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Pharmacogenomics in psychiatry: the relevance of receptor and transporter polymorphisms

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The treatment of severe mental illness, and of psychiatric disorders in general, is limited in its efficacy and tolerability. There appear to be substantial interindividual differences in response to psychiatric drug treatments that are generally far greater than the differences between individual drugs; likewise, the occurrence of adverse effects also varies profoundly between individuals. These differences are thought to reflect, at least in part, genetic variability. The action of psychiatric drugs primarily involves effects on synaptic neurotransmission; the genes for neurotransmitter receptors and transporters have provided strong candidates in pharmacogenetic research in psychiatry. This paper reviews some aspects of the pharmacogenetics of neurotransmitter receptors and transporters in the treatment of psychiatric disorders. A focus on serotonin, catecholamines and amino acid transmitter systems reflects the direction of research efforts, while relevant results from some genome-wide association studies are also presented. There are many inconsistencies, particularly between candidate gene and genome-wide association studies. However, some consistency is seen in candidate gene studies supporting established pharmacological mechanisms of antipsychotic and antidepressant response with associations of functional genetic polymorphisms in, respectively, the dopamine D_2 receptor and serotonin transporter and receptors. More recently identified effects of genes related to amino acid neurotransmission on the outcome of treatment of schizophrenia, bipolar illness or depression reflect the growing understanding of the roles of glutamate and γ-aminobutyric acid dysfunction in severe mental illness. A complete understanding of psychiatric pharmacogenomics will also need to take into account epigenetic factors, such as DNA methylation, that influence individual responses to drugs.

Introduction

Drug action in psychiatric disease

The development and introduction of specific drug treatments for schizophrenia, depression and bipolar disorder in the middle of the last century revolutionized the way in which these disorders are managed. Nevertheless, severe mental illness still represents a huge burden to society in general and healthcare in particular. This reflects the limited efficacy of current treatment; while the past half-century has seen further developments in the drug treatment of psychosis and mood disorders, there has been little improvement in efficacy. Most newly introduced drugs have offered incremental changes, primarily in side-effect profile rather than symptom response. Even now, the pharmacotherapy of depression achieves response rates of little more than 50%, while even lower proportions of patients with schizophrenia achieve adequate response to their antipsychotic drug treatment.

Thus, while there may be small differences between psychiatric drug treatments in terms of their efficacy, there are clearly major differences between individuals in their response to these treatments. Although the psychiatric drugs may differ more in their adverse effect profiles than their efficacies, again the experience of adverse effects varies profoundly between individuals. These unexplained differences in response and side-effects are thought to reflect, at least in part, genetic differences between patients; thus, pharmacogenetics in psychiatry has much to offer in the eventual identification of risk factors for these limitations of drug treatment. Furthermore, it should be born in mind that the information exchange between

pharmacology and pharmacogenetics is a two-way process; while our understanding of psychopharmacology provides us with good candidates for pharmacogenetic study, pharmacogenetic findings can also provide clues relating to underlying pharmacological mechanisms.

The pharmacological mechanisms underlying the actions of the major psychiatric drugs are at least partly understood. Thus, the antipsychotic drugs act at dopamine D_2 receptors to diminish dopaminergic neurotransmission in the mesolimbic pathway, resulting in relief of some psychotic and manic symptoms. Dopamine D_2 receptor blockade in other pathways is also responsible for certain side-effects of these drugs, namely hyperprolactinaemia and the acute extrapyramidal motor symptoms (EPS). The antidepressant action of the selective serotonin reuptake inhibitors (SSRIs) is thought to be the consequence of an initial increase in synaptic serotonin which, via effects including changes in receptor expression, results in alterations in the activity and regulation of serotoninergic neurons.

However, there are still many pharmacological mechanisms that remain elusive. The unique efficacy of clozapine in bringing relief to a good proportion of psychotic patients not responding to other antipsychotic drugs is still not well understood, despite over 40 years of research. The role and importance of the effects of antidepressant drugs on neurogenesis is still debated, and the pharmacological mechanisms behind some adverse effects of psychiatric drug treatments are not fully understood.

