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A Call for Clear and Consistent Communications Regarding the Role of Pharmacogenetics in Antidepressant Pharmacotherapy

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INTRODUCTION

Recent regulatory and industry communications pertaining to the clinical importance of pharmacogenetic information, along with related language included in the product labeling of some U.S. Food and Drug Administration (FDA) approved drugs, has resulted in confusing and inconsistent information. In particular, specific statements regarding the relevance of pharmacogenetics in relation to treatment outcomes from certain antidepressants deserve clarification. There clearly is not only the need for clarification, but also an opportunity to educate the clinical and scientific community in this relevant area.

Depression and anxiety disorders are major health issues affecting millions of individuals worldwide that can severely impair quality of life along with potentiating comorbidities and mortality. Initial treatment success is often low, with 30–50% of patients estimated to fail first-line antidepressant pharmacotherapy due to ineffectiveness or intolerance (1). Furthermore, in the United States approximately 25,000 patients per year present to emergency departments due to antidepressant-induced adverse events (2). Patients often try numerous antidepressant regimens before finding a drug that improves depressive symptoms with limited side effects. Because antidepressant pharmacotherapy trials often take a minimum of 6–8 weeks, the personal and societal costs of iteratively taking medications that ‘do not work’ can be devastating for the individual and underscores the need to improve drug selection and dosing strategies.

Decades of research have established associations between genetic variation and drug response phenotypes, with evidence sufficiently strong for some antidepressant gene-drug pairs to warrant consideration of translation into clinical practice (3, 4). The majority of antidepressants are catabolized by polymorphic drug metabolizing enzymes, particularly CYP2D6 and CYP2C19. Interindividual differences in antidepressant drug exposure are attributed to either genetic variation that alter metabolic capacity, or drug-drug interactions that inhibit or induce CYP2D6 or CYP2C19 activity. Over ten medications approved for treating depression have pharmacogenetic-related information for *CYP2D6* or *CYP2C19* in their product label that addresses drug exposure (5) (Table S1). In some of those drug labels, statements are made that poor metabolizers, i.e. patients with no or little enzyme activity, may have differences in drug exposure that could be small or quite large (e.g., 8-fold increase in plasma AUC for individuals who are CYP2D6 poor metabolizers taking certain tricyclic antidepressants), although no specific dosing recommendations are provided. In other cases, dosing recommendations are provided. For example, patients prescribed

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brexpiprazole or vortioxetine who are known CYP2D6 poor metabolizers are recommended to receive a specific dose reduction. Similarly, the product label for citalopram recommends a maximum dose of 20 mg per day for CYP2C19 poor metabolizers, which is half the maximum recommended dose for normal metabolizers. Although specific dosing recommendations for particular drug metabolizing phenotypes are provided in some antidepressant drug labels, the FDA does not comment on pharmacogenetic testing before drug prescribing which has the potential to create confusion among clinicians on how to determine phenotype status.

Based on strong clinical evidence and FDA drug labeling, a number of healthcare systems and clinical genetic testing laboratories offer pharmacogenetic testing to help guide antidepressant treatment strategies. However, concerns regarding how these pharmacogenetic tests were marketed prompted the FDA to recently issue statements and warning letters related to pharmacogenetic testing. A safety communication issued October 31, 2018 cautioned that there may be a lack of clinical evidence supporting the utility of clinical pharmacogenetic testing. This safety communication specifically highlighted the use of pharmacogenetic testing to guide antidepressant drug prescribing stating that “the relationship between DNA variations and the effectiveness of antidepressant medication has never been established” (6).

In addition to the 2018 safety communication on pharmacogenetics, the FDA recently issued a warning letter to Inova Genomics Laboratory regarding the marketing and gene content of their clinical pharmacogenetic tests (7). In addition to these concerns about their test offerings, the FDA again explicitly highlighted the use of pharmacogenetic tests to guide antidepressant drug selection as problematic. The letter specifically noted that “the relationship between *CYP2C19* genotype and drug response to escitalopram and sertraline is not established and this relationship is not described in the FDA-approved labeling for these drugs.” However, the FDA product label for escitalopram does include language stating that “the exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.” This statement suggests that CYP2C19 poor metabolizers are at an increased risk of supratherapeutic drug exposure following administration of an approved dosage of escitalopram 20 mg once daily.

