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The Promise and Reality of Pharmacogenetics in Psychiatry

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Summary

Existing psychotropic medications for the treatment of mental illnesses, including antidepressants, mood stabilizers, and antipsychotics, are clinically sub-optimal. They are effective in only a subset of patients or produce partial responses, and they are often associated with debilitating side effects that discourage adherence. There is growing enthusiasm in the promise of pharmacogenetics to personalize the use of these treatments to maximize their efficacy and tolerability. However, there is still a long way to go before this promise becomes a reality. In this article, we review the progress that has been made in research towards understanding how genetic factors influence psychotropic drug responses and the challenges that lie ahead in translating the research findings into clinical practices that yield tangible benefits for patients with mental illnesses.

Keywords

Pharmacogenetics; pharmacogenomics; antidepressants; antipsychotics; mood stabilizers; genome-wide association study; efficacy; side-effects

Introduction

The primary means of treating mental illnesses is with an arsenal of psychotropic medications, including antidepressants, antipsychotics and mood stabilizers. Despite progress over the past several decades in developing new classes of such medications that are presumably safer and more effective, the ability to treat mental illnesses remains clinically sub-optimal. These medications are effective in only a subset of patients or produce partial responses, and they are often associated with debilitating side effects that discourage adherence (1).

The results from the latest and largest treatment effectiveness trials of psychotropic medications sponsored by the National Institute of Mental Health (NIMH) reinforce the notion that there is still a long way to go in the war against mental illnesses. In the recently completed Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study in which patients with non-psychotic major depression were followed for up to six years through a sequence of alternative treatment regimens, only 37% achieved remission on first line therapy with a selective serotonin reuptake inhibitor (SSRI) while another 16.3% withdrew completely from treatment due to drug intolerance (2). Even worse, in the Clinical

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Antipsychotic Trials of Intervention Effectiveness (CATIE) in which patients with schizophrenia were treated with a menu of leading antipsychotics under conditions meant to reflect realistic clinical practice and followed for up to 18 months, over 74% eventually discontinued their study medication either due to lack of efficacy or tolerability (3). Similarly, in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial in which patients with bipolar disorder were enrolled and provided treatments with mood stabilizers and antidepressants that followed expert consensus guidelines, up to 75% experienced symptom relapse sometime over the course of follow-up (4). These figures are sobering and suggest considerable room for improvement in psychiatric treatments.

With the advent of the genomics revolution, there has been growing excitement that pharmacogenetics can pave the way to improved treatments. The term pharmacogenetics was first coined nearly a half century ago when it was recognized that inherited variation can influence responses to medications (5). Since then, an ever growing number of pharmacogenetic traits have been studied. Earlier studies focused on variation in candidate genes or gene systems believed to influence the absorption, distribution, or clearance of drugs (i.e., pharmacokinetics) or mediate their mechanisms of actions via interactions with receptors and/or transporters and downstream second messengers (i.e., pharmacodynamics). However, the completion of the Human Genome Project and the emergence of new tools to interrogate the entire genome on an unprecedented scale have accelerated interest in studying the relevance of variation across the entire genome. These advances have spawned a new term, pharmacogenomics. Pharmacogenomics and pharmacogenetics are used interchangeably, and in both cases refer to the study of how genetic variation influences response to drug treatments in terms of efficacy (i.e., efficacy pharmacogenetics) or tolerability (i.e., safety pharmacogenetics).

The hope is that through pharmacogenetics we will be able to discover genetic profiles that can be determined by simple genetic tests and that predict how patients will respond to different psychotropic treatments before they are initiated. The benefits are obvious as it would allow physicians to tailor medications to their patients in such a way that maximizes their efficacy and tolerability, thus ushering in an era of “personalized medicine.” In addition, by elucidating the pathways by which drugs act to treat illness and provoke unwanted side effects, pharmacogenetics may inform the rational development of new treatments that are ever more safe and efficacious. Thus, the promise of pharmacogenetics in psychiatry is that it will lead to the smarter use of our existing weapons and, in turn, the development of even smarter weapons to combat mental illness.

However, there is clearly still a long way to go before the promise becomes a reality. In this article, we review the progress that has been made in research towards understanding how genetic factors influence psychotropic drug response and the challenges that lie ahead in translating the research findings into clinical practice that yield tangible benefits for patients. We discuss antidepressants, mood stabilizers, and antipsychotics in turn, and for each we review the pharmacogenetic studies that have been carried out on them, including candidate gene studies of pharmakcokinetic or pharmacodynamic factors and genome-wide studies. We then examine the few examples of pharmacogenetic biomarkers and corresponding tests that have begun to penetrate into clinical practice in psychiatry and assess their impact on patient care. Finally, we conclude with a discussion of the challenges to advancing the goals of personalized care in psychiatry.