Nevertheless, the drug treatment of severe mental illness and other psychiatric disorders primarily involves effects on, and/or regulation of, neurotransmission. Consequently, the genes coding for proteins involved in neurotransmitter action have provided valuable candidates for pharmacogenetic research in psychiatry. It is these studies, the association with drug effects of functional polymorphisms in genes involved in the neurochemical processes of synaptic transmission, on which this review will focus. In addition to these important pharmacokinetic aspects of psychiatric pharmacogenetics, variation in genes associated with pharmacodynamic processes, such as the cytochrome P450 drug-metabolizing enzymes, can also influence the effectiveness of psychiatric drug treatments; however, consideration of these is outside the scope of this review.

Neurochemistry of synaptic transmission

Synaptic chemical neurotransmission is the essential mechanism of communication between neurons; hence, it is central to brain function. Its associated neurochemical processes provide the major point at which we can influence neuronal activity through the effects of drug treatment. Each of the presynaptic processes of transmitter synthesis, storage, release and reuptake, the metabolic removal of transmitter, and the various presynaptic and postsynaptic receptor sites are all potential, if not actual, targets for neuro- and psychoactive drugs.

Transmitters are synthesized by the action of enzymes on readily available precursors; generally, these initial enzymes are fairly specific to the neurons containing the neurotransmitter. Thus, tyrosine hydroxylase and tryptophan hydroxylase are responsible for the initial step in the synthesis of catecholamines and serotonin, glutamic acid decarboxylase for γ-aminobutyric acid (GABA) and choline acetyltransferase for acetylcholine. Storage of transmitter in vesicles is effected by vesicular transporters (e.g. VGluT1 and 2 for glutamate; VMAT2 for monoamines in the central nervous system), while other transporters selective for particular transmitters are involved in transmitter reuptake from the synapse. A wide variety of specific neurotransmitter receptors mediate synaptic neurotransmission or modulate presynaptic neuronal activity and transmitter release. Finally, enzymes such as monoamine oxidase (MAO), catechol-*O*-methyltransferase and acetylcholinesterase provide a mechanism for metabolic inactivation of neurotransmitter molecules. This is a substantial list of processes, with many candidate proteins to study; this review will focus solely on the two processes involving proteins that recognize the neurotransmitter in the synapse, i.e. receptors and transporters. While receptors mediate the action of neurotransmitters on postsynaptic cells, and occasionally elsewhere, the reuptake transporters are the major mechanism for removal of the transmitter from the synapse, limiting its action.

This restricted focus is inevitably a limitation of our review, undertaken in order to provide a manageable and comprehensible, rather than comprehensive, overview of the current 'state of the art'. For the same reason, we have not undertaken a systematic approach, but rather provided a critical review with, where possible, some emphasis on genotype functionality. There is a focus on positive findings, again for reasons of space limitation and comprehensibility; it is likely that any attempt to include negative findings systematically will suffer from the fact that many will remain unpublished. Table 1 provides a summary of the findings that we discuss below.

Pharmacogenetic approaches

Given that their effects in influencing synaptic transmitter concentrations and/or synaptic transmission, the genes for these proteins provide strong candidate genes for both psychiatric disorders and, inevitably, individual variability in response to psychiatric pharmacotherapy. In the past, psychiatric pharmacogenetics has concentrated particularly on genes coding for the proteins involved in monoamine neurotransmission, because it is at the dopamine, noradrenaline and serotonin synapses that many of the psychoactive drugs have their effects. Hence, these monoamine-associated genes may provide strong candidates for psychiatric pharmacogenetic associations. However, an increasing focus on the amino acid

Table 1

Association studies of single nucleotide polymorphisms in neurotransmitter receptor and transmitter genes with psychiatric treatment response and side-effects

