Pharmacogenetics of Schizophrenia: Bringing ‘Order to Chaos’ in the Psychopharmacology of Schizophrenia?

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Abstract

The inherent wide interindividual variability in response and tolerability of side effects in the treatment of schizophrenia itself provides a compelling rationale for the great potential of pharmacogenetics. Moreover, this potential is consonant with the broader public health directive toward personalized medicine. Within schizophrenia, the progress thus far has been modest in both the treatment response and adverse effect domains. This chapter chronicles the progress made in the quest for pharmacogenetic predictors in the treatment of schizophrenia.

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By any measure – and especially with regard to its treatment – schizophrenia is a highly heterogeneous disorder. A continued debate in our field that is of great relevance to the area of pharmacogenetics is whether schizophrenia is actually etiologically heterogeneous – that is a collection of several conditions that arise from different pathobiological bases – or whether schizophrenia is (merely) symptomatically heterogeneous [1]. Certainly, every clinician knows well that the presentation and course of illness varies widely between patients. Irrespective of whether you ascribe this heterogeneity to neurobiology or course alone, this variability in schizophrenia itself is the ‘baseline condition’ upon which pharmacogenetic examinations begin. This is an important consideration.

Clinicians also know that there is wide variability in patients’ response and tolerability of any given antipsychotic medication. The advent of second-generation antipsychotic medications (SGAs) alongside the first-generation antipsychotic medications (FGAs) has broadened the treatment options for patients. However, in large part the dilemma remains the same: at present, the selection of an antipsychotic is more on a ‘trial and error’ basis rather than based upon any robust rationale.

Table 1. Current contextual issues in the psychopharmacology of schizophrenia

Diagnostic	Drug choice	Drug profile
– Overlap between schizophrenia and bipolar disorder. – Is schizoaffective disorder a valid and useful nosological entity? – Can we really identify schizophrenia in its prodromal stages?	– Are older and new anti-psychotics really different in efficacy? – Do SGAs really differ in efficacy among each other? – What is the best drug to start with? – When should other drugs be used? – Does antipsychotic polypharmacy work?	– How do we predict and manage weight gain and metabolic disturbances? – Is dopamine D₂ receptor binding necessary and sufficient for antipsychotic efficacy? – How do you balance drug efficacy and drug tolerability over the course of illness? – Can biomarkers help to guide clinical decisions?

Set against both the variability of schizophrenia and its treatment, pharmacogenetics at least offers the promise of ‘bringing order to the chaos’ in the psychopharmacology of schizophrenia [2]. However, ‘promise’ is the operative term, and there are substantial theoretical and methodological challenges in this emergent field of pharmacogenetics. Thus, in this chapter we will describe and discuss these important contextual issues rather than simply recount findings from disparate pharmacogenetics studies. We will also, however, enumerate key studies that provide important findings for treatment responsivity and medication tolerability in schizophrenia.

Pharmacotherapy of Schizophrenia: Contextual Issues for Pharmacogenetics

In considering pharmacogenetics, the state of pharmacotherapy in schizophrenia first needs to be briefly reviewed (table 1). Several excellent recent reviews and meta-analyses provide the reader with a more comprehensive evaluation. At the present time, our field is hotly debating the relative merits of FGAs versus SGAs [3, 4]. Several large pragmatic studies have been published [5–9] which, when taken collectively, affirm the earlier observation of great inherent variability between patients so that ‘mapping the right drug to the right patient’ remains challenging. Thus far, drugs with antipsychotic activity appear to bear at least some relationship to a blockade of dopamine receptors. Antipsychotic efficacy appears to be tied – at least to some extent – to dopamine (D₂) blockade. Recent enthusiasm that glutamate alone might be a distinct target has been dampened by the results of a recent trial of a glutamatergic drug that had shown initial promise [10]. Additionally, these drugs have highly variable pharmacologic profiles at several other neuroreceptors. This

has also been an important area of focus in pharmacogenetics (see below). Perhaps the area of greatest clinical distinction between antipsychotics is in adverse effect profiles. Extrapyramidal side effects and tardive dyskinesia (TD) are more common with FGAs than SGAs [11]. Rates of TD are still about 10 times less with SGAs. On the other hand, SGAs are more associated with weight gain and metabolic disturbances [12]. In the large CATIE study, 40% of patients met the criteria for the metabolic syndrome [13]. In a first-episode study (CAFE), 13% of patients met the criteria for the metabolic syndrome [14]. Prediction of weight gain and risk for metabolic syndrome has been a productive area of current pharmacogenetic research (see below).

