The impact of pharmacogenetics on the development and use of antipsychotic drugs

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There are substantial differences between individuals in the effects of antipsychotic drugs in the treatment of schizophrenia. This is apparent in symptom response, as well as in the emergence of side effects, such as tardive dyskinesia or weight gain. Genetic variation is likely to contribute substantially; in the past decade genetic polymorphisms in candidate genes have been identified which are associated with these individual differences. Whether pharmacogenetics will prove valuable in antipsychotic drug discovery is unclear, although it is already elucidating mechanisms of antipsychotic drug action, and genetic testing may well lead to a future of individualised drug treatment.

Introduction

Despite the huge impact that psychiatric illness has on society, treatment of the major psychiatric disorders remains very limited in its efficacy. Response rates of little more than 50% are common for treatment of depression, while even lower proportions of patients with schizophrenia may achieve adequate response to their antipsychotic drug treatment.

Antipsychotic drugs are widely prescribed, to over 1% of the population. Primarily, but not exclusively, these are patients with schizophrenia (Box 1); however, antipsychotic drugs are also used in treating a variety of behavioural problems from childhood autism to psychosis in neurodegenerative disorders. Patients with psychotic illnesses demonstrate substantial unexplained individual variability in their clinical response to this drug treatment. There is little understanding of the reasons for, or correlates of, these profound differences between individuals, although genetic factors are likely to contribute.

Thus, pharmacogenetics potentially has much to offer in identifying what may underlie these differences in the consequences of antipsychotic drug treatment. The pharmacogenetics of antipsychotics has received substantial research effort over the past decade. This has been driven by an awareness of the varied, but generally limited, effectiveness of antipsychotic drugs both in controlling symptoms of schizophrenia and in inducing unwanted side effects that may, in turn, result in reduced treatment compliance and/or further morbidity.

The target phenotypes: symptom response

Antipsychotic drugs are often effective at controlling the positive psychotic symptoms, such as hallucinations and delusions, but less so with respect to the negative and cognitive features of schizophrenia. These include social withdrawal, blunted mood, lack of self-care, poor executive function and poor working memory and, along with depressed mood, are the symptoms that are most problematic in returning the patient to society. Pharmacogenetic analysis of response to antipsychotic treatment is beginning to recognise the differential effects of drugs on positive and negative or cognitive symptoms.

Some patients respond particularly poorly, with minimal symptom improvement, following treatment with several antipsychotic drugs. Clozapine is the only pharmacotherapy indicated for these patients and is essentially their last therapeutic hope, although it provides adequate symptom relief in only approximately 50% of cases. Due to the occasional (approximately 1%) risk of developing a potentially fatal agranulocytosis, treatment with clozapine requires regular blood monitoring. Thus, clozapine response has been a prime target for pharmacogenetic investigation, with the importance of the problem being assisted by the pragmatic advantage of sample availability and regular patient monitoring in retrospective studies.
The target phenotypes: side effects

The side effects of antipsychotic drugs are limiting and problematic. The extrapyramidal side effects (EPS) are various movement disorders suffered as a result of antipsychotic drug treatment and which have been apparent since the introduction of chlorpromazine over half a century ago. They include the relatively immediate effects of akathisia, dystonia and parkinsonism, believed to be consequences of acute inhibition of dopaminergic neurotransmission via antipsychotic drug antagonism of the D2 receptor, as well as chronic motor problems, of which the greatest is tardive dyskinesia (TD). TD is characterised by the delayed appearance of involuntary movements and is particularly associated with long-term medication with the older antipsychotic drugs, such as chlorpromazine and haloperidol. There are several risk factors known to predispose to TD; however its familial concordance suggests that susceptibility to TD and other EPS may, in part, be genetic.

The identification of effective antipsychotic drugs that have diminished propensity to produce EPS underlies the concept of atypicality; “atypical” is a label applied to all antipsychotics introduced in the past 20 years. In addition to clozapine, these include olanzapine, quetiapine and risperidone; these and most other atypical antipsychotics combine D2 dopamine receptor antagonism with a strong antagonist action at the 5-HT2A receptor, often with a variety of other receptor actions. Aripiprazole has been recently introduced; as well as having 5-HT2A antagonist effects, it has a unique partial agonist action at the D2 receptor which is thought to be responsible for its lack of acute EPS or hyperprolactinaemia.