Gene	Polymorphism	Functional effect of polymorphism	Type of study/patient cohort	Drug(s)	Number of patients	Length of study	Effect observed	Reference
SLC6A4	5-HTTLPR s/l	S allele is associated with reduced expression						[4, 7]
			Primary/MDD	Fluvoxamine	102	6 weeks	l allele carriers had better response	[7]
			Primary/depression in elderly	Paroxetine	34	12 weeks	l allele carriers had better response	[8]
			Primary/depression in elderly	Nortriptyline	23	12 weeks	No effect	[8]
			Meta-analysis/MDD	SSRIs	1435	4 weeks	Patients with ss alleles took longer to respond and were less likely to achieve remission	[9]
			Meta-analysis/MDD	SSRIs/other antidepressants	5408	varied	No effect on response to SSRIs	[10]
			Meta-analysis/MDD Caucasian/Asian	SSRIs/other antidepressants	5479	2–18 weeks	In Caucasians, l allele carriers on SSRIs had better response and remission; weaker effect was seen in an Asian population on mixed antidepressants	[13]
			Primary/MDD (STAR*D study)	Citalopram	1762	Varied, with side-effects	No association with treatment outcome; l allele was associated with side-effects	[17]
			Primary/MDD	Paroxetine	124	2–7 weeks	s allele was associated with severe adverse events during study	[18]
			Primary/MDD	Mirtazapine	122	2–7 weeks	ll genotype was associated with adverse side-effects	[18]
			Primary/MDD/anxiety in adolescents and children	Citalopram	83	8 weeks	l allele in combination with –703G SNP in tryptophan hydroxylase gene was associated with improved treatment response	[21]
SLC6A4	rs25531 A/G in l allele of 5-HTTLPR	G allele associated with reduced expression						[5]
			Primary/dementia	Citalopram Risperidone	92	12 weeks	s allele of 5-HTTLPR in combination with G allele of rs25531 predicted greater side-effects	[20]
SLC6A4	STin2 VNTR	Influences gene expression						
			Systematic review/MDD	SSRIs	650	2–18 weeks	Greater effect in Asians than seen with 5-HTTLPR	[14]
			Meta-analysis/MDD	SSRIs/other antidepressants	1546	Varied	No effect on treatment response seen	[15]
			Primary/bipolar	Lithium	122	Varied	Treatment response in combination with HTTLPR	[16]
			Primary/premature ejaculation	Sertraline	246	12 weeks	12/12 genotype was associated with treatment response	[19]

HTR1A	–1019 C/G rs6295	G allele is associated with increased receptor expression and reduced neuronal transmission						[22]
			Review/MDD	SSRIs/other antidepressants	NA	NA	G allele was associated with poorer response	[24]
			Primary/panic disorder	Sertraline/paroxetine	102	6 weeks	C allele was associated with improved initial response	[25]
			Primary/schizophrenia	Risperidone	130	8 weeks	G allele was associated with poorer response	[27]
			Primary/schizophrenia	Mixed antipsychotics	130	4 weeks	G allele was associated with poorer response	[28]
HTR1B	rs6298 A/G	Functional relevance unknown	Primary/MDD	SSRIs/other antidepressants	308	6 weeks	AA genotype was associated with poorer response to treatment; interaction with negative life events	[29]
HTR2A	–1438 A/G rs6311 102 T/C rs6313	SNPs are in linkage disquilibrium; 102 C allele is associated with lower expression						[30]
			Primary/schizophrenia	Risperidone	100	6 weeks	102 CC genotype was associated with better clinical response	[31]
			Primary/schizophrenia	Typical antipsychotics	102	Long term	102 CC genotype was associated with poorer clinical response	[32]
			Meta-analysis/schizophrenia	Clozapine	733	Varied	102 CC genotype was associated with poorer clinical response	[33]
			Primary/MDD (STAR*D study)	Citalopram	1953	6 weeks	AA genotype was more likely to respond to treatment	[35]
			Primary/MDD (Korean cohort)	Citalopram	71	4 weeks	GG genotype was more likely to respond to treatment	[36]
			Primary/schizophrenia	Typical/mixed antipsychotics	635	Varied	102 CC genotype was associated with increased risk of tardive dyskinesia	[38]
			Primary/schizophrenia	Olanzapine	164	Varied	102 T allele was associated with weight gain	[46]
HTR2C	–759C/T rs3813929	Influences gene expression						[44, 45]
			Primary/schizophrenia	Antipsychotics	96	10 weeks	C allele was associated with weight gain	[42]
HTR4	rs1011427 C/T	Intronic SNP, functional relevance unknown	Primary/schizophrenia (CATIE study)	Antipsychotics	400+	8 weeks	Treatment response – cognitive measures	[34]
HTR7	rs7916403 G/T	Intronic SNP, functional relevance unknown	Primary/alcohol dependence	NA	1064	NA	G allele is associated with alcohol dependence	[47]
DRD2	Taq1A rs1800497	1A carriers have reduced striatal dopamine D_2 receptor density and reduced dopaminergic activity						[51]
			Meta-analysis/schizophrenia	Antipsychotics	748	Varied	No association seen with response to treatment	[59]
			Primary/schizophrenia	Antipsychotics	206	6 weeks	Taq1A polymorphism is associated with weight gain	[60]
DRD2	–141 ins/del	Del allele is associated with lower dopamine D_2 receptor expression						[53, 54]
			Meta-analysis/schizophrenia	Antipsychotics	687	8 weeks	Del allele is associated with poorer response to treatment	[59]
			Primary/schizophrenia	Risperidone Olanzapine	58	6 weeks	Del allele is associated with weight gain	[61]
DRD3	Gly/Ser rs6280	Gly allele is associated with increased binding of dopamine						[67]
			Schizophrenia	Clozapine, risperidone	32; 75;68; 100	Varied	Studies 68 and 69 show that Gly allele is associated with improved treatment; 70 and 71 find no effect	[68, 69, 70, 71]
			Meta-analyses/schizophrenia	Antipsychotics	1610;2126	Varied	Risk of tardive dyskinesia was associated with Gly allele in early studies; effect not seen in later studies	[75, 76]
			Primary/schizophrenia (CATIE study)	Antipsychotics	710	Varied	No effect of polymorphism on tardive dyskinesia risk	[77]

