Mental Health Breakout Session

Will Heise MD FACMT

Division of Medical Toxicology and Precision Medicine

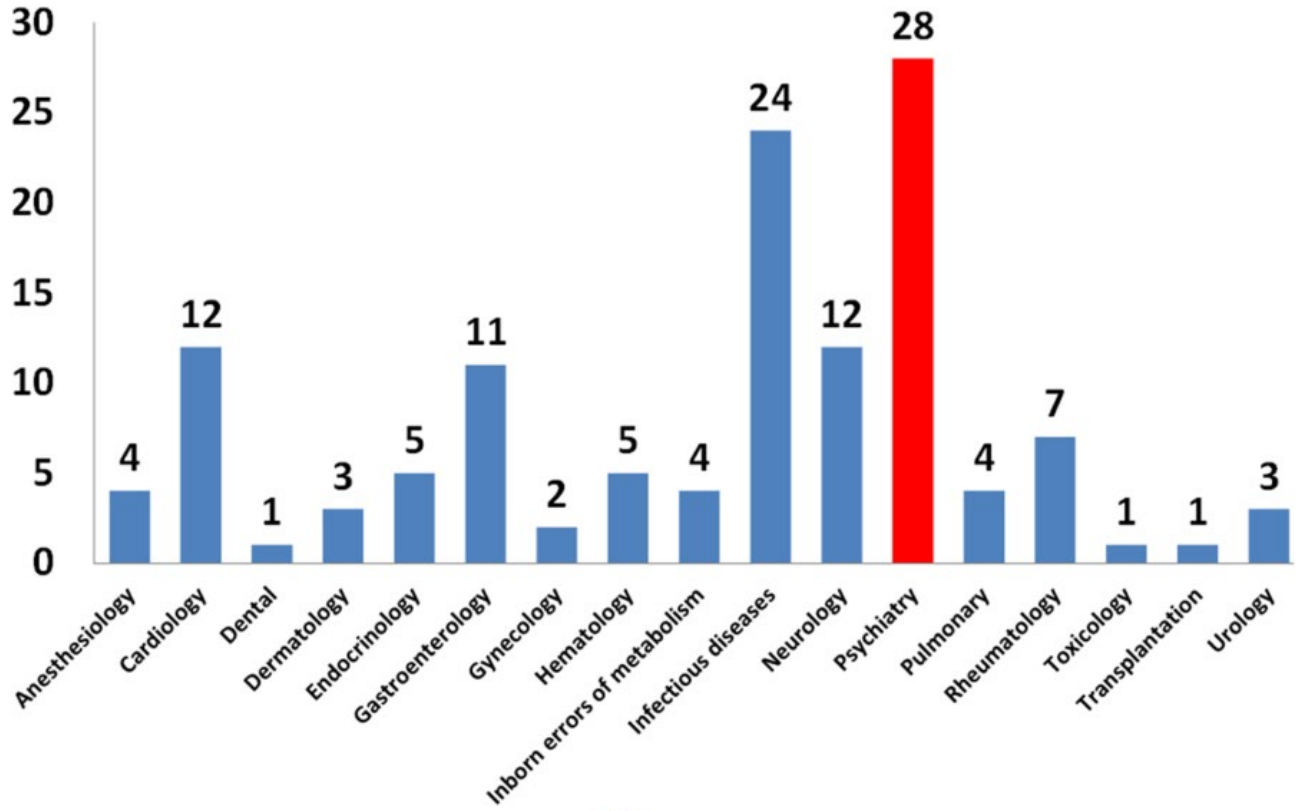
THE UNIVERSITY OF ARIZONA

No conflicts of financial interest

Objectives

- Consider emerging precision medicine approaches to mental health.
- Recognize current impact of psychiatric pharmacogenomics.
- Synthesize approaches to overcome current barriers to the use of psychiatric PGX.

Therapeutic Agents by Category



Benefits of and Barriers to Pharmacogenomics-Guided Treatment for Major Depressive Disorder

Clinical Pharmacology & Therapeutics, Volume: 103, Issue: 5, Pages: 767-769, First published: 01 February 2018, DOI: (10.1002/cpt.1009)

What medications are impacted by the PHASER panel?

