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MOOD AND ANXIETY DISORDERS (D IOSIFESCU, SECTION EDITOR)

The Role of Pharmacogenomics to Guide Treatment in Mood and Anxiety Disorders

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Abstract Interest has grown in genetic testing to personalize treatment approaches in psychiatry, especially mood disorders and to a lesser extent anxiety. However, numerous studies of genetic variants of metabolizing enzymes, along with fewer studies of single nucleotide polymorphisms of drug transporter proteins, receptors, and other putative drug targets such as neurotransmitter reuptake pumps and receptors, have reported contradictory findings that have not translated into practical, cost-effective treatment recommendations. In this article, we review basic principles of genetic testing and highlight selected elements of genetic testing in cancer. We then critically review the current status of genetic research in pharmacokinetics and pharmacodynamics, as well as the few clinical trials that have been performed. After discussing the limited clinical applications of current research, we make recommendations for developing more clinically useful studies of cost-effective approaches to genetic testing in the treatment of mood and anxiety disorders.

Keywords Pharmacogenetic · Pharmacodynamics · CYP450 · P-glycoprotein · Drug transporter · Depression · Anxiety

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Introduction

The clinical and genetic heterogeneity of even the most clearly defined illnesses makes therapeutics largely empirical, with the choice and dose of most medications being derived from clinical trials of homogeneous samples, particularly in psychiatry [1]. However, different cases of the same disorder can vary substantially at a molecular level, making it difficult to know exactly which treatment, and at which dose, is optimal [2]. Despite the continued release of new medications for depression and anxiety, nothing has emerged that is clearly superior, although a particular treatment may be optimal for a specific patient. As a result, multiple medication trials may be necessary before an effective treatment is found.

Research linking disease phenotypes to mutations in more than 3000 of the 25,000 mapped genes in the human genome, completion of the Human Genome Project, and decreased costs of genome sequencing have increased confidence that genetic approaches may identify clinically meaningful predictors of effectiveness and/or side effect burden of psychiatric medications [3–5]. This article expands on recent reviews [6–9] to address dimensions of genetic testing in the diagnosis and treatment of anxiety and depression that include studies of the relationship between genotype and phenotype, with a critical discussion of the nature of the evidence of utility of any type of genetic testing in actual clinical practice.

Principles and Methodologies of Genetic Testing

Pharmacogenomics is the study of variations in the structure or expression of multiple specific genes on medication actions. The term pharmacogenetics is often used to refer to the same approach, but technically it involves single gene-drug effects. Preemptive pharmacogenetic testing (PGx)

involves batteries of pharmacogenetic tests in unselected patients in order to inform future treatment [10].

Pharmacogenetic and pharmacogenomic approaches involve pharmacokinetics and pharmacodynamics. Pharmacokinetics in this context is the study of the impact of genetic polymorphisms on drug metabolism, primarily by hepatic enzymes, and transport, especially by drug transporter proteins. Pharmacodynamics refers to target site actions (e.g., receptors) that mediate drug effects [11]. Genetic polymorphisms affecting drug targets (pharmacodynamics) and metabolism and disposition (pharmacokinetics) are both important sources of individual variability in therapeutic and adverse effects of medications [5].

The usefulness of genetic testing depends on analytical validity, clinical validity, and clinical utility [12]. Analytical validity is a measure of the performance of a test in identifying a genetic variant. Clinical validity refers to the statistical association between the variant and the outcome of drug therapy. Clinical utility refers to the value of the test in health care, the definition of which depends on who is evaluating it; in many cases, the definition includes the likelihood that the test will improve clinical decision-making and outcomes [12]. Considerable debate remains about the nature of the data that should be required as evidence of a favorable balance between benefit versus risk and cost in clinical practice [12].

Both genome-wide association studies (GWASs), which assess millions of single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and other genetic variations, and candidate gene association studies (CGASs), which investigate hundreds of a priori variants based on preliminary studies, examine a potential association of genotype with a broad phenotype such as treatment response [6]. A GWAS requires a much larger sample to maintain statistical power after adjustment for the probability of a type I error [6]. In order to work with a smaller sample, convergent functional genomics (CFG) is an approach to prioritizing candidate genes for further study [13]. This approach aims to integrate findings from gene expression studies in animal studies of apparent drug-induced phenotypes of a disorder (e.g., yohimbine-induced anxiety) and treatments for the disorder (e.g., diazepam), databases of gene expression studies, and human experiments involving blood or postmortem brain, applying Bayesian theory to derive a composite CFG score representing the combination of previous evidence with new findings [13].

Pharmacokinetics

Cytochrome P450 (CYP450) enzymes, which have been most widely studied in psychiatry [5], catalyze phase I metabolism through oxidation, reduction, *N*-demethylation, hydrolysis, and cyclization [14–16]. CYP450 enzymes in the small intestine influence gastrointestinal absorption of substrates, while hepatic enzymes determine phase I hepatic metabolism; the expression of these enzymes in target tissues, which may be different from their expression in the intestine and liver, influences final drug action [14]. CYP1A2, 2C9, 2E1, and 3A4 are the most abundant CYP enzymes [17], and CYP1A2, 2D6, 2C9, 2C19, and 3A4 account for 60 % of psychiatric drug metabolism [14]. CYP3A enzymes are involved in the metabolism of half of all marketed drugs [18], but it exhibits little in the way of genetic polymorphisms [19]. CYP2D6 is involved in the metabolism of just 25 % of medications, including at least 30 psychiatric medications [5], but it exhibits considerable genetic variability in the general population. Most CYP enzymes metabolize more than one drug, and most drugs are metabolized by more than one enzyme [14, 16]. Regardless of expression in the liver and intestine, a number of CYP450 enzymes are overexpressed in the brain [14].

Even if genotyping metabolizing enzymes reliably predicted phenotype (i.e., drug metabolism as measured by serum level), a clear correlation between the latter and clinical response has only been demonstrated for a small number of medications, perhaps because brain levels do not correlate well with serum levels due to transport in and out of the central nervous system [20]. One important drug transporter that comprises a component of the blood-brain barrier is P-glycoprotein (P-gp), a 170-kDa glycoprotein efflux transporter that is also found in the intestine, liver, and kidney [21]. Polymorphisms of its gene, ABCB1 (MDR1), contribute to differences in efficacy and adverse effects of many psychiatric drugs because P-gp regulates how much of the drug remains in the brain [22]. A number of other drug transporter proteins discussed below that are also involved in the access of a psychotropic medication to targets in the brain also contribute to overall likelihood of treatment response. Once in the central nervous system, the role of target polymorphisms is much harder to assess than the role of metabolizing enzymes, and the relationship of target genotype to responder status is unknown in most cases [23].