Antidepressants

The monoamine oxidase inhibitors and tricyclics were the first antidepressants introduced back in the 1950’s. They heralded a major breakthrough in the treatment of depression, but

their wider use was limited by partial efficacy and significant concerns about side effects, like sedation (6). In the late 1980's a new class of antidepressants became available known as the selective serotonin reuptake inhibitors (SSRIs). Because of their improved efficacy and tolerability, the SSRIs quickly gained popularity and are now the most widely used antidepressants (7). They are among the first line choices for the treatment of depression (8, 9), but they are still only effective in a subset of patients (10) and are associated with certain common side effects as well, such as weight gain, insomnia and sexual dysfunction that are leading causes of non-adherence (11). More recently, a number of other new classes of antidepressants have been introduced with mixed pharmacodynamic profiles. These include serotonin-norepinephrine reuptake inhibitors (SNRIs), the dopamine-norepinephrine reuptake inihibitors (DNRIs), serotonin modulators, norepinephrine-serotonin modulators, and selective norepinephrine reuptake inhibitors (NRIs).

Overview of Pharmacogenetic Studies

At least 119 pharmacogenetic studies of candidate genes and the efficacy or tolerability of treatment with antidepressants have been reported in the literature (12–130). The overwhelming majority of these have studied SSRIs, although several have examined SNRIs or other older agents such as the monoamine oxidase inhibitors or tricyclics. Approximately 65% of the studies have been on Caucasian samples, while the remaining studies have mostly studied Asian samples, including Chinese, Japanese or Korean. The samples sizes have been generally small with a median of less than 150 subjects, and each of the studies have investigated no more than a handful of specific candidate gene polymorphisms at a time. The exceptions to this include several reports (71, 87, 90, 97, 108, 115, 123, 124, 127) from STAR*D in which pharmacogenetic studies with over 1,900 subjects who provided a DNA sample have been carried out to examine the association between a number of different candidate genes and treatment response to citalopram, including efficacy, treatment emergent suicide ideation and sexual dysfunction. In addition to these studies, three genome-wide association studies of antidepressant treatment response have recently been reported in the literature (131–133). (See Table 1 for a description of candidate genes studies from STAR*D and genome-wide association studies of treatment responses to antidepressants.)

Pharmacokinetic Studies

Multiple pharmacogenetic studies have been carried out on the relationship between genes coding for CYP450 enzymes, which are involved in the metabolism of many different xenobiotics, and antidepressant treatment responses. CYP2D6 and CYP2C19, which together with CYP2C9 metabolize virtually all SSRIs (134), have received the greatest attention.

CYP2D6 is constitutively expressed in the liver and is responsible for metabolizing approximately 25% of drugs known to be metabolized by CYP450 enzymes (135). It is the key enzyme in the metabolic pathway of many antidepressants (136). Because CYP2D6 is not inducible (137), functional genetic variation and "environmental" inhibitors of the enzyme are the only factors that can modify its activity, making it a good candidate for pharmacogenetic testing (138). Over 90 genetic variants have been identified in *CYP2D6* (139). These variants have been functionally classified into four phenotypic groups based on their effects on enzyme activity: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs). There are considerable differences in the frequencies of these classes across racial and ethnic groups (138). *CYP2C19* is also polymorphic with two main phenotypic groups: EMs and the more rare PMs (138).

The contention is that CYP related PMs are at an increased risk of side effects from antidepressants, while UMs, and to a lesser extent IMs, are less likely to show positive response to treatment (138). A commercially available pharmacogenetic test has been clinically approved to test for the *CYP2D6* and *CYP2C19* genetic variants based on this characterization (140). However, at least 13 different studies have examined the relationship between variation in these genes and treatment response to antidepressants (12, 22, 24, 39, 40, 48, 54, 55, 59, 75, 82, 83, 108), and the results have been decidedly mixed. The largest study from STAR*D included 1,877 genotyped subjects and found no association between variation in *CYP2D6* or *CYP2C19* and either efficacy or tolerability (108). Moreover, a recent review of existing studies found little overall evidence of an association between these two CYP450 genes and antidepressant response, calling into question the clinical utility of testing for these variants (141). The commercially available pharmacogenetic test and its potential use in clinic practice are discussed in further detail below.

Pharmacodynamic Studies

The therapeutic action of antidepressants is thought to be mediated at least partially through their effects on monoaminergic transmission and primarily the serotonergic pathway. Consequently, genes in the serotonergic pathway have been of great interest in pharmacogenetic studies of antidepressants. *5HTT*, which codes for the pre-synaptic membrane bound serotonin transporter protein that is the target of SSRIs, is by far the most widely studied of these. It has a variable length repeat polymorphism in the promoter region (5HTTLPR), in which a 44 bp long stretch of DNA is either present in the “long” form of the gene or absent in the “short” form. Experimental data suggest the long form is associated with greater expression of the gene (142), although recent findings have suggested this locus may actually be triallelic due the presence of a SNP nearby which leads to further variability in the effect on gene expression (143). Other common variants are found in the gene, including a variable number of tandem repeats in intron 2 (STin2) which has been shown to influence gene transcription (144) and has also been examined in multiple pharmacogenetic studies.