Like EPS, hyperprolactinaemia, leading to galactorrhoea, can be limiting in the pharmacotherapy of schizophrenia. Such drug effects on the hypothalamic–pituitary–gonadal axis have further consequences, including sexual dysfunction and, potentially, osteoporosis. Hyperprolactinaemia is most likely a consequence of pituitary dopamine D2 receptor antagonism; this side effect has a reduced occurrence with some, but not all, atypical antipsychotic drugs.

There are side effects relating to other receptor mechanisms, however, not all of which have diminished with the introduction of the atypical drugs. These include sedation, postural hypotension and weight gain. Weight gain in particular is increasingly recognised as a major limitation of current antipsychotic therapies, potentially leading to cardiovascular disease and type II diabetes, which are well-established consequences of obesity. There is substantial evidence from studies of obesity in the general population to suggest genetic influences; the unexplained and substantial inter-individual variation in drug-induced weight gain strongly indicates the involvement of genetic factors here too.

The candidate genes

The pharmacogenetics of antipsychotic drug action has concentrated primarily on investigation of common variations in the DNA sequence (polymorphisms) in genes that have been implicated by the known pharmacology and neurochemical mechanisms of these drugs (reviewed in [4]). The target receptors for the antipsychotic drugs thus provide valuable ‘candidate’ genes. It is the dopamine D2 receptor that is considered the major site of antipsychotic action and this, along with other D2-like receptors, D3 and D4, has been an important candidate. D3, in particular, may be an important site for some antipsychotics, while there is little evidence that D4 has a major role in antipsychotic action [4].

The newer antipsychotic drugs all demonstrate a relatively high affinity for the 5-HT2A receptor, which has long been considered to contribute to the reduced incidence of EPS, with most of these atypical antipsychotics. Thus, effects at the 5-HT2A receptor, in addition to other serotonin receptors, including 5-HT2C and 5-HT1A, have provided useful working hypotheses relating to mechanisms of drug action [4]. These receptors, therefore, also provide valuable candidate genes, as do other components in the neurophysiological processes associated with neurotransmission by dopamine and serotonin. Such genes include the neuronal transporters, as well as the enzymes involved in synthesis and metabolic removal of transmitter, the latter group including monoamine oxidases (MAO) A and B and catechol-O-methyltransferase (COMT).

These receptors, and other candidate genes, are often as equally implicated in association with side effects as with symptom response. Antagonism at the dopamine D2 receptor underlies EPS and hyperprolactinaemia, as well as the main antipsychotic mechanism, and 5-HT2A receptor antagonism may contribute to improved symptom response, as well as diminished EPS. Sedation and postural hypotension may relate to antagonism at the histamine H1 and alpha1 adrenergic receptors, although such candidate genes have yet to be investigated adequately.

Although these pharmacodynamic aspects of drug action provide the major candidate gene hypotheses for antipsychotic drug pharmacogenetics, elsewhere in pharmacology, genetic approaches have drawn more from pharmacokinetics. In particular, the cytochrome P450 drug-metabolizing enzymes have attracted attention, since some have well-established variability in phenotype (poor versus extensive metabolizers) that reflects genotype variation. The CYP2D6 gene demonstrates a large amount of genetic variability, with several polymorphisms profoundly influencing enzyme activity and, hence, the rate of metabolic deactivation of substrate drugs. It has effects on several antipsychotics, including risperidone and aripiprazole, as well as several of the older antipsychotic drugs; two further enzymes,
CYP1A2 (clozapine and olanzapine) and CYP3A4 (quetiapine, ziprasidone and risperidone), are also involved in metabolism of atypical antipsychotics [5]. Polymorphisms in these genes may not only influence rate of metabolism and, hence, plasma concentrations, they may also be differentially sensitive to inhibition or, for CYP1A2 and CYP3A4, differentially induced by other drugs, xenobiotics or toxins, such as cigarette smoke. Several companies undertake commercial testing for CPY gene polymorphisms, although their routine use in antipsychotic treatment is not easily justified in the absence of a strong evidence base relating enzyme genotype to plasma concentrations of drug, or even a clear understanding of the relationship between plasma drug concentration and efficacy.