Regardless of genotype, a number of factors influence gene expression, including promoters and regulatory regions, transcription factors, genes encoding transcription factors, mRNA stability, and posttranscriptional regulation. Gene expression is influenced by epigenetic factors, which act through DNA methylation, histone modification, and noncoding RNA such as short interfering RNA (siRNA), all of which can alter gene expression without altering DNA sequence [17, 24]. In particular, the activity of many CYP enzymes is altered by DNA methylation of the promoter region [17].

Gene Expression

Gene expression can be modified by a number of epigenetic factors, including histone methylation and demethylation and

noncoding RNA. MicroRNAs (miRNAs) are short, noncoding posttranslational regulators of gene expression, directly or via nuclear receptors [17, 25]. They regulate mRNA stability and translation by targeting hundreds of mRNA transcripts to influence gene networks [26]. Some miRNAs, which are associated with inflammation and other illnesses, alter drug metabolism by most CYP enzymes [17]. MicroRNAs may be targets of medications such as antipsychotic drugs [25]. In a genome-wide gene and miRNA study in lymphocytes after exposure to some of these medications, 68 genes were differentially expressed in similar directions after acute and subacute exposure to haloperidol and clozapine [25].

MicroRNAs have been implicated in a number of disorders [26]. One variant, miR-132, is involved in circadian clock machinery, which is associated with bipolar disorder and major depression [26]. Postmortem gene expression profiling has found a number of miRNAs downregulated in bipolar disorder versus controls [26]. Major depression in the context of excessive stress may be associated with disruption of a circadian clock by perturbation of its regulation by miRNAs [26]. Despite these findings, the usefulness of miRNAs as biomarkers for psychiatric disorders is limited by their association with multiple disorders and the heterogeneity of patient populations [26].

Cancer Genomics

The best established clinical use of genetic testing has been in oncology. The Cancer Genome Atlas (TCGA), which is scheduled for completion in 2015 and cost $375 million, is generating a comprehensive summary of genetic alterations in known tumor types [27]. TCGA has characterized 10,000 tumors from 25 different cancers, with data on 10 million mutations, and is now moving to coordinate findings with clinical data [27].

Some tumor phenotypes that seem very similar are clinically heterogeneous, and specific clinical features may not predict treatment response [28]. Histologic grade of breast cancer is a good predictor of survival at the well-differentiated and slow growing, and poorly differentiated and highly proliferative, ends of the spectrum, but not for moderately differentiated tumors, which comprise 50 % of breast cancers [28]. Gene expression signatures may provide better stratification of prognosis [28]. Analyzing 44,928 probe sets in 347 primary breast tumors, two different methods found 18 probe sets representing 18 genes, and six probe sets representing five genes, that correctly classified 96 % of well-differentiated and 95 % of poorly differentiated tumors. Of the intermediate groups, 94–98 % were correctly classified by genetic analysis as closer to well or poorly differentiated. Genetic signatures also were as good as or better than lymph node status and tumor size in predicting recurrence [28]. Among the differences between more or less differentiated tumors were genes for VEGF, p53, and markers of genomic instability. Overall, expression of five genes involved in mitotic index, angiogenic potential, p53 mutational status, and estrogen and progesterone dependence distinguished between moderately differentiated tumors with different metastatic potentials [28]. However, despite advances in computation, there is still not much clear integration between genomics and clinical practice [27].

Diagnosis and Assessment

In psychiatric disorders, genetic factors interact with the environment to contribute both to illness susceptibility and clinical presentation [29]. Modifier genes appear to influence disease characteristics but not disease liability [29]. Although considerable research has been devoted to polymorphisms associated with anxiety and mood disorders, overlap with other disorders has interfered with applications of the results to diagnosis or treatment in the same way that such approaches have been useful in cancer.

In a cohort of 29 bipolar I subjects, 13 had low mood self-reported on a visual analogue scale (VAS), 13 had high mood, and 3 had intermediate mood [30]. A replication sample included 30 subjects with schizophrenia, schizoaffective disorder, or substance-induced psychosis with similar mood self-ratings, 9 with low, 7 with intermediate, and 14 with high mood, and a second bipolar cohort of 19 subjects, 6 with low, 3 with intermediate, and 10 with high mood. A panel of five genes involved in myelination and six genes involved in growth factor signaling reported in human postmortem brains from mood disorder subjects predicted high or low mood in the three samples with 67–85 % sensitivity and 62–81 % specificity [30]. The authors contend that their panel of genes involved in cell survival and proliferation associated with high mood, and cell shrinkage and apoptosis associated with low mood, could be used to assess mood state. However, there was no suggestion of usefulness for actual diagnosis, and the results are probably more useful for indicating that high and low mood may have different impacts on cellular function.

The same group derived a CFG score for genes induced by the anxiogenic compound yohimbine and suppressed by the anxiolytic drug diazepam, in rodent experiments, as well as published human and animal data, to propose a set of candidate genes for anxiety disorders [13]. These genes included FBJ murine osteosarcoma viral oncogene homolog (FOS), an immediate early-response gene and oncogene, gamma aminobutyric acid receptor B receptor 1 (GABBR1), nuclear receptor subfamily 4, group A, member 2 (NR4A2), a transcription factor and adrenal steroid receptor gene, dopamine receptor 1 (DRD1), adenosine A2a receptor (ADORA2A), as well as genes for an RNA-binding protein,

signal transduction, and response to the environment. A number of these genes were also implicated in schizophrenia, and the data suggest that they are involved in the regulation of arousal and the stress response rather than markers for specific disorders.