Drug List

Amitriptyline	Codeine	Imipramine	Ribavirin*	Trimipramine
Atomoxetine	Desipramine	Interferon, pegylated*	Sertraline	Tropisetron
Azathioprine	Doxepin	Mercaptopurine	Simvastatin	Voriconazole
Capecitabine	Escitalopram	Nortriptyline	Tacrolimus	Warfarin
Citalopram	Fluorouracil	Ondansetron	Tamoxifen	
Clomipramine	Fluvoxamine	Paroxetine	Thioguanine	
Clopidogrel	Fosphenytoin	Phenytoin	Tramadol	*coming soon

Promise/Potential

Known Issues

- Evidence sufficiency
  - Payer issues
- Testing before/after plan to prescribe
- Specialized interpretation
- Match to AZ population

Clinical Pharmacology & Therapeutics

PERSPECTIVES

PERSPECTIVE

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

J. Kevin Hicks[1], Jeffrey R. Bishop[2], Roseann S. Gammal[3,4], Katrin Sangkuhl[5], Chad A. Bousman[6,7,8], J. Steven Leeder[9], Adrián Llerena[10,11], Daniel J. Mueller[12,13], Laura B. Ramsey[14,15], Stuart A. Scott[16,17], Todd C. Skaar[18], Kelly E. Caudle[4], Teri E. Klein[5] and Andrea Gaedigk[9,*]

Recent regulatory and industry communications pertaining to the clinical importance of pharmacogenetic information, along with related language included in the product labeling of some US 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

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 cytochrome isoenzymes are referring to both CYP2D and

Reproducible Genetic Risk Loci for Anxiety: Results From ~200,000 Participants in the Million Veteran Program

Daniel F. Levey, Ph.D., Joel Gelernter, M.D., Renato Polimanti, Ph.D., Hang Zhou, Ph.D., Zhongshan Cheng, Ph.D., Mihaela Aslan, Ph.D., Rachel Quaden, M.A., John Concato, M.D., M.P.H., Krishnan Radhakrishnan, M.D., Ph.D., Julien Bryois, Ph.D., Patrick F. Sullivan, M.D., the Million Veteran Program, Murray B. Stein, M.D., M.P.H.

Objective: Anxiety disorders are common and often disabling. The goal of this study was to examine the genetic architecture of anxiety disorders and anxiety symptoms, which are also frequently comorbid with other mental disorders, such as major depressive disorder.

Methods: Using one of the world's largest biobanks including genetic, environmental, and medical information, the Million Veteran Program, the authors performed a genome-wide association study (GWAS) of a continuous trait for anxiety (based on score on the Generalized Anxiety Disorder 2-item scale [GAD-2], N=199,611) as the primary analysis and self-report of physician diagnosis of anxiety disorder (N=224,330) as a secondary analysis.

Results: The authors identified five genome-wide significant signals for European Americans and one for African Americans on GAD-2 score. The strongest were on chromosome 3 (rs4603973) near *SATB1*, a global regulator of gene expression, and on chromosome 6 (rs6557168) near *ESR1*, which encodes an estrogen receptor. The locus identified on chromosome 7 (rs56226325, MAF=0.17) near *MAD1L1* was previously identified in GWASs of bipolar disorder and schizophrenia. The authors replicated these findings in the summary statistics of two major published GWASs for anxiety, and also found evidence of significant genetic correlation between the GAD-2 score results and previous GWASs for anxiety (r_g=0.75), depression (r_g=0.81), and neuroticism (r_g=0.75).

Conclusions: This is the largest GWAS of anxiety traits to date. The authors identified novel genome-wide significant associations near genes involved with global regulation of gene expression (*SATB1*) and the estrogen receptor alpha (*ESR1*). Additionally, the authors identified a locus (*MAD1L1*) that may have implications for genetic vulnerability across several psychiatric disorders. This work provides new insights into genetic risk mechanisms underpinning anxiety and related psychiatric disorders.

AJP in Advance (doi: 10.1176/appi.ajp.2019.19030256)

THE UNIVERSITY OF ARIZONA

JAMA Network Open

Original Investigation | Psychiatry

Use of Machine Learning for Predicting Escitalopram Treatment Outcome From Electroencephalography Recordings in Adult Patients With Depression

Andrey Zhdanov, PhD; Sravya Atluri, PhD; Willy Wong, PhD; Yasaman Vaghei, MSc; Zafiris J. Daskalakis, MD, PhD; Daniel M. Blumberger, MD; Benicio N. Frey, MD, PhD; Peter Giacobbe, MD; Raymond W. Lam, MD; Roumen Milev, MD, PhD; Daniel J. Mueller, MD, PhD; Gustavo Turecki, MD, PhD; Sagar V. Parikh, MD; Susan Rotzinger, PhD; Claudio N. Soares, MD, PhD; Colleen A. Brenner, PhD; Fidel Vila-Rodriguez, MD, PhD; Mary Pat McAndrews, PhD; Killian Kleffner, MSc; Esther Alonso-Prieto, PhD; Stephen R. Arnott, PhD; Jane A. Foster, PhD; Stephen C. Strother, PhD; Rudolf Uher, MD, PhD; Sidney H. Kennedy, MD; Faranak Farzan, PhD

Abstract

IMPORTANCE Social and economic costs of depression are exacerbated by prolonged periods spent identifying treatments that would be effective for a particular patient. Thus, a tool that reliably predicts an individual patient's response to treatment could significantly reduce the burden of depression.