Other pharmacokinetic processes need to be considered. P-glycoprotein (P-gp) is one further factor in determining the availability of drug; this protein acts as an efflux pump for xenobiotics, and many drugs. The MDR1 gene coding for P-gp also demonstrates substantial genetic, and hence phenotypic, variability which can influence bioavailability of a wide variety of drugs, including some antipsychotics [6].

Further candidate genes may be unrelated to direct aspects of drug action, but be disease-modifying or risk factors. These include genes for COMT, dysbindin, neuregulin-1, metabotropic glutamate receptor 3 amongst many more [3]. They have been little investigated in terms of pharmacogenetics, apart from COMT, and yet offer substantial potential. Thus, for example, genetic variation in dysbindin appears to influence cognitive performance [7], perhaps by affecting activity at the glutamatergic synapse [8]; it would seem likely that an “at risk” polymorphism in this gene might well influence response and remission, since cognitive function will contribute to the symptom profile in treated patients. A review of genetic risk factors for schizophrenia is beyond the scope of this article, although it is still worth noting that the identification of such risk factors provides insight into the pathological processes underlying the disease and can point towards novel targets for antipsychotic drug development [9].

Thus, a variety of mechanisms underlying pharmacogenetic association with response to treatment can be distinguished, ranging from these complex interactions relating to the various genetic contributors to the pathology of the disease down to simple pharmacokinetic effects influencing drug availability (Box 2).

Genetic polymorphisms

Genetic variation in candidate genes can take a variety of forms. The classical non-synonymous single nucleotide polymorphism (SNP) in a coding region of DNA results in an amino acid change in protein product, with likely effects on its structure and function. There are many further genetic polymorphisms that can influence biological function, however. SNPs or other polymorphisms (e.g. sequence insertion/deletion, variable number tandem repeat and so on) occurring in the 5’ promoter region of the gene can affect binding of transcription factors, while other non-coding or synonymous coding SNPs may influence mRNA stability and folding, all of which can potentially affect the transcription and/or translation of gene product. However, investigated polymorphisms may not necessarily be functional, even if they exhibit a significant pharmacogenetic association; this may reflect their being in linkage disequilibrium with a functional, but uninvestigated, polymorphism. Such linkage may underlie the reported differences in risk genotype between pharmacogenetic studies of a single SNP in different populations. Thus, the SNP may demonstrate different linkage with the (uninvestigated) true functional polymorphism in different ethnic populations. Some attempt to minimise these problems and produce more reliable results has been the reporting of haplotype data, whereby association with not one, but a group of several SNPs, usually in close proximity and linkage is reported.

Pharmacogenetic associations – symptom response

The past decade has seen a steady growth of reports of genetic associations with antipsychotic response to antipsychotic drug treatment; however, these studies have many limitations. A brief search of recent reports show that 4 out of 10 have sample sizes substantially less than 100, and 2 had fewer than 50 subjects, suggesting they were inadequately powered to identify reliably anything other than the strongest of genetic associations. Confounds relating to variability in ethnicity, sample selection, prior treatment, symptom severity and many other factors may underlie the inconsistencies between studies. Some of these influences may be minimised by investigating patients first receiving drug treatment, which would also avoid the inevitable lack of subjects responding well to initial treatments within cohorts of chronic patients. However, very few studies have had the opportunity to assess first-episode drug-naïve patients.

It is beyond the scope of this short review to provide a comprehensive assessment of the whole of this literature. Nevertheless, we can identify some consistency and concordance that is beginning to emerge from published reports. Recent reviews [11,12] highlight how genes for three receptors: dopamine D2, dopamine D3 and serotonin 5-HT2A each have several papers demonstrating association between their genetic polymorphisms, often proven or presumed functional polymorphisms, and response to antipsychotic treatment. The emphasis on these receptors, particularly D2, the primary site of antipsychotic action, and 5-HT2A, the major target proposed to differentiate the atypical antipsychotics from the older drugs, is reassuring, but almost certainly is influenced by a research bias towards testing these most obvious of hypotheses. Variation in these genes still only explains a small percentage of the variance in response, and it is likely many further factors will contribute to antipsychotic-induced improvement in symptoms.