Brief Overview of the Genetics of Schizophrenia: Implications for Pharmacogenetics

Although the genetics of schizophrenia are highly complex, overwhelmingly the evidence from familial, twin, and now a host of association studies collectively points to a genetic basis for schizophrenia [15–19]. While a comprehensive review of genetic studies is clearly beyond the scope and intent of this section of the paper [for a synthesis of recent findings, see 15, 17, 19], most notably the study of the genetics of schizophrenia has advanced alongside traditional familial and twin association studies to now also become increasingly molecular in focus [18, 20]. There has been a great deal of interest in polymorphisms in the Val/Met alleles of the catecholamine-O-methyl transferase gene in explaining frontal lobe functional deficits in schizophrenia [21]. Many other studies have shown abnormalities in several genes that code for neurodevelopment (e.g. dysbindin, neuregulin, DISC, SNAP-25) and for trophic factors (e.g. BDNF) [16, 18, 22, 23]. These ‘susceptibility genes’ regulate proteins and/or biological processes that have also been implicated through other neurobiological (e.g. postmortem) studies in schizophrenia. For example, dysbindin is a neurodevelopmental protein gene that is found on chromosome 6. Decreased levels of dysbindin mRNA have been noted in the dorsolateral prefrontal cortex in schizophrenia patients [24], and variants in expression of components of the dysbindin gene have been reported in patients with schizophrenia [25–27]. Studies of large pedigrees have also shown a linkage signal on chromosome 10 as well as genetic variations in the gene that encodes for neuregulin [28, 29] – another neurodevelopmental gene that has been implicated in schizophrenia [30]. At present, these genetics investigations do not converge in mechanistic approaches that are used to inform pharmacogenetic investigations. Perhaps some greater confluence may occur as the field of pharmacogenetics matures further.

Findings Thus Far from Pharmacogenetic Studies in Schizophrenia

Pharmacogenetic studies of antipsychotic response and adverse effects in schizophrenia have examined both the pharmacodynamic and pharmacokinetic attributes of antipsychotic medications. Research on genetic variations of pharmacodynamic factors involved in the antipsychotic response has focused on polymorphisms of genes that code for dopamine, serotonin, histamine, muscarine, glutamate and adrenergic receptors (neurotransmitters observed to be altered in patients with schizophrenia). The pharmacokinetic studies have investigated genetic variants in enzymes known to be involved in antipsychotic metabolism.

Pharmacodynamic Factors

Numerous studies have evaluated the potential of pharmacogenetics to predict the response to antipsychotic medications [31, 32]. In a first-episode study comparing risperidone and olanzapine, Lenz et al. [33] reported that a polymorphism of the dopamine D₂ promoter gene (specifically the possession of either the -241C allele or the -141C Del allele) was associated with an enhanced treatment response during 12 weeks of treatment. There were no differences between either risperidone- or olanzapine-treated patients. Lane et al. [34] examined another polymorphism of the dopamine D₂ receptor – in this instance a polymorphism of serine (Ser 311 Cys) – in 123 patients with schizophrenia. Patients with the Ser 311 Cys allele (n = 12) showed a more robust response to antipsychotics. In a study of Chinese patients with first episode psychosis, Reynolds et al. [35] found no association between another dopamine receptor polymorphism – the Ta21A polymorphism of the dopamine D₃ receptor – and treatment response in 117 patients treated for 10 weeks with either risperidone or chlorpromazine.

However, Reynolds et al. [36] did find an association between the polymorphism (-759D C/T) in the 5HTR2C promoter region that was associated with improvements in general and negative (but not positive) symptoms. Ellingrod et al. [37] found a relationship between response to olanzapine and another 5HTR2C polymorphism (Cys 23 Ser) in a study of 41 patients with chronic schizophrenia. Polymorphisms of the 5HT2 A receptor have been shown to be associated with treatment response, most notably in an initial and influential early study by Arranz et al. [38] which reported that possession of the 102C allele of the 5HT2 A receptor predicted a poor response to clozapine. Lane et al. [39] reported contradictory findings in relation to treatment with risperidone.

