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EDITORIAL

Panacea, placebo or poison? Genetically guided treatment for depression

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Understanding pharmacogenomic influences on drug response and adverse effects is critical to precision health, a major goal for modern healthcare. The ability to transcend the current trial-and-error process of treatment matching in psychiatry would prevent harm, improve outcomes and enhance patient quality of life.[1] Public enthusiasm for using genetic information to guide prescribing is nearly universal and physician support is strong.[1] However, although the world is ready for pharmacogenomics, pharmacogenomics is not ready for the world!

Our grasp of the mechanism of disease and drug action remains primitive in psychiatry. Genetic risk for mental illness has only recently begun to be mapped to specific variants and pathways. Very large, well-controlled, unbiased studies are needed to identify genetic factors that influence drug response. The small candidate gene studies nominating most proposed pharmacogenomic variants are known to produce unreliable, false-positive results. More research is required before pharmacogenomic testing can identify the best drug for a patient.[2]

A profoundly uneven knowledge base supports the two classes of genetic variation that influence drug effects. Pharmacokinetic variants that regulate the absorption, metabolism and disposition of drugs impact what the body does to the drug. Pharmacodynamic variants that modify target receptors and mechanistic pathways affect what the drug does to the body. Both types can alter drug efficacy and side effects. A solid evidence base exists for many pharmacokinetic variants that alter drug metabolism.[3,4] Common variants in two enzymes that process the majority of psychotropic drugs, CYP2D6 and CYP2C19, have been shown to impact serum levels of serotonin reuptake inhibitors (SRIs),[4] tricyclic antidepressants (TCAs),[3] and antipsychotic medications, among others. The only validated pharmacodynamic variants are HLA variants that confer a high risk of cutaneous adverse effects in response to some mood stabilizers. The U.S. Federal Drug Administration (FDA) has advised genetic testing for HLA-B*1502 when prescribing carbamazepine to patients of Asian descent and CYP2C19 testing when prescribing citalopram to prevent cardiac arrhythmia in poor metabolizers with other cardiac risk factors. Thirty-two FDA-approved psychiatric drugs have genetic information in their labeling, most recommending caution or

dosing adjustment when metabolism is impaired by inactivating variants. The Clinical Pharmacogenetics Implementation Consortium has published guidelines for pharmacogenetic testing of CYP2D6 and CYPC19 when prescribing SRI[4] and TCA[3] antidepressants and the attention-deficit/hyperactivity disorder drug atomoxetine. These guidelines suggest changes to dosing or drug choice when inactivating or enhancing variants are present.

Despite the small number of clinically actionable variants, private industry has reached far beyond the evidence base to combine dozens of variants, many of dubious significance, into sweeping proprietary algorithms advertised to match a patient with the right drug.[2] The literature supporting the clinical implementation of this testing is entirely industry-sponsored and highly biased. A few randomized controlled trials have been performed, but the majority have not met their primary outcomes.[2,5] The typical reporting format uses green, yellow, and red boxes to highlight lists of drugs with absent, minor or major gene-drug effects, respectively. Since newer drugs have been designed to have fewer CYP interactions, drugs in the green box are often the most expensive and are supported by the least amount of evidence. Tragically, physicians will discontinue, by request of the patient or their own judgment, an effective, well-tolerated medication because it maps to the red box. When starting a new treatment, physicians commonly choose a medication without evidence for the patient's indication because none of the appropriate medications appear in the green box. The reality that most patients and many physicians don't understand is that these tests reveal nothing about which medication will work best for a patient. The most they can tell us is whether the patient may have more or less beneficial or adverse effects at standard doses. A more responsible approach for reporting would list medications that should be prescribed as expected vs. those that may need altered dosing or titration speed.

The FDA has acknowledged that the irresponsible marketing and interpretation of genetic testing is causing harm to patients. In November 2018, it issued a warning that these tests are not supported by enough scientific information or clinical evidence and should not be used to guide prescribing. Further, the FDA has requested that multiple companies change their tests. It is speculated

that the FDA will continue to increase its regulation of genetic tests and may even prohibit references to specific drugs in commercial reports.

Currently, the most responsible approach for clinicians is to rely primarily on clinical judgment and the scientific evidence base when treating mental illness.[1] However, genetic testing is not necessarily avoidable. If a patient provides testing results ordered by a former provider, a physician could be considered legally and ethically obligated to at least consider the available data. In certain situations, such as rapidly optimizing the dose or avoiding side effects in a vulnerable patient, testing can help produce an efficient treatment plan.[1,2]

Clearly, genetically informed prescribing is far from a panacea and currently is beneficial in limited, specific cases. Such testing may give patients more confidence that the prescribed medication is going to work, thereby enhancing treatment adherence and causing powerful placebo effects. However, this is beneficial only if the testing supports an evidence-based treatment, because allowing the testing to override clinical judgment and scientific evidence is undoubtedly doing harm. When the evidence-based medication for your patient's condition lies in the red, don't be afraid to prescribe outside the green box!

Disclosure

The author reports no conflicts of interest.

References

1 Bousman CA, Forbes M, Jayaram M, Eyre H, Reynolds CF, Berk M, et al. Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. BMC Psychiatry. 2017;17:60.

2 Fabbri C, Zohar J, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: comparison of the available testing kits and clinical trials. Prog Neuropsychopharmacol Biol Psychiatry. 2018;86:36-44.

3 Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102:37-44.

4 Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015; 98:127-34.

5 Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. J Affect Disord. 2018; 241:484-91.