Chapter 25

Pharmacogenomics in bipolar disorder: towards precision psychiatry and personalized treatment

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25.1 Background

"*The right drug for the right patient at the right dose at the right time*."

Precision medicine is formally defined as "an emerging approach for treatment and prevention that takes into account each person's variability in genes, environment, and lifestyle." Incorporating precision medicine into clinical practice is a recognized priority, as it is shown by the "Precision Medicine Initiative" launched by President Obama in 2015. This initiative's goal is to bring medicine into a new era by changing our concepts of how medicine is traditionally understood and applied in all clinical areas (Collins & Varmus, 2015; Fernandes et al., 2017). In particular, being able to predict response to a particular therapy, what has been called "choosing the right treatment for the right patient at the right dose at the right time," one of the pillars of precision medicine, is perhaps the most important (Fig. 25.1) (Fernandes et al., 2017).

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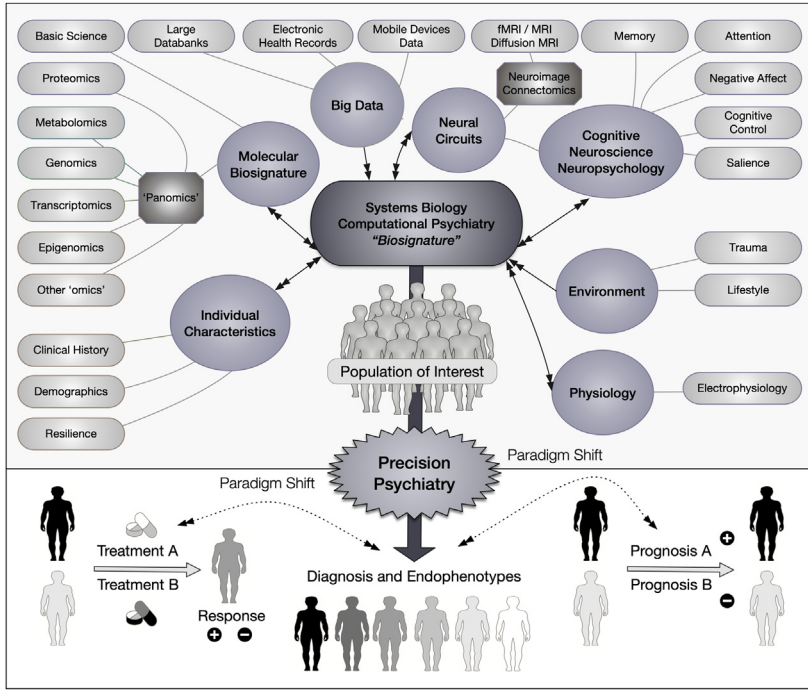

FIGURE 25.1 Domains related to "Precision Psychiatry." Diverse approaches and techniques, such as "omics," neuroimaging, cognition, and clinical characteristics, converge to several domains that can be analyzed using systems biology and computational psychiatry tools in order to produce a biosignature—a set of biomarkers—that, when applied to individuals and populations will produce better diagnosis, endophenotypes—measurable components unseen by the unaided eye along the pathway between disease and distal genotype—classifications, and prognosis, as well as tailored interventions for better outcomes. The bottom-up approach from specific areas (such as metabolomics) to domains (such as molecular biosignature) to systems biology and computational psychiatry to a resultant biosignature can also be reverted to a top-down approach, with specific biosignatures being analyzed to better understand domains and its specific components. Each components and domains are not mutually exclusive, and a subject can belong to more than one component or domain, such, for instance, "large databanks" can belong to data from "neuroimaging," "mobile devices," and "panomics," all of which are put as different domains. After the establishment of precision psychiatry, persons considered to belong to the same group (agglomerate of persons in *gray*) will be reclassified into different diagnosis and endophenotypes. Also, after accomplishing precision psychiatry, it will be possible to better predict response or nonresponse to treatment, and also better prognosis. *Annotations:* Light warm *gray* rectangles, specific components; medium cool *gray* circles, domains; agglomerate of persons in *gray*, different individuals grouped together that, after precision psychiatry, will be better recognized. Bidirectional arrows, bidirectional relationships; unidirectional arrows, unidirectional relationships. *Data from Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. (2017). The new field of 'precision psychiatry'. BMC Medicine,* 15*, 7.*

Pharmacogenetics and pharmacogenomics study the genetic variation of each person that is related to drug response and occurrence of adverse events. This field began with studies of enzymes responsible for drug metabolism, which is related to pharmacokinetics, and evolved to studies analyzing drug transporters, which are related to pharmacodynamics (Cuellar-Barboza et al., 2020), and are one of the earlier focus of precision psychiatry (Fernandes et al., 2017).