Pharmacokinetic Studies

CYP2D6 has been subjected to considerable pharmacokinetic research [5]. CYP2D6 alleles are classified as wild type (normal), reduced function, or nonfunctional [31], and about 35 % of the population has an abnormally functional 2D6 allele [5]. Assortment of the 100 or so reported CYP2D6 genotypes are generally thought to be responsible for four major phenotypes: poor metabolizer (PM; 5–10 % of Caucasians and 1–2 % of Asians), intermediate metabolizer (IM; 2–11 % of patients), rapid (extensive) metabolizer (EM; 77–92 % of patients), and ultrarapid metabolizer (UM; 1–2 % of patients) [3, 31, 32]. However, gene duplication can alter phenotype [31] depending on whether the duplicated genes are active or inactive. The frequency of 2D6 phenotype varies in different ethnic populations [18, 19, 33]. Studies of antidepressants and antipsychotics that are CYP2D6 substrates show a stronger correlation of CYP2D6 status with medication levels than with clinical response [32]. Even in this domain, genotype does not inevitably predict phenotype because CYP2D6 can be inhibited by a number of medications, including fluoxetine, paroxetine, and several antipsychotic drugs, although it is not known to be induced by exogenous factors [16, 31]. Coadministration of a CYP2D6 inhibitor converts an ultrarapid metabolizer to the PM phenotype [32]. In an open study of 900 patients treated with venlafaxine who were genotyped and phenotyped for CYP2D6, 4 % were genotypic PMs, while 27 % were phenotypic PMs, suggesting that 24 % of patients with other genotypes had converted to a PM phenotype as a result of concomitant medications [34].

Like CYP2D6, 2C19 exhibits well-defined polymorphisms [35]. Approximately 3 % of the population are poor, 20 % are intermediate, and 77 % are extensive 2C19 metabolizers [35]; 2C19 poor metabolizers are more common in Asian populations (13–23 %) [19]. About 1 in 500 Caucasians is deficient in both 2D6 and 2C19 [35]. It has been recommended that poor 2C19 metabolizers should receive lower doses of some antidepressants (e.g., citalopram), but this is not based on any clinical trials [35].

CYP3A4 is inhibited by medications such as nefazodone and fluvoxamine, as well as a variety of substances, including grapefruit products, kale, and green tea [17, 36, 37]. Grapefruit juice (and Seville oranges and pomelos) contains furanocoumarins, which irreversibly inhibit CYP3A4, primarily in the small intestine [38], probably by means of reduced gene translation or possibly increased enzyme degradation [21]. The net effect is excessive absorption of 3A4 substrates, which, after acute administration of grapefruit products, can last for 2–3 days, even without a change in systemic metabolism [15, 21, 38]. This can be offset to some extent by inhibition by flavonoids of the intestinal influx transporter organic anion transporter protein (OATP) for about 4 h and inhibition of intestinal P-glycoprotein, both of which decrease systemic availability of the drug [21, 38]. Hepatic 3A4 may be inhibited by repeated ingestion of grapefruit juice, elevating levels of many substrates. CYP3A4 can be induced by St. John's wort [15]. Since enzyme induction involves de novo RNA and protein synthesis, this process can take several weeks, while the time to reversal of enzyme induction depends on the half-lives of the new enzyme and the inducing substance [39].

A number of recommendations based on genotype have been made for CYP2D6 and CYP2C19 substrates, but these do not take into account ethnic differences in gene activity, lack of linear kinetics for many drugs, and therapeutic windows for some of them [33]. Most of the recommendations for adjustment of substrates based on genotype have not been studied in clinical trials and are based on assumptions about the relationship between genotype and drug activity [33]. In addition, as was already noted, the relationship between CYP genotype and CYP phenotype is not necessarily straightforward [40]. Because most genotyping studies have not accounted for induction or inhibition of CYP enzymes by concomitant medications or other substances, either through direct interaction with the enzyme or alteration of gene expression [14], recommendations for dosage adjustments based on single-dose or short-term studies of such drugs in normal subjects, or patients without comorbidity or concomitant medications [19], may not predict actions in the clinic. Conversely, in two retrospective studies, clinicians blind to CYP2D6 genotype prescribed lower doses of 2D6 substrates, or fewer of these substrates for shorter periods of time, for 2D6 poor metabolizers, even though they did not know the patients' actual 2D6 status [7].

Drug Transporter Studies

Drug transporters, including P-gp, organic cation transporters, and multidrug and toxin extrusion (MATE) proteins, account for a significant amount of pharmacokinetic findings because they influence tissue uptake and renal elimination [41].

In the International Study to Predict Optimized Treatment in Depression (iSPOT-D), 10 ABCB1 (MDR1) SNPs in or near the ABCB1 gene were examined as possible predictors of remission and side effects of 3 antidepressants in major depressive disorder (MDD) patients with and without intact cognition [20]. In this study, 888 patients (mean age 39, mean duration of MDD 15 years) had MDR1 genotyping, 683 completed at least 2 weeks of treatment (intent to treat sample),

and 576 completed 8 weeks of treatment (per protocol sample). Mean baseline HDRS was 21.7, and mean Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score was 14.5. Patients were randomly assigned to escitalopram, sertraline, or venlafaxine ER. Remission was defined as QIDS score ≤5. Because age and baseline QIDS scores significantly predicted remission, retrospective genetic analyses controlled for these variables. Within the overall model, homozygotes but not heterozygotes for the common rs10235483 allele responded significantly better to escitalopram and sertraline, while minor allele homozygotes responded significantly better to venlafaxine. The same SNP also had a significant effect on side effects corrected for multiple tests (O.R. 3.07). Major allele carriers had fewer side effects with escitalopram, while minor allele homozygotes had fewer side effects with venlafaxine. Controlling for age and baseline QIDS, rs10235483 significantly predicted remission (O.R. 3.70) in the per protocol model. The T minor allele results in higher Pgp expression, which could result in more clearance of escitalopram and sertraline from the brain. However, it does not explain a better response to venlafaxine. MDR1 variants that predict less efficacy but more side effects could reflect higher doses being used, with more peripheral side effects [41].

ABCB1 variation therefore seems to have a different impact on different medications. Variable results of studies of ABCB1 polymorphisms in antidepressant outcome may reflect heterogeneity of patients, small sample sizes, specific alleles studied, and different interactions of antidepressants with P-gp, and collection of DNA after results are known rather than prospectively [20]. In many cases, even if drug disposition can be predicted to some extent, the impact of transporter and target (e.g., receptor) genotype may be more relevant to disease susceptibility than treatment response [23].

