Psychiatry Research 271 (2019) 604–613

Contents lists available at ScienceDirect

Psychiatry Research

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

Does obtaining CYP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions?

Haley V. Solomon[a,b,c,*], Kevin W. Cates[a,b,c], Kevin J. Li[a,b,c]

[a] Harvard South Shore Psychiatry Residency Training Program, Brockton, MA, USA
[b] Department of Psychiatry, Veterans Affairs Boston Healthcare System, Boston, MA, USA
[c] Department of Psychiatry, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
CYP450
Pharmacogenomic
Major depressive disorder
Obsessive compulsive disorder
Anxiety disorder
SSRI

ABSTRACT

Treatment non-response and adverse reactions are common in patients receiving antidepressants. Personalizing psychiatric treatment based on pharmacogenetic testing has been proposed to help clinicians guide antidepressant selection and dosing. This systematic literature review assesses the two most robustly studied drug-metabolizing enzymes, CYP2D6 and CYP2C19, and examines whether obtaining CYP2D6 and CYP2C19 testing can be used to predict antidepressant response or adverse drug reactions in order to improve clinical outcomes. In general, literature reviews published prior to 2013 indicated that results have been inconsistent linking CYP2D6 and CYP2C19 to antidepressant treatment outcomes, suggesting that more evidence is required to support the clinical implementation of genotyping to predict outcomes. We thus performed an extensive and systematic literature review, focusing on studies published from 2013 through 2018. Sixteen studies were found to be relevant. The results yielded inconsistent findings, suggesting that CYP2D6 and CYP2C19 testing may predict response in certain individuals, but it remains unclear if this will translate to improved clinical outcomes. Further research is required to determine when pharmacogenetic testing should be utilized and in which populations it is indicated. Randomized, controlled, prospective trials with adequate sample sizes would best clarify whether genotype-guided antidepressant selection will ultimately improve clinical outcomes.

1. Introduction

Antidepressants (AD) are considered the cornerstone of pharmacological treatment for a number of psychiatric conditions, but non-response rates are high and adverse reactions are common (Mrazek, 2010). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that only one-third of patients being treated for Major Depressive Disorder (MDD) experienced remission when treated with a first-line Selective Serotonin Reuptake Inhibitor (SSRI) (Trivedi et al., 2006; Warden et al., 2007). Furthermore, compliance with AD therapy is poor, and it is estimated that less than 30% of patients prescribed an AD will continue taking it 90 days after treatment initiation (Olfson et al., 2006). Adverse drug reactions (ADR) are cited as the most frequent reason for discontinuing SSRI treatment, and the usage of tricyclic antidepressants (TCA) has declined in part due to undesirable adverse effects (Bull et al., 2002; Hicks et al., 2016). Interestingly, interindividual variation in drug metabolism may account for almost 50% of ADRs (Phillips et al., 2001). Historically, predicting AD response and tolerability has been problematic and clinicians often select drugs by trial and error (Fabbri et al., 2013).

It has been hypothesized that personalizing psychiatric treatment based on genetic variation of both pharmacokinetic and pharmacodynamic genes will help guide AD selection and dosing (Amare et al., 2017; de Leon, 2006). In terms of pharmacokinetics, the interindividual variability in AD response may be explained in part by inherited or acquired differences in drug metabolism (Preskorn, 2010). The most robust pharmacokinetic data implicates the cytochrome P450 (CYP) family, given the role of CYP2D6 and CYP2C19 in metabolizing many commonly prescribed ADs (Müller et al., 2013), as detailed in Table 1.

The cytochrome P450 enzymes (CYPs) are responsible for catalyzing oxidative reactions of both endogenous and exogenous substances (Zhou, 2009a). CYP2D6 and CYP2C19 are both highly polymorphic with the frequency of allelic variants differing considerably between ethnic groups (Zanger et al., 2008). These genetic variants can predict clinical metabolizer status and are classified phenotypically as ultra-rapid metabolizer (UM) for increased enzymatic function, extensive metabolizer (EM- also termed normal metabolizer), intermediate metabolizer (IM) for decreased enzymatic function and poor metabolizer

* Corresponding author at: VA Boston Healthcare, Harvard Medical School, 940 Belmont Street, Building 5, Brockton, MA 02301, USA.
E-mail address: haley.solomon@va.gov (H.V. Solomon).

https://doi.org/10.1016/j.psychres.2018.12.053
Received 4 October 2018; Received in revised form 6 December 2018; Accepted 7 December 2018
Available online 08 December 2018
0165-1781/ Published by Elsevier B.V.

Table 1
Primary CYP metabolism of commonly prescribed ADs and pharmacologic activity of each AD metabolite.

Antidepressant	Primary metabolism	Minor metabolism	Metabolites	Reference
Amitriptyline	2C19, 2D6	3A4/5, 1A2, 2C9	Via 2C19 to nortriptyline (active) Via 2D6 to 10-hydroxyamitriptyline (weakly active)	Hicks et al., (2016) and Samer et al. (2013)
Bupropion	2B6		Hydroxybupropion (active)	Berm et al. (2016) and Samer et al. (2013)
Citalopram	2C19	2D6, 3A4	Desmethylcitalopram (inactive) Didesmethylcitalopram (inactive)	Kumar et al. (2014)
Clomipramine	1A2, 2D6, 3A4/5	2C19	Desmethylclomipramine (active)	Samer et al. (2013)
Desipramine	2D6		2-Hydroxydesipramine (active)	Nguyen et al. (2016)
Doxepin	2D6	2C19	Desmethyldoxepin (active)	Haufroid and Hantson (2015)
Duloxetine	2D6, 1A2		Various, (inactive)	Lantz et al. (2003) and Samer et al. (2013)
Escitalopram	2C19		Desmethylescitalopram (inactive)	Hicks et al. (2015)
Fluoxetine	2C9, 2D6	2C19, 3A4/5	Via 2D6 to S-Norfluoxetine (active) Via 2D6, 2C9 to R-norfluoxetine (inactive)	Hicks et al. (2015) and Samer et al. (2013)
Fluvoxamine	2D6	1A2	Fluvoxamino acid (inactive)	Hicks et al. (2015) nad Kirchheiner et al. (2004) Samer et al. (2013) and Zastrozhin et al. (2018)
Imipramine	2D6, 3A4/5, 1A2	2C19	Desipramine (active)	Samer et al. (2013)
Mirtazapine	2D6, 3A4/5	1A2	Desmethylmirtazapine (active)	Brockmoller et al., (2007) and Samer et al. (2013)
Nortriptyline	2D6	2C19, 1A2, 3A4/5	10-hydroxynortriptyline (active)	Hicks et al. (2016), Kirchheiner et al. (2004), Nordin and Bertilsson (1995), and Samer et al. (2013)
Paroxetine	2D6		Paroxetine-catechol (inactive)	Agrawal et al. (2014) and Samer et al. (2013)
Sertraline	2C19	2B6, 2D6, 3A4/5	N-desmethylsertraline (active, weakly active)	Hicks et al. (2015), Saiz-Rodriguez et al. (2018), and Sprouse et al. (1996)
Trazodone	3A4/5	2D6	m-chlorophenylpiperazine (active)	Rotzinger et al. (1998) and Saiz-Rodriguez et al. (2017)
Venlafaxine	2D6	3A4/5	O-desmethyl-venflafaxine (active)	Kirchheiner et al. (2004) and Samer et al. (2013)

(PM) for absent enzymatic function (Hicks et al., 2015; Samer et al., 2013). The most commonly reported CYP2D6 allelic variants are CYP2D6*1, *2 (normal function), CYP2D6*9, *10, *41 (decreased function), and CYP2D6*3–6 (absent function) (Hicks et al., 2015). Similarly, the most commonly reported CYP2C19 allelic variants are CYP2C19*1 (normal function), CYP2C19*2, *3 (absent function), and CYP2C19*17 (increased function) (Fabbri et al., 2018a; Hicks et al., 2015).