Yamanouchi et al. [40] found no association between 5HT2A polymorphisms and treatment response in a short-term study of 73 patients with schizophrenia. Lane et al. [34] reported several associations between polymorphisms of the 5HTR6 gene and treatment response. Lin et al. [41] examined treatment response in relation to a polymorphism of a gene that codes for P-glycoprotein, which has been shown to transport certain SGAs across the blood brain barrier. They found that the 3435 genotype pre-

dicted positive symptom response to olanzapine treatment. Most recently, genotypic analysis was incorporated into the registration clinical trials for a novel antipsychotic, iloperidone [42]. Here a 6-marker genetic combination was associated with treatment response to iloperidone during a 4-week study. Seventy-five percent of patients with this genetic combination showed a response to iloperidone, as opposed to the response rate of 37% among the remainder of patients. Incorporating genetic analyses into antipsychotic drug development and early clinical trials programs is a substantial advance for our field. However, to date, pharmaceutical companies have been reluctant to use this approach, particularly as it has the potential to limit or ‘pigeon-hole’ the use of a new compound toward a subset of patients. In contrast, federally funded treatment studies proved a great opportunity to search for pharmacogenetic markers of treatment response. In this regard, the results of pharmacogenetic evaluations of treatment response in the schizophrenia CATIE study are rather salutary [43, 44]. Despite a large sample size and excellent clinical trial methodology, the assessments and analyses of polymorphism of many of the genes noted above failed to reveal any robust relationship to treatment response. A later and broad analysis of some 2,767 polymorphisms detected some weak associations, although the authors acknowledge that this may in part be due to the large number of comparisons in this analysis [44]. In balance then, examining functional polymorphisms of both dopamine and serotonin receptor genes has provided some associations with treatment response, although overall the signal appears weak and no reproducible focus emerges from these studies.

The relationship of receptor polymorphisms to adverse effects of antipsychotic medications appears to be more robust – as evident from the literature thus far. Several studies have examined polymorphisms of the dopamine D₂, D₃, and D₄ receptor substance and presence of TD. The results of these studies have been largely positive, with exceptions noted. These associations appear more robust than for 5HT_{2A} or 5HT_{2C} and the presence of TD. Early on, it was reported that patients of Ashkenaz Jewish ethnicity had a heightened risk of developing agranulocytosis during treatment with clozapine [45]. This relationship was not confirmed in subsequent studies. However, a commercial genetic test for clozapine-induced agranulocytosis has been developed [46]. Potentially, this could predict whether a patient might be at risk of developing agranulocytosis upon exposure to clozapine. Such a test could influence the selection of patients for clozapine and/or the closer hematologic monitoring of patients who might be at risk early on during treatment with clozapine.

Although agranulocytosis was the adverse effect of greatest concern to clinicians when clozapine became available, it soon emerged that weight gain and metabolic disturbances are more worrisome side effects of this drug – and now this also appears to be the case for all SGAs [47]. Accordingly, the prediction of weight gain and metabolic disturbances during treatment with SGAs is a major focus of pharmacogenetics in schizophrenia. Reynolds et al. [48] first reported that possession of a T allele of the 5HT₂ receptor was associated with weight gain during treatment with

either risperidone or chlorpromazine. They found a similar relationship for clozapine therapy, also partly replicated in a study by Miller et al. [49] in a population receiving 6 months of clozapine therapy. However, studies by Basile et al. [50] and by Tsai et al. [51] did not replicate this association in clozapine-treated patients. Ellingrod et al. [52] did replicate this association in patients who were being treated with olanzapine.