Table 1

Continued

Gene	Polymorphism	Functional effect of polymorphism	Type of study/patient cohort	Drug(s)	Number of patients	Length of study	Effect observed	Reference
SLC6A3/DAT1	VNTR 2–11 repeats	Conflicting evidence of effect of repeat number on binding						[78]
			Primary/ADHD	Methylphenidate	11	8 weeks	10-repeat was associated with poorer treatment outcome	[80]
			Meta-analysis/ADHD	Methylphenidate	1572	varied	No effect of repeat number on treatment response	[81]
			Primary/schizophrenia	Clozapine	160	8 weeks	Effect on treatment response	[82]
			Primary/schizophrenia	Risperidone	130	8 weeks	No effect of repeat number on treatment response	[83]
			Primary/MDD	SSRIs	190	3 weeks	Poorer response associated with nine-repeat allele	[84]
ADRA1A	–4884 A/G rs922733	May influence gene expression	Primary/schizophrenia	Clozapine	289	3 months	No effect of polymorphism on treatment response	[85]
			Primary/schizophrenia	Risperidone/other antipsychotics	427	11 months	AA genotype was associated with weight gain	[88]
ADRA2A	–1291 C/G rs1800544	May influence gene expression	Primary/schizophrenia	Clozapine	93	Varied	G allele was associated with weight gain	[90]
			Primary/schizophrenia	Clozapine	129	6–14 weeks	C allele was associated with weight gain	[91]
			Primary/schizophrenia	Antipsychotics	139	6–14 weeks	SNP only has an effect on weight gain in association with the u-VNTR polymorphism in the *MAOA* gene	[92]
			Primary/ADHD	Methylphenidate	450+	Varied	G allele was associated with treatment response in children but not in adults	[93–98]
			Primary/MDD	Milnacipran	93	4 weeks	C allele carriers had improved response to treatment	[101]
SLC6A2/NET	–182 T/C rs2242446	May influence gene expression	Primary/MDD	Milnacipran	96	6 weeks	T allele was associated with improved response	[99]
	1287 G/A rs5569	May affect transmitter binding or affinity						[99]
			Primary/MDD	Milnacipran	96	6 weeks	AA genotype was associated with slower response to treatment	[99]
SLC1A2 (EAAT2)	rs4354668 –181 A/C (T/G)	C allele is associated with lower transporter activity						[104]
			Primary/bipolar disorder	Lithium	110	≥6 months	TT homozygotes had improved response to treatment	[105]
SLC1A1 (EAAT3)	rs2228622 A/G rs3780413 C/G rs 3780412 A/G	Synonymous exonic and intronic SNPs, functionality unknown	Primary/schizophrenia	Mixed antipsychotics	94	≥24 months	A/C/G haplotype is associated with increased risk of development of obsessive–compulsive disorder	[106] [107]