A systematic review of pharmacogenetic studies of antidepressants (145, 146) was recently reported in which the published associations between treatment response and these two well-characterized *5HTT* variants were comprehensively examined. In this review, a meta-analysis of 15 studies (13–16, 21, 27, 28, 34, 37, 38, 44, 49, 73, 74, 88) showed the long allele of the promoter polymorphism was associated with better response and remission rates, while another meta-analysis of nine studies (35, 41, 46, 74, 81, 87, 100, 118, 121) indicated the long allele was also associated with lower rates of side-effects. The review of studies on the intronic variant was less clear, although a meta-analysis of seven studies (14, 30, 51, 73, 84, 110, 121) suggested an influence on efficacy, particularly among Asians. Enthusiasm for these findings are dampened by the fact that another study (90) from the STAR*D trial found no evidence of an association between any variants in *5HTT* and treatment outcomes, despite having one of the largest samples to test the relationship.

The systematic review (146) also examined variants in 16 other candidate genes thought to play a role in the pharmacodynamics of antidepressants and reported on by at least two different studies. Of these, variants in four of the genes were found upon meta-analysis to be significantly associated with either efficacy or side effects. The four genes were *5HT1A*, *5HT2A*, *TPH1*, and *BDNF*. *5HT1A* and *5HT2A* code for serotonin receptors that are the targets of certain antidepressants and atypical antipsychotics. Interestingly, an association between *5HT2A* and antidepressant efficacy was one of the leading pharmacogenetic findings from STAR*D (71). *TPH1* codes for tryptophan hydroxylase which is the rate-limiting enzyme in the biosynthesis of serotonin. It is more commonly expressed in the periphery (147), but there is some evidence from the mouse that it is also expressed in the

brain during the late developmental stages (148). *BDNF* is a neurotrophic factor that is involved in the development, survival and functional maintenance of neurons (149).

Genome-wide Studies

Three genome-wide association studies of antidepressant response have been published (131–133). In the first study (131) 90 Caucasians who developed treatment emergent suicidal ideation (TESI) with citalopram in STAR*D and an equal number of sex and race matched treated controls were genotyped at 109,365 SNPs on the Illumina Human-1 BeadChip. One marker was significant after correction for multiple testing in the gene *PAPLN*. This gene encodes a proteoglycan-like sulfated glycoprotein, but little else is known about its function and potential relevance to TESI.

The second study (132) examined efficacy responses to citalopram in 1,491 STAR*D subjects who were genotyped at 430,198 SNPs with the Affymetrix 500K and 5.0 platforms. No SNPs met criteria for genome-wide significance, but there were three with suggestive evidence in or near the genes *UBE3C*, *BMP7*, and *RORA*. The biological relevance of these genes to treatment response is not immediately obvious.

The most recent study (133) was carried out in the Munich Antidepressant Response Signature (MARS) project in which patients who were treated with antidepressants according to the choice of their physicians were naturalistically followed for efficacy response. A total of 339 patients were genotyped on almost 410,000 non-overlapping SNPs with the Illumina Sentrix Human-1 and HumanHap300 BeadChip arrays. A multilocus genetic variable that described the individual number of alleles of select SNPs associated with beneficial treatment outcome was constructed and then dichotomized. The dichotomized variable describing carriers with high and low number of response alleles was associated with positive outcome in the MARS sample as well as in a replication sample derived from STAR*D. This finding suggests that treatment response may in fact be multifactorial and under the control of a number of additive genetic loci instead of a limited number with large effects.

Mood Stabilizers

The leading mood stabilizers include lithium and the anticonvulsants, such as valproate, carbamazepine, and lamotrigine. Lithium has been a remarkably successful drug, but its introduction into psychiatry has had a complicated and somewhat controversial history (150). Its use in practice dates back to the mid-19th century, but it was not until the 1970's that it was finally approved in the United States for the treatment and prophylaxis of mania. Considerable evidence has accumulated since then about the positive benefits of lithium (151), yet it lacks universal effectiveness and can provoke side effects, such as hand tremor, frequent urination, and weight gain. Despite the benefits and relatively cheap cost of lithium, its use has been steadily eclipsed over the past couple decades by the introduction of the anticonvulsants (152). The comparative safety and efficacy of lithium versus the rival anticonvulsants, however, remains a matter of debate (153).