The unique efficacy of clozapine has attracted substantial investigation into the genetic basis of response to treatment with this drug. Much early work on antipsychotic pharmacogenetics addressed this problem. Arranz et al. [13] undertook a study of a range of candidate genes, many chosen on the basis of the known pharmacology of clozapine. They looked for association of response with 19 polymorphisms in 10 genes; 6 polymorphisms in genes for the 5-HT2A and 5-HT2C receptors, the 5-HT transporter and the histamine H2 receptor gave a sensitivity of 96% in identifying clozapine responders. The strongest components in this profile of polymorphisms are two coding region SNPs in the 5-HT2A receptor: one synonymous (silent) 1027C/T in linkage disequilibrium with a promoter SNP (−1438A/G) with functional activity [14] and one nonsynonymous his452tyr. These findings have not been consistently replicated [12], but the work of Arranz and colleagues has, nevertheless, led to the establishment of a
Pharmacogenetics of antipsychotic drug action – mechanisms of association

There are several levels of pharmacogenetic association with antipsychotic drug effects, dependent on the mechanism of the drug–gene interaction:

(I) Variation in pharmacokinetic genes. Here genetic variation influences drug disposition and availability through, for example, metabolism or active cellular efflux.

(II) Genetic variation in a target (e.g., the dopamine D2 receptor) that mediates the clinical effect of the drug. Here the functional genetic polymorphism might influence drug affinity for, or activity of, the target molecule. Such hypotheses have probably driven most pharmacogenetic studies of candidate genes.

(III) Genetic variation influencing the consequences of the initial drug mechanism by indirectly modifying the responses to drug action. This is probably at least as common in pharmacogenetics as level II above, and may be hard to distinguish, given that we know so little of antipsychotic drug mechanisms.

(IV) Genetic variation modifying disease pathology. Here there will be no clear relationship to drug action, but the genetic variation is itself a risk factor that may contribute to disease pathogenesis in some patients. The consequent disease pathology may then be more or less responsive to the pharmacotherapeutic approach offered. An example is provided by the report of an association of a genotype in the dysbindin schizophrenia risk gene with severity of negative symptoms [10]; this was in patients who had received antipsychotic treatment and thereby defines a group in whom these symptoms had not responded adequately.

A pharmacogenetic test for clozapine response, marketed by LGC (Teddington, UK). However, a confirmatory prospective trial to assess the predictability and value in practice of such pharmacogenetic testing has yet to be undertaken.

Commercial pharmacogenetic testing for antipsychotic drug efficacy has not been extended to treatment with the antipsychotics available for initial treatment of psychosis. In developing such an approach, it seems more valuable to differentiate groups of symptoms in terms of their response to treatment. As mentioned above, the negative features of the disease respond poorly to antipsychotic drugs, and it is these rather than the positive symptoms that are more important in determining functional recovery in patients. From the few studies where subdivision of the symptoms has been investigated, some interesting trends seem to be emerging, albeit with many inconsistencies and failed replications between studies. Associations of dopamine D2 and, to a lesser extent, D3 receptor gene polymorphisms are found with positive symptom changes, while effects on negative symptoms appear to be more associated with serotonergic genes, particularly the 5-HT2A receptor (Table 1). There are some other recently identified genetic associations of drug-induced changes in these more problematic negative and cognitive symptoms in schizophrenia, including the val/met COMT polymorphism [24,25], thought to modulate frontal cortical dopamine activity, and the glutamate metabotropic receptor-3 gene [26], a risk factor for schizophrenia.

Reading the literature may give an impression that there are drug-specific genetic associations with response. A major goal of pharmacogenetics is to inform drug selection and so, a genetic test that identified responders specific to particular drug treatments would be of huge value in guiding prescribing practice. However, there is, as yet, no concrete evidence demonstrating significant differences between drugs in terms of genetic association with their effects on symptom response. In fact, some findings indicate that genetic associations with response can generalise across drug treatments [23].

