Clinical Insights Into Pharmacogenetics and Schizophrenia, Part 2

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference "Clinical Insights Into Pharmacogenetics and Schizophrenia," which was held January 24, 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Vanda Pharmaceuticals, Inc.*

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Introduction

Dr. Kane: We discussed the clinical relevance that the field of pharmacogenetics has for diagnosing and potentially individualizing treatment for patients with schizophrenia in Part 1 of this ACADEMIC HIGHLIGHTS.[1] In this discussion, we will explore how pharmacogenetics might help us to identify the relationship between schizophrenia and bipolar disorder as well as manage peripheral problems associated with schizophrenia and bipolar disorder such as cognitive dysfunction and treatment-associated side effects.

Potential Gene Candidates for Neurocognitive Function

Dr. Kane: Cognitive dysfunction is a problem in both schizophrenia and bipolar disorder, although more so in schizophrenia, and has an enormous influence on course, outcome, and functional disability. Progress has been made in understanding the genetic factors that might contribute to various dimensions of cognition. Would you describe how much progress has been made and what the implications are?

Dr. Malhotra: Candidate genes that seem to influence specific aspects of neurocognitive function, both in healthy volunteers and in patients with schizophrenia, have been identified (Table 1).[2] The implication of pharmacogenetics is that once these genes are identified and validated, they may represent novel targets for pharmacologic studies that specifically focus on neurocognitive enhancement.

Catechol-*O*-methyltransferase (*COMT*) is one candidate gene suggested to be associated with cognitive dysfunction susceptibility in patients with schizophrenia.[3] While the link between *COMT* and schizophrenia is controversial,[4] data suggest that a functional polymorphism in *COMT* influences aspects of neurocognitive function, particularly executive function.[5,6] Cognitive enhancement mediated by the *COMT* inhibitor tolcapone may be influenced by the *COMT* genotype.[3]

Dr. Perlis: Catechol-*O*-methyltransferase is an interesting candidate gene, although much of the evidence has shown only small effects in patients with schizophrenia. However, a recent meta-analysis[7] reported an effect of *COMT* on cognition in healthy controls. The valine-to-methionine (Val/Met) polymorphism is the most studied for its effect on the functioning of *COMT*, but it may not be the most important one in mediating the effects of *COMT* on cognition.[4] In particular, recent data[4,8] suggest that other common polymorphisms in this gene may be associated with prefrontal functioning in both healthy adults and patients.

Dr. Malhotra: My colleagues and I[9,10] have worked with another candidate susceptibility gene called dysbindin (*DTNBP1*), which, in our data set, influences general cognitive ability in patients with schizophrenia or schizoaffective disorder and in healthy volunteers and seems to affect the severity of cognitive decline in patients. Unfortunately, no obvious drug target has been suggested, so we are unable to test a dysbindin-active drug and its effects on neurocognitive function.

Table 1. Genes With Potential to Affect Cognition in Schizophrenia[a]

Catechol-*O*-methyltransferase (*COMT*)
Dysbindin (*DTNBP1*)
Disrupted-in-schizophrenia (*DISC1*)
Neuregulin-1 (*NRGI*)
Regulator of G Protein signaling 4 (*RGS4*)
Proline dehydrogenase (*PRODH*)

[a]Data from O'Tuathaigh et al.[2]

Dr. Kane: Would a dysbindin-knockout animal model be informative for drug development?

Dr. Malhotra: Yes. Work is being done with the *Sdy* mouse, which has a naturally occurring deletion of the *DTNBP1* gene and therefore produces no dysbindin protein.[11,12] To date, the data on cognitive dysfunction in the *Sdy* mouse are relatively limited.

Dr. Perlis: If appropriately defined, the animal models can help determine gene involvement in mental illness and cognition.[2] Unfortunately, many of these candidate genes tend to be lethal to and/or have profound effects on brain development. The *Sdy* mice that Dr. Malhotra mentioned provide an exception to the trend of having to use convoluted manipulations to "condition" the knockout or induce the deletion in adult animals to understand variations that would otherwise be lethal.