Pharmacodynamic Studies

The serotonin transporter (SERT; reuptake pump) is a site of action of serotonin reuptake inhibitor antidepressants (SSRIs), but it remains to be demonstrated that this action is responsible for the therapeutic effect of these medications. Studies of its gene (SCL6A4) have involved a deletion (short polymorphism or s-allele) or insertion (long polymorphism or l-allele) within the promoter region, which is called 5HTTLPR [32]. The short polymorphism decreases, and the long polymorphism increases, SLC6A4 transcription rates, resulting in less or more SERT expression, respectively [32]. A systematic review of 33 studies found a stronger association of l genotypes (one or two copies of the l allele) than s homozygous (s/s) genotypes with both response and remission with SSRIs, but not other antidepressants, in Caucasians but not Asians [42]. However, differences in efficacy were not clinically impressive and a meta-analysis reported the opposite result [43]. The 5HTTLPR genotype explains at most 5 % of the variance in antidepressant response [15], and the predictive utility of 5HTTLPR genotyping has not been studied prospectively [6]. In 108 patients with major depressive disorder, higher SLC6A4 promoter methylation was significantly associated with childhood adversity and more severe depression but not outcome after 12 weeks of antidepressant treatment [44].

A retrospective analysis of data from an 18-month study of venlafaxine XR for generalized anxiety disorder (GAD) assessed the relationship of the rx25531 SNP of the 5HTTLPR, which has the highest transcription rate of all promoter polymorphisms, and the 5HT2A SNP rs7997012 which, although it has no known function, has also been associated with venlafaxine response, in the outcome of 112 patients of European descent in the initial 6-month open-label phase of this study [45]. The 6-month Hamilton Anxiety Rating Scale (HAM-A) score was 10.7 points lower in patients who were homozygous for both SNPs (N=28) than in patients with neither marker (N=12, p<0.0001). Interpretation of the results is limited by collection of genetic data at the end of the study, a study that was not designed to examine gene-treatment response interactions, retrospective data analysis without correction for multiple statistical tests, and the small number of subjects with both and neither marker.

The involvement of the endogenous opioid system in the modulation of stress and arousal, and the association of reduced μ-opioid receptor binding in women who did not respond to antidepressants in one study, led to a study of the A118G variant of the μ-opioid receptor gene OPRM1 in 112 Caucasian patients with generalized anxiety disorder treated for 6 months with venlafaxine XR [46]. No association was found between this SNP and response to venlafaxine.

Gene Network Studies

Drug action is a function of the net of absorption, distribution, metabolism, excretion, and interaction with target sites, which are influenced by different genetic factors [24] that are not necessarily additive [17]. Genotyping a single enzyme system therefore is not likely to be clinically meaningful unless a medication is only metabolized by one of those enzymes and the medication is not transported, which is not true of most antidepressants and other psychiatric medications [18]. Positive and negative effects of medications may depend on enzymes and other proteins in target organs, which as has already been discussed may distribute differently from metabolizing enzymes [18]. Because treatment outcome seems to be influenced by multiple genetic polymorphisms, each with a

small effect [5, 47], research has moved toward analysis of networks of genes in the hope of developing more clinically useful information [6, 7, 48].

Although larger studies have been conducted to demonstrate the ability of genotyping a combination of drug-metabolizing, transport, and target genes to predict treatment response in depression than is true for pharmacokinetic studies [22], none has produced clinically meaningful results [6, 7]. The Genome-Based Therapeutic Drugs for Depression study (GENDEP; N=811), a sub-study of the Sequenced Treatment Alternatives to Relive Depression (STAR*D; N=1491) study, and the Munich Antidepressant Response study (N=339), did not find any combination of genetic markers than influenced treatment response in depression [3, 7].

In an 8-week trial in 499 Caucasian outpatients with nonbipolar, nonpsychotic, major depressive disorder (MDD) with mild to moderate depression treated openly with SSRIs, 398 of whom completed the protocol, genome-wide association studies did not reveal any SNPs associated with response or remission [49]. Similarly, DNA from patients in the STAR*D study did not reveal any positive GWA findings, and the top 25 SNPs from the STAR*D GWA analysis did not have any significant associations with treatment response [49]. In a secondary STAR*D analysis, an SNP of the riboflavin kinase gene was associated with 8-week treatment response and an SNP of the G protein-coupled receptor kinase 5 gene was associated with 8-week remission [49]. However, this was not in the primary hypothesis and is mainly a finding requiring independent evaluation.

A German genome-wide transcriptomics study of 24 moderately depressed inpatients, openly treated for 5 weeks with their physicians' choice of antidepressant, compared 12 remitters (equivalent to 17-item Hamilton Rating Scale for Depression [HRSD] score <7) with 12 age- and severity-matched nonresponders (<25 % improvement) [50]. The authors identified 127 gene transcripts that had a significant association with remission. A replication study in a separate sample of 142 depressed inpatients supported a significant association with treatment response with lower expression of retinoid-related orphan receptor alpha (RORa), germinal center expressed transcript 2 (GCET2), and chitinase 3-like protein 2 (CHI3L2). Lower expression of RORa, a clock gene involved in generating circadian rhythms and steroid hormone receptors, was also found to be associated with higher plasma corticosterone levels in stress reactive mice in this study [50]. While significant, the association of RORa with treatment response was "slight," and in the absence of non-depressed controls, it is not clear that the reported association was with a response of depression rather than a nonspecific element of the stress response. No prospective confirmation of the findings has been reported.

In a post-hoc analysis of data from a European study of 170 patients with major depressive disorder and 61 with bipolar disorder, an association was studied between treatment resistance and two genes involved in the inflammatory response, "mitogen-activated protein kinase 1 (MAPK1) and cyclic AMP-responsive-element binding protein 1 (CREB1)," which is a transcription factor that is a downstream target of the MAPK pathway [51]. In the primary outcome analysis, neither gene had an SNP associated with treatment resistance. A secondary analysis found a significant association between the GG genotype of CREB1 and remission in major depressive disorder. Insofar as this represented a secondary evaluation of a post-hoc study, the finding does not appear to justify an association with variants of either of these genes and treatment response in depression. Expression of a panel of genes was studied before and after treatment in an open study of 63 outpatients with nonpsychotic MDD treated for 8 weeks with citalopram [52]. Within 32 probesets differentially expressed in citalopram responders, upregulation of interferon regulatory factor 7 (IRF7) was most significant, while decreased IRF7 was found in the prefrontal cortex of untreated depressed patients. Whereas the goal of the study was to study potential markers of citalopram response, following gene expression over the course of treatment does not seem particularly practical since it would be evident clinically whether patients were responding. The result therefore seems more likely to be useful in demonstrating an impact of antidepressant treatment on expression of a gene involved in immune regulation.