An example of a relatively strong genetic association with a response to antipsychotic drugs comes from the recent study of the −1019C/G SNP of the 5-HT1A receptor gene. This promoter SNP is found to influence receptor expression by influencing the binding of transcription factors, as well as being associated with suicide and diagnosis of depression [27]. A strong association with negative and depressive symptoms and their response to treatment with two atypical antipsychotic drugs was found, although the 5-HT1A receptor polymorphism had no influence on the response of positive symptoms to antipsychotic drug treatment [23]. As well as explaining much of the variance between patients with schizophrenia in negative and depressive symptom response, this pharmacogenetic finding provides further evidence for involvement of the 5-HT1A receptor in the action of atypical antipsychotics [28], in turn emphasising the potential of this site as a developmental drug target.

Pharmacogenetic associations – side effects

Given the close relationship between the emergence of acute EPS and dose, it is hardly surprising that for some drugs metabolised by CYP2D6, polymorphisms in this gene underlying poor metabolism may be associated with these side effects in initial treatment [29], but not in patients stabilised and on, presumably optimised, maintenance doses [30]. Perhaps for similar reasons, reports into the influence of dopamine D2 receptor SNPs on EPS are inconsistent, although a large study found no significant effect [31]. The chronic side effect of TD has been studied much more comprehensively, where not only associations with several candidate genes have been reported (Box 3), but also some interesting synergistic interactions between polymorphisms in different genes have been identified. These include interactions between dopamine D3 and 5-HT2C [33], and D3 and Mn-superoxide dismutase [34]. The role of the latter is notable in the context of suggestions that oxidative stress may be involved in the pathogenesis of TD [36].

Recently, weight gain has received much pharmacogenetic attention, reflecting the increased clinical concern over this side effect and its long-term consequences. The two genes with the strongest evidence for association with antipsychotic-induced weight gain [38], those for the 5-HT2C receptor and leptin, explain a substantial proportion of the variance in initially drug-naïve subjects [41], and also provide some clues relating to the underlying mechanism of the side effect. Both polymorphisms are associated with blood concentrations of the circulating anorexigenic hormone leptin [41]; it is likely that antipsychotics cause weight gain by interfering with the inhibitory effect of leptin on food intake, possibly by antagonism at the 5-HT2C receptor in the hypothalamus.

A true pharmacogenomic approach to understanding drug-induced obesity has been undertaken using a genome-wide
TABLE 1

Differentiating positive and negative symptom response to antipsychotic drugs – some reports of association with dopamine and serotonin receptor genes

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Association with symptoms</th>
<th>Drug treatment</th>
<th>Refs</th>
</tr>
</thead>
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<tr>
<td>Dopamine D2 receptor (DRD2)</td>
<td>Ser311cys</td>
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<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Taq1A</td>
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<td>No</td>
</tr>
<tr>
<td>Dopamine D3 receptor (DRD3)</td>
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<td>No</td>
</tr>
<tr>
<td></td>
<td>Ser9Gly</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>−205A/G, ser9Gly</td>
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<td>No</td>
</tr>
<tr>
<td>5-HT2A receptor (HTR2A)</td>
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<td>Yes</td>
</tr>
<tr>
<td></td>
<td>−1438A/G</td>
<td>No</td>
<td>Yes</td>
</tr>
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<td></td>
<td>−1438A/G</td>
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</tr>
<tr>
<td>5-HT2C receptor (HTR2C)</td>
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<tr>
<td>5-HT1A receptor (HTR1A)</td>
<td>−1019C/G</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

study, which identified linkage in a region including the gene for pro-melanin-concentrating hormone [43]; in a follow-up study, association with obesity in patients treated with olanzapine was found for a SNP in this candidate gene [44]. Recent work on the genetics of obesity (e.g. [45]) has provided new candidate genes from genome scans for investigation in antipsychotic drug-induced weight gain. Future studies need to address the emergence of metabolic syndrome, type 2 diabetes and cardiovascular disease, contributors to the increased incidence of physical illness in patients with schizophrenia treated with antipsychotics.