Dr. Malhotra: The disrupted-in-schizophrenia 1 (*DISC1*) gene has been shown to influence risk for schizophrenia and seems to disrupt working memory and reduce gray matter density.[13,14] Research on *DISC1* is still in the preclinical stage, but data strongly support its involvement in the development of major mental illness.[15]

Dr. Perlis: Family studies have been informative in understanding *DISC1*.[16,17] A study of a large Scottish pedigree[17] reported significant associations between *DISC1* and bipolar disorder ($p = .0016$) as well as schizophrenia ($p = .0056$). The *DISC1* gene seems to be important in neuronal differentiation, making it a particularly intriguing candidate gene. In contrast with *COMT*, which simply confirms the importance of catecholamines in psychiatric disorders, *DISC1* and *DTNBP1* offer the potential to open up entirely new pharmacologic targets.

Dr. Malhotra: In the original Scottish family study,[18] the logarithm of the odds (likelihood of 2 genes being within a measurable distance of each other) score for schizophrenia alone was 3.6; it was 7.1 when bipolar disorder, major depressive disorder, and schizophrenia were classified together. My colleagues and I[19] are seeing a *DISC1* association between schizophrenia, schizoaffective disorder, and bipolar disorder, so an overlap between these disorders exists at the genetic level. Whether that translates into an overlap at the pharmacogenetic level is still an open question, but the fact that second-generation antipsychotics are now being used almost ubiquitously in bipolar disorder as well as schizophrenia suggests some pharmacogenetic commonality.

Dr. Perlis: The overlap between bipolar disorder and schizophrenia, specifically in cognition, is important because the perception traditionally has been that schizophrenia has profound cognitive effects, while bipolar disorder, except during acute episodes, does not. However, 2 recent meta-analyses[20,21] provide evidence for the presence of cognitive deficits in euthymic patients with bipolar disorder. Even after controlling for mood symptoms and medication effects, cognitive and functional deficits were found to contribute to chronic impairment in euthymic patients—the kind of impairment that we might expect in schizophrenia but not traditionally in bipolar disorder.

Dr. Malhotra: A recent study[22] of bipolar I disorder probands and a healthy control group found that a genetic variation of *COMT* was associated with cognitive effects in patients and in the control group, suggesting a potential genetic diathesis to the cognition problems in these patients.

Measures of Cognitive Dysfunction

Dr. Kane: Would either of you suggest that the distribution of cognitive dysfunction is similar in bipolar disorder and schizophrenia?

Dr. Perlis: Unfortunately, at least until recently, many cognitive studies used different kinds of batteries, making it difficult to compare individual studies, much less disorders. However, the pattern of deficits does seem to differ somewhat between the 2 disorders and is not necessarily a continuum.

Dr. Malhotra: Yes, there may be differences in the cognitive profiles between the disorders. Bipolar disorder seems to have deficits in attention, verbal learning, and memory functioning,[21,22] as opposed to the more global deficits observed in schizophrenia.[23] In schizophrenia, deficits in cognitive function begin as early as the first episode of illness and perhaps even prior to the onset of illness.[24]

Dr. Perlis: That is a key distinction. As a rule, patients with bipolar disorder have deficits in verbal memory and perhaps executive functioning and attention, but overall cognitive functioning based on a global measure, for example, IQ, tends to fall in the normal range.[23,24]

Dr. Kane: Have there been studies of prodromal symptoms in bipolar disorder that might indicate when the dysfunction begins or what the trajectory is prior to illness onset?

Dr. Perlis: Deficits tend to occur fairly early in the course of bipolar disorder, so even patients who recover from their index episode may exhibit profound functional impairment.[25] Less attention has been paid to prodrome in bipolar disorder than in schizophrenia. Identifying when the disease begins is often difficult because children and adolescents tend to exhibit mood lability and impulsivity, at least early in the course of their illness, rather than discrete mood episodes. So, the trajectory of cognitive dysfunction is not well established. Often no clear euthymic

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period exists for quite a while before these patients are diagnosed.

Dr. Kane: It would be interesting to get a prior history, such as school records, for adults with bipolar disorder, in order to search for evidence of cognitive dysfunction during their early school years.

Dr. Perlis: The kind of progressive decline that is associated with prodromal schizophrenia is not typically seen in bipolar disorder. However, whether subtle changes occur early on deserves to be studied.

The 2 major effectiveness studies in psychiatry, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[26] and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[27] differed in their assessment of cognitive function. CATIE was careful to include cognitive measures, while STEP-BD did not include detailed cognitive assessments. Notably, STEP-BD did include functional measures, which indicated clear impairment in many patients even outside of mood episodes. In addition to the widespread use of pharmacotherapies known to have cognitive effects, one common illness feature that complicates the study of cognitive symptoms in bipolar patients is the presence of residual mood symptoms. As a result, finding patients who are in remission and taking minimal medication can be difficult.