Prospective Studies

The studies cited thus far have involved genotyping conducted after a clinical trial is completed, and retrospective data analysis, potentially biasing the results. A small number of reports have involved prospective use of genotyping to make treatment decisions. A German study of 58 depressed inpatients noted that use of genotyping for ABCB1 was associated with a shorter hospital stay because patients with the TT/GG genotype were more likely to have an increase in the dose of an antidepressant that was a P-gp substrate, while a change to a non-P-gp substrate did not affect outcome [53]. However, the study was not randomized, and numerous intervening variables, including pharmacokinetics, comorbidity, and past history, were not considered.

A commercially supported approach to using genotypes for multiple metabolizing and target genes in predicting response to treatment of depression involved a proprietary survey (GeneSight) that involves genotyping a buccal swab for CYP2D6, 2C19, 2C9, and 1A2, the serotonin transporter gene (SLC6A4), and the serotonin 5HT2A receptor gene (5HTR2A). A summary "composite report" is generated that classifies antidepressants and antipsychotic drugs used in the treatment of depression into three categories: "use as

directed," "use with caution," and "use with caution and with more frequent monitoring." In an 8-week open study of the composite report in a multidisciplinary mental health clinic providing pharmacotherapy and psychotherapy [54], 44 patients with MDD were assigned in a nonrandom manner to treatment guided by the composite report (guided treatment) or non-guided treatment by the same group of clinicians. Patients in the guided group were less likely to receive medications in the use with caution and with more frequent monitoring category, presumably because of reluctance by the guided clinicians to prescribe medications that required more monitoring. Some patients also took medications not mentioned in the composite report.

Depression improved similarly in both groups for the first 4 weeks of treatment, but a final measure 4 weeks after that revealed an increase in depression scores for the non-guided but not the guided group, resulting in a significant final difference between groups in decrease in depression from baseline to 8 weeks. No explanation was offered for the final increase in depression scores in the non-guided group when multiple earlier ratings demonstrated a steady decrease in scores. Improvement in the non-guided group was not impressive, and it is impossible to know whether comorbid factors, concomitant medications, treatment adherence, patient enthusiasm, substance use, adjunctive psychotherapy, clinician knowledge of treatment condition, and open ratings affected the conduct of treatment or the outcome assessment.

The same clinicians conducted a larger industry-sponsored open study in a clinic with a proprietary interest in the genomic survey [55]. The same categories were utilized in the composite report, with the addition of notations about the reason why a medication was classified in a particular group (e.g., serum level too high, increased risk of side effects). Of 227 mildly-moderately depressed patients, 165 completed 8 weeks of treatment. Patients in the guided group had significantly greater reductions in depression rating scale scores at 8 weeks, and the odds ratio for response was about twice as high in the guided group. The primary limitations of this replication were the use of a non-randomized sample, lack of correction for multiple statistical tests, and the open method. Since clinicians reported substantial levels of confidence in the genetic reports, and they made more changes in medication in response to them, it is possible that they worked more vigorously with patients in the guided group or that patients were more adherent with a treatment approach they thought would be more effective. Since patients were aware of their treatment group, it is equally likely that those in the guided group were encouraged to report better results.

A double-blind, randomized, controlled trial of the gene profile assigned 25 depressed patients to treatment as usual (TAU) and 26 patients to treatment informed by the pharmacogenomic profile (i.e., guided treatment) [56]. Improvement was numerically greater in patients in the guided than in the TAU group, but none of the group differences were statistically significant. It is conceivable that a small advantage of guided treatment was missed in this smaller sample, but in that case, the difference does not appear to have been clinically important.

In a fourth report from the same company [57], 97 patients with a depressive or anxiety disorder treated openly by a single psychiatrist with one of the medications in the genetic survey received genotyping that assigned each of the 26 medications on that list into one of the three categories noted above. After 1 year of open observation, the 9 patients taking at least one medication in the use with caution category had significantly more total health care visits and non-psychiatric medical visits than the other subjects. However, these patients also took more medications than the other subjects, and there was a significant correlation between the number of medications taken and the two significant outcome variables. The overall cost of care over the observation year was an average of $5188 higher for patients taking medications in the use with caution category. When different statistical analyses were performed on the same data (e.g., analysis of variance and *t* tests), some were significant and some were not; no correction was made for multiple statistical tests. Although the authors concluded that their genetic analysis could save health care costs, this hypothesis was not actually tested. Since no data were available on medical comorbidity and severity of psychiatric illness, the possibility was not considered that the small number of patients in the use with caution category had more health care visits and took more medications because they are sicker psychiatrically or had more medical comorbidity.

Genotype and Adverse Effects

A prospective study found that screening for the HLA-B*1502 allele, which in retrospective studies appeared to increase the risk of a severe rash with carbamazepine, at least in some Asian patients [58], was associated with no new rashes in 5000 Taiwanese patients, when 10 rashes were predicted to occur based on overall population risk [59]. However, other Asian populations, let alone different ethnic groups, may have different HLA risk factors for a medically important rash with carbamazepine [7], whereas rashes that are less dangerous may occur in 10 % of patients taking carbamazepine. Juvenile patients who are homozygous for an allele of the gene for the melanocortin 4 receptor may be more likely to gain weight with some atypical antipsychotic drugs [7], but there is no evidence of a benefit of prospective genotyping for preventing weight gain. The STAR*D study found that CYP450 polymorphisms did not predict side effects from citalopram in the treatment of depression [60].