Several studies have also examined the mechanistic pathways to weight gain and metabolic disturbances. Polymorphisms in the leptin gene have been associated with weight gain [53]. Jin et al. [54] provide a comprehensive review of the relationships of leptin, weight gain, and antipsychotic treatment. Ellingrod et al. [52] evaluated the relationships between methylenetetrahydrofolate reductase (MTHFR) activity and indices of the metabolic syndrome in 58 patients with schizophrenia. They observed a 4-fold increased risk of metabolic syndrome in patients with the 677T allele of MTHFR. They also found elevated insulin levels in patients with the 677T allele. Souza et al. [55] report a meta-analysis of association studies of the GNB3 gene and weight gain with antipsychotics. Overall, there appears a more consistent pattern of pharmacogenetic associations for antipsychotic-related side effects than for therapeutic response.

Pharmacokinetic Factors

Various cytochrome P450 (CYP) isoenzymes have been shown to affect the metabolism of various antipsychotics leading to interest in whether mutations in the genes that code for the enzymes predict response and adverse effects with antipsychotics. CYP2D6 is the main metabolic pathway of a number of older antipsychotics (chlorpromazine, thioridazine and haloperidol) as well as several newer antipsychotics (risperidone and aripiprazole). In a naturalistic study of haloperidol treatment, Brockmoller et al. [56] found a trend towards increased CYP2D6 activity and lower therapeutic efficacy and significantly higher ratings of parkinsonism in poor metabolizers of CYP2D6. The other studies that have investigated CYP2D6 activity have found no relationship between CYP2D6 genotype and therapeutic effects of the older antipsychotic drugs. Several studies have shown that CYP2D6 variants did not predict response to risperidone, but predicted the ratio of the parent drug to metabolite and adverse effects [57–59]. Another CYP enzyme, CYP1A2, is involved in the main metabolic pathway of clozapine and olanzapine. However, CYP1A2 polymorphisms have not been shown to significantly influence clozapine metabolism [60], but delays in response to clozapine have been observed in individuals with the ultrametabolizer phenotype [61, 62]. In addition, the combination of high inducibility CYP1A2 alleles and smoking has been found to result in reduced clozapine plasma concentrations [63]. The CYP3A4 enzyme has been shown to be involved in the metabolism of aripiprazole, quetiapine, risperidone and to a lesser extent clozapine and ziprasidone. To date, no significant reports of an association of the identified variants of CYP3A4 with antipsychotic variability or response have been published. Likewise no signifi-

Table 2. Considerations that could impact the therapeutic potential of pharmacogenetics in schizophrenia

Patient variables	Measurement variables	Treatment variables
– Diagnosis – Illness onset and duration – Clinical heterogeneity – Medical and psychiatric comorbidities – Extent of prior treatment-refractoriness	– Definition(s) of treatment responses – Measurement scale(s) used – Duration of observation – Physiological indices (e.g. insulin sensitivity, leptin levels) and their measurement issues – Technical aspects of pharmacogenetic blood tests	– Study durations – Drug use – Presence of concomitant medications

cant response associations have been reported with the polymorphic CYP3A5, an enzyme reported to contribute to antipsychotic metabolism [64].

Thus at the present time, the use of pharmacogenetics of antipsychotic kinetics may be clinically useful for predicting dose in special cases and for certain antipsychotics, while their usefulness in predicting clinical response must be further explored.

There is also a series of studies examining the association between TD and the cytochrome P450 genes CYP2D6 and CYP1A2. The majority of studies found that mutations resulting in reduced 2D6 activity (and presumably in higher plasma concentrations of antipsychotic medications) were positively correlated with higher AIMS scores and the development of TD [65–68]. Conversely, Sachse et al. [67] found that the CYP2D6 polymorphisms did not predict TD but that CYP1A2 polymorphisms were significantly associated with TD. Basile et al. [69] reported that patients who were homozygous for the C allele of the CYP1A2 gene had significantly higher AIMS scale scores. This finding was not replicated in a study by Schulze et al. [70].