Dr. Malhotra: One of the studies we are currently conducting is specifically focused on cognitive dysfunction in bipolar disorder. Stable patients with bipolar disorder undergoing treatment with an antipsychotic agent are randomly assigned to treatment with the dopamine D_2/D_3 receptor agonist pramipexole versus placebo to test for an effect on neurocognitive function over time. The preliminary data is encouraging, but we are still in the early stages of the study.

Dr. Perlis: Similar studies are ongoing at Massachusetts General Hospital as well, and interestingly, those studies have reported effects even on patients' self-report measures.

Dr. Malhotra: Burdick et al.[28] examined the relationship between subjective complaints of cognitive impairment and objective neuropsychological function in patients with bipolar disorder. Results showed that patients' self-reports were not predictive of cognitive impairment. In fact, some cognitive scores had an inverse correlation with patients' self-reports. Patients who believed that they were cognitively impaired performed better on some measures than patients who did not think they were cognitively impaired. This finding demonstrates the importance of having both subjective measures as well as formal neurocognitive testing in these studies.

Dr. Perlis: Some of the best predictors of recurrence in the STEP-BD study[29] have been certain kinds of residual mood symptoms, which may include cognitive symptoms. Cognitive markers may be indicative of course of illness, not just functional status, even before drug or genetic effects are factored in.

Pharmacogenetics and the Schizophrenia-Bipolar Spectrum

Dr. Kane: Clearly, the prodrome in schizophrenia has gotten a lot of attention. The prodrome in bipolar disorder is beginning to receive more attention, but we also see early-onset cases of schizophrenia and bipolar disorder. To what extent do the genetic findings help us understand whether these early-onset cases are part of a continuum or actually represent discrete disease entities?

Dr. Perlis: Once a bipolar liability gene is convincingly replicated, the obvious hypothesis to test would be that individuals with early onset of illness might carry greater genetic loading—in this case, that they might be more likely to carry early-onset risk genes. Early-onset samples are a more homogeneous group than samples with later onset. Interestingly, in the context of our previous discussion,[1] the early-onset group tends to have more chronic depressive symptoms and more functional impairment than patients with later onset.[30] However, only about one third of patients have onset before the age of 13 years, yielding a relatively small group to study, so it is difficult to determine how much additional statistical power would be available despite the heavy genetic loading and homogeneity.

Dr. Malhotra: Few studies on the genetics of early-onset schizophrenia exist, as well. Rapoport et al.[31] from the National Institute of Mental Health have conducted much of the work on early-onset schizophrenia. Prior to the advent of genetic research, most of the biological work done in schizophrenia showed little difference between patients with early-onset and adult-onset schizophrenia, suggesting that the 2 types lie on a continuum. Patients with early-onset schizophrenia may develop schizophrenia earlier due to heavy environmental loading as well as genetic loading. For example, many of these patients may be living in a highly stressful or a low socioeconomic status situation. And again, as Dr. Perlis mentioned is the case with bipolar disorder, the low incidence of early-onset schizophrenia makes for small sample sizes. Further, prodromal symptoms for schizophrenia and bipolar disorder often overlap.[32] Evidence of these overlapping phenotypes is an attractive area of genetic investigation.

Dr. Perlis: As we have discussed, recent reports[33,34] support an association between a variation in *DISC1* and bipolar disorder and schizophrenia. These findings suggest an overlap in genetic susceptibility for psychosis and bipolar disorder. Cognitive impairment may be one of the phenotypes that we should be looking at in these groups.

Soon we will be examining phenotypic and genetic overlap in data from

the CATIE and STEP-BD studies, as well as the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of major depressive disorder. Although assessments among the 3 studies were different, we may be able to get a first look at overlapping genetic liability.

Pharmacogenetics in Pharmacotherapy Research

Dr. Kane: Dr. Perlis, you have been researching the pharmacogenomics of lithium response. Do you have any findings about the vulnerability that some patients have to the cognitive effects of lithium?