Limitations of Pharmacogenetic Testing

It has been argued that even though prospective studies do not demonstrate its clinical usefulness, easy methods of obtaining relevant DNA samples through blood or saliva and decreasing cost of genotyping [3, 6] should make genotyping a routine component of medical care because this recommendation is no less evidence based than many existing practice standards, and the results may be useful later [61]. This recommendation is limited by a number of shortcomings of the current database. Sample sizes in most existing studies has been too small to produce meaningful, replicable, results because of the genetic heterogeneity of psychiatric disorders [30], and the combined influence of multiple genes, each with a small effect size [3, 12, 62]. Most studies have utilized retrospective or post-hoc analyses of outcomes rather than prospective studies based on a priori hypotheses [10], and statistical significance is often inflated by lack of correction for multiple statistical tests [12]. The majority of studies lack replication in independent samples, especially by different investigators [12]. Furthermore, complicating factors such as comorbid disorders, concomitant medications, and other patient factors discussed below that influence drug levels and disposition, as well as end organ response, are usually not considered [3].

A technical complication in predicting medication effects from genotype is that the illness, as well as medications used to treat it, can alter the relationship between pharmacologic genotype and phenotype. For example, altered levels of inflammatory cytokines have been reported in mood and anxiety disorders [63]. As a result of effects on transcription or post-translational protein modification, many pro-inflammatory cytokines and acute phase proteins downregulate some CYP450 genes and upregulate others [64]. At the same time, suppression of inflammatory cytokines by antidepressants can alter gene expression in directions opposite to the direct effect of the antidepressant [16].

While genotyping of metabolizing enzymes has been most widely recommended in the treatment of depression and anxiety, many pharmacokinetic studies have been conducted in normal subjects or patients who are not taking other medications and who do not have other illnesses, limiting extrapolation to clinical samples [35]. Assessment of rare functional polymorphisms of CYP450 genes is done from a blood sample, whereas the enzyme is concentrated in the liver [17]. Even clear demonstration of a genotype/blood level relationship in a single dose study in patients may not correlate with chronic treatment, in which compensatory changes in secondary metabolic pathways and drug transporters, gene up- or downregulation, saturation pharmacokinetics, and other factors may modify the impact of one or even a few oxidative enzyme polymorphisms on final drug action [14, 19]. With chronic treatment, some psychotropic drug metabolites form complexes with P450 enzymes that alter or even reverse the acute effect on metabolism [16]. Similar long-term changes in P450 enzymes occur in the brain, with further unpredictable effects, not only on the substrate drug but also on neurotransmitters and neurosteroids metabolized by the same enzymes and implicated in the disorder for which the medication is used [16].

Additional factors complicate clinical correlations of pharmacogenetic studies. For medications that are chiral mixtures of enantiomers with different actions, metabolism of each enantiomer may be by different enzymes [18]. Active metabolites with their own metabolic pathways may enhance or interfere with therapeutic or toxic effects predicted by presumed metabolism of the parent drug [19, 65]. In most instances, more than one genetic factor affects drug levels and disposition [5], and interactions between these factors can be difficult to predict. Even a reliable relationship between genotype and treatment response in populations of patients does not necessarily translate into prediction of treatment response in a particular patient [3]. As a result, most studies of pharmacogenetic technologies have not demonstrated clinical utility, even when a significant number of people carry actionable variants of genes that have been studied [10].

Patient factors not addressed in most studies also influence the predictive value of genetic testing in actual practice. Expression of CYP450 and other genes involved in response to treatment for anxiety and depression changes with age [17]. Smoking induces enzymes such as CYP1A2, which metabolizes a number of antidepressants to reduce levels by 50 % [15], but which is usually not controlled in clinical studies [35]. Use of alcohol, hormones, herbal remedies (especially St. John's wort), caffeine, cabbage, grapefruit juice, and other substances alter CYP phenotype in patients with the same genotype [15]. It is also necessary to take into consideration ethnic differences in drug metabolism by the same CYP enzyme. For example, there are more Swedish than Chinese CYP2D6 poor metabolizers, but Chinese extensive metabolizers break down substrates more slowly than Swedish extensive metabolizers [15]. Genetic studies of treatment for anxiety and depression have not controlled for nonadherence, which occurs in half of all depressed patients [66]. As the rate of nonadherence increases in any population, statistical power to detect a genotype effect decreases substantially [3].

Should a pattern of genotypes be found to be clinically useful, implementation may be slow. A survey of American physicians found that only 29 % had received any training in pharmacogenetics [2]. When genotyping for HLA-B*15:02 because it was found to predict risk of severe skin reactions with carbamazepine in some Asian patients as noted earlier was introduced in Hong Kong, prescriptions for carbamazepine decreased and alternative drugs were prescribed, apparently out of a desire to avoid genetic testing; as a result, there was no decrease in the percentage of patients with this severe side effect [2].

Conclusions

Results of association studies in pharmacogenetics and pharmacogenomics have been provocative, and automated genotyping is becoming more affordable. It has been hoped that pharmacogenetic testing in psychiatry will result in the kind of "personalized medicine" for depression and anxiety that has led to selection of therapies with a higher likelihood of effectiveness and tolerability for specific types of cancer (e.g., trastuzumab for patients with human epidermal growth factor receptor-2 [HER2] positive breast cancer). While this is an exciting prospect, there are still important differences between genotyping in cancer and anxiety and depression. In the former, a specific allelic variation of the HER2 gene conveys a propensity toward aggressive growth as well as a receptor conformation that fits a specific drug that is not likely to work well for other breast cancers. Even in this case, the clinical impact of HER2 testing has had a variable clinical impact [10]. In depression and anxiety, no polymorphism or group of polymorphisms has been found to reliably predict a specific course or a need for a specific medication, the choice of which remains largely empirical.

Therapeutic and adverse effects in the treatment of anxiety and depression are the result of complex factors that are several steps removed from simple biological pathways such as metabolism by one or even a combination of enzymes, or a particular receptor or transporter [7]. Prediction of treatment outcome may be more successful using discrete intermediate endophenotypes (e.g., anhedonia, energy, sensory gating, information processing, heart rate variability, or mood) rather than overall response of complex and heterogeneous disorders like depression and anxiety [8, 47, 67]. Genetic studies of such features should assess gene pathways, networks and interactions, epigenetics, gene-disease interactions, noncoding RNA, and behavior [5]. If targeting more discrete genetic variants associated with an endophenotype proves effective, broader categorical diagnoses could be enriched for it, reducing the sample size necessary for prospective studies.