GRIK4	rs1954787 C/T	Intronic SNP may influence gene expression						[109]
			Primary/MDD (STAR*D study)	Citalopram	1816	Varied	C allele was predictive of improved treatment outcome when combined with *HTR2A* genotype	[109]
			Primary/MDD	Antidepressants	387	5 weeks	G allele was associated with remission	[110]
GRIK4	rs 12800734 A/G	Intronic SNP may influence gene expression	Primary/MDD	Antidepressants	223	Varied	No effect of genotype	[111]
			Primary/MDD	Antidepressants	281	Varied (≥6 weeks)	G allele and the GG genotype are associated with better response	[112]
GABRP	rs10036156 C/T	Synonymous exonic SNP, functionality unknown	Primary/MDD	Antidepressants	281	Varied (≥6 weeks)	G allele was associated with better response, specifically in the SNRI subgroup	[112]
GABRQ	Phe/Ile rs3810651	May influence binding						[112]
			Primary/MDD	Antidepressants	281	Varied (≥6 weeks)	A allele was associated with better response	[112]
GABRA6	rs1992647 C/T (G/A)	May influence gene expression	Primary/MDD	Antidepressants	281	Varied (≥6 weeks)	AA was associated with nonresponse	[112]
GRIA4	rs2513265 A/T	May influence gene expression	Primary/schizophrenia	Iloperidone	407	Up to 7 months	TT genotype was associated with poorer response to treatment	[113]
			Primary/schizophrenia	Ziprasidone	409	4 weeks	Treatment response (negative result)	[114]
			Primary/schizophrenia	Risperidone	145	12 weeks	TT genotype was associated with poorer response to treatment	[115]
GRM3	rs724226 A/G	Intronic SNP, functional relevance unknown	Primary/schizophrenia and related disorders	Risperidone	143	2–12 weeks	G allele was associated with remission and change in PANSS	[117]
	rs274622 C/T	May influence gene expression	Primary/schizophrenia	Olanzapine	42	6 weeks	C allele was associated with improved response to treatment	[119]
GR1A2	rs3813296 G/T	Intronic SNP, functional relevance unknown	Primary/schizophrenia	Antipsychotics	221	Varied	T allele was associated with poorer response to treatment	[120]
SLC6A11	rs4684742 A/G	Intronic SNP, functional relevance unknown	Primary/schizophrenia	Antipsychotics	272	Long term	Association of A allele with tardive dyskinesia	[123]
SLC6A5	rs2298826 A/G	Intronic SNP, functional relevance unknown	Primary/schizophrenia	Haloperidol	290	4 weeks	Dyskinesia and EPS	[124]

Abbreviations are as follows: ADHD, attention deficit hyperactivity disorder; EPS, extrapyramidal motor symptoms; NA, not applicable; SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor.

neurotransmitter genes has reflected a growing interest in the roles that disturbances of GABA and glutamate neurotransmission may play in mental illness.

As the relevant technology has developed, such candidate gene approaches, driven by mechanism-based hypotheses, are increasingly being supplemented by hypothesis-free genome-wide association studies (GWAS). These are not without limitations themselves, because the handling and statistical analysis of typically over 100 million data points has its inherent difficulties; the relative lack of interstudy consistency as well as poor consistency with candidate gene findings are further concerns.

Response to treatment with psychiatric drugs is not dichotomous, although it might be treated as such for purposes of data analysis. The apparently continuous variability generally observed in symptom relief or side-effects cannot be explained by a single genetic variant [1] but must involve multiple factors. These may be multiple genes within a transmitter system or pathway, or different additive or interactive effects across systems. Research is beginning to address this multiplicity of risk factors although, as will be apparent, the majority of studies, even when assessing the effects of multiple genes and systems, look for discrete associations rather than additive and interactive genetic influences.