Dr. Perlis: Almost 2 decades ago, Goodwin and Jamison[35] summarized the profound effects that lithium can have on cognition, and, in the future, my colleagues and I hope to examine those underlying mechanisms of action. However, currently we are focused on using pharmacogenetics to find predictors of response to lithium. In a study[36] to examine genes related to lithium mechanism of action in bipolar I disorder, none of the genes that had been chosen to examine the action of lithium were associated with bipolar disorder, but other genes were suggested as candidate genes associated with bipolar disorder (Table 2).

The pharmacogenetics of bipolar disorder has lagged behind the pharmacogenetics of schizophrenia, in part because no one agrees on how to define treatment response. Treatment response research may require long-term observation rather than short-term trials. One set of definitions relies on the clinical improvement observed following lithium initiation and has been used to identify bipolar patients who are particularly responsive to lithium.[37]

Dr. Malhotra: Many bipolar treatment studies are using a relapse prevention model, and these studies may be more difficult to conduct than acute efficacy trials of shorter duration.

Dr. Perlis: It is certainly more resource-intensive, because we are thinking about 1- or 2-year studies, at minimum, compared with typical 4- or 8-week acute studies. Of course, few cohorts are available, even for examining acute outcomes in bipolar disorder, so schizophrenia research has a head start in that regard.

Dr. Malhotra: An attractive pharmacogenetic target is the response to second-generation antipsychotic drugs in acute mania, which are almost the standard of care now. The advantage of an acute efficacy design is the potential rapid response to second-generation antipsychotics, sometimes as early as 2 to 4 days. Thus, the pharmacogenetic trial could have a shorter duration.

Table 2. Putative Susceptibility Genes for Bipolar Disorder[a]

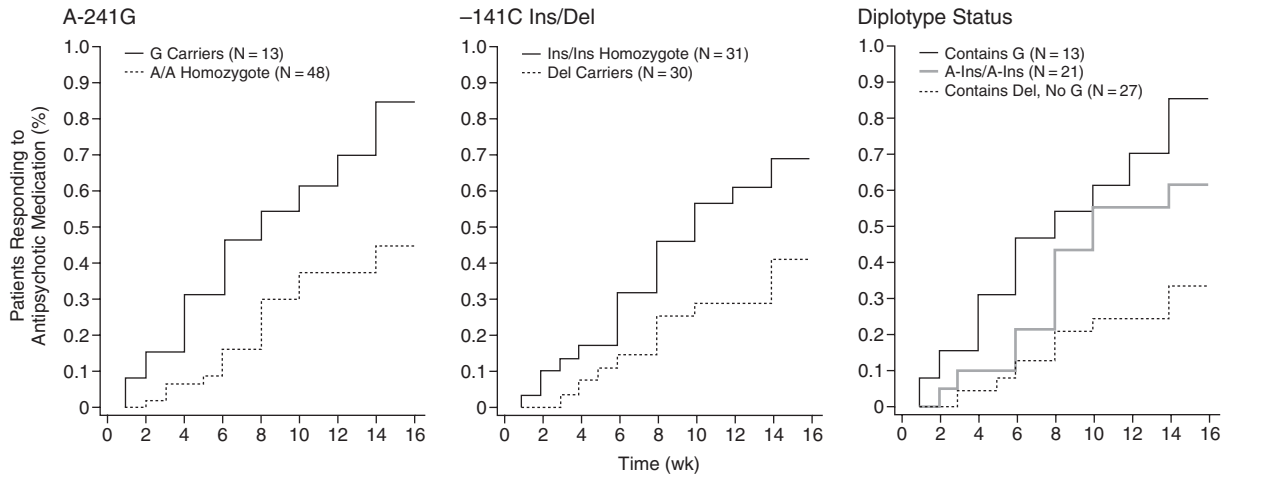
Sialytransferase 4A (*SIAT4A*)
Tachykinin receptor 1 (*TACR1*)
γ-Aminobutyric acid (A) β2 receptor subunit (*GABRB2*)
Disrupted-in-schizophrenia (*DISC1*)

[a]Data from Perlis et al.[36]

Dr. Perlis: Placebo response is still a problem, even in acute mania trials, but less so than in depression studies.[38] A large cohort is necessary for an adequately powered trial, which takes time. On the other hand, the advantage is that these trials should produce a more homogenous phenotype than most studies in psychiatric genetics.

Dr. Kane: Lencz et al.[39] found a significant effect with just 61 patients in a study showing that dopamine-2 (D_2) receptor gene polymorphisms may have an effect on the timing of clinical response to antipsychotic treatment in first-episode schizophrenia (Figure 1).