To demonstrate the true clinical benefit of genotyping for predicting treatment response or adverse effects, it would be necessary to conduct prospective head-to-head comparisons of different specific treatments chosen by genotype, which have not yet been performed [3]. Useful studies should control for comorbidity, polypharmacy, environmental exposure, age, gender, ethnicity, substance use, and treatment adherence [7]. Studies integrating findings in multiple pharmacogenetic domains have the greatest likelihood of success in this regard [19], but funding sufficiently powered controlled studies of genotyping effectiveness is likely to be more of a challenge in psychiatry than it has been in cancer.

Until evidence emerges of clinical benefit and cost-effectiveness of routine genetic testing [68], it might be reasonable to consider genotyping CYP2D6 and 2C19 to determine whether they are in the small number of poor metabolizers in both classes, for compliant patients taking a single medication who have severe side effects with small initial doses or unexpected severe interactions with other drugs that act on P450 enzymes or drug transporter proteins [69]. CYP2D6 poor metabolizers may be more likely to have adverse effects with tricyclic antidepressants (TCAs) [7], but adjustment based on metabolizer status is valid only within certain dosage ranges because elimination of some medications (e.g., clomipramine, desipramine, imipramine, trimipramine) by 2D6 is saturable, and dose/blood-level relationships are not linear for medications such as imipramine, desipramine, and fluvoxamine [35], and desipramine, nortriptyline, imipramine, and possibly amitriptyline often require therapeutic monitoring anyway. Whenever pharmacogenetic testing is implemented, it is important to ensure that patients are not ingesting substances or foods likely to interact with the enzymes being studied. Treatment choice otherwise remains based on clinical judgment to a greater degree than might be desirable but a degree that permits rational decision-making based on clinical features.

Compliance with Ethics Guidelines

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References

1. Dubovsky SL, Dubovsky AN. Psychotropic drug prescriber's survival guide: ethical prescribing in the age of Big Pharma. New York: W.W. Norton; 2007.
2. Yip V, Hawcutt DB, Pirmohamed M. Pharmacogenetic markers of drug efficacy and toxicity. Clin Pharmacol Ther. 2015;98(1):61–70.
3. Malhotra AK, Zhang J-P, Lencz T. Pharmacogenetics in psychiatry: translating research into clinical practice. Mol Psychiatry. 2012;17:760–9.
4. Cox DBT, Platt RJ, Zhang F. Therapeutic genome editing: prospects and challenges. Nat Med. 2015;21:121–31.
5. Trembplay J, Hamet P. Role of genomics on the path to personalized medicine. Metabolism. 2013;62:S2–5.
6. Singh AB, Bousman CA, Ng C, Berk M. Antidepressant pharmacogenetics. Curr Opin Psychiatry. 2014;27:43–51.
7. Hamilton SP. The promise of psychiatric pharmacogenomics. Biol Psychiatry. 2015;77:29–35.
8. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: the way toward the personalization of antidepressant treatment. Can J Psychiatry. 2014;59:62–75.