There remains much inconsistency in the results of pharmacogenetic studies; one contributing factor is thought to be inadequate power due to small sample sizes. However, we would argue that the current focus on quantity rather than quality of the sample is misdirected. Pragmatic investigation of patients who have had a variety of previous drug treatments and treatment periods introduces variance in measures of symptoms and side-effects that can be avoided by, for example, studying first episode, initially drug-naïve, subjects. But the large, systematic and prospective multicentre studies of treatment efficacy, such as CATIE for schizophrenia [2] and STAR*D for depression [3], also provide strong and comprehensive clinical data that have proved useful in pharmacogenetic investigations, and some emphasis will be placed on findings from these and similar studies in our review.

The serotonin system

A large proportion, if not the majority, of pharmacogenetic studies has addressed genes governing or influencing serotonin neurotransmission. Perhaps the most studied of these is the 5-hydroxytryptamine (5-HT) transporter (5-HTT) gene (*SLC6A4*), which has a common length polymorphism (the HTTLPR) that results in a partial deletion of a tandem repeat sequence within the promoter region. This is found to influence activity of the transporter, in which the deletion (short or s allele) is associated with lower expression [4]. There are other promoter polymorphisms in *SLC6A4*, of which one is found within the deletion sequence (rs25531; A/G), where the G allele in the l allele reduces expression in a similar manner to the HTTLPR deletion s allele [5]. Another polymorphism has been described in intron 2 of *SLC6A4* consisting of a 17 bp variable number of tandem repeats (termed STin2 VNTR). This also has functional activity with an influence on gene expression [6].

As 5-HTT is the main site of action of SSRIs, its gene has been much studied in association with depression and antidepressant action. The pharmacogenetics of the HTTLPR (l/s) polymorphism has been investigated as a potential marker for symptom response to SSRIs. Thus, Smeraldi *et al*. [7] showed that in patients with major depression, l allele carriers showed a better response to fluvoxamine than homozygotes for the short variant (s/s). Pollock *et al*. [8] reported a similar effect on treatment response for paroxetine in major depression, but found no effect on treatment outcome in patients treated with the tricyclic antidepressant nortriptyline. Meta-analyses assessing the remission rate, response rate and response within the first 4 week period of treatment with SSRIs [9] revealed that patients with ss alleles took longer to respond and were less likely to achieve remission. However, results are not always clear cut. A meta-analysis of data obtained from 28 studies with 5408 participants found no significant effect of the HTTLPR on response to SSRI medication [10]. This may be because opposite effects in Asians have been reported, with the s allele being associated with better SSRI response [11, 12].

Porcelli *et al*. [13] reviewed 19 studies performed on Caucasians and 11 on Asians. Evaluations were performed separately for SSRIs and mixed/other drugs. There was positive association of the l allele with response and remission in Caucasians within the SSRI group and only a marginal association between the l allele and remission in the mixed antidepressant treatment group. In Asians, however, only a small effect of HTTLPR on remission for mixed antidepressants was detected. Interestingly, an early systematic review suggested that while the HTTLPR influenced antidepressant response in Caucasian subjects, it was the STin2 VNTR that had a greater effect in Asians [14]. A recent meta-analysis of candidate gene studies of antidepressant efficacy by Niitsu *et al*. [15] showed, after exclusion of HTTLPR, no major effect of any single gene variant, but some positive association with STin2 driven by one or two studies. Effects of 5-HTT polymorphisms are seen in response to treatments other than antidepressants; Tharoor *et al*. [16] reported an association of STin2 polymorphism and its combined effect with 5-HTTLPR variants with lithium response in treatment of bipolar disorder.

Results of the major STAR*D study of citalopram treatment have been summarized by Lin and Chen [17]. There was no association observed between treatment outcome and HTTLPR in over 1700 subjects, although presence of the l allele was associated with side-effects.

Others have also reported association with SSRI side-effects. Murphy *et al*. [18] found that among paroxetine-treated subjects, s allele carriers experienced more severe adverse events during the course of the study (gastrointestinal complaints, fatigue, agitation, sweating and dizziness), which caused early discontinuation of treatment. However, in mirtazapine-treated subjects, adverse effects were associated with the ll genotype and included drowsiness, dizziness and anxiety. Interestingly, Safarinejad [19] described an association of STin2 12/12