OBJECTIVE To estimate how accurately an outcome of escitalopram treatment can be predicted from electroencephalographic (EEG) data on patients with depression.

DESIGN, SETTING, AND PARTICIPANTS This prognostic study used a support vector machine classifier to predict treatment outcome using data from the first Canadian Biomarker Integration Network in Depression (CAN-BIND-1) study. The CAN-BIND-1 study comprised 180 patients (aged 18-60 years) diagnosed with major depressive disorder who had completed 8 weeks of treatment. Of this group, 122 patients had EEG data recorded before the treatment; 115 also had EEG data recorded after the first 2 weeks of treatment.

INTERVENTIONS All participants completed 8 weeks of open-label escitalopram (10-20 mg) treatment.

Key Points

Question Is it possible to predict whether the condition of a patient with depression will improve after escitalopram treatment by analyzing their resting-state electroencephalographic signals?

Findings In this prognostic study of data from 122 patients diagnosed with major depressive disorder, support vector machine classifiers demonstrated an accuracy of 82.4% for predicting escitalopram treatment outcome.

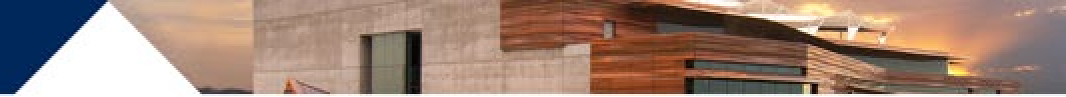
Meaning When complemented by appropriate analysis methods, resting-state electroencephalographic recordings may be instrumental in improving treatment of patients with depression.

Annual Review of Pharmacology and Toxicology

Gene-Based Dose Optimization in Children

Laura B. Ramsey,[1,2] Jacob T. Brown,[3] Susan I. Vear,[4]
Jeffrey R. Bishop,[5] and Sara L. Van Driest[6]

Pharmacogenetics is a key component of precision medicine. Genetic variation in drug metabolism enzymes can lead to variable exposure to drugs and metabolites, potentially leading to inefficacy and drug toxicity. Although the evidence for pharmacogenetic associations in children is not as extensive as for adults, there are several drugs across diverse therapeutic areas with robust pediatric data indicating important, and relatively common, drug–gene interactions. Guidelines to assist gene-based dose optimization are available for codeine, thiopurine drugs, selective serotonin reuptake inhibitors, atomoxetine, tacrolimus, and voriconazole. For each of these drugs, there is an opportunity to clinically implement precision medicine approaches with children for whom genetic test results are known or are obtained at the time of prescribing. For many more drugs that are commonly used in pediatric patients, additional investigation is needed to determine the genetic factors influencing appropriate dose.



Drug Prescribing and Outcomes After Pharmacogenomic Testing in a Developmental and Behavioral Health Pediatric Clinic

Jai N. Patel, PharmD, BCOP,* Maxine K. Mueller, PharmD,† William J. Guffey, PharmD,‡ Joseph Stegman, MD§

ABSTRACT: *Objective:* To describe drug prescribing and outcomes after pharmacogenomic (PGx) testing in children with developmental and/or behavioral disorders. *Methods:* This is a single-clinic retrospective analysis of patients aged 5 to 17 years with documented behavioral and/or development disorder(s) and having received PGx testing between May 2015 and May 2017. The primary endpoint was frequency of PGx-guided medication changes after testing. Secondary endpoints included frequency of medications in each category from the PGx report (use as directed, use with caution, and use with increased caution), changes in therapy within each category, frequency and type of actionable genes, symptomatic improvement, and frequency of medication changes up to 6 months after PGx-guided therapy. *Results:* Of 200 patients, 75% were male, 78% were white, 83% had attention-deficit/hyperactivity disorder, and 45% had anxiety, and their mean age was 10 years. Most common reasons for ordering PGx testing were lack of response (83%) and/or adverse events (42%). Approximately 84% had PGx-guided medication change(s) after testing. At baseline, 50% of medications were categorized in "use as directed," 40% in "use with caution," and 11% in "use with increased caution." After testing, 8%, 29%, and 30% of medications in "use as directed," "use with caution," and "use with increased caution" categories were discontinued; 85% were added or continued from "use as directed" category. The most common actionable genes were *ADRA2A* (47%), *COMT* (22%), and *CYP2D6* (20%). Sixty percent were on the same medication(s) suggested by the PGx report 6 months later, and 64% had provider-documented symptomatic improvement. *Conclusion:* Pharmacogenomic testing may affect drug prescribing and clinical outcomes in a pediatric behavioral health clinic.