9. Dubovsky SL. The usefulness of genotyping cytochrome P450 enzymes in the treatment of depression. Expert Opin Drug Metab Toxicol. 2015;11:369–79.
10. Janssens ACJW, Deverka PA. Useless until proven effective: the clinical utility of preemptive pharmacogenetic testing. Clin Pharmacol Ther. 2014;96:652–4.
11. Lombard J, Doraiswamy PM. What is the role of pharmacogenetics in clinical psychiatry? Expert Opin Drug Metab Toxicol. 2013;9:1–4.
12. Gillis NK, Innocenti F. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. Clin Pharmacol Ther. 2014;96:655–7.
13. Le-Niculescu H, Balaraman Y, Patel SD, et al. Convergent functional genomics of anxiety disorders: translational identification of genes, biomarkers, pathways and mechanisms. Transl Psychiatry. 2011;1, e9.
14. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS ONE. 2013;8, e82562.
15. Jones DS, Perlis RH. Pharmacogenetics, race, and psychiatry: prospects and challenges. Harv Rev Psychiatry. 2006;14:92–108.
16. Wladyslawa AD. The influence of long-term treatment with psychotropic drugs on cytochrome P450: the involvement of different mechanisms. Expert Opin Drug Metab Toxicol. 2005;1:203–17.
17. Zanger UM, Klein K, Thomas M, et al. Genetics, epigenetics, and regulation of drug-metabolizing cytochrome P450 enzymes. Clin Pharmacol Ther. 2014;95:258–61.
18. Crettol S, de Leon J, Hiemke C, Eap CB. Pharmacogenomics in psychiatry: from therapeutic drug monitoring to genomic medicine. Clin Pharmacol Ther. 2014;95:254–7.
19. Kirchheiner J, Nickchen K, Bauer M, Wong M-L, Roots I, Brockmoller J. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry. 2004;9:442–73.
20. Schatzberg AF, DeBattista C, Lazzeroni LC, Etkin A, Murphy GM, Williams LM. ABCB1 genetic effects on antidepressant outcomes: a report from the iSPOT-D trial. Am J Psychiatry. 2015;1–9.
21. Seden K, Dickinson L, Khoo S, Back D. Grapefruit-drug interactions. Drugs. 2010;70:2373–407.
22. Rosenhagen MC, Uhr M. The clinical impact of ABCB1 polymorphisms in the treatment of psychiatric diseases. Curr Pharm Des. 2011;17:2843–51.
23. Lanni C, Racchi M, Govoni S. Do we need pharmacogenetics to personalize antidepressant therapy? Cell Mol Life Sci. 2013;70:3327–40.
24. Xu Q, Wu X, Xiong Y, Xing Q, He L, Qin S. Pharmacogenomics can improve antipsychotic treatment in schizophrenia. Front Med. 2013;7:180–90.
25. Gardiner E, Carroll A, Tooney PA, Cairns MJ. Antipsychotic drug-associated gene-miRNA interaction in T-lymphocytes. Int J Neuropsychopharmacol. 2014;17:929–43.
26. Geaghan M, Cairns MJ. MicroRNA and post-transcriptional dysregulation in psychiatry. Biol Psychiatry. 2014. doi:10.1016/j.biopsych.2014.12.009
27. Anonymous. The future of cancer genomics. Nature Medicine. 2015;21:99.
28. Ivshina AV, George J, Senko O, et al. Genetic reclassifcation of histologic grade delineates new clinical subtypes of breast cancer. Cancer Res. 2006;66:10292–301.
29. Fanous AH, Kendler KS. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. Mol Psychiatry. 2005;10:6–13.
30. Le-Niculescu H, Kurian SM, Yehyawi N, et al. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry. 2009;14:156–74.
31. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95:376–82.
32. Alter CN, Hornberger J, Shewade A, Cruz V, Garrison J, Mrazek D. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. Int Rev Psychiatry. 2013;25:509–33.
33. de Leon J, Arranz GR. Pharmacogenetic testing in psychiatry: a review of features and clinical realities. Clin Lab Med. 2008;28:599–617.
34. Preskorn SH, Kane CP, Lobello K, et al. Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine. J Clin Psychiatry. 2013;74:614–21.
35. Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand. 2001;104:173–92.
36. Misaka S, Kawabe K, Onoue S, et al. Effects of green tea catechins on cytochrome P450 2B6, 2C8, 2C19, 2D6 and 3A activities in human liver and intestinal microsomes. Drug Metab Pharmacokinet. 2013;28:244–9.
37. Yamasaki I, Yamada M, Uotsu N, Teramoto S, Takayanagi R, Yamada Y. Inhibitory effects of kale ingestion on metabolism by cytochrome P450 enzymes. Biomed Res. 2012;33:235–42.
38. Pirmohamed M. Drug-grapefruit juice interactions. Two mechanisms are clear but individual responses vary. BMJ. 2013;346:f1.
39. Nadkarni A, Oldham MA, Howard M, Berenbaum I. Psychotropics: updated review of the literature. Pharmacotherapy. 2012;32:932–42.
40. Preskorn SH. Complexities of personalized medicine: how genes, drug-drug interactions, dosing schedules, and other factors can combine to produce clinically meaningful differences in a drug's effect. J Psychiatric Practice. 2013;19:397–405.
41. Goswami S, Yee SW, Stocker S, et al. Genetic variants in transcription factors are associated with the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2014;96:370–9.
42. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. 2012;22:239–58.
43. Taylor MJ, Sen S, Bhagwagar Z. Antidepressant response and the serotonin transporter-linked polymorphic region. Biol Psychiatry. 2010;68:536–43.
44. Kang HJ, Kim JM, Stewart R, et al. Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2013;44:23–8.
45. Lohoff FW, Narasimhan S, Rickels K. Interaction between polymorphisms in serotonin transporter (SLC6A4) and serotonin receptor 2A (5HT2A) genes predict treatment response to venlafaxine XR in generalized anxiety disorder. Pharmacogenomics J. 2013;13:464–9.
46. Cooper AJ, Rickels K, Lohoff FW. Association analysis between the A118G polymorphism in the OPRM1 gene and treatment response to venlafaxine XR in generalized anxiety disorder. Hum Psychopharmacol. 2013;28:258–62.
47. Keers R, Aitchison KJ. Pharmacokinetics of antidepressant response. Expert Rev Neurother. 2011;11:101–25.
48. Costa e Silva JA. Personalized medicine in psychiatry: new technologies and approaches. Metab Clin Exp. 2013;62:S40–S4.
49. Ji Y, Biernacka JM, Hebbring S, et al. Pharmacogenomics of selective serotonin reuptake inhibitor treatment for major depressive disorder: genome-wide associations and functional genomics. Pharmacogenomics J. 2013;13:456–63.
50. Hennings JM, Uhr M, Klengel T, et al. RNA expression profiling in depressed patients suggests retinoid-related orphan receptor alpha as a biomarker for antidepressant response. Transl Psychiatry. 2015;5, e538.

51. Calati R, Crisafulli C, Balestri M, et al. Evaluation of the role of MAPK1 and CREB1 polymorphisms on treatment resistance, response and remission in mood disorder patients. Prog Neuro-Psychopharmacol Biol Psychiatry. 2013;44:271–8.
52. Mamdani F, Berlim MT, Beaulieu M-M, Labbe A, Merette C, Turecki G. Gene expression biomarkers of response to citalopram treatment in major depressive disorder. Transl Psychiatry. 2011;1, e13.
53. Breitenstein B, Scheuer S, Pfister H, et al. The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. CNS Spectr. 2014;19:165–75.
54. Hall-Flavin DK, Winner JG, Allen J, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2, e172.
55. Hall-Flavin DK, Winner JG, Allen J, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenet Genomics. 2013;23:535–48.
56. Winner JG, Carhart JM, Alter CN, Allen J, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013;16:219–27.
57. Winner JG, Allen J, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013;3, e242.
58. Chung WH, Hung SI, Hong HS, et al. Medical genetics. A marker for Stevens-Johnson syndrome. Nature. 2004;428:486.
59. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011;364:1126–33.
60. Peters EJ, Slager SL, Kraft JB, et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One. 2008;3, e1872.
61. Ratain MJ, Johnson JA. Meaningful use of pharmacogenetics. Clin Pharmacol Ther. 2014;96:650–2.
62. Consortium GoP. Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depression. JAMA Psychiatry. 2015.
63. Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. J Affect Disord. 2014;169:15–20.
64. Harvey RD, Morgan ET. Cancer, inflammation, and therapy: effects on cytochrome P450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clin Pharmacol Ther. 2014;96:449–57.
65. Seeringer A, Kirchheiner J. Pharmacogenetics-guided dose modifications of antidepressants. Clin Lab Med. 2008;28:619–26.
66. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry. 1998;55:1128–32.
67. Domschke K. Clinical and molecular genetics of psychotic depression. Schizophr Bull. 2013;39:766–75.
68. Levy KD, Decker BS, Carpenter JS, et al. Prerequisites to implementing a pharmacogenomics program in a large healthcare system. Clin Pharmacol Ther. 2014;96:307–9.
69. Wall CA, Croarkin PE, Swintak C, Koplin BA. Psychiatric pharmacogenomics in pediatric psychopharmacology. Child Adolesc Psychiatr Clin N Am. 2013;21:773–88.