Since CYP2D6 and CYP2C19 polymorphisms may alter biotransformation of ADs or modify drug clearance, previous literature reviews sought to analyze the contribution of allelic variations to therapeutic response. In 2004, Kirchheiner et al. analyzed all published pharmacogenetic data between 1970 and 2003, and found that dose alterations were required in 14 out of 20 ADs due to CYP2D6 and CYP2C19 polymorphisms. However, authors concluded that response is more likely a "combinatorial outcome of complex systems that interact at multiple levels," and that it was not yet possible to translate pharmacogenetic parameters into therapeutic recommendations (Kirchheiner et al., 2004). Similarly, in 2009, Zhou et al. concluded that dose adjustments of prescribed TCAs or SSRIs based on CYP2D6 genotype/phenotype was premature (Zhou, 2009b). In 2011, Porcelli et al. reported that 17 studies published between 1996 and 2010 found no association between CYP2D6 genotype and SSRI or TCA related effects. Positive associations were found mainly in case reports, and only a handful of positive studies were performed on larger samples. Authors concluded that testing was potentially useful in order to anticipate clinical outcomes of certain ADs (Porcelli et al., 2011). In an industry-sponsored review of literature published between 2008 and 2013, Altar et al. found positive associations in seven of 19 studies assessing CYP2D6 phenotype and AD response as well as positive associations in five of eight studies assessing CYP2D6 phenotype and ADRs (Altar et al., 2013). Muller et al. also reviewed 21 studies published between 2008 and 2013 and reported inconsistent results linking variants of CYP2D6 and CYP2C19 to treatment response (Müller et al., 2013). Samer et al. concluded that pharmacogenetic testing has remained limited due to the paucity of studies showing that testing leads to improved clinical outcomes (Samer et al., 2013). Nevertheless, given the growing literature, in 2013, the Clinical Pharmacogenetics Implementation Consortium (CPIC), supported by the Pharmacogenetics Knowledgebase (PharmGKB), began producing SSRI and TCA dosage guidelines based on CYP2D6 and CYP2C19 phenotype (Hicks et al., 2015; Hicks et al., 2016; Whirl-Carrillo et al., 2012). Additionally, the Food and Drug Administration (FDA) made recommendations regarding maximum dosages of ADs for patients with certain metabolizer phenotypes (Conrado et al., 2013).

Building upon the aforementioned reviews, and given those reviews were inconclusive regarding the clinical utility of CYP pharmacogenetic testing, the following is a systematic review of the pharmacogenetic literature from 2013 to August 2018. This systematic review specifically focuses on whether studies in this interval challenge the conclusions of prior reviews, namely whether or not there is strong evidence supporting the clinical implementation of CYP2D6 and CYP2C19 pharmacogenetic testing to predict clinical response to ADs or ADRs. Of note, this paper does not evaluate available commercial pharmacogenetic testing panels, which utilize proprietary algorithms to generate medication recommendations for patients. These have been extensively reviewed elsewhere (Fabbri et al., 2018b; Rosenblat et al., 2017; Rosenblat et al., 2018).

2. Methods

2.1. Pharmacogenetic testing and treatment outcomes

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were followed for the current systematic review (Moher et al., 2009); however, the protocol for this systematic review was not registered prior to conducting the review. MEDLINE/PubMed was searched for reviews, meta-analyses, and primary studies published in print between 2013 through August 2018 that evaluate the impact of pharmacogenomic testing, specifically CYP2D6 and/or CYP2C19 on psychiatric treatment outcomes and ADRs. Search terms included Boolean combinations of the following: *major depressive disorder (MDD), obsessive compulsive disorder (OCD), anxiety disorder, antidepressant, SSRI, SNRI, TCA, response, pharmacogenetics, pharmacogenomics, cytochrome, CYP, CYP450, CYP2D6, and CYP2C19*.

Two rounds of screening were conducted. During stage one of the search, all records were screened based on title and abstract. Articles that were clearly outside the scope of the review and articles not

written in English were removed prior to the next round of screening. In the subsequent stage of screening, full texts of articles were thoroughly reviewed for inclusion. All published adult human studies, written in English, assessing the utilization of CYP2D6 and/or CYP2C19 pharmacogenetic testing on objectively predicting clinical outcomes in patients treated with an AD were included. Due to the limited number of studies, there were no restrictions regarding quality of study, randomization, or use of a control group. One study was published online in 2012, but included in this review because it was published in print in 2013. Studies that utilized commercial pharmacogenetic testing algorithms to guide treatment were excluded from this review because of the proprietary algorithm used by commercial companies, which cannot be validated externally (Altar et al., 2015; Fabbri et al., 2018b; Zubenko et al., 2018). Finally, we excluded studies that did not provide data regarding the genotypes or phenotypes examined.

2.2. Antidepressant metabolism

Additionally, a non-systematic MEDLINE/PubMed search was conducted to identify the CYP enzymes that are primarily responsible for the metabolism of commonly prescribed ADs. The pharmacologic activity of each AD metabolite was also identified. The results are described in Table 1.

2.3. Standardized levels of evidence

Once the relevant articles were identified, three reviewers independently examined two of the articles using the Good Research for Comparative Effectiveness (GRACE) checklist (Dreyer et al., 2016). Afterwards, discussion yielded consensus scoring of the articles and aided in creating a unified standard of grading amongst the reviewers. The remaining articles were divided amongst the reviewers and examined independently (Supplementary Table 1).

3. Results

3.1. Search results

After removal of duplicates, the initial search yielded 220 articles (Fig. 1). In the subsequent round of screening, 23 full-text articles were thoroughly reviewed for inclusion. Evaluation of full-text articles yielded 16 studies that were included in this current systematic review. These publications are detailed in both the results section and table 2, organized chronologically by finding.

3.2. Studies with negative findings

In 2013, Ng et al. conducted a multi-site prospective, naturalistic study to examine the effects of several candidate genes on AD response and tolerability over the course of eight weeks (Ng et al., 2013). A total of 106 adults (75% Caucasian, 24% Han Chinese; 60% female) with a diagnosis of MDD were treated in a non-randomized, open-label fashion with escitalopram (n = 62) or venlafaxine (n = 44). The results indicated no significant difference in the reduction of Hamilton Depression Rating Scale (HAM-D), between either CYP2C19 or CYP2D6 PM/IM and EM/UM polymorphisms. Despite the eight-week study duration, ADRs were only measured during week one, because drug dosing was fixed at this stage of the trial. At week one there were no significant associations found on the Udvalg for Kliniske Undersogelser (UKU) ADR scale, except an unexpected finding that Caucasian CYP2C19 EMs and UMs taking escitalopram reported increased autonomic symptoms, such as sweating and gastrointestinal complaints (p = 0.038). Several limitations are worth noting. First, this study is non-randomized and underpowered with a small Han Chinese subsample, limiting the ability to make conclusive comparisons between these ethnic groups. Next, data regarding ADRs was taken at week one of treatment, and it is unclear if there would have been significant ADRs with higher dosages at later points in the trial. Finally, the authors report that at least 25% of the patients were taking unknown herbal remedies, which could independently induce or inhibit CYP2D6 and/or CYP2C19 thus confounding any potential conclusions.

In 2014, Hodgson et al. conducted a post-hoc analysis with data from the Genome Based Therapeutic Drugs for Depression (GENDEP) study to explore the relationship between CYP2D6 and/or CYP2C19 and response to treatment with either escitalopram or nortriptyline. GENDEP was a 12-week open-label part-randomized multicenter study with 868 Caucasian European adults (63% female) diagnosed with moderate to severe depression (Hodgson et al., 2014). At week eight of the study, serum AD levels and dosages were available for 235 patients taking escitalopram and 169 patients taking nortriptyline. Despite finding that genotypes with greater enzymatic activity were linked to lower serum drug concentrations and higher metabolite to drug ratios, these authors concluded there was no significant association between CYP450 genotype and response to AD treatment (escitalopram, n = 443, ß = 0.165, SE = 0.233, p = 0.478; nortriptyline, n = 334, ß = 0.127, SE = 0.524, p = 0.807). A year later, Hodgson et al., performed another post-hoc analysis from GENDEP data to determine the association between genotype and escitalopram or nortriptyline ADRs (Hodgson et al., 2015). The analysis revealed that genotype did not predict ADRs (nortriptyline, n = 251, p = 0.5638, β = − 0.133, standard error (SE) = 0.229; escitalopram, n = 340, p = 0.9627, β = − 0.004, SE = 0.085) or study discontinuation (nortriptyline, n = 284, hazard ratio (HR) = 1.300, p = 0.174; escitalopram, n = 376, HR = 0.870, p = 0.118). In terms of study limitations, 23 out of 266 patients taking escitalopram had serum measurements below the therapeutic boundary (10 mg/day), resulting in exclusion from analysis. While this could have been due to non-compliance, it also could have been due to ultrarapid metabolism, which may have altered the study's overall treatment response statistics. Additionally, these studies have limited power given the small number of subjects with the CYP2C19 PM metabolic phenotype.