Bipolar disorder (BD) is a common and disabling psychiatric condition, associated with severe socioeconomic impact. BD can be treated with a myriad of drugs, including mood stabilizers, among which lithium represents the first-line treatment (Vieta et al., 2018). Anticonvulsants, antipsychotics, and antidepressants are also commonly used to treat this debilitating disorder. Many studies published have aimed to identify molecular and genetic markers that could help clinicians to predict response to drugs employed to treat BD or the risk for adverse reactions to psychiatric medications. The majority of pharmacogenetic studies have focused on major depressive disorder (MDD), not BD, though.

In this review, we will outline available studies investigating the pharmacogenetics and pharmacogenomics of drugs routinely prescribed to people with BD.

25.2 Pharmacogenomics and genetic variation

The human genome is comprised of approximately 3.1 billion nucleotide bases. Recently, the 1000 Genomes Project sequenced the genomes of 2504 persons representing more than 26 different populations groups and described over 88 million genetic variants, of which 84.7 million are single-nucleotide polymorphisms (SNPs), 3.6 million are short insertions/deletions (indels), and other 60,000 are structural variants. Our genome has around 30,000 genes, and every individual inherits two copies of most genes, one from each parent (Genomes Project et al., 2015).

Genetic variants in metabolism enzymes can result in functional activity changes that potentially can inform and predict different pharmacological metabolizer phenotypes. Polymorphisms in genes implicated in drug metabolism that may affect function include SNPs, small insertions/deletions, gene duplications or deletions, or larger copy number variants that affect gene expression or protein conformation. The National Center for Biotechnology Information (NCBI) has a public repository for SNP data, the Single-Nucleotide Polymorphism Database (dbSNP), which assigns unique reference SNP identifiers (*rs* number) for each genetic variant. For genes responsible for producing enzymes necessary for drug metabolism, combinations of these polymorphisms are used to define alleles, which, by definition, have a star "*" designation (Scott et al., 2013). Diplotypes (star allele combinations, for instance, CYP2D6 *1/*4) are then used for defining the metabolizer

groups according to genetics, which is generally classified into four main categories. *Extensive or normal metabolizers* display enzyme activity that is normal, marked by, in most situations, either two normal functional alleles or one normal and one partly reduced function allele. *Intermediate metabolizers* present reduced enzyme activity only partially and are distinguished by one decreased-function and one no-function allele or one normal-function allele and a decreased- or no-function allele. *Poor metabolizers* display little or no enzyme activity, characterized by two nonfunctional alleles. Finally, *rapid and ultrarapid metabolizers* display increased enzyme activity, characterized by multiple copies of functional alleles or alleles with greater-than-normal activity (Eum, Lee, & Bishop, 2016).

25.3 Pharmacokinetic: drug metabolism

The superfamily of proteins 2D6, 2C9, 2C19, and 3A4, from the Cytochrome P450 (CYP), is crucial for phase I drug metabolism (Crettol, Petrovic, & Murray, 2010). Phase I biotransformation reactions introduce or expose functional groups on the drug and increases the polarity of the compounds. Phase I drug metabolism occurs in several different tissues, but the primary and first-pass metabolism site occurs during hepatic circulation. Inside the cell, most phase I enzymes are located in the endoplasmic reticulum (Thompson, Watkins, Gregus, & Klaassen, 1982). Phase I reactions are, generally speaking, grouped into three categories, which are oxidation, reduction, and hydrolysis. As most small molecule drugs are lipophilic in nature, drug metabolism converts these hydrophobic compounds into more water-soluble compounds that can be excreted (David Josephy, Peter Guengerich, & Miners, 2005). Usually, the most common phase I reaction is oxidation. The cytochrome P450 complex is the most important of all phase I oxidation systems. Pharmacokinetics mostly started with the study of the genotyping, coupled with metabolic phenotyping, of CYP in the hope that would shed light and guide treatment selection and dosage by identifying drug classes that would be associated with clinical response and side effects (Nassan et al., 2016). Most pharmacogenetic tests focus on the CYP and usually classify individuals according to the metabolism capacity of this cytochrome in *poor, intermediate, extensive (normal, or "wild type," the default type), and ultrarapid*. This categorization has some utility mostly to identify some individuals who might experience severe adverse events, most notably related to identifying those individuals who are poor metabolizers. Poor metabolizers have two inactive allele copies of the gene encoding for the enzyme. Thus those poor metabolizers possess a lack of ability to produce a functional enzyme, which causes an increase in the plasma levels of the drugs and, consequentially, more adverse events for drugs that have a dose-dependent increase in toxicity. In this sense, poor metabolizers of 2C19 and 2D6 are at increased risk of presenting severe arrhythmia adverse events

related to prolonging the QT interval, and the Food and Drug Administration (FDA) has demanded drug label revisions (Eum et al., 2016). Following this same rational, poor metabolizers also have less capacity to metabolize and activate prodrugs, which can, possibly, decrease the efficacy of the drug (Crews et al., 2014). Ultrarapid metabolizers possess the capacity of metabolizing medications at high speed and, consequently, propitiate, probably, lower bioavailability of the drugs and thus efficacy (Nassan et al., 2016).