The fortunately rare, but potentially fatal, side effect of clozapine treatment, neutropenia leading to agranulocytosis, is considered a possible immunotoxic response. A series of studies have pointed to the role of genetic variation in human leucocyte antigens (HLAs) in this side effect [46,47], which has resulted in the development of a genetic test marketed by PGxHealth (New Haven, USA). Again, there has been no report of a prospective trial of the value of this test, without which we cannot objectively assess its effects on clinical treatment and decision-making.

Past limitations, future prospects

In summary, the pharmacogenetics of antipsychotic drug treatment has attracted much effort and yet is still in its infancy. It is driven by the problems of current treatment with these drugs, in which there is substantial individual variability in both symptom response and the incidence of side effects. The work has almost entirely been based on candidate gene studies, and these candidates have been provided primarily by the known pharmacology of the antipsychotic drugs and the receptor mechanisms implicated in their actions. Nevertheless, some studies are identifying genetic associations that inform us about possible mechanisms, such as the processes involved in antipsychotic-induced weight gain, and highlight potential new approaches to drug development.

Whether pharmacogenetics will have a positive influence on antipsychotic drug discovery remains questionable. Little is known of antipsychotic mechanisms, other than the central role of the dopamine D2 receptor, and even the assumed improved effectiveness of the atypical drugs has been called into question by some large and independent trials [48]. Nevertheless, it is part of the undisputed dogma of antipsychotic pharmacology that action at other receptors is essential to the unique efficacy of clozapine, and few would argue against extrapolating from this “rich pharmacology” to implicate actions beyond the dopamine D2 receptor in the beneficial effects of most of the newer antipsychotic drugs.

The emphasis on dopamine D3 receptor SNPs in symptom response indicates that this receptor may be more important a drug target than has been considered in the past. Similarly, the repeatedly reported role of polymorphisms in 5-HT-related genes, consistent as a theme, if not always in the identification of specific genes, does indicate that this system may well be central to drug effects in relieving negative symptoms of schizophrenia. A better understanding of the role of 5-HT neurotransmission in these more intransigent symptoms and their treatment could lead to improved pharmacotherapies.

Current approaches to drug development include a focus on the cognitive symptoms of schizophrenia [49], and drugs targeting these symptoms may be acceptable adjuncts to standard antipsychotic treatment. Here there is a biology-driven emphasis on the role of glutamatergic systems, which thereby provides an interesting convergence towards some genetic risk factors [3].
The employment of genotyping in neuroimaging studies is a recent development which has much to offer. Valuable in understanding the pathology associated with genetic risk factors in disease [50], and in identifying relationships between genotype, brain function and drug response [51,52], functional neuroimaging is also beginning to tell us about the role of genotype in modifying neurotransmitter systems. For example, the 5-HT transporter insertion/deletion polymorphism, perhaps the most studied in psychiatric pharmacogenetics [53], can influence activity, not only of its own gene product, but also of the 5-HT1A receptor [54]. Thus, we can envisage how genetic polymorphisms in several genes, in this example related to serotonergic neurotransmission, may have a convergent influence on neuronal function and hence on drug response.

As the technical and cost boundaries are pushed back, the future in pharmacogenomics is likely to see much more in the way of whole genome association studies, which will inevitably identify novel candidate genes. A major limitation that is very apparent now is the imprecise definition and reproducibility of phenotype due, in part, to the assessment of often subjective measures of symptoms. These problems are compounded by the heterogeneity of patient groups; nevertheless, some attempt to address this limitation is in the initial study of patients soon after the emergence of psychosis and ideally in a drug-free state. There are also many well-designed drug trials with DNA samples available to the pharmaceutical industry, which are of a size and value beyond the scope of most publicly funded projects. These could contribute much to our understanding of pharmacogenetic risk, yet there is a substantial reluctance within many companies to “bite the bullet” and recognise the long-term advantages of individualised drug treatment for industry, as well as for the patient. Finally, as we move towards predictive testing for response, outcome and side effects of antipsychotic drug treatments, it will be essential to have properly designed prospective trials and economic assessment to determine the effectiveness and value of genetic testing. Concurrently, education of clinical staff will be essential in translating genetic information into clinical and prescribing practice.

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