In 2016, Sanchez-Iglesias et al. investigated the significance of CYP2D6 pharmacogenetic testing to predict ADRs. 224 adults from Spain being treated for a variety of psychiatric diagnoses were genotyped and ADRs were assessed with the Clinical Global Impression (CGI) and UKU scales (Sanchez-Iglesias et al., 2016). There were no associations found between CYP2D6 genotype or predicted phenotype and ADRs, although no p-value was reported. Interestingly, investigators found that three out of three Bipolar Type I PMs experienced a manic episode while receiving simultaneous treatment with a CYP2D6 substrate and inhibitor. It is difficult to draw conclusions regarding this finding given the small sample size, but it warrants further exploration in the future. This study has numerous limitations, preventing the generalizability of the results. This was a non-randomized, non-controlled study with a poor description of the methods including unavailable data regarding scores on standardized measures, lack of clear timeline for the intervention, unavailable data regarding which medications were administered to patients, and scant discussion of the primary outcome. Furthermore, there was incomplete statistical analysis of the data.

In 2017, Taranu et al. conducted a prospective cohort study in France examining the relationship between CYP2D6 and CYP2C19 phenotype and venlafaxine treatment outcomes in 87 patients (Taranu et al. 2017). There were no associations found between CYP2D6 or CYP2C19 and response to treatment or remission of depression at six months. The lack of association between phenotype and treatment response may be explained by the metabolism of venlafaxine to its pharmacologically active metabolite, O-desmethyl-venlafaxine (ODV), which is thought to contribute to overall treatment response. Regardless, it is difficult to draw conclusions since serum concentrations of venlafaxine and its metabolite were not measured. Additionally, this study had high drop out rates and it is unclear if drop out was due to

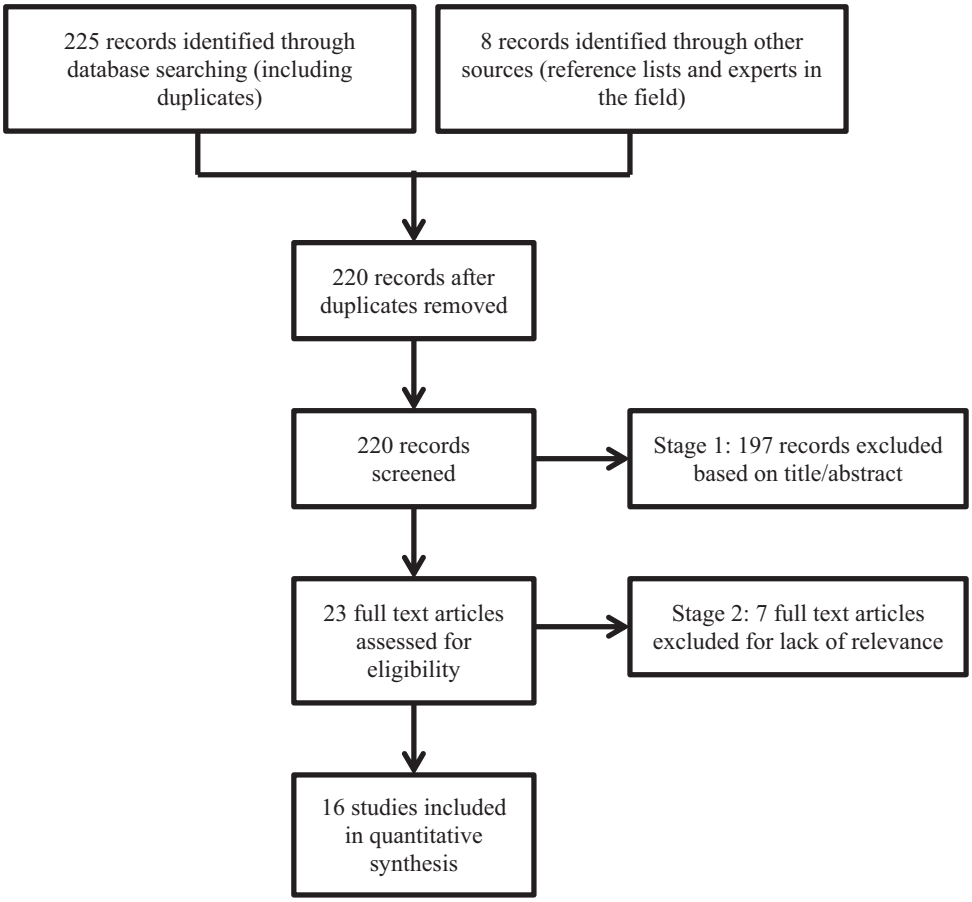

Fig. 1. PRISMA flow diagram.

ADRs or therapeutic failure. While this was a multicenter study with a prospective design, it was non-randomized, there were a small number of PMs and UMs, and data regarding co-medication were unavailable.

3.3. Studies with mixed findings

In order to expand upon results from a prior pilot study, Brandl et al. investigated the influence of CYP2D6 and CYP2C19 genotype on AD treatment response in patients (n = 184) with obsessive compulsive disorder (OCD) (Brandl et al., 2014). In this retrospective study, patients who had been treated with one of 10 ADs for greater than 10 weeks were grouped into metabolizer phenotypes. Then, in a structured clinical interview, response and ADRs to previously trialed ADs were assessed via standardized scales. No significant differences were found in terms of CYP2D6 or CYP2C19 metabolizer status and overall treatment response or ADRs. However, CYP2D6 UM, IM and PMs had significantly more failed medication trials than EMs ($p = 0.007$). This suggests these patients had either not responded sufficiently or developed ADRs due to their altered metabolizer phenotype. Additionally, CYP2D6 EMs taking venlafaxine had a significantly higher rate of self-reported side effects than non-EMs ($p = 0.022$). Authors hypothesized this unexpected finding could be explained by venlafaxine's active metabolite, ODV, but it is difficult to draw conclusions given the small sample size of venlafaxine trials (n = 53). This study did not account for disease severity or the total length of treatment when assessing symptom improvement. Additionally, response and ADRs were assessed via clinical interview, not chart review, raising the possibility for recall bias and thus limiting the conclusions that may be drawn from these results.

In 2016, Berm et al. performed a post-hoc analysis to assess for potential phenoconversion in elderly patients, with a secondary outcome of evaluating drug response in relation to CYP2D6 genotype and phenotype (Berm et al., 2016). Elderly patients may have decreased function of certain CYP enzymes, but it is generally reported that CYP2D6 function does not decrease with age (Abbott et al., 2018). Data was obtained from a prior randomized controlled trial with adults (age 60+, 73% female), started on nortriptyline (n = 40) or venlafaxine (n = 35). The authors controlled for the use of CYP2D6 strong inhibitor co-medications. Response was defined as reduction of at least 50% from baseline score on the Montgomery-Asberg Depression Scale (MADRS) and the HAM-D, and was measured at 12 weeks. In terms of clinical outcomes, the PMs had significantly higher rates of non-response based on the HAM-D (Fisher's exact test: $p < 0.01$), but not on the MADRS scale (Fisher's exact test: $p < 0.16$). It is possible this discrepancy stems from the greater focus on somatic symptoms (gastrointestinal, dizziness, insomnia, dry mouth) in the HAM-D, compared to the MADRS. An important limitation was the incomplete availability of genetic data. Specifically, only two mutations were included in the analysis and UMs could not be incorporated because there was no data on gene duplications.

3.4. Studies with positive findings

In 2013, Penas-Lledo et al. examined the relationship between CYP2D6 genotype and the discontinuation of ADs by designing a naturalistic, observational study for 100 patients in Mexico who were diagnosed with MDD and treated with either amitriptyline at <75 mg (n = 45) or fluoxetine at 20 mg (n = 55) (Penas-Lledo et al., 2013). Starting dosages of the medications were intentionally low, given the trend for practitioners to start ADs at low dosages to minimize potential ADRs. This study found that all CYP2D6 UM patients (n = 4) discontinued treatment within the first four weeks of the trial. While these

Table 2
(summary of results).