Figure 1. Time to Sustained Antipsychotic Medication Response in 61 First-Episode Schizophrenia Patients as a Function of Dopamine-2 (D_2) Receptor Gene Promoter Region Single Nucleotide Polymorphisms[a,b]



[a]Reprinted with permission from Lencz et al.[39]
[b]Note that time of response is marked from the beginning of the period of sustained response.

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Disease Susceptibility

Dr. Kane: Are there new genetic strategies that might influence how the field will evolve?

Dr. Malhotra: My colleagues and I recently conducted a study[40] using a different approach to genome association data. Current genome association studies are predicated on the common disease/common variant model for disease susceptibility, which assesses the additive effects of any individual allele on disease risk. In our study, we identified relatively lengthy runs of homozygous single nucleotide polymorphism genotypes that occurred more often than expected by chance in the general population and occurred even more frequently in patients with schizophrenia. The high penetrance yet rare incidence of these recessive loci suggests that there may be multiple ways to develop the schizophrenia phenotype. However, these rare alleles may explain only a small proportion of the overall illness.

Treatment response may be different among patients who carry these runs of homozygosity (ROH). However, because these are rare alleles, small numbers of subjects are available in which to study these ROHs. As data sets such as those from CATIE become publicly available, a larger pool from which to examine treatment response in patients with these ROHs may become available. Although this strategy is currently underpowered, it is a new way of looking at genome association data that may have some relevance to pharmacogenetics.

Dr. Perlis: Another new approach is to study genetic structural variation, such as copy number variation. Weiss et al.[41] used copy number variation in locating risk alleles associated with autism. However, copy number variation may be difficult to examine in other disorders until larger cohorts are available, because such variation is typically much less common than the single nucleotide polymorphisms we have been focusing on.

Dr. Malhotra: Despite relatively small sample sizes, however, Sebat et al.[42] found an overrepresentation of rare copy number variants in genes related to disease, neurologic function, and regulation of metabolism and cell growth.

Dr. Perlis: While the field is beginning to identify attractive candidate genes or pathways, emphasis should also be placed on expression studies in animal models, and treatment studies will be needed to confirm the effects of these candidates. Many of the signals that are being found in genetic association studies are in areas where genes have no known regulatory importance.

Dr. Malhotra: I agree. I tend to think of genetics essentially as a screening paradigm for which results should be validated with a biological measure of function. Whether by in vitro, in vivo, animal model, or treatment response, we have to show that the genetic finding has some meaning beyond the purely statistical p value. But genetics can be an effective screening strategy because it is not influenced by confounds that affect other potential screening strategies like the effects of prior or ongoing drug treatment, illicit drug use, or other environmental confounds.

Population Stratification and Study Groups

Dr. Perlis: Will problems of population stratification found in standard genetic association studies become a larger problem in pharmacogenetic treatment studies, or will the fact that these studies tend to use nested case-control cohorts help us get around that problem?

Dr. Malhotra: I am not as concerned about population stratification in pharmacogenetic studies as I would be in a simple case-control disease susceptibility study. Few data suggest that ethnicity plays a role in differential drug response, and for population stratification to have an effect, there has to be a difference in the frequency of the phenotype, not just the genotype. In pharmacogenetic studies, we hope to include all available subjects and examine stratification in the data analysis phase.

Dr. Perlis: In the past, a concern with antipsychotic treatment has been the drug interaction potential of certain cytochrome P450 enzymes.[43,44] Should we still be concerned about adjusting the antipsychotic dose to account for the metabolism of these enzymes, or does the genetic variation supersede this concern?

Dr. Malhotra: Drug metabolism is still a concern. Data[45–47] suggest that certain ethnic groups may require higher doses of medication to reach the same plasma drug concentration and level of treatment response. White patients and African American patients, for example, appear to require higher doses than Asian or Hispanic patients.[45–47] However, these data may not have been generated in randomized clinical trials, and other biases may have led to higher doses being used.

Genetic Predisposition to Suicidality

Dr. Kane: What have we learned in recent years about genetic predisposition to suicidality in patients with schizophrenia and bipolar disorder?