The CYP2D6 genotype is also important when prescribing fluoxetine and paroxetine since they are metabolized by the CYP2D6, in addition to other less critical enzymes with lower affinity. This factor may be relevant in the FDA black-box warning that short-term treatment-emergent suicidal ideation and short-term antidepressant-induced mania both typically occur early in the course of treatment (Eum et al., 2016). This might be of particular relevance to people with BD, which present an increased suicide risk and antidepressant-induced manic switch. However, it should be acknowledged that there are some drawbacks in the studies of CYP profiles and the use of pharmacogenetic tests, for instance, the allele frequency of CYP genes possess great variability among different races and ethnicities, as well as great variability among different people, and the fact that CYP genes are heavily influenced by several environmental factors and concurrent use of other medications, all of which are difficult to take into consideration when performing a pharmacogenetic test (McGraw, Gerhardt, & Morris, 2018). Polymorphisms of CYP2C19 and CYP2D6 genes are the most commonly used in pharmacogenetic tests for psychiatric drugs since they are crucial to enzymes that metabolize most selective reuptake inhibitors and approximately half of antipsychotics, medications commonly used in BD (Bousman, Jaksa, & Pantelis, 2017). Below, some central polymorphisms of the CYP complex and its influence in psychiatric medications are discussed in more detail.

25.3.1 CYP2D6

The most common and important polymorphism of the hepatic CYP complex related to psychiatric medications is, arguably, the one involving CYP2D6. CYP2D6 is involved in the metabolism, and is heavily inhibited, by several antidepressants and antipsychotics, for instance, paroxetine, fluoxetine, venlafaxine, perphenazine, and thioridazine, which are sometimes prescribed to people with BD. Decreases or increases in CYP2D6 function impact pharmacokinetics and has the potential, at least theoretically, of impacting dose-related outcomes of these drugs (Ravyn, Ravyn, Lowney, & Nasrallah, 2013). Until now, more than 1400 allelic variants have been discovered in CYP2D6, of which at least 105 are considered as major variants (Nassan et al., 2016; Smigielski, Sirotkin, Ward, & Sherry, 2000). Statistics and prevalence of the different CYP2D6 polymorphisms differ widely across the

world. Regarding race and ethnicity, Europeans are overrepresented among the poor metabolizers (approximately 5%), whereas Asians, Oceanians, and Middle Eastern populations present the lowest prevalence among poor metabolizers (less than 1%). In contrast, ultrarapid metabolizers are overrepresented among Oceanians (21%) and Middle Eastern populations (11%) and are subrepresented in East Asia (approximately 1%) (Cuellar-Barboza et al., 2020; Eum et al., 2016). This great variability in CYP2D6 genotype confounds the actual metabolism phenotype of a given person, therefore, it is difficult to predict response to treatment or adverse events.

With the exception of ziprasidone, which is metabolized through CYP1A2 and CYP3A4, and of quetiapine, which is metabolized through CYP3A4 and CYP3A5, most antipsychotics are substrates of CYP2D6 (Eum et al., 2016). CYP2D6 is responsible for metabolizing risperidone to its active metabolite 9OH-risperidone and aripiprazole to its active metabolite dehydroaripiprazole. Those who are CYP2D6 poor metabolizers show an increase in the serum concentrations of aripiprazole and an increase in the half-life of both aripiprazole and risperidone (Eum et al., 2016; Jukic, Smith, Haslemo, Molden, & Ingelman-Sundberg, 2019). A retrospective cohort study, published in 2019, investigated CYP2D6-genotyped individuals who received aripiprazole or risperidone, and showed a decrease in the metabolic ratios, which is the ratio between the metabolite and the parent drug, for both risperidone and aripiprazole in those who are poor or intermediate metabolizers. However, greater metabolic ratios were found only for risperidone, not for aripiprazole. Thus these drugs theoretically should be used with caution in those who are poor metabolizers regarding CYP2D6, although the real implications are still unclear at this stage of research (Jukic et al., 2019).

