toxicol. 3 (1), 21–31.

Borges, S., Desta, Z., Jin, Y., Faouzi, A., Robarge, J.D., Philips, S., Nguyen, A., Stearns, V., Hayes, D., Rae, J.M., Skaar, T.C., Flockhart, D.A., Li, L., 2010. Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. J. Clin. Pharmacol. 50 (4), 450–458.

Brandl, E.J., Tiwari, A.K., Zhou, X., Deluce, J., Kennedy, J.L., Muller, D.J., Richter, M.A., 2014. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharm. J. 14 (2), 176–181.

Clinical Pharmacogenetics Implementation, C, 2015. CYP2C19 Dosing Recommendations. 〈https://www.pharmgkb.org/gene/PA124#tabview=table0&subtab=31〉 (Accessed 10 July 2015).

Cronin-Fenton, D.P., Lash, T.L., 2011. Clinical epidemiology and pharmacology of CYP2D6 inhibition related to breast cancer outcomes. Expert Rev. Clin. Pharmacol. 4 (3), 363–377.

Gaedigk, A., Simon, S.D., Pearce, R.E., Bradford, L.D., Kennedy, M.J., Leeder, J.S., 2008. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin. Pharmacol. Ther. 83 (2), 234–242.

Hicks, J.K., Bishop, J.R., Sangkuhl, K., Muller, D.J., Ji, Y., Leckband, S.G., Leeder, J.S., Graham, R.L., Chiulli, D.L., A, L.L., Skaar, T.C., Scott, S.A., Stingl, J.C., Klein, T.E., Caudle, K.E., Gaedigk, A., Clinical Pharmacogenetics Implementation, C., 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.

Hicks, J.K., Sangkuhl, K., Swen, J.J., Ellingrod, V.L., Muller, D.J., Shimoda, K., Bishop, J.R., Kharasch, E.D., Skaar, T.C., Gaedigk, A., Dunnenberger, H.M., Klein, T.E., Caudle, K.E., Stingl, J.C., 2016. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin. Pharmacol. Ther.

Hicks, J.K., Swen, J.J., Thorn, C.F., Sangkuhl, K., Kharasch, E.D., Ellingrod, V.L., Skaar, T.C., Müller, D.J., Gaedigk, A., Stingl, J.C., 2013. Clinical pharmacogenetics implementation consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin. Pharmacol. Therap. 93, 402–408. http://dx.doi.org/10.1038/clpt.2013.2.

Hodgson, K., Tansey, K., Dernovsek, M.Z., Hauser, J., Henigsberg, N., Maier, W., Mors, O., Placentino, A., Rietschel, M., Souery, D., Smith, R., Craig, I.W., Farmer, A.E., Aitchison, K.J., Belsey, S., Davis, O.S., Uher, R., McGuffin, P., 2014. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J. Psychopharmacol. 28 (2), 133–141.

Hoop, J.G., Lapid, M.I., Paulson, R.M., Roberts, L.W., 2010. Clinical and ethical considerations in pharmacogenetic testing: views of physicians in 3 “early adopting” departments of psychiatry. J. Clin. Psychiatry 71 (6), 745–753.

Kalman, L.V., Agundez, J., Appell, M.L., Black, J.L., Bell, G.C., Boukouvala, S., Bruckner, C., Bruford, E., Caudle, K., Coulthard, S.A., Daly, A.K., Del Tredici, A., den Dunnen, J.T., Drozda, K., Everts, R.E., Flockhart, D., Freimuth, R.R., Gaedigk, A., Hachad, H., Hartshorne, T., Ingelman-Sundberg, M., Klein, T.E., Lauschke, V.M., Maglott, D.R., McLeod, H.L., McMillin, G.A., Meyer, U.A., Muller, D.J., Nickerson, D.A., Oetting, W.S., Pacanowski, M., Pratt, V.M., Relling, M.V., Roberts, A., Rubinstein, W.S., Sangkuhl, K., Schwab, M., Scott, S.A., Sim, S.C., Thirumaran, R.K., Toji, L.H., Tyndale, R.F., van Schaik, R., Whirl-Carrillo, M., Yeo, K., Zanger, U.M., 2016. Pharmacogenetic allele nomenclature: international workgroup recommendations for test result reporting. Clin. Pharmacol. Ther. 99 (2), 172–185.