Study *Negative Findings:*	Gene	Population	Study Design	Primary Endpoint	Main Findings
Ng et al. (2013)	5−HTTLPR	n = 106, (76% Caucasians, 24% Singapore Han Chinese, 60% female)	Prospective cohort	*Response*: HAM-D, CGI	1. No difference (p = 0.22) in reduction of HAM-D in CYP2D6 or CYP2C19 PM/IM compared to EM/UM.
	STin2 CYP2D6 CYP2C19	Dx: DSM-IV MDD	ESC (n = 62) or VEN (n = 44)	*ADR*: UKU over 8 weeks	2. Neither CYP2C19 nor CYP2D6 PM/IM associated with increased ADRs.
Hodgson et al. (2014)	CYP2D6	n = 404, (100% Caucasian, 63% female); GENDEP cohort	Post-hoc analysis	*Response*: MADRS	1. No association between CYP2D6 or CYP2C19 genotype and response to AD treatment (ESC, n = 443, ß = 0.165, SE = 0.233, p = 0.478; NTP, n = 334, ß = 0.127, SE = 0.524, p = 0.807).
	CYP2C19	Dx: DSM-IV MDD	ESC (10–30 mg/d) or NTP (50–150 mg/d)	at 12 weeks	2. Greater enzymatic activity linked to lower serum drug concentrations and higher metabolite to drug ratio.
Hodgson et al. (2015)	CYP2D6	n = 404, (100% Caucasian, 63% female); GENDEP cohort	Post-hoc analysis	*ADR*: ASEC	1. CYP2D6 and CYP2C19 genotype did not predict ADRs (NTP, n = 251, p = 0.5638, β = − 0.133, SE = 0.229; ESC, n = 340, p = 0.9627, β = − 0.004, SE = 0.085), study discontinuation (NPT, n = 284, hazard ratio (HR) = 1.300, p = 0.174; ESC, n = 376, HR = 0.870, p = 0.118) or specific ADRs.
	CYP2C19	Dx: DSM-IV MDD	ESC (10–30 mg/d) or NTP (50–150 mg/d)	at 12 weeks	2. Serum drug concentrations related to dry mouth, dizziness, diarrhea.
Sanchez-Iglesias et al. (2016)	CYP2D6	n = 224, (96% Caucasian, 57% female); Spain	Prospective cohort	*Response*: CGI	1. No association between CYP2D6 genotype or predicted phenotype and ADRs (no reported p value).
		Dx: variety	Variety of AD and/or antipsychotics	*ADR*: UKU	2. 3/ 3 Bipolar PMs had manic episode while treated with CYP2D6 substrate and simultaneous inhibitor.
Taranu et al. (2017)	CY2D6	n = 87, (100% Caucasian, 66% female); METADAP cohort, France	Prospective cohort	*Response*: HAM-D	1. No difference in response for CYP2C19 or CYP2D6 phenotypes at sixth month.
	CYP2C19	Dx: DSM-IV MDD	VEN	at 6 months	
Mixed Findings:					
Brandl et al. (2014)	CYP2D6 CYP2C19	n = 184, (90% European, 61% female); Toronto	Retrospective	*Response*: Y-BOCS, CGI	1. More failed AD trials in CYP2D6 UM, IM, PMs compared to EMs (P = 0.007).
		Dx: DSM-IV OCD	Variety of ADs	*ADR*: side effect report at 10 weeks	2. CYP2D6 EMs had more ADRs to VEN (p = 0.022), compared to non-EM. 3. No impact of CYP2D6 (p = 0.743) or CYP2C19 (p = 0.939) metabolizer status on overall treatment response. 4. No impact of CYP2D6 (p = 0.619) or CYP2C19 (p = 0.391) metabolizer status on overall ADRs
Berm et al. (2016)	CYP2D6	n = 81, (mean age 72.2, 73% female)	Post-hoc analysis	*Response*: MADRS, HAM-D	1. CYP2D6 PM had higher risk of non-response based on HAM-D scale, but not MADRS.
		Dx: DSM-IV MDD	NTP (n = 40) or VEN (n = 35)	at 12 weeks	

Study *Positive Findings:*	Gene	Population	Study Design	Primary Endpoint	Main Findings
Penas-Lledo et al. (2013)	CYP2D6	n = 100, Mexico	Prospective cohort	*Response*: AD discontinuation, measured by dropout	1. All CYP2D6 UMs discontinued FLU or ATP within first 4 weeks, whereas no PM did within 12 weeks.
		Dx: DSM-IV MDD	ATP at < 75 mg (n = 45) or FLU at 20 mg (n = 55)	over 12 weeks	
Rolla et al. (2014)	CYP2D6	n = 47, (61% female); Italy	Prospective cohort	*Response*: CGI	1. UM (n = 1) responded to high dose of VEN (375 mg) without ADRs
		Dx: DSM-IV MDD	VEN (75–300 mg/d)	at 6 weeks, 6 months, 1 year	
Kumar et al. (2014)	CYP2C19	n = 155, (87% Caucasian, 71% female); MN, USA	Retrospective cohort	*ADR*: QTc prolongation	1. CYP2C19 associated with QTc length for CIT users but not ESC users.
		Dx: no data	CIT (n = 75) and ESC (n = 80)		2. CIT: EMs had shorter QTc than IMs, PMs (427.1 ± 23.6 ms vs. 440.1 ± 26.6 ms, one-tailed *t*-test, p = 0.029). 3. No dose-dependent relationship between CIT (p = 0.62) or ESC (p = 0.30) and QTc interval prolongation.

(*continued on next page*)

Table 2 (*continued*)

Study *Positive Findings:*	Gene	Population	Study Design	Primary Endpoint	Main Findings
Berard et al. (2017)	CYP2D6	n = 246, pregnant females; US and Canada	Prospective cohort	*Response*: EPDS, BAI	1. CYP2D6 PMs or IMs were 4 fold more likely to discontinue AD during pregnancy compared to EMs or UMs (OR = 3.57 (95% CI:1.15–11.11)).
		Dx: anxiety, depression	Variety of ADs	at 1st, 2nd trimesters	
Torrellas et al. (2017)	CYP2D6 CYP2C9 CYP2C19 CYP3A4/5	N = 30, (43.3% female); Spain	Pre-post intervention	*Response*: HAM-D	1. Improved HAM-D in group with AD adjusted by individual genotyping (p = 0.002), compared to trial and error prescribing.
		Dx: HAM-D ≥ 8.	Variety of ADs (48% SSRI)	at 3 months	2. High "error" rate in trial and error prescribing (error = prescribing medication "not best suited to the genetic profile").
He et al., 2017	CYP2C19	n = 78, China	Prospective cohort	*Response*: PDSS-CV, HAMA-14	1. CYP2C19 PMs had higher response ratio compared to EMs at 2nd and 4th weeks of treatment ($p < 0.05$).
		Dx: DSM-V panic disorder	ESC (10 mg/d)	over 8 weeks	2. CYP2C19 PMs had greater reductions in PDSS-CV, HAMA-14 compared to EMs at 4th and 8th weeks of tx ($p < 0.05$).
Jukic et al. (2018)	CYP2C19	n = 2,087, (100% European, 63% female); Norway	Retrospective	*Response*: AD switch and sub-therapeutic ESC concentrations	1. CYP2C19 PMs and UMs had higher rates of switching from ESC to another AD, compared with EMs (OR = 3.3, $p < 0.001$for PM; OR = 1.5, p = 0.003 for CYP2C19*1/*17; OR = 3.0, $p < 0.001$ for CYP2C19*17/*17).
		Dx: no data	ESC		2. Compared with EMs, ESC serum concentration was 3.3x greater for PMs and ESC serum concentration was 10% lower for CYP2C19*1/*17 ($p < 0.003$) and 20% lower for CYP2C19*17/*17 ($p < 0.002$).
					3. OR of ESC serum concentration below the therapeutic boundary (25 nm) was 1.5 (CYP2C19*1/*17) and 1.7 (CYP2C19*17/*17).
Zastrozhin et al. (2018)	CYP2D6	n = 45, (0% female); Moscow	Prospective cohort	*Response*: CGI, HADS, HAM-D, BDS	1. Significantly reduced efficacy ($p < 0.001$) and increased ADRs ($p < 0.001$) of fluvoxamine in patients with heterozygous polymorphism 1846G > A of CYP2D6 (rs3892097) compared to wild type (GG).
		Dx: MDD and alcohol use disorder	Fluvoxamine (median = 100 mg/d)	*ADR*: UKU day 2, 9, 16 of fluvoxamine	
Fabbri et al. (2018a)	CYP2C19	n = 2558, (60–67% female); GENDEP, STAR*D, GenPod, PGRN-AMPS cohorts	Meta-analysis	*Response:* HAM-D, QIDS-C16, BDS	1. Compared to EMs, PMs had higher symptom improvement rates (SMD = 0.43, CI = 0.19–0.66, $p = 0.00037$) and higher remission rates (OR = 1.55, CI = 1.23–1.96, $p = 0.00025$).
		Dx: DSM-IV MDD	CIT and ESC	*ADR*: ASEC, PRISE	2. At weeks 2–4, PMs had increased GI ADRs (OR = 1.26, CI = 1.08–1.47, $p = 0.0033$), CNS ADRs (OR = 1.28, CI = 1.07–1.53, $p = 0.0068$) & sexual ADRs (OR = 1.52, CI = 1.23– 1.87, $p = 0.0001$). No difference seen at week 8–9.
				Over 8 or 12 weeks	