Overview of Pharmacogenetic Studies

There is a relative dearth of pharmacogenetic studies of mood stabilizers. Some 36 candidate gene studies have been reported (154–189). Almost all of these examined lithium. With few exceptions, the studies were based on Caucasian samples with exceedingly small numbers (median = 111), and in the majority of cases they relied on retrospective characterization of response to lithium. One genome-wide association study of lithium responsiveness was recently reported (190). (See Table 2 for a description of the genome-wide association study of treatment response to mood stabilizers.)

Pharmacodynamic Studies

As far as we are aware, no pharmacogenetic studies have been reported on the pharmacokinetics of mood stabilizers. Published studies have instead concentrated on pharmacodynamic factors. Although the mechanisms of action of lithium and the other anticonvulsant mood stabilizers are not completely known, there are two leading hypotheses. The first involves the phosphoinositide pathway and has been referred to as the "inositol depletion hypothesis" (191). It posits that lithium, and perhaps valproate and carbamazepine as well (192), inhibit the activity of two enzymes, inositol monophosphatase (IMPA) and inositol polyphosphate 1-polyphosphatase (INPP1) which causes a reduction in the amount of free inositol available for the regeneration of phosphatidylinositol-4, 5-bisphosphate (PIP2). PIP2 is a substrate needed for the generation of important intracellular signaling molecules, inositol-1, 4, 5-triphosphate (IP3) and diacylglycerol (DAG) via activation of the enzyme G-protein-coupled phospholipase C. IP3 mediates Ca+2 release from intracellular stores and mediates a range of signaling pathways. Both Ca+2 and DAG further stimulate protein kinase C which is also a component of other signaling pathways. There have been at least seven studies (156, 157, 159, 167, 169, 179, 181) on the relationship between variation in genes coding for key enzymes in this pathway and treatment response to lithium, but the findings have been largely inconclusive.

The leading alternative hypothesis for lithium's mechanism of action is its effects on cell survival through the inhibition of GSK3b (193). Lithium acts in the same manner as the Wnt pathway to inhibit GSK3b, leading to the translocation of β-catenin to the cell nucleus where it becomes part of complexes that regulate the transcription of genetic components involved in cell survival (194, 195). It has been shown that valproate may have similar effects (196). Motivated by these considerations, several pharmacogenetic studies of *GSK3b* (175, 176) have been reported, again with mixed findings.

There has also been interest in examining some of the usual suspects in psychiatric genetics including, for example, *MAOA*, *COMT*, *5HTT*, *TPH1*, *BDNF* (e.g., (161, 163, 168, 170, 173, 174, 177, 179, 182, 184)). As yet, there remains no conclusive evidence that variation in any of these genes influence treatment response to mood stabilizers.

Genome-wide Studies

One genome-wide association study of lithium response has been reported (190). In this prospective study from STEP-BD, the associations between 1.4 million genotyped and imputed SNPs and the risk of mood disorder recurrence were examined among 1,177 patients with bipolar disorder, including 458 who were treated with lithium alone or in combination with other psychotropic medications. SNPs found to be associated at the threshold of $p<5\times10^{-4}$ were examined in a replication sample from the University College London in which 359 patients with bipolar disorder were retrospectively assessed for lithium response. These SNPs were also tested to determine if their association with recurrence was specific to treatment lithium in the STEP-BD cohort. None of the SNPs tested in the STEP-BD cohort met genome-wide significant criteria for association. However, 140 SNPs were carried forward for replication, and of these 9 were significant in the UCL sample at $p<0.05$. Of these, five had the same direction of effect as in the STEP-BD cohort, and three displayed associations that were specific to lithium treatment. The latter three SNPs point to associations with *GRIA2*, which has been found to be downregulated by chronic lithium treatment in a human neuronal cell line (197, 198); *SDC2*, which codes for a cell-surface proteoglycan that may play a role in dendritic spine formation in the hippocampus (197); and *ODZ4*, which has been implicated in brain patterning (199). These findings implicate novel candidate genes for lithium response that merit further investigation, but more

generally they suggest there are few if any genes with large effects on lithium response and, instead, as with other complex traits, multiple loci may be involved.

Antipsychotics

The first generation of antipsychotics (FGAs), including the phenothiazine deriviates such as chlorpromazine, dates back to the 1950s. Their introduction was responsible for large decreases in psychiatric inpatient populations (200). However, because of side effects such as extrapyramidal symptoms (EPS) including parkinsonism, akathisia and tardive dyskinesia (TD), their appeal was limited. In the 1990s a second generation of antipsychotics (SGAs) with a more diverse mechanism of action that targeted various serotonin and dopamine receptors was developed. The first of these, clozapine, has been shown to be effective against treatment-resistant schizophrenia (201), but it is also associated with life-threatening agranulocytosis. Several other SGAs, such as risperidone, olanzapine, and quetiapine, have since been introduced. The conventional notion is that compared to FGAs these so-called “atypical antipsychotics” have better safety profiles and greater efficacy, particularly against the negative symptoms of schizophrenia (200). However, a recent meta-analysis suggested that only a few are actually more effective at reducing symptoms and have less tendency for inducing EPS (202). SGAs are also associated with notable adverse effects of their own, such as weight gain, diabetes, metabolic syndrome and sedation (203).