Methodological Considerations in Optimizing Pharmacogenetic ‘Signals’ in Schizophrenia Research

The extent to which the ‘promise’ of pharmacogenetics might be realized in schizophrenia research – ‘bringing order to chaos’ and heralding the clinical expression of personalized medicine – is in part dependent on several factors (table 2). Just as in ‘classical genetics’, the ability to detect any meaningful signal in pharmacogenetics studies is dependent upon careful diagnostic assessment. This may seem too intuitive to merit attention, yet the trend in clinical trials research today toward large pragmatic trials may be contributory. These studies include heterogeneous patient populations with psychiatric and medical comorbidities which might obfuscate pharmacogenetic associations, especially if these are weak and/or only observed in combination. The lack of

robust associations in the CATIE schizophrenia study is noteworthy and this study, while exceptionally large, did enroll an impressively heterogeneous patient population.

Another very important consideration here is ethnicity of the study population [31, 71]. It is likely that the results in various studies of response and adverse effects may also be related to ethnicity. This is most evident for investigations of the CYP2D6 cytochrome system which is well known to vary substantially in expression according to ethnicity.

It is also unclear whether pharmacogenetic associations are likely to emerge as class related (i.e. weight gain associated with all SGAs) or drug-specific (e.g. 5HT₂ receptor -759C/T association with clozapine-related weight gain but not with other SGAs). Clearly, clues in either direction would support a more tailored research focus in later studies.

It is also important to appreciate that pharmacogenetic studies are subject to the same methodological issues that conspire against positive therapeutic findings in psychopharmacologic research: Was the right dose of the antipsychotic used for the study? Was the duration of the study long enough to observe a therapeutic response? Was this a study population ‘capable’ of showing a therapeutic response or did the investigators unwittingly choose a more refractory patient sample for this treatment study?

It is also evident that definitions of treatment response differ substantially across studies, reflecting the current state of methodology within psychopharmacology. For example, the study of Arranz et al. [38], which showed an association between symptom response to clozapine therapy and 5HT_{2C}, was based upon scores on the Global Assessment of Functioning Scale. This is a reasonable approach. However, of course it should not be a surprise that subsequent studies using the Brief Psychiatric Rating Scale or other measures did not replicate this initial finding. The conventions for defining treatment response in schizophrenia also vary across studies – some apply a percent change from baseline ratings, some apply composite measures, and increasingly studies are considering remission and recovery as therapeutic outcomes [72]. In terms of evaluating the capacity of pharmacogenetics to provide a predictive signal, this variance in measurement and definition of treatment response is indeed shifting ground which must surely contribute to the inconsistency in results across pharmacogenetic studies. In this regard, it may well be that adverse effect profiles may be a more tangible measure to advance pharmacogenetic investigations in schizophrenia.

Pharmacogenetics: ‘Bringing Order to Chaos?’

Personalized medicine, while not quite inculcated into current clinical care, is looming large as the next transformation of healthcare [73–75]. Synderman and Dinan [76] articulate a fundamental shift from a ‘find it, fix it’ model of care to a ‘personalize it, predict it’ model (table 3). This is extremely exciting and provocative. Already, we can

Table 3. Evolution toward personalized medicine

Current approaches	Personalized care
– Disease diagnosis	– Risk identification and analysis
– Identifying overall risk factors	– Delineating personalized ‘risk factor’ profile
– Developing a treatment plan	– Constructing personalized care plan
– Algorithm-based care	– Personalized individual risk-based care
– Global preventative approaches	– Individual wellness and risk reduction management

Derived from Snyderman and Dinan [76].

see glimpses of this potential, as evidenced in the pharmacogenetics of anticoagulant therapy [77] and in increasingly refined and genetics-guided approaches to cancer chemotherapy [78]. Psychiatry – and in this instance, the treatment of schizophrenia – deserves no less.

If either therapeutic response and/or tolerability to antipsychotic medications have a neurobiological basis that is genetically regulated, then the promise of pharmacogenetics remains considerable. If we could select the initial choice of antipsychotic for a first-episode psychosis patient based upon his/her genetic profile, this would be paradigm-breaking for psychopharmacology. If we could predict which patient is going to develop antipsychotic-induced diabetes mellitus for a given drug, we would avoid exposure to that agent. If we knew which genes were important to treatment response with one drug and that they differed between drugs, we could make rational decisions about which drug to try next when the patient fails on the present antipsychotic. All, or even any, of these advances would represent substantial progress in psychopharmacology and they would take us well beyond the repeated ‘trial and error’ of current treatment.

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