Table 2. Key:
ASEC: Antidepressant Side Effect Checklist, ATP: amitriptyline, BAI: Beck Anxiety Inventory, BDS: Beck Depression Scale, CGI: Clinical Global Impression Scale, CIT: citalopram, EPDS: Edinburgh Postnatal Depression Scale, ESC: escitalopram, FLU: fluoxetine, GENDEP: Genome Based Therapeutic Drugs for Depression, GenPod: The GENetic and clinical Predictors Of treatment response, HADS: Hospital Anxiety and Depression Scale, HAMA-14: Hamilton Anxiety Scale, HAM-D: Hamilton Rating Scale for Depression, MADRS: Montgomery-Asberg Depression Scale, MDD: Major Depressive Disorder, NTP: Nortriptyline, PDSS-CV: Panic Disorder Severity Scale – Chinese Version, PGRN-AMPS: The Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study, PRISE: Patient-Rated Inventory of Side Effects, QIDS-C16: 16-item Quick Inventory of Depressive Symptomatology-Clinical Rated, STAR*D: The Sequenced Treatment Alternatives to Relieve Depression (STAR*D), UKU: Udvalg for Kliniske Undersogelser, VEN: venlafaxine, Y-BOCS: Yale-Brown Obsessive Compulsive Scale

results emphasize the utility of identifying patients who are less likely to respond to AD treatment due to rapid drug metabolism, there are numerous limitations of this study and results should be cautiously interpreted. These limitations include the lack of patient demographic data, lack of exclusion criteria, small sample size with four UMs and four PMs, non-randomized design, incomplete methods description, unavailability of data regarding co-medication, lack of serum drug concentrations, and incomplete data regarding methods for genotyping.

In a small observational study (n = 47) conducted in Novara, Italy, investigators studied the relationship between CYP2D6 and venlafaxine treatment outcomes at six weeks, six months, and one year of treatment (Rolla et al., 2014). In this study, participants were treated with venlafaxine and were not allowed to take any additional medications. The authors observed that the CYP2D6 UM (n = 1) responded to a rather high dosage of venlafaxine (375 mg/d) without side effects, suggesting an association between CYP2D6 gene duplication and therapeutic efficacy. None of the PMs and IMs (n = 4) developed ADRs despite taking a median venlafaxine dosage of 225 mg/d. Results of this study should be interpreted with caution for many reasons, but most notably because of the small sample size, particularly of UM, IM, and PMs. Additionally, this study did not utilize a rating scale for the assessment of depression symptoms and did not measure serum drug or drug metabolite concentrations. Despite these limitations, an important strength is the strict selection criteria, which ensured patients were not taking medications with CYP2D6 inducing or inhibiting properties.

Given the FDAs recommendation against dosing citalopram more than 20 mg/day for CYP2C19 PMs (Conrado et al., 2013), in 2014 Kumar et al. sought to evaluate whether CYP2C19 genetic variation was linked with QTc prolongation (Kumar et al., 2014). This retrospective cohort study included 155 adults (87% Caucasian, 71% female) with complete records of genotyping, ECG and consistent usage of either escitalopram (n = 80) or citalopram (n = 75). Overall, findings suggested that CYP2C19 was associated with QTc length in patients taking citalopram, but not escitalopram. Specifically, in citalopram users, CYP2C19 EMs had a significantly shorter QTc than IMs or PMs (427.1 ± 23.6 ms vs. 440.1 ± 26.6 ms, one-tailed *t*-test, p = 0.029). Interestingly, there was no dose-dependent relationship between either citalopram (p = 0.62) or escitalopram (p = 0.30) and QTc prolongation. These results suggest citalopram dosage may be less helpful than CYP2C19 genotype to predict QTc prolongation. However, this study had a small sample size with only one PM who had a prolonged QTc. When excluding the one PM, there was a trend for EMs to have a shorter QTc than IMs, but this was not statistically significant (427.1 ± 23.6 ms vs. 437.4 ± 25.1 ms, one-tailed *t*-test, p = 0.066). Additionally, given the retrospective design there was no time correlation between when the serum citalopram level was drawn and when the ECG was obtained.

Berard et al. also sought to understand the relationship between CYP2D6 genotype and AD discontinuation, but instead aimed to investigate this relationship during pregnancy given the lack of prior studies (Berard et al., 2017). This prospective study included 246 pregnant adult women (91% Caucasian) from multiple sites in the US and Canada, who were within the first 14 weeks of gestation and taking an AD. Depression and anxiety symptoms were measured every trimester over the phone using the Edinburgh Postnatal Depression Scale (EPDS) and Beck Anxiety Inventory (BAI) respectively. The results indicated that CYP2D6 PM or IMs were almost four times more likely to discontinue their AD during pregnancy compared to EM or UMs (OR = 3.57, 95% CI: 1.15–11.11). While this study has many strengths, namely it's prospective design and it's inclusion of patients from various locations in the US and Canada, there are limitations worth discussing. First, AD usage was self-reported, which has the potential to introduce biases. Next, this study had a relatively small sample size with few PMs and IMs. Finally, discontinuation of the drug could have been a multifactorial decision, given the risks of taking medication during pregnancy.

In 2017, Torrellas et al. examined 291 patients being treated with ADs at a biomedical research center in Spain (Torrellas et al., 2017). Patients were genotyped and the authors identified a sub-cohort of 30 patients who subsequently underwent AD medication changes. Compared to patients treated by trial and error, the sub-cohort of patients whose medication was changed in accordance with the results of genotype analysis experienced a significant improvement in treatment response. In trial and error prescribing, 62.2% of prescriptions were discordant with the results of genotypic analysis. The investigators observed improvement in outcomes when prescribing medications informed by pharmacogenetic testing. A major strength of this study is that it compares the results of treatment via trial and error with treatment informed by genotype data. However, the study is limited by its non-randomized design, small sample size, poorly described inclusion diagnoses, and lack of clear exclusion criteria from the original cohort.

In order to explore the association between CYP2C19 genotype and escitalopram treatment outcomes, He et al. designed a prospective, open-label observational study in Chinese adults (n = 78) diagnosed with panic disorder (He et al., 2017). Patients were grouped into metabolizer phenotypes and response to fixed dose escitalopram 10 mg was observed over eight weeks. Results of this study indicated that CYP2C19 PMs had a higher response ratio at the second and fourth weeks of treatment ($p < 0.05$) compared to EMs. Additionally, PMs had significantly greater rating reductions on the Panic Disorder Severity Scale-Chinese Version (PDSS-CV) and the Hamilton Anxiety Scale (HAMA-14) at the fourth and eighth weeks of treatment ($p < 0.05$). The authors concluded that CYP2C19 PMs experienced an earlier treatment response compared to EMs. Limitations include inability to detect any UMs in the sample, lack of serum concentrations of escitalopram, and the fact that 12 out of 90 patients dropped out due to anxiety, side effects, and unwillingness to continue.