Overview of PGx Studies

At least 274 pharmacogenetic studies of candidate genes and antipsychotic treatment response have been published (204–476). The majority of these studies examined the use of multiple antipsychotics, although FGAs were typically considered separately from SGAs. Approximately 40% of the studies examined only one antipsychotic, with clozapine being the most widely studied, followed by olanzapine and risperidone. The outcomes of interest were split evenly between efficacy and side effects. Among the latter, TD and weight gain were mostly commonly studied, with a subset of studies focused on agranulocytosis associated with clozapine. Just over half the studies were on Caucasian samples, while the rest were mostly of Chinese, Japanese or Korean samples. As with the pharmacogenetic studies of antidepressants and mood stabilizers, the sample sizes were generally small with a median of 115, not counting four reports (398, 403, 441, 442) from the CATIE trial which each included approximately 700 patients. Five genome-wide association studies of antipsychotic treatment response have been published (477–481). (See Table 3 for a description of candidate genes studies from CATIE and genome-wide association studies of treatment responses to antipsychotics.)

Pharmacokinetics

Just as they do with antidepressants, the CYP450 enzymes play a leading role in the pharmacokinetics of antipsychotics. Along with CYP2D6, CYP1A2, CYP3A4, and CYP3A5 are the key enzymes responsible for metabolizing most commonly used antipsychotics (482). A number of studies (205, 222, 232, 236, 245, 260, 262, 270, 271, 281, 292, 294, 310, 311, 324, 331, 341, 342, 348, 367, 377, 388, 389, 404, 420, 451, 459, 461, 463) have examined the association between variants in the genes coding for these enzymes and antipsychotic response. The majority of these have studied adverse effects, and in particular TD. A meta-analysis (483) of studies on TD provided evidence of an increased risk with loss of function alleles in *CYP2D6*. However, further analysis suggested that publication bias could not be entirely ruled out. In addition, a recent report (398) from the CATIE trial in which a number of variants across the key CYP450 genes, as well as several other Phase II and transporter genes, were examined found no strong associations with dosing, safety or efficacy of the antipsychotic treatments used in the trial.

Pharmacodynamics

Dysregulation of the dopaminergic system was among the first pathological findings observed in schizophrenia, and dopamine inhibition is a common feature of most antipsychotics, particularly the FGAs. Evidence suggests that dopamine antagonism may be required for antipsychotic activity, with PET studies showing that a certain level of blockade of dopaminergic receptors in the striatrum is needed to sustain a therapeutic effect, while excess blockade can lead to extrapyramidal side effects (484–486). There are five subtypes of dopamine receptors (D1–D5), and of these D2 and D3 are the most widely implicated in pharmacogenetic studies of antipsychotics.

Three polymorphisms in *DRD2* which encodes the D2 receptor have received the greatest attention. These include the Taq1A polymorphism, which is located approximately 10 kb from the 3' end of the gene and has no known functional effect; the −141-C Ins/Del polymorphism in the promoter region, which has been associated with lower expression of the D2 receptor in vitro (487) and higher D2 density in the striatum in vivo (488); and Ser311Cys, a relatively common coding polymorphism that has been shown to reduce signal transduction via the receptor (489). At least fourteen studies (250, 261, 265, 273, 306, 330, 345, 349, 351, 390, 392, 411, 420, 421) have examined the relationship between *DRD2* polymorphisms and efficacy of both FGAs and SGAs, while twenty-one studies (243, 255, 259, 264, 274, 278, 289, 293, 295, 300, 352, 372, 375, 382, 395, 401, 421, 421, 422, 444, 452) have investigated adverse effects, including TD, weight gain and neuromalignant syndrome. In a recent meta-analysis (490) of four different genes and TD, a significant association was found with the Taq1A polymorphism in *DRD2*.

The *DRD3* gene, which has also been extensively studied, contains a Ser9Gly polymorphism that has been shown in vitro to influence dopamine binding affinity (491). Several studies have examined the association between this polymorphism and efficacy (227, 238, 250, 284, 316, 334, 339, 400, 418, 420, 439, 446, 449) and adverse effects like TD (211, 215, 223, 228, 237, 242, 244, 252, 257, 278, 286, 375, 401, 416, 443, 452, 473, 492). A mega-analysis of combined data from several studies on 780 patients (276) suggested the Gly9 allele conferred a small, but significant, increase in risk of TD. This finding was corroborated by a later meta-analysis (492) which suggested the association was stronger in non-Asian versus Asian populations.