The majority of studies investigating the role of CYP2D6 genotype in the pharmacokinetics of antidepressants and subsequent antidepressant response have been done in individuals with MDD, not BD. There is no influence of the CYP2D6 genotype profile in response to escitalopram, venlafaxine, and nortriptyline (Hodgson et al., 2014, 2015; Ng et al., 2013). One study with the a population composed exclusively of pregnant women showed that those who are poor or intermediate metabolizers had a nearly four times higher risk of discontinuing antidepressants when compared to those who are normal or ultrarapid metabolizers. However, predicted metabolizer CYP2D6 status had no influence on change of antidepressant dosage. However, since only women during pregnancy were included in this study, we cannot generalize its results to the general population or even to nonpregnant women. As it is the case for antipsychotics, the real clinical implications are still open to debate (Berard et al., 2017).

There is also an effect called *iatrogenic poor phenotype* (phenocopy or phenoconversion) that might occur with paroxetine and fluoxetine, which occurs due to the fact that these drugs are also potent inhibitors of CYP2D6 (Spina, Santoro, & D'Arrigo, 2008), which in turn might lead to individuals

behaving as if they were poor metabolizers, thus, if an individual is on fluoxetine or paroxetine and is prescribed another drug that is also metabolized by CYP2D6 they might face toxicity (Berm, Risselada, Mulder, Hak, & Wilffert, 2013; Preskorn et al., 2013). For instance, there are data showing that, in the long-term (more than 2 weeks), 43% of extensive metabolizers who were on fluoxetine 20 mg/day iatrogenically converted to a poor metabolizers phenotype, and that 95% converted at a dosage of 40 mg/day. This effect is lower with paroxetine than with fluoxetine, though. Long-term treatment with paroxetine 20 mg/day converted 70% of those with an extensive phenotype into poor metabolizers (Preskorn, 2003a,b).

Regarding venlafaxine, those who are CYP2D6 poor metabolizers show an increase in the plasma levels of this drug. This has been linked with an increased risk of a range of adverse events, from nausea, diarrhea, and vomiting, to potentially more serious events such as hyponatremia and cardiotoxicity (Alexandrino-Silva, Nadalini Maua, de Andrade, & de Toledo Ferraz Alves, 2008; Chua, Foulds, Miller, & Kennedy, 2013; Vinetti et al., 2011). O-desmethylvenlafaxine is the active metabolite of venlafaxine. Those who possess a poor CYP2D6 metabolizer genotype are reported to have a decreased ratio of plasma O-desmethylvenlafaxine to venlafaxine and more adverse events when compared to individuals with all the other CYP2D6 metabolizers genotypes (Shams et al., 2006).

Another point of interest in the field of pharmacokinetics of antidepressants prescribed to individuals with BD is the emergence of a manic switch induced by antidepressant. In one study, all participants with BD who were poor metabolizers regarding the CYP2D6 genotype presented manic switching with antidepressants (Sanchez-Iglesias et al., 2016).

At this stage, for both antipsychotics and antidepressants, the role and clinical utility of routinely performing genotyping of the CYP2D6 remains unclear when it comes to people with BD. Future studies investigating the clinical utility of CYP2D6 genotyping guiding prescription of antipsychotics and antidepressants in BD are necessary to clarify this.

25.3.2 CYP2C19

Another polymorphism of importance is that of CYP2C19, which has 35 major genetic allelic variants (Nassan et al., 2016). Commonly prescribed psychiatric drugs involving CYP2C19 are selective serotonin reuptake inhibitors (SSRIs) (citalopram and escitalopram), tricyclic antidepressants, and benzodiazepines, and there is some evidence that those who are poor metabolizers when it concerns CYP2C19 have higher concentrations of these drugs, and caution might be necessary in this population according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) (Hicks et al., 2015, 2017). Interestingly, and potentially relevant to the management of people with BD, a 10-year retrospective cohort study showed that the

frequency of poor metabolizers regarding CYP2C19 were more commonly found in participants with BD than with MDD (16 times more common in BD than in MDD, 9.8% compared to 0.6%) (Veldic et al., 2019).

Regarding SSRIs, sertraline, citalopram, and escitalopram, drugs commonly prescribed to individuals with BD, present increased serum levels in those who are poor CYP2C19 metabolizers (Spina & de Leon, 2015). In this line, a *meta*-analysis of genome-wide association studies (GWAS) showed that CYP2C19 poor metabolizers presented higher occurrence of side effects with escitalopram or citalopram compared to those who are extensive metabolizers, but also that they had more important improvement in depressive symptoms (Fabbri et al., 2018). In spite these data, the current role and benefit of routinely genotyping CYP2C19 before initiating escitalopram or citalopram, and the actual impact of the CYP2C19 in different clinical response or remission with these drugs, remains open for debate.

25.3.3 CYP2C9

The role of different genotypes of CYP2C9 appears to be considerable less important than the CYP2D6 and CYP2C19 (Spina & de Leon, 2015). One notable exception is, perhaps, that its genotyping might be clinically relevant in children on valproate (Llerena, Dorado, Berecz, Gonzalez, & Penas, 2004).