Dr. Perlis: The existence of a suicidality phenotype is still controversial, but evidence from studies of both suicidal behavior[48] and suicidal thinking[49] suggests that genetics strongly contributes to the risk for suicide. The STAR*D study[49] identified 2 genetic markers associated with suicidality related to antidepressant treatment. A third gene, cyclic adenosine monophosphate response element binding (*CREB1*) protein, may be related to mood reactivity and aggression and has also been associated with treatment-emergent suicidality.[50] Of the 1447 participants observed, 8.6% reported treatment-emergent suicidality.[50]

Among these patients, a genetic association with suicidality was found in the men. Of course, for all 3 reported associations, it is important to point out that these findings have not yet been replicated. Replication of these outcomes poses a problem because replication often requires even larger cohorts than the initial detection cohort. However, these studies are an example of a way in which pharmacogenetics may ultimately prove to be clinically viable, not just for predicting efficacy, but for predicting clinically meaningful adverse effects as well.

Dr. Kane: What about suicidality in patients with schizophrenia?

Dr. Malhotra: Clozapine is indicated for the treatment of suicidality in patients with schizophrenia. So, the opposite approach could be taken in schizophrenia pharmacogenetics. That is, because patients who were suicidal had to be studied in the research[51,52] leading up to clozapine's receiving that indication, it stands to reason that we could test whether the drug's efficacy on suicidality was mediated by genetic factors in those patients.

As more data are acquired on suicidality measures, such as the Columbia Suicide Severity Rating Scale, we may get a better sense of how valid and reliable those assessments will be for use in pharmacogenetic studies.

Dr. Perlis: Detailed assessment scales should also be more sensitive to milder symptoms associated with suicidality, even in the absence of over suicide attempts or plans.

Dr. Malhotra: Suicide assessments are now required in many clinical trials, not just those focused on psychiatric drugs.[53] It is possible that a number of subjects who have had treatment-emergent suicidality with a number of different treatments may be collected in a relatively short period of time. If DNA is collected from those subjects, suicidality may be an interesting phenotype to study independent of specific treatment; such a large number of subjects could allow for careful matching across many different domains of suicidality.

Dr. Perlis: Looking at treatment-emergent suicidality across disorders may lead us to a common genetic pathway—that is, it may help us to understand why suicide risk is elevated in so many different psychiatric disorders.

Using Pharmacogenetics to Identify Side Effect Risk

Dr. Kane: What progress has the field of pharmacogenomics made in identifying genetic factors that contribute to the metabolic adverse effects of atypical antipsychotic drugs?

Dr. Malhotra: Reynolds et al.[54] has examined genetic polymorphisms associated with antipsychotic-induced weight gain. Promoter region variations in the serotonin-2C (5-HT_{2C}) receptor have been found to be associated with protection from weight gain in patients with schizophrenia who were taking risperidone,[55] olanzapine,[56] or clozapine.[57]

Weight gain is clearly a multidetermined effect, and environmental factors certainly play a role, but the idea that genetic factors could predict who is at risk for antipsychotic-induced weight gain is attractive. Results from CATIE trials[58] suggested that olanzapine was a more effective treatment than other antipsychotics but had a higher incidence of weight gain. Pharmacogenetics could help to identify a subpopulation of patients with schizophrenia who are not at risk for weight gain and thus might benefit from olanzapine. Because patients with bipolar disorder are also often treated with antipsychotics, this information could be beneficial for bipolar treatment as well.

For pharmacogenetic studies of weight gain, studying antipsychotic-naïve treatment groups would help to avoid the variability of prior treatment, which could make it difficult to detect a subtle genetic effect. However, finding patients who have not previously been treated is increasingly difficult because patients are being treated with medications at younger ages now.

Conclusion

Dr. Kane: Pharmacogenetics can provide us with strategies for deciphering the bipolar disorder/schizophrenia overlap, particularly in the area of neurocognition and pharmacotherapy. Several genotypes are currently being studied that may represent phenotypes associated with antipsychotic side effects. Potentially, pharmacogenetics could lead to screening patients for susceptibility to common adverse events and influence the outcomes of pharmacotherapy. For example, the identification of a gene that influences neurocognition could be used to select a pharmacologic agent whose effects on neurocognition could be mediated by genotypes.[3] Pharmacogenetic testing may lead to individualized treatments that will increase adherence as well as lead to optimal patient outcomes.

Drug names: clozapine (FazaClo, Clozaril, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), pramipexole (Mirapex and others), risperidone (Risperdal), and tolcapone (Tasmar).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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