Kobylecki, C.J., Jakobsen, K.D., Hansen, T., Jakobsen, I.V., Rasmussen, H.B., Werge, T., 2009. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. Neuropsychobiology 59 (4), 222–226.

Lineweaver, T.T., Bondi, M.W., Galasko, D., Salmon, D.P., 2014. Effect of knowledge of APOE genotype on subjective and objective memory performance in healthy older adults. Am. J. Psychiatry 171 (2), 201–208.

Lingjaerde, O., Ahlfors, U.G., Bech, P., Dencker, S.J., Elgen, K., 1987. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr. Scand. Suppl. 334, 1–100.

Muller, D.J., Kekin, I., Kao, A.C., Brandl, E.J., 2013. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. Int Rev. Psychiatry 25 (5), 554–571.

Peters, E.J., Slager, S.L., Kraft, J.B., Jenkins, G.D., Reinalda, M.S., McGrath, P.J., Hamilton, S.P., 2008. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 3 (4), e1872.

Plothner, M., Ribbentrop, D., Hartman, J.P., Frank, M., 2016. Cost-Effectiveness of pharmacogenomic and pharmacogenetic test-guided personalized therapies: a systematic review of the approved active substances for personalized medicine in Germany. Adv. Ther. 33 (9), 1461–1480.

Pouget, J.G., Shams, T.A., Tiwari, A.K., Muller, D.J., 2014. Pharmacogenetics and outcome with antipsychotic drugs. Dialog-. Clin. Neurosci. 16 (4), 555–566.

Ravyn, D., Ravyn, V., Lowney, R., Nasrallah, H.A., 2013. CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence. Schizophr. Res. 149 (1–3), 1–14.

Shams, M.E.E., Arneth, B., Hiemke, C., Dragicevic, A., Muller, M.J., Kaiser, R., Lackner, K., Hartter, S., 2006. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J. Clin. Pharm. Therap. 31, 493–502. http://dx.doi.org/10.1111/j.1365-2710.2006.00763.x.

Shin, J.G., Kane, K., Flockhart, D.A., 2001. Potent inhibition of CYP2D6 by haloperidol metabolites: stereoselective inhibition by reduced haloperidol. Br. J. Clin. Pharmacol. 51 (1), 45–52.

Skinner, M.H., Kuan, H.Y., Pan, A., Sathirakul, K., Knadler, M.P., Gonzales, C.R., Yeo, K.P., Reddy, S., Lim, M., Ayan-Oshodi, M., Wise, S.D., 2003. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin. Pharmacol. Ther. 73 (3), 170–177.

Spina, E., de Leon, J., 2015. Clinical applications of CYP genotyping in psychiatry. J. Neural Transm. 122 (1), 5–28.

Stingl, J., Viviani, R., 2015. Polymorphism in CYP2D6 and CYP2C19, members of the cytochrome P450 mixed-function oxidase system, in the metabolism of psychotropic drugs. J. Intern. Med. 277 (2), 167–177.

U.S Food and Drug Administration, 2015. Table of pharmacogenomic biomarkers in drug labeling. 〈http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm〉 (Accessed 1 August 2015).

Walden, L.M., Brandl, E.J., Changasi, A., Sturgess, J.E., Soibel, A., Notario, J.F., Cheema, S., Braganza, N., Marshe, V.S., Freeman, N., Tiwari, A.K., Kennedy, J.L., Muller, D.J., 2015. Physicians' opinions following pharmacogenetic testing for psychotropic medication. Psychiatry Res. 229 (3), 913–918.

Winner, J., Allen, J.D., Altar, C.A., Spahic-Mihajlovic, A., 2013. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl. Psychiatry 3, e242.