Given the prior conflicting literature, in 2018, Jukic et al. sought to determine the contribution of CYP2C19 polymorphisms to escitalopram exposure and therapeutic failure (Jukic et al., 2018). This retrospective study included 2,087 genotyped European adults from Oslo, Norway being treated with escitalopram. The primary endpoint was determining if CYP2C19 genotype was associated with therapeutic failure, as measured by a switch from escitalopram to another AD. A secondary endpoint was sub-therapeutic concentration of escitalopram in relation to genotype. In terms of the primary endpoint, results indicated that CYP2C19 PM and UM patients were linked with therapeutic failure, as measured by significantly higher frequencies of switching from escitalopram to another AD compared with EMs (OR = 3.3, $p < 0.001$for PM; OR = 1.5, p = 0.003 for CYP2C19*1/*17 subgroup; OR = 3.0, $p < 0.001$ for CYP2C19*17/*17 subgroup). For the secondary endpoint, escitalopram serum concentrations were 3.3 times greater for PMs compared with EMs and 20% lower for UMs (CYP2C19*17/17) compared with EMs. Furthermore, the odds ratio of escitalopram serum concentrations below the lower therapeutic boundary (10 mg/day) was 1.7 for UMs (CYP2C19*17/17) compared with EMs, which may explain the higher likelihood of therapeutic failure in this subgroup. Given the data, these authors concluded that preemptive CYP2C19 genotyping could help individualize escitalopram treatment to improve efficacy. Major strengths of this study included the large sample size and the fact that UM and PM patients represented 33% of the study population. However, limitations include the lack of a control group, and unavailability of data regarding psychiatric diagnosis, exclusion criteria, and co-medications.

Also in 2018, Zastrozhin et al. studied the correlation between CYP2D6 polymorphisms and the efficacy and safety of fluvoxamine in 45 adult Russian males receiving inpatient treatment for depressive disorder and comorbid alcohol use disorder (Zastrozhin et al., 2018). CYP2D6 genotyping by polymorphic marker 1846G > A (rs3892097) was performed and patients were grouped into either genotype GG (64.4%) or heterozygous polymorphism genotype GA (25.6%). No

patients were found to be homozygous for the mutation genotype AA. Fluvoxamine efficacy and ADRs were evaluated with several scales, including the HAM-D, Hospital Anxiety And Depression Scale (HADS) and UKU scale at days two, nine and 16 of medication therapy. Investigators observed that patients with the heterozygous polymorphism 1846G > A (rs3892097) had significantly reduced efficacy ($p < 0.001$) and increased ADRs ($p < 0.001$) of fluvoxamine compared to wild type. The authors proposed that patients with poor metabolism of fluvoxamine likely had reduced biotransformation and elimination of the drug, leading to ADRs and toxic concentrations, thereby reducing antidepressant efficacy. Notable limitations include the small sample size with no patients carrying homozygous mutant alleles, analysis of only one polymorphism, unavailable serum concentrations of fluvoxamine, and short duration of trial with lack of longer-term follow-up. Furthermore, all patients in this study had comorbid alcohol use disorder and were simultaneously undergoing alcohol detoxification treatment, which may confound results.

Also in 2018, Fabrri et al. conducted a meta-analysis including data from GENDEP, STAR*D, The GENetic and clinical Predictors Of treatment response (GenPod) and The Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS) to investigate how CYP2C19 polymorphisms predicted escitalopram/citalopram treatment response ($n = 2,558$) and ADRs ($n = 2,037$) (Fabbri et al., 2018a). All patients had a diagnosis of MDD and were treated with either escitalopram or citalopram for eight weeks (PGRN-AMPS) or 12 weeks (GENDEP, STAR*D, GenPod). Investigators found that compared to EMs, PMs had higher symptom improvement scores (SMD = 0.43, CI = 0.19–0.66, $p = 0.00037$), and higher remission rates (OR = 1.55, CI = 1.23–1.96, $p = 0.00025$) without increased dropout rates. Investigators indicated that their finding is discordant with CPIC recommendations to reduce the starting dose of escitalopram/citalopram in CYP2C19 PMs (Hicks et al., 2015). In terms of ADRs, PMs had statistically higher risk of gastrointestinal (GI), central nervous system (CNS) and sexual side effects during weeks two through four, but no significant difference was seen during weeks eight through nine. A major strength of this study is the large sample size. However, authors acknowledged that PMs are rare in the Caucasian population, and this meta-analysis only included 51 PMs. Also, the confounding effect of CYP2C19 enhancing/inhibiting co-medications was not assessed.

4. Discussion

It is estimated that mental and substance use disorders account for 7.4% of total worldwide disease burden. Within this category, depression and anxiety are the leading causes of disability adjusted life years (DALYs) (Whiteford et al., 2013). Researchers and clinicians have been hopeful that advancements in pharmacogenetics will translate into improved treatment outcomes, thus easing the global burden of psychiatric disease. In general, previous literature reviews indicated that results have been inconsistent linking CYP2D6 and CYP2C19 to AD treatment outcomes, suggesting that more evidence is required to support the clinical implementation of genotyping to predict outcomes and guide psychiatric treatment (Altar et al., 2013; Kirchheiner et al., 2004; Müller et al., 2013; Porcelli et al., 2011; Samer et al., 2013; Zhou, 2009b).

In the present review of the literature since 2013, studies continue to find mixed results. Four authors reported no significant differences in AD treatment response based on CYP2D6 or CYP2C19 metabolizer status (Brandl et al., 2014; Hodgson et al., 2014; Ng et al., 2013; Taranu et al. 2017). In contrast, eight authors reported positive associations including improved AD response based on CYP2C19 metabolizer status (Fabbri et al., 2018a; He et al., 2017), reduced AD efficacy in 1846G > A CYP2D6 polymorphism (Zastrozhin et al., 2018), improved response based on individual genotyping (Torrellas et al., 2017), as well as higher rates of AD discontinuation or failed AD trials associated with CYP2D6 (Berard et al., 2017; Brandl et al., 2014; Penas-Lledo et al., 2013), and CYP2C19 genotype (Jukic et al., 2018). Two authors had mixed (Brandl et al., 2014) or inconclusive results (Berm et al., 2016). In terms of ADRs, four authors found no significant differences in ADRs based on CYP2D6 metabolizer status (Brandl et al., 2014; Hodgson et al., 2015; Ng et al., 2013; Sanchez-Iglesias et al., 2016), and three authors found no significant differences in ADRs based on CYP2C19 metabolizer status (Brandl et al., 2014; Hodgson et al., 2015; Ng et al., 2013). In contrast, four authors reported positive ADR associations including increased GI, CNS and sexual side effects at weeks two through four in CYP2C19 PMs (Fabbri et al., 2018a), increased ADRs in 1846G > A CYP2D6 polymorphism (Zastrozhin et al., 2018), lack of ADRs despite high dosage venlafaxine in a CYP2D6 UM (Rolla et al., 2014), and shorter QTc intervals in CYP2C19 EMs compared to IMs and PMs (Kumar et al., 2014).

The results of these studies have a litany of limitations. First, most studies in this review were underpowered with small samples of PMs and UMs, making it difficult to produce meaningful, replicable results given the heterogeneity of psychiatric disorders. Second, study designs were heterogeneous and there was significant variability between definitions of response as well as classification of phenotype based on genotype. Furthermore, as listed in Table 3, the alleles tested in each study were highly variable, making it difficult to compare findings. Additionally, many studies did not exclude or account for patients taking other medications. Co-medication can obscure treatment response because drugs with CYP-inhibiting or inducing properties can cause phenoconversion, or a discrepancy between genotype and phenotype. Lastly, most studies in this review utilized flexible dosing protocols, which reflects actual prescribing in clinical practice, but may also cause selection bias. Overall, many studies in this review were of poor quality due to non-randomization, insufficient description of methods, unclear inclusion and exclusion criteria, high dropout rates, and lack of serum drug concentration monitoring.