The serotonergic system has also been implicated in treatment responses to antipsychotics. SGAs in particular display high affinities for serotonin receptors which have been hypothesized to mediate, at least partially, their therapeutic action (493, 494). Seven distinct families of serotonin receptors have been identified (5HT1 – 5HT7) (495). Of greatest interest is the 5HT2 receptor family, especially 5-HT2A and 5-HT2C. Several polymorphisms in both *5HT2A* (−1438-G/A and 102-T/C in the promoter and His425Tyr in the coding region) and *5HT2C* (a VNTR, −759-T/C, and −995-G/A in the promoter and Cys23Ser in the coding region) have been investigated in multiple studies of treatment response and adverse effects (204, 206–210, 212, 214, 218, 220, 225, 226, 230, 246, 248, 249, 263, 266, 268, 269, 275, 280, 283, 285, 288, 290, 297, 308, 320, 327–329, 336, 365, 367, 370, 375, 384, 385, 387, 401, 402, 409, 413, 418, 429, 430, 443, 445, 448, 453, 456, 468, 473). Several meta-analyses of these studies have been conducted including one showing an association between the 102-T/C and His425Tyr polymorphisms in *5HT2A* and treatment response to clozpaine (496), a second showing an association between the 102-T/C polymorphism in *5HT2A* and TD (497), and a third showing an association between the −759C/T polymorphism in *5HT2C* and weight gain (498).

A number of other genes have been investigated in relation to antipsychotic responses. These studies have been motivated by various hypotheses about the mechanisms of action of

antipsychotics, such as, for example, the role of the glutamatergic system or neuronal genesis and plasticity (for a more detailed review see (482)). In addition, several pharmacogenetic studies from the CATIE trial have examined a range of candidate genes with inconclusive results (441, 442).

Genome-wide Studies

Five genome-wide association studies of antipsychotic treatment response have been reported in the literature (477–481). Three of these came from the CATIE trial in which patients with schizophrenia were randomized to treatment with either a SGA (olanzapine, quetiapine, risperidone, or ziprasidone) or a FGA (perphenazine). The first study (477) tested for genome-wide predictors of efficacy among 738 patients genotyped using the Affymetrix 500K genotyping platform supplemented with a custom 164K chip to improve genome-wide coverage. Efficacy was measured by changes over time in positive and negative symptom scores. Because the patients were allowed to switch among treatments due to lack of efficacy or tolerability, associations were examined relative to the first drug to which the patient was randomized. Only one finding, in an intergenic region on chromosome 4p15, reached the pre-specified threshold for genome-wide significance. Two other findings were close to this threshold in *ANKS1B* and *CNTNAP5*, which were found to mediate negative symptom response to olanzapine and risperidone, respectively.

The two other studies (478, 479) from CATIE were partially overlapping. The more inclusive study (479) examined symptoms of parkinsonism, akathasia, and abnormal involuntary movements among the 738 patients included in the efficacy study described above. Three findings met genome-wide significance in novel regions that have not been previously implicated in the pharmacogenetics of extrapyramidal symptoms. Two were located in an intergenic region on chromosome 11q24, and the other was in *ZNF202*, which is a transcriptional repressor controlling PLP1, a major component of myelin.

The remaining two genome-wide association studies (480, 481) came from a phase 3 randomized trial of iloperidone, an investigational new drug for the treatment of schizophrenia from Vanda Pharmaceuticals. The 28 day trial was double-blinded as well as placebo and ziprasidone-controlled. In the first study (480), genome-wide associations with efficacy were examined. A total of 426 patients genotyped on the Affymetrix 500K platform were included, including 218 on iloperidone, 103 on active comparator, and 103 on placebo. The outcome was change from baseline to last scheduled observation in positive and negative total symptom scores. Three complimentary analyses were carried out, and six loci were identified with consistent findings across these analyses. The single best finding was in *NPAS3*, a gene which circumstantial evidence has previously implicated in schizophrenia. In the second study (481), genome-wide associations with QT interval prolongation, a potentially life-threatening side effect of treatment with iloperidone and other antipsychotics, were examined. A total of 183 patients on iloperidone treatment with QT interval measurements at day 14 of the trial were included in this analysis. The top findings implicated two genes in particular, *CERKL* and *SLC03A1*, with plausible roles in this adverse effect. CERKL is thought to be part of the ceramide pathway, which regulates currents conducted by various potassium channels including the hERG channel, which, when inhibited, can prolong the QT interval. SLC03A1 plays a role in translocation of prostaglandins which may have cardioprotective effects.

Pharmacogenetics in Clinical Practice

Only one pharmacogenetics test has been approved by the Food & Drug Administration (FDA) for clinical use in psychiatry (140). This is the AmpliChip CYP450 Test marketed by Roche Molecular Systems. It uses Affymetrix microarray-based genotyping technology with

more than 15,000 oligonucleotide probes to assay for 20 *CYP2D6* alleles, 7 *CYP2D6* duplications, and 3 *CYP2C19* alleles. The test includes software with an algorithm to predict CYP2D6 and CYP2C19 phenotypes (i.e., PM, IM, EM, and UM) based on the identified alleles.