25.4 Pharmacogenomics of drugs commonly used in bipolar disorder

GWAS have consistently shown that psychiatric disorders are highly polygenic, with a large number of genetic variants with small effect underlining the susceptibility to the disorders (Gratten, Wray, Keller, & Visscher, 2014). Thus, a similarly high variation is expected in response to different drugs by different individuals. In addition to drug-metabolizing enzymes and drug transporters, pharmacogenetic research has also focused on genes encoding therapeutic targets of drug therapies. We discuss below the most common drugs employed in the treatment for BD from a pharmacogenomics perspective.

25.4.1 Valproic acid

Valproic acid (VPA) is formally recommended in all phases of BD (mania, depression, and euthymia). It is broadly accepted that one of the mechanisms of action of valproate is through the blockage of sodium channels (Swainson et al., 2020; Yatham et al., 2018). Understandably, pharmacogenomics research on valproate early focused on the genetics of the family of the SCN genes (Cuellar-Barboza et al., 2020), particularly SCN2A, which is

responsible for encoding the sodium channels. Despite this reasoning, there is no clear evidence that variations in SCN2A influence clinical response to valproate (Haerian et al., 2013; Haug et al., 2001). Another gene that encodes for sodium channels is CACNA1C, and, similarly to SCN, results on its variation and clinical response to valproate were disappointing. One important point to note is that these studies were conducted in people with epilepsy and not BD (Lv et al., 2015). Finally, specifically in people with BD, one study presented an association between the polymorphism XBP1−116 C/G (Kim, Kim, Lee, & Joo, 2009).

25.4.2 Lamotrigine and carbamazepine

The FDA formally recommends that all those who are of Asian ancestry be tested in order to identify carriers of the HLA-B*15:02 allele before commencing carbamazepine due to increased risk of severe and potentially fatal adverse events, particularly Stevens−Johnson syndrome (Drozda, Pacanowski, Grimstein, & Zineh, 2018). Carriers of the HLA-B*15:02 allele are also at increased risk of dermatological adverse events with lamotrigine, however, routinely testing for the HLA-B*15:02 allele is not recommended prior commencing lamotrigine by the FDA (Bloch, Sills, Pirmohamed, & Alfirevic, 2014).

25.4.3 Lithium

Lithium is the mainstream treatment of BD and thus attracted attention as a target of pharmacogenomics studies since the beginning. Lithium in monotherapy or in combination is effective in approximately 60% of chronically treated patients, but the response remains heterogeneous, and a large number of individuals require a change in treatment after several weeks or months (Yatham et al., 2018). The International Consortium on Lithium Genetics, ConLiGen, completed a genome-wide association multicentric study (GWAS) in a large cohort of people with BD and found a hit in a group of SNPs in chromosome 21. A follow-up subgroup study by this group showed that alterations in this region of chromosome 21 were associated with a lower chance of relapse in a 2 years period (Hou et al., 2016). Also, a *meta*-analysis of GWAS suggested that 15 genetic variants, most of which were related to HLA antigen complex, might influence response to lithium (International Consortium on Lithium et al., 2018). However, another large GWAS in people with BD not only did not replicate these findings as it also not found any association of any genetic variant and objective lithium response (Song et al., 2016). The clinical importance and utility of the findings discussed here are still to be determined.

25.4.4 Antidepressants

Antidepressants, although not first-line treatment in BD, are very commonly prescribed medication to people with BD. Clinically, the main concern related to antidepressant use in BD is the occurrence of a manic switch. Given the potential severity of this phenomenon, researchers have tried to identify polymorphisms that might help in the prediction of its occurrence, and the main focus of such efforts have been on the gene responsible for serotonin transport reuptake, SLC6A4, and its variants. Of major interest are the short (S) and long (L) alleles of 5-HTTLPR, and there is borderline *meta*-analytic evidence suggesting that the S allele of 5-HTTLPR is possibly associated with the occurrence of manic switch induced by antidepressants in people with BD (Frye et al., 2015). This study also suggested that those who possess the L-A-10 haplotype in the SNP rs25531 (A/G) presented a lower risk of a manic switch with antidepressants (Frye et al., 2015).

25.4.5 Atypical antipsychotics

The Systematic Treatment Enhancement Program for Bipolar Disorder analyzed if any genotypic profile could emerge as a potential predictor of antipsychotic-induced weight gain, specifically in BD. However, none was found to significantly impact this outcome (Creta, Fabbri, & Serretti, 2015). In 2016 a large *meta*-analysis on the topic of antipsychotics induced weight gain and genetics was published. Most of the included population, almost 7000 participants, possessed Asian or Caucasian origins and were not limited to BD. The results showed that thirteen SNPs, from nine different genes, ADRA2A, ADRB3, BDNF, DRD2, GNB3, HTR2C, INSIG2, MC4R, and SNAP25, were associated with weight gain due to antipsychotics (Zhang et al., 2016).