Despite uncertainty and mixed evidence regarding how well the science translates to the clinical setting, psychiatric practitioners are beginning to order pharmacogenetic testing for their patients. There are a number of companies that have created proprietary algorithms based partly on the aforementioned evidence in order to recommend certain medication trials. A recent meta-analysis of six industry-funded studies concluded that compared to treatment as usual, commercial pharmacogenetic panel testing may improve AD response and MDD remission rates (Rosenblat et al., 2018). However, clinicians should be cautious in taking these recommendations given the algorithms are not made public, and there may be non-genetic factors used to issue medication recommendations. Notably, the FDA issued a recent consumer warning describing the paucity of evidence to support the clinical utility of pharmacogenetic testing (FDA, 2018). Our review highlights important considerations for practitioners, namely the lack of consensus regarding who should receive pharmacogenetic testing or the point at which testing should be utilized during psychiatric treatment.

In conclusion, this paper reviewed the literature from 2013 to August 2018 to ascertain whether CYP2D6 and CYP2C19 pharmacogenetic testing could predict AD response or ADRs. The literature reviewed had mixed findings, suggesting that CYP2D6 and CYP2C19 testing may predict response in certain individuals but it remains unclear if this will translate to improved or safer clinical outcomes. Further research is required to determine when pharmacogenetic testing should be utilized and in which populations it is indicated. Randomized, controlled, prospective trials with adequate sample sizes would best clarify whether CYP450 genotype-guided AD selection will ultimately lead to significantly better and safer clinical outcomes compared to treatment as usual.

Acknowledgements

We would like to acknowledge Elaine Alligood for her assistance in

Table 3
Genes and alleles tested.

Study	Genes	Alleles
Negative Findings:		
Ng et al. (2013)	5-HTTLPR STin2 CYP2D6 CYP2C19	Not specified
Hodgson et al. (2014)	CYP2D6 CYP2C19	AmpliChip and CYP2C19*17
Hodgson et al. (2015)	CYP2D6 CYP2C19	AmpliChip and CYP2C19*17
Sanchez-Iglesias et al. (2016)	CYP2D6	AmpliChip and CYP2C19*2, CYP2C19*3
Taranu et al. (2017)	CY2D6 CYP2C19	CYP2D6: *2xN dup, *3 (rs35742686), *4 (rs3892097), *6 (rs5030655), *5 del, *10 (rs1065852), *41 (rs28371725) CYP2C19: *2 (rs4244285), *3 (rs4986893), *4 (rs28399504), *5 (rs56337013), *17 (rs12248560)
Mixed Findings:		
Brandl et al. (2014)	CYP2D6 CYP2C19	CYP2D6: *3 (rs35742686), *4 (rs3892097), *5 del, *10 (rs1065852), *17 (rs28371706), *41 (rs28371725) CYP2C19: *2 (rs4244285), *3 (rs4986893), *17 (rs12248560)
Berm et al. (2016)	CYP2D6	CYP2D6: *3 (rs35742686), *4 (rs3892097)
Positive Findings:		
Penas-Lledo et al. (2013)	CYP2D6	CYPD2D6: *1,*1xN, *2, *2xN, *3, *4, *4xN, *5, *6, *10, *17
Rolla et al. (2014)	CYP2D6	BioFilm Chip CYP4502D6 INFINITI, Autogenomics: *1,*2, *2A, *3, *4, *5 del, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41, *1 (*XN)
Kumar et al. (2014)	CYP2C19	Not specified
Berard et al. (2017)	CYP2D6	CYP2D6: *2 (rs16947), *3 (rs35742686), *4 (rs3892097), *5del, *6 (rs5030655), *7 (rs5030867) *9 (rs5030656), *10 (rs1065852), *13 (2D6/2D7 hybrid genes), *17 (rs28371706), *29 (rs59421388), *41 (rs28371725), *56 (rs147960066), 1862ins18bp, 1846 G>A (rs1800716)
Torrellas et al. (2017)	CYP2D6 CYP2C9 CYP2C19 CYP3A4/5	CYP2D6: *3 (rs35742686), *4 (rs3892097), *5 del, *6 (rs5030655) CYP2C19: *2 (rs4244285), *17 (rs12248560)
He et al. (2017)	CYP2C19	CYP2C19: *2 (rs4244285), *3 (rs4986893), *17 (−3402C>T)
Jukic et al., 2018	CYP2C19	CYP2C19: *2 (rs4244285), *3 (rs4986893/rs57081121), *4 (rs28399504), *17 (rs12248560)
Zastrozhin et al. (2018)	CYP2D6	CYP2D6: *4 (rs3892097)
Fabbri et al. (2018)	CYP2C19	CYP2C19: *2 (rs4244285), *17 *rs12248560)

obtaining full-text versions of the articles.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.053.

References

Abbott, R., Chang, D.D., Eyre, H.A., Bousman, C.A., Merrill, D.A., Lavretsky, H., 2018. Pharmacogenetic decision support tools: a new paradigm for late-life depression? Am. J. Geriatr. Psychiatr. 26 (2), 125–133.

Agrawal, N., Marco-Peiro, S., Esteve-Romero, J., Durgbanshi, A., Bose, D., Peris-Vicente, J., Carda-Broch, S., 2014. Determination of paroxetine in blood and urine using micellar liquid chromatography with electrochemical detection. J. Chromatogr. Sci. 52 (10), 1217–1223.

Altar, C.A., Carhart, J.M., Allen, J.D., Hall-Flavin, D.K., Dechairo, B.M., Winner, J.G., 2015. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenomics J. 15 (5), 443–451.

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. Psychiatr. 25 (5), 509–533.

Amare, A.T., Schubert, K.O., Baune, B.T., 2017. Pharmacogenomics in the treatment of mood disorders: strategies and opportunities for personalized psychiatry. Epma. J. 8 (3), 211–227.

Berard, A., Gaedigk, A., Sheehy, O., Chambers, C., Roth, M., Bozzo, P., Johnson, D., Kao, K., Lavigne, S., Wolfe, L., Quinn, D., Dieter, K., Zhao, J.P., Committee, O.C.R., 2017. Association between CYP2D6 genotypes and the risk of antidepressant discontinuation, dosage modification and the occurrence of maternal depression during pregnancy. Front Pharmacol. 8, 402.

Berm, E., Kok, R., Hak, E., Wilffert, B., 2016. Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry. Pharmacopsychiatry 49 (5), 186–190.

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. Pharmacogenomics J. 14 (2), 176–181.

Brockmoller, J., Meineke, I., Kirchheiner, J., 2007. Pharmacokinetics of mirtazapine: enantioselective effects of the CYP2D6 ultra rapid metabolizer genotype and correlation with adverse effects. Clin. Pharmacol. Ther. 81 (5), 699–707.

Bull, S.A., Hunkeler, E.M., Lee, J.Y., Rowland, C.R., Williamson, T.E., Schwab, J.R., Hurt, S.W., 2002. Discontinuing or switching selective serotonin-reuptake inhibitors. Ann. Pharmacother. 36 (4), 578–584.

Conrado, D.J., Rogers, H.L., Zineh, I., Pacanowski, M.A., 2013. Consistency of drug-drug and gene-drug interaction information in US FDA-approved drug labels. Pharmacogenomics 14 (2), 215–223.

de Leon, J., 2006. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics 47 (1), 75–85.

Dreyer, N., Bryant, A., Velentgas, P., 2016. The GRACE checklist: a validated assessment tool for high quality observational studies of comparative effectiveness. J. Manag. Care Spec. Pharm. 22 (10), 1107–1113.

Fabbri, C., Di Girolamo, G., Serretti, A., 2013. Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. Am. J. Med. Genet. B Neuropsychiatr. Genet 162B (6), 487–520.

Fabbri, C., Tansey, K.E., Perlis, R.H., Hauser, J., Henigsberg, N., Maier, W., Mors, O., Placentino, A., Rietschel, M., Souery, D., Breen, G., Curtis, C., Lee, S.H., Newhouse, S., Patel, H., O'Donovan, M., Lewis, G., Jenkins, G., Weinshilboum, R.M., Farmer, A., Aitchison, K.J., Craig, I., McGuffin, P., Schruers, K., Biernacka, J.M., Uher, R., Lewis, C.M., 2018a. 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.

Fabbri, C., Zohar, J., Serretti, A., 2018b. Pharmacogenetic tests to guide drug treatment in depression: comparison of the available testing kits and clinical trials. Prog. Neuro-Psychopharmacol. Biol. Psychiatr. 86, 36–44.