The intended use of the chip cleared by the FDA is very general and does not refer to any specific drug. Instead, it states that information about the two CYP450 genes assayed, "may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized" by products of these genes (499). Consequently, the FDA cleared the Roche AmpliChip without clinical studies demonstrating that it is actually beneficial for selection or dosing of any psychotropic medication, despite the fact that it has been marketed, often direct-to-consumer, for use with these medications, especially the SSRIs (500). This is consistent with the FDA's approach to other diagnostic devices such as MRIs where it has left demonstration of clinical benefit to clinicians and payers.

The Center for Disease Control and Prevention (CDC) commissioned an independent panel to examine the analytic validity, clinical validity and clinical utility of CYP450 genotyping when prescribing SSRI antidepressants (501). These three key characteristics of a pharmacogenetics test are defined, respectively, as, the ability to a) detect different alleles accurately, b) predict clinically meaningful outcomes, and c) provide information that improves the risk/benefit ratio of clinical treatment. In their review, the independent panel determined there was strong evidence for the analytic validity of CYP450 genotyping, but only marginal evidence for its clinical validity and almost no evidence for its clinical utility (141). Thus, the independent panel concluded (501) there was, "insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment," and further noted that, "in the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed."

In addition to regulating pharmacogenetic tests, the FDA also oversees the incorporation of information about relevant pharmacogenetic biomarkers into the drug labels. Biomarkers are defined as characteristics that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic interventions (502). Genetic variants associated with therapeutic responses to a pharmacological agent are pharmarcogenetics biomarkers. The FDA collects information on pharmacogenetic biomarkers and their analytic validity, clinical validity and clinical utility from pharmaceutical companies during the drug application process (503), and then incorporates this information into approved drug labels as deemed appropriate.

In a recent survey (504) of drug labels approved between 1945–2005, it was reported that a total of 121 contained pharmacogenetic information. Of these, 69 labels referred to human genomic biomarkers, and the remainder referred to microbial genomic biomarkers. Of the labels referring to human genomic biomarkers, 43 (62%) pertained to polymorphisms in CYP450 genes, with *CYP2D6* being the most common. Approximately 17% of the labels were for psychiatric drugs. In most cases the drug labels merely provided pharmacogenetic information. Only one label went further and recommended, but did not require, a specific action before making a therapeutic decision. This was for testing urea cycle enzyme deficiencies before prescribing valproic acid. Thus, while pharmacogenetic information has begun to penetrate into clinical practice, it has not yet had a meaningful impact on therapeutic decision making in psychiatry.

Challenges to Clinical Translation

Despite notable progress in research over the past decade, the promise of pharmacogenetics in psychiatry has not yet been fully realized. The biggest obstacle to translating the promise into reality is that we still do not have a clear understanding of how genetic factors influence treatment response to psychotropic medications. The studies carried out to date suggest a number of intriguing hypotheses that merit further investigation, but they do not point to any definitive associations that can be used with confidence to predict how a patient will respond to a particular treatment. The difficulty with the pharamcogenetic associations thus far reported is the lack of consistent findings. For every positive association, there are typically several negative studies that cast doubt on the finding. As a result, it is difficult to draw firm conclusions about the clinical relevance of any genes that may be implicated.

There are several reasons for the difficulty. First, treatment responses to psychotropic medications are complex phenotypes. They may, in fact, be as complex as the diseases for which they are used to treat. Psychotropic medications may act on a number of different molecular pathways to exert their therapeutic effect, and in turn they may be acted on by a number of different molecular pathways in the process of their absorption, distribution and elimination. Consequently, multiple variants in distinct and converging genetic pathways may independently and interactively contribute to a particular drug response. In addition, multiple environmental factors may further contribute to variability in the response. Demographic factors, diet, substance abuse, smoking, concomitant treatments and co-morbidities may all affect the actions of psychotropic drugs (505). For example, it has been shown that smoking induces CYP450 activity and promotes the metabolism of substrate drugs (506, 507), while conversely SSRI's are known to inhibit CYP450 activity and may disrupt the metabolism of other concomitant medications (508). Thus, treatment responses may be the sum of a number of impinging genetic and environmental factors, making it difficult to identify any one factor in isolation and to construct more complete models of the determinants of drug response.

Second, it is particularly challenging to conduct appropriately designed pharmacogenetic studies that can illuminate the complex architecture of treatment responses. The studies carried out to date have had rather small sample sizes and short periods of follow-up, largely because it is costly and logistically challenging to ascertain and prospectively evaluate patients in such studies. Even the largest studies that have been reported are significantly underpowered to detect genes with effect sizes likely involved in treatment responses. To address this issue, efforts have been made to combine data across studies in meta or mega analyses. While this can be a useful strategy, existing studies frequently differ so considerably in design, patient populations and outcome measures that it raises serious questions about the comparability of results across studies. Finally, to complicate matters, within each study, patients often take multiple medications and have erratic patterns of adherence. As a result, the responses to any one drug during follow-up may be hopelessly obscured. Clearly, new approaches are needed to overcome these limitations in order to further advance the goals of pharmacogenetics.

Conclusions

By personalizing treatments to psychotropic medications, pharmacogenetics holds great promise to dramatically improve care in psychiatry. The genomics revolution has provided us with an unprecedented set of tools to pursue the goal of pharmacogenetics. As reviewed here, a great deal of work has begun to use these tools to unravel the complex pharmacogenetic underpinnings of treatment responses. While considerable progress has been made, much work remains to be done. It appears we are only at the end of the beginning of a long venture.

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Table 1

Candidate Gene Studies from STAR*D and Genome-wide Association Studies of Treatment Responses to Antidepressants.

Author (Year)	Drug	Gene(s)	Outcome	Sample Size	Key Finding(s)
*Candidate gene studies from STAR*D*					
McMahon (2006)	Citalopram	68 genes	Efficacy	1,953 (split sample design)	Association with *5-HTR2A*
Hu (2007)	Citalopram	*5-HTT*	Efficacy Remission Tolerance Adverse effects	1,775	Association with adverse effect burden
Kraft (2007)	Citalopram	*5-HTT*	Efficacy	1,914	No association
Paddock (2007)	Citalopram	68 genes	Efficacy	1,816 (full sample)	Association with *GRIK4*
Peters (2008)	Citalopram	*CYP2D6, CYP2C19, CYP3A4, CYP3A5, ABCB1*	Efficacy Tolerance	1,953 (split sample design)	No associations
Lekman (2008)	Citalopram	*FKBP5*	Efficacy	1,809	Association with response
Cabanero (2009)	Citalopram	*PDE11A, PDE1A, PDE9A*	Efficacy	1,914	No association
Domschke (2009)	Citalopram	*BDNF*	Efficacy	1,914	No association
Perlis (2009)	Citalopram	68 genes	Sexual Dysfunction	1,473	Associations with *GRIA3, GRIK2, GRIA1, GRIN3A*
Genome-wide association studies					
Laje (2009)	Citalopram	Illumina Human-1 Bead Chip	Treatment emergent suicidal ideation	180	Association with *PAPLN*
Garriock (2009)	Citalopram	Affymetrix 500K and 5.0	Efficacy	1,491	Suggestive associations with *UBE3C, BMP7, RORA*
Ising (2009)	Antidepressants	Illumina Human-1 and HumanHap300 Bead Chips	Efficacy	339	Association with a multifactorial SNP score

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Table 2

Genome-wide Association Studies of Treatment Responses to Mood Stabilizers.

Author (Year)	Drug	Gene(s)	Outcome	Sample Size	Key Finding(s)
Perlis (2009)	Lithium (alone or in combination with other psychotropic medications)	Affymetrix 500K	Efficacy (recurrence)	458	Suggestive associations with *GRIA2*, *SDC2*, *ODZ4*

Table 3

Candidate Gene Studies From CATIE and Genome-wide Association Studies of Treatment Responses to Antipsychotics

Author (Year)	Drug	Gene(s)	Outcome	Sample Size	Key Finding(s)
Candidate gene studies from CATIE					
Grossman (2008)	CATIE*	*CYP2D6, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP1A4, CYP3A5, CYP3A4, ABCB1, FMO3 UGT1A4*	Optimized dose Treatment stop due to side effects Tardive dyskinesia	750	No associations
Campbell (2008)	CATIE*	*RGS4*	Efficacy	678	Suggestive association
Need (2009)	CATIE*	118 genes	21 phenotypes	756	Multiple suggestive associations
Tsai (2009)	CATIE*	128 genes	Tardive dyskinesia	710	No associations
Genome-wide association studies					
McClay (2009)	CATIE*	Affymetrix 500K	Efficacy	738	Significant association in 4p15
Alkelai (2009)	CATIE*	Affymetrix 500K plus custom 164K fill-in chip	Antipsychotic-induced parkinsonism	397	Suggesitve associations in *EPF1, NOVA1, FIGN*
Aberg (2009)	CATIE*	Affymetrix 500K	Extra-pyramidal side effects	738	Significant associations in 11q24 and *ZNF202*
Lavedan (2009)	Iloperidone	Affymetrix 500K	Efficacy	426	Suggestive association with *NPAS3*
Volpi (2009)	Iloperidone	Affymetrix 500K	QT interval prolongation	183	Suggestive association with CERKL and SLCO3A1

* In CATIE, patients were treated with up to 5 different antipsychotics: olanzapine, quetiapine, risperidone, ziprasidone, perphenazine