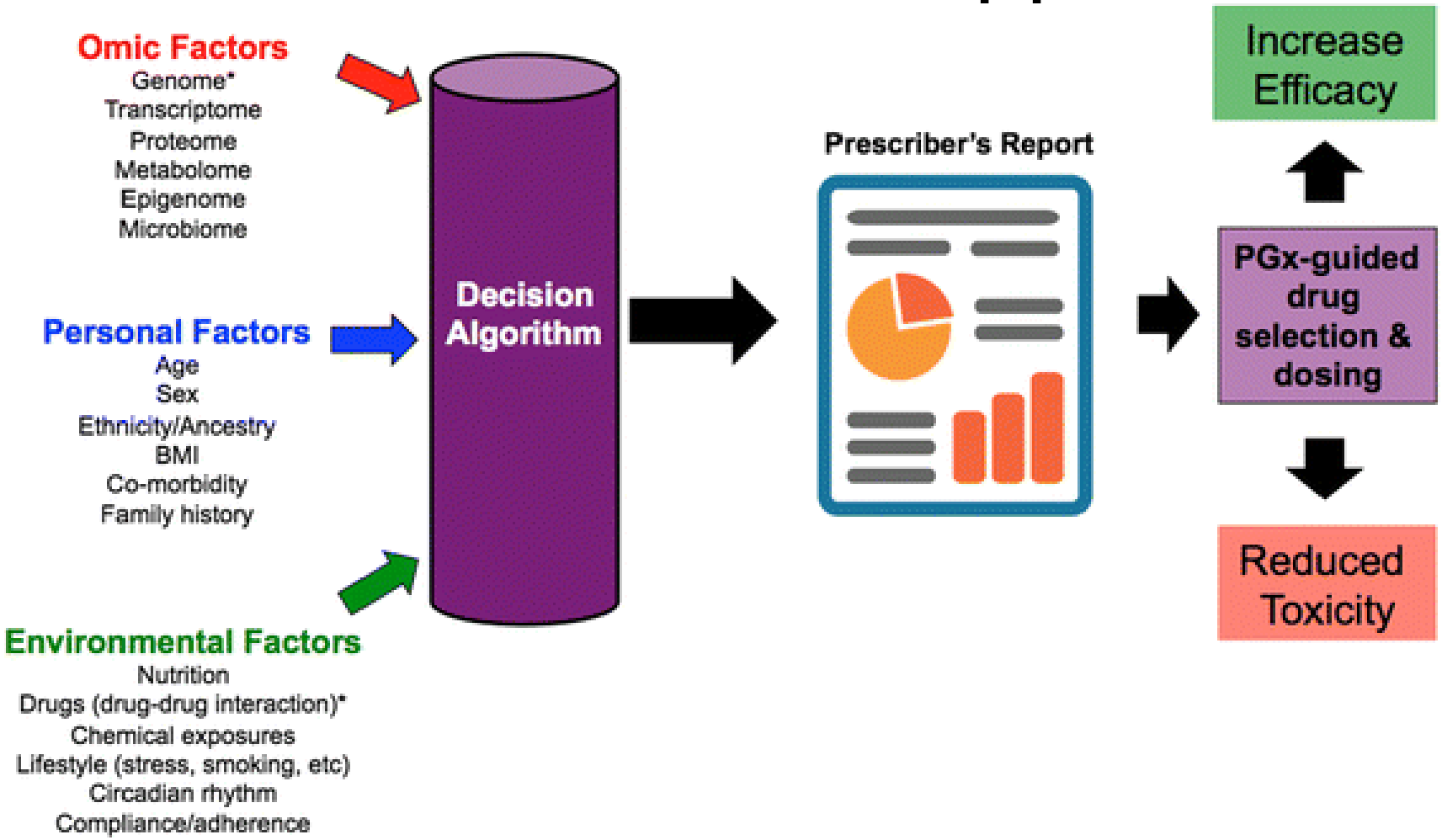
(*J Dev Behav Pediatr* 41:65–70, 2020) **Index terms:** pharmacogenomics, pediatrics, developmental disorders, behavioral disorders.

Downloaded from https://journals.lww.com/

Barriers to Clinical Use Discussion

Solutions to Clinical Use

Future Decision Support



Bousman CA, Forbes M, Jayaram M, Eyre H, Reynolds CF, Berk M, Hopwood M, Ng C. Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. BMC psychiatry. 2017.