Haufroid, V., Hantson, P., 2015. CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants. Clin. Toxicol. (Phila) 53 (6), 501–510.

He, Q., Yuan, Z., Liu, Y., Zhang, J., Yan, H., Shen, L., Luo, X., Zhang, Y., 2017. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenet. Genom. 27 (8), 279–284.

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., 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. 102 (1), 37–44.

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.

Hodgson, K., Tansey, K.E., Uher, R., Dernovsek, M.Z., Mors, O., Hauser, J., Souery, D., Maier, W., Henigsberg, N., Rietschel, M., Placentino, A., Craig, I.W., Aitchison, K.J., Farmer, A.E., Dobson, R.J., McGuffin, P., 2015. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 232 (14),

2609–2617.
Jukic, M.M., Haslemo, T., Molden, E., Ingelman-Sundberg, M., 2018. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am. J. Psychiatr. 175 (5), 463–470.
Kirchheiner, J., Nickchen, K., Bauer, M., Wong, M.L., Licinio, J., Roots, I., Brockmöller, J., 2004. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol. Psychiatr. 9 (5), 442–473.
Kumar, Y., Kung, S., Shinozaki, G., 2014. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J. Psychopharmacol. 28 (12), 1143–1148.
Lantz, R.J., Gillespie, T.A., Rash, T.J., Kuo, F., Skinner, M., Kuan, H.Y., Knadler, M.P., 2003. Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. Drug. Metab. Dispos. 31 (9), 1142–1150.
Moher, D., Liberati, A, Tetzlaff, J, Atlman, DG, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), 1–6.
Mrazek, D.A., 2010. Psychiatric pharmacogenomic testing in clinical practice. Dialogues Clin. Neurosci. 12 (1), 69–76.
Müller, D.J., Kekin, I., Kao, A.C.C., Brandl, E.J., 2013. Towards the implementation ofCYP2D6andCYP2C19genotypes in clinical practice: Update and report from a pharmacogenetic service clinic. Int. Rev. Psychiatr. 25 (5), 554–571.
Ng, C., Sarris, J., Singh, A., Bousman, C., Byron, K., Peh, L.H., Smith, D.J., Tan, C.H., Schweitzer, I., 2013. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum. Psychopharmacol. 28 (5), 516–522.
Nguyen, H.Q., Callegari, E., Obach, R.S., 2016. The use of in vitro data and physiologically-based pharmacokinetic modeling to predict drug metabolite exposure: desipramine exposure in cytochrome P4502D6 extensive and poor metabolizers following administration of imipramine. Drug. Metab. Dispos. 44 (10), 1569–1578.
Nordin, C., Bertilsson, L., 1995. Active hydroxymetabolites of antidepressants. Emphasis on E-10-hydroxy-nortriptyline. Clin. Pharmacokinet. 28 (1), 26–40.
Olfson, M., Marcus, S.C., Tedeschi, M., Wan, G.J., 2006. Continuity of antidepressant treatment for adults with depression in the united states. Am. J. Psychiatr. 163 (1), 101–108.
Penas-Lledo, E.M., Trejo, H.D., Dorado, P., Ortega, A., Jung, H., Alonso, E., Naranjo, M.E., Lopez-Lopez, M., Llerena, A., 2013. CYP2D6 ultrarapid metabolism and early dropout from fluoxetine or amitriptyline monotherapy treatment in major depressive patients. Mol. Psychiatr. 18 (1), 8–9.
Phillips, K.A., Veenstra, D.L., Oren, E., Lee, J.K., Sadee, W., 2001. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA 286 (18), 2270–2279.
Porcelli, S., Fabbri, C., Spina, E., Serretti, A., De Ronchi, D., 2011. Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert. Opin. Drug. Metab. Toxicol. 7 (9), 1101–1115.
Preskorn, S.H., 2010. Understanding outliers on the usual dose-response curve: venlafaxine as a way to phenotype patients in terms of their CYP 2D6 status and why it matters. J. Psychiatr. Pract. 16 (1), 46–49.
Rolla, R., Gramaglia, C., Dalo, V., Ressico, F., Prosperini, P., Vidali, M., Meola, S., Pollarolo, P., Bellomo, G., Torre, E., Zeppegno, P., 2014. An observational study of Venlafaxine and CYP2D6 in clinical practice. Clin. Lab. 60 (2), 225–231.
Rosenblat, J.D., Lee, Y., McIntyre, R.S., 2017. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? J. Clin. Psychiatr. 78 (06), 720–729.
Rosenblat, J.D., Lee, Y., McIntyre, R.S., 2018. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. J. Affect Disord. 241, 484–491.
Rotzinger, S., Fang, J., Baker, G.B., 1998. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. Drug. Metab. Dispos. 26 (6), 572–575.
Saiz-Rodriguez, M., Belmonte, C., Derqui-Fernandez, N., Cabaleiro, T., Roman, M., Ochoa, D., Talegon, M., Ovejero-Benito, M.C., Abad-Santos, F., 2017. Pharmacogenetics of trazodone in healthy volunteers: association with pharmacokinetics, pharmacodynamics and safety. Pharmacogenomics 18 (16), 1491–1502.
Saiz-Rodriguez, M., Belmonte, C., Roman, M., Ochoa, D., Koller, D., Talegon, M., Ovejero-Benito, M.C., Lopez-Rodriguez, R., Cabaleiro, T., Abad-Santos, F., 2018. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. Basic. Clin. Pharmacol. Toxicol. 122 (5), 501–511.
Samer, C.F., Lorenzini, K.I., Rollason, V., Daali, Y., Desmeules, J.A., 2013. Applications of CYP450 testing in the clinical setting. Mol. Diagn. Ther. 17 (3), 165–184.
Sanchez-Iglesias, S., Garcia-Solaesa, V., Garcia-Berrocal, B., Sanchez-Martin, A., Lorenzo-Romo, C., Martin-Pinto, T., Gaedigk, A., Gonzalez-Buitrago, J.M., Isidoro-Garcia, M., 2016. Role of pharmacogenetics in improving the safety of psychiatric care by predicting the potential risks of mania in CYP2D6 poor metabolizers diagnosed with bipolar disorder. Medicine (Baltimore) 95 (6), e2473.
Sprouse, J., Clarke, T., Reynolds, L., Heym, J., Rollema, H., 1996. Comparison of the effects of sertraline and its metabolite desmethylsertraline on blockade of central 5-HT reuptake in vivo. Neuropsychopharmacology 14 (4), 225–231.
Taranu, A., Colle, R., Gressier, F., El Asmar, K., Becquemont, L., Corruble, E., Verstuyft, C., 2017. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics 18 (7), 639–650.
Torrellas, C., Carril, J.C., Cacabelos, R., 2017. Optimization of antidepressant use with pharmacogenetic strategies. Curr. Genomics. 18 (5), 442–449.
Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., Team, S.D.S., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatr. 163 (1), 28–40.
Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D Project results: a comprehensive review of findings. Curr. Psychiatr. Rep. 9 (6), 449–459.
Whirl-Carrillo, M., McDonagh, E.M., Hebert, J.M., Gong, L., Sangkuhl, K., Thorn, C.F., Altman, R.B., Klein, T.E., 2012. Pharmacogenomics knowledge for personalized medicine. Clin. Pharmacol. Ther. 92 (4), 414–417.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382 (9904), 1575–1586.
Zanger, U.M., Turpeinen, M., Klein, K., Schwab, M., 2008. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal. Bioanal. Chem. 392 (6), 1093–1108.
Zastrozhin, M.S., Grishina, E.A., Denisenko, N.P., Skryabin, V.Y., Markov, D.D., Savchenko, L.M., Bryun, E.A., Sychev, D.A., 2018. Effects of CYP2D6 genetic polymorphisms on the efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorder. Pharmgenomics. Pers. Med. 11, 113–119.
Zhou, S.F., 2009a. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. Clin. Pharmacokinet. 48 (11), 689–723.
Zhou, S.F., 2009b. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin. Pharmacokinet. 48 (12), 761–804.
Zubenko, G.S., Sommer, B.R., Cohen, B.M., 2018. On the marketing and use of pharmacogenetic tests for psychiatric treatment. JAMA Psychiatr. 75 (8), 769–770.

Web references

FDA, 2018. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm Date Accessed: Nov 15, 2018.