Numerous research studies have established a robust relationship between escitalopram plasma concentrations and *CYP2C19* genotype. Those with genetic variants predictive of poor metabolism (i.e. *CYP2C19*2* and **3*) have significantly higher plasma concentrations and, conversely, those with genetic variants predictive of ultrarapid metabolism (i.e. *CYP2C19*17*) have significantly lower plasma concentrations (Table S2). Clinically, drug exposure can be associated with both efficacy and toxicity. For example, a recent study by Aldrich *et al.* demonstrated that pediatric patients with CYP2C19 poor metabolizer genotypes had a greater number of escitalopram-induced side effects when compared to other genotype-defined metabolizer groups (8). Furthermore, large population studies demonstrated that genetically-mediated CYP2C19 ultrarapid or poor metabolizers were approximately three times more likely to switch from escitalopram to an alternative antidepressant as compared to normal metabolizers (9). One challenge however, is that the

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FDA does not explicitly state their meanings of ‘effectiveness’ and ‘response’, which could potentially be defined as reduction of depressive systems, occurrence of toxicities, or a combination of both. Implicit, but often not specifically addressed in any discussion of the relationship between ‘dose’ and ‘response’ is the issue of systemic exposure, or more specifically, exposure at the site of action. While a number of studies have established relationships between antidepressant dose and efficacy or side effects it is often challenging connecting drug dose and response/outcome with drug exposure and response/outcome as studies have largely not been designed to address this question (10).

Although the FDA product labeling for sertraline does not include information about the importance of CYP2C19 for its metabolism or impact of genetic metabolizer status, the importance of CYP2C19 phenotype for sertraline metabolism has been reported in the scientific literature (Table S3). The body of literature on the relationship between *CYP2C19* genotype and sertraline is smaller when compared to escitalopram, but there is evidence indicating that CYP2C19 poor metabolizers have higher exposure to sertraline (approximately 3-fold) compared to normal metabolizers (Table S3).

The National Institutes of Health (NIH)-supported Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org) was established in 2009 to provide guidance on how to use gene-drug information in the clinical setting. As part of this mandate, CPIC has a rigorous process for reviewing the available evidence for gene-drug pairs by clinicians and researchers knowledgeable about the gene, drug, and applicable disease states. An extensive review of the pharmacogenetic evidence pertinent to tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) over the past 40 years resulted in CPIC guidelines for *CYP2C19*/*CYP2D6*-TCAs and *CYP2C19*/*CYP2D6*-SSRIs (3, 4). Specifically, for escitalopram and sertraline CPIC guidelines state that for CYP2C19 poor metabolizers consideration should be given to a 50% dose reduction and titration to response or to select an alternative antidepressant not metabolized predominantly by CYP2C19 due to the risk of increased side effects. CPIC guidelines also state that consideration should be given to avoiding escitalopram in CYP2C19 ultrarapid metabolizers and select an alternative antidepressant not metabolized predominantly by CYP2C19 due to the risk of therapeutic failure. Collectively this significant body of evidence supports a clinically relevant relationship between *CYP2C19* genotype and both escitalopram and sertraline response. As such, it is incorrect to state that “the relationship between DNA variations and the effectiveness of antidepressant medication has never been established” and that “the relationship between *CYP2C19* genotype and drug response to escitalopram and sertraline is not established” (3, 4) (Tables S2 and S3).

We strongly agree that caution should be exercised when marketing pharmacogenetic tests to both providers and patients. However, it is important to acknowledge that pharmacogenetic tests for genes representing drug clearance pathways, such as CYP2C19 or CYP2D6, influence the relationship between the dose prescribed and the amount of the drug measurable in the blood or plasma, and subsequently the clinical response. Therefore, pharmacogenetic test results provide valuable information for the treatment of individual patients by identifying the most appropriate starting dose or dosing strategy (including dose titration) of a medication based on that individual’s genotype, an approach analogous to the

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use of surrogate markers of hepatic and renal function to guide therapeutic decisions for individual patients. Pharmacogenetic data could also identify patients that may need closer clinical management for further treatment individualization. The guidelines developed by CPIC to guide the dosing of SSRIs and TCAs, including escitalopram and sertraline, are based on critical review of the available evidence. The process is transparent, and the literature providing the data upon which the guidelines are based is readily available for review. In some cases, the guideline authors may determine that there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time, as was the case for *CYP2D6* and fluoxetine. Furthermore, each of the guidelines is subject to peer-review prior to final publication. Of note, the FDA, along with the NIH, is an observer of the CPIC process and included in communications at all stages of the guideline development process.

In conclusion, we would like to stress that we fully support efforts to improve drug safety, minimize risk to patients, and mitigate inappropriate claims and marketing as they pertain to pharmacogenetic testing. However, our extensive evaluation of the literature firmly supports relationships between genetically defined drug metabolism status and outcomes from antidepressants including escitalopram and sertraline. We respectfully urge the FDA to release a statement clarifying what evidence they require to establish a relationship between a pharmacogenetic test or drug-gene pair and clinical outcome(s), and specifically detail what additional evidence they seek to support the relationship between *CYP2C19* genetic variation and escitalopram and sertraline response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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