25.5 Future directions for the field

The future of therapeutic interventions in psychiatry lies in identifying subsets of patients who will benefit from particular therapies, using predictive biomarkers. The final aim of pharmacogenetics is to complement clinical criteria used in medication choice with information on the individual's genetic profile to personalize treatment prescription. Until now, none of the genes suggested by pharmacogenetic studies on mood stabilizers have been included in any of the genetic tests approved by the FDA for drug efficacy. On the other hand, genetic information has been included in drug labels to test for carbamazepine and valproate safety.

One factor that makes conducting pharmacogenomics research in BD challenging is that BD is a highly heterogeneous disorder; in tandem with a modern understanding of psychiatric disorders, BD is probably constituted

by several different subtypes, each one possessing better odds of responding to a given treatment than the other. The selection of the most successful treatment would thus require identification of characteristics of each individual person, such as clinical characteristics and biological characteristics (biomarkers), that would predict if that given individual patient will respond or not to a given treatment, and, ideally if a given treatment is superior to another. There is still a lot of research that needs to be done until we can answer these questions. In the future, sizeable clinical trials comparing treatment as usual to pharmacogenomics-guided treatment for BD patients are essential to help answer these questions.

References

Alexandrino-Silva, C., Nadalini Maua, F. H., de Andrade, A. G., & de Toledo Ferraz Alves, T. C. (2008). Hypotension caused by therapeutic doses of venlafaxine: Case report and proposed pathophysiological mechanisms. *Journal of Psychopharmacology (Oxford, England)*, *22*, 214–216.

Berard, A., Gaedigk, A., Sheehy, O., Chambers, C., Roth, M., Bozzo, 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. *Frontiers in Pharmacology*, *8*, 402.

Berm, E. J., Risselada, A. J., Mulder, H., Hak, E., & Wilffert, B. (2013). Phenoconversion of cytochrome P450 2D6: The need for identifying the intermediate metabolizer genotype. *The Journal of Clinical Psychiatry*, *74*, 1025.

Bloch, K. M., Sills, G. J., Pirmohamed, M., & Alfirevic, A. (2014). Pharmacogenetics of antiepileptic drug-induced hypersensitivity. *Pharmacogenomics*, *15*, 857–868.

Bousman, C. A., Jaksa, P., & Pantelis, C. (2017). Systematic evaluation of commercial pharmacogenetic testing in psychiatry: A focus on CYP2D6 and CYP2C19 allele coverage and results reporting. *Pharmacogenetics and Genomics*, *27*, 387–393.

Chua, E. W., Foulds, J., Miller, A. L., & Kennedy, M. A. (2013). Novel CYP2D6 and CYP2C19 variants identified in a patient with adverse reactions towards venlafaxine monotherapy and dual therapy with nortriptyline and fluoxetine. *Pharmacogenetics and Genomics*, *23*, 494–497.

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine*, *372*, 793–795.

Creta, E., Fabbri, C., & Serretti, A. (2015). Genetics of second-generation antipsychotic and mood stabilizer-induced weight gain in bipolar disorder: Common and specific effects of key regulators of fat-mass homoeostasis genes. *Pharmacogenetics and Genomics*, *25*, 354–362.

Crettol, S., Petrovic, N., & Murray, M. (2010). Pharmacogenetics of phase I and phase II drug metabolism. *Current Pharmaceutical Design*, *16*, 204–219.

Crews, K. R., Gaedigk, A., Dunnenberger, H. M., Leeder, J. S., Klein, T. E., Caudle, K. E., … Clinical Pharmacogenetics Implementation. (2014). Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clinical Pharmacology and Therapeutics*, *95*, 376–382.

Cuellar-Barboza, A. B., McElroy, S. L., Veldic, M., Singh, B., Kung, S., Romo-Nava, F., … Frye, M. A. (2020). Potential pharmacogenomic targets in bipolar disorder: Considerations

for current testing and the development of decision support tools to individualize treatment selection. *International Journal of Bipolar Disorders*, *8*, 23.

David Josephy, P., Peter Guengerich, F., & Miners, J. O. (2005). "Phase I and Phase II" drug metabolism: Terminology that we should phase out? *Drug Metabolism Reviews*, *37*, 575–580.

Drozda, K., Pacanowski, M. A., Grimstein, C., & Zineh, I. (2018). Pharmacogenetic labeling of FDA-approved drugs: A regulatory retrospective. *JACC Basic to Translational Science*, *3*, 545–549.

Eum, S., Lee, A. M., & Bishop, J. R. (2016). Pharmacogenetic tests for antipsychotic medications: Clinical implications and considerations. *Dialogues in Clinical Neuroscience*, *18*, 323–337.

Fabbri, C., Tansey, K. E., Perlis, R. H., Hauser, J., Henigsberg, N., Maier, W., … Lewis, C. M. (2018). Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: *Meta*-analysis of data from genome-wide association studies. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *28*, 945–954.

Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. (2017). The new field of 'precision psychiatry'. *BMC Medicine*, *15*, 7.

Frye, M. A., McElroy, S. L., Prieto, M. L., Harper, K. L., Walker, D. L., Kung, S., … Biernacka, J. M. (2015). Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. *The Journal of Clinical Psychiatry*, *76*, 174–180.

Genomes Project, C., Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., Korbel, J. O., … Abecasis, G. R. (2015). A global reference for human genetic variation. *Nature*, *526*, 68–74.

Gratten, J., Wray, N. R., Keller, M. C., & Visscher, P. M. (2014). Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Neuroscience*, *17*, 782–790.

Haerian, B. S., Baum, L., Kwan, P., Tan, H. J., Raymond, A. A., & Mohamed, Z. (2013). SCN1A, SCN2A and SCN3A gene polymorphisms and responsiveness to antiepileptic drugs: A multicenter cohort study and *meta*-analysis. *Pharmacogenomics*, *14*, 1153–1166.

Haug, K., Hallmann, K., Rebstock, J., Dullinger, J., Muth, S., Haverkamp, F., … Heils, A. (2001). The voltage-gated sodium channel gene SCN2A and idiopathic generalized epilepsy. *Epilepsy Research*, *47*, 243–246.

Hicks, J. K., Bishop, J. R., Sangkuhl, K., Muller, D. J., Ji, Y., Leckband, S. G., … Clinical Pharmacogenetics Implementation, C. (2015). Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clinical Pharmacology and Therapeutics*, *98*, 127–134.

Hicks, J. K., Sangkuhl, K., Swen, J. J., Ellingrod, V. L., Muller, D. J., Shimoda, K., … Stingl, J. C. (2017). Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clinical Pharmacology and Therapeutics*, *102*, 37–44.

Hodgson, K., Tansey, K. E., Uher, R., Dernovsek, M. Z., Mors, O., Hauser, J., … McGuffin, P. (2015). Exploring the role of drug-metabolising enzymes in antidepressant side effects. *Psychopharmacology*, *232*, 2609–2617.

Hodgson, K., Tansey, K., Dernovsek, M. Z., Hauser, J., Henigsberg, N., Maier, W., … McGuffin, P. (2014). Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. *Journal of Psychopharmacology (Oxford, England)*, *28*, 133–141.

Hou, L., Heilbronner, U., Degenhardt, F., Adli, M., Akiyama, K., Akula, N., ... Schulze, T. G. (2016). Genetic variants associated with response to lithium treatment in bipolar disorder: A genome-wide association study. *Lancet*, *387*, 1085–1093.

International Consortium on Lithium, G., Amare, A. T., Schubert, K. O., Hou, L., Clark, S. R., Papiol, S., ... Baune, B. T. (2018). Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: A genome-wide association study. *JAMA Psychiatry*, *75*, 65–74.

Jukic, M. M., Smith, R. L., Haslemo, T., Molden, E., & Ingelman-Sundberg, M. (2019). Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: A retrospective, cohort study. *Lancet Psychiatry*, *6*, 418–426.

Kim, B., Kim, C. Y., Lee, M. J., & Joo, Y. H. (2009). Preliminary evidence on the association between XBP1–116C/G polymorphism and response to prophylactic treatment with valproate in bipolar disorders. *Psychiatry Research*, *168*, 209–212.

Llerena, A., Dorado, P., Berecz, R., Gonzalez, A. P., & Penas, L. E. M. (2004). Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. *European Journal of Clinical Pharmacology*, *59*, 869–873.

Lv, N., Qu, J., Long, H., Zhou, L., Cao, Y., Long, L., ... Xiao, B. (2015). Association study between polymorphisms in the CACNA1A, CACNA1C, and CACNA1H genes and drug-resistant epilepsy in the Chinese Han population. *Seizure: The Journal of the British Epilepsy Association*, *30*, 64–69.

McGraw, J., Gerhardt, A., & Morris, T. C. (2018). Opportunities and obstacles in genotypic prediction of cytochrome P450 phenotypes. *Expert Opinion on Drug Metabolism & Toxicology*, *14*, 659–661.

Nassan, M., Nicholson, W. T., Elliott, M. A., Rohrer Vitek, C. R., Black, J. L., & Frye, M. A. (2016). Pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants: A template for psychiatric precision medicine. *Mayo Clinic Proceedings. Mayo Clinic*, *91*, 897–907.

Ng, C., Sarris, J., Singh, A., Bousman, C., Byron, K., Peh, L. H., ... Schweitzer, I. (2013). Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. *Human Psychopharmacology*, *28*, 516–522.

Preskorn, S. H. (2003a). Reproducibility of the in vivo effect of the selective serotonin reuptake inhibitors on the in vivo function of cytochrome P450 2D6: An update (part I). *Journal of Psychiatric Practice*, *9*, 150–158.

Preskorn, S. H. (2003b). Reproducibility of the in vivo effect of the selective serotonin reuptake inhibitors on the in vivo function of cytochrome P450 2D6: An update (part II). *Journal of Psychiatric Practice*, *9*, 228–236.

Preskorn, S. H., Kane, C. P., Lobello, K., Nichols, A. I., Fayyad, R., Buckley, G., ... Guico-Pabia, C. J. (2013). Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: Implications for personalized medicine. *The Journal of Clinical Psychiatry*, *74*, 614–621.

Ravyn, D., Ravyn, V., Lowney, R., & Nasrallah, H. A. (2013). CYP450 pharmacogenetic treatment strategies for antipsychotics: A review of the evidence. *Schizophrenia Research*, *149*, 1–14.

Sanchez-Iglesias, S., Garcia-Solaesa, V., Garcia-Berrocal, B., Sanchez-Martin, A., Lorenzo-Romo, C., Martin-Pinto, T., ... 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*, *95*, e2473.

Scott, S. A., Sangkuhl, K., Stein, C. M., Hulot, J. S., Mega, J. L., Roden, D. M., … Clinical Pharmacogenetics Implementation, C. (2013). Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clinical Pharmacology and Therapeutics*, *94*, 317–323.

Shams, M. E., Arneth, B., Hiemke, C., Dragicevic, A., Muller, M. J., Kaiser, R., … Hartter, S. (2006). CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *Journal of Clinical Pharmacy and Therapeutics*, *31*, 493–502.

Smigielski, E. M., Sirotkin, K., Ward, M., & Sherry, S. T. (2000). dbSNP: A database of single nucleotide polymorphisms. *Nucleic Acids Research*, *28*, 352–355.

Song, J., Bergen, S. E., Di Florio, A., Karlsson, R., Charney, A., Ruderfer, D. M., … Belliveau, R. A. (2016). Genome-wide association study identifies SESTD1 as a novel risk gene for lithium-responsive bipolar disorder. *Molecular Psychiatry*, *21*, 1290–1297.

Spina, E., & de Leon, J. (2015). Clinical applications of CYP genotyping in psychiatry. *Journal of Neural Transmission (Vienna)*, *122*, 5–28.

Spina, E., Santoro, V., & D'Arrigo, C. (2008). Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: An update. *Clinical Therapeutics*, *30*, 1206–1227.

Swainson, J., McGirr, A., Blier, P., Brietzke, E., Richard-Devantoy, S., Ravindran, N., … Lam, R. W. (2020). The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the use of racemic ketamine in adults with major depressive disorder: Recommandations Du Groupe De Travail Du Reseau Canadien Pour Les Traitements De L'humeur Et De L'anxiete (Canmat) Concernant L'utilisation De La Ketamine Racemique Chez Les Adultes Souffrant De Trouble Depressif Majeur. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 706743720970860.

Thompson, T. N., Watkins, J. B., Gregus, Z., & Klaassen, C. D. (1982). Effect of microsomal enzyme inducers on the soluble enzymes of hepatic phase II biotransformation. *Toxicology and Applied Pharmacology*, *66*, 400–408.

Veldic, M., Ahmed, A. T., Blacker, C. J., Geske, J. R., Biernacka, J. M., Borreggine, K. L., … Frye, M. A. (2019). Cytochrome P450 2C19 poor metabolizer phenotype in treatment resistant depression: Treatment and diagnostic implications. *Frontiers in Pharmacology*, *10*, 83.

Vieta, E., Salagre, E., Grande, I., Carvalho, A. F., Fernandes, B. S., Berk, M., … Suppes, T. (2018). Early intervention in bipolar disorder. *The American Journal of Psychiatry*, *175*, 411–426.

Vinetti, M., Haufroid, V., Capron, A., Classen, J. F., Marchandise, S., & Hantson, P. (2011). Severe acute cardiomyopathy associated with venlafaxine overdose and possible role of CYP2D6 and CYP2C19 polymorphisms. *Clinical Toxicology (Philadelphia, Pa.)*, *49*, 865–869.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*, 97–170.

Zhang, J. P., Lencz, T., Zhang, R. X., Nitta, M., Maayan, L., John, M., … orrell, C. U. (2016). Pharmacogenetic associations of antipsychotic drug-related weight gain: A systematic review and *meta*-analysis. *Schizophrenia Bulletin*, *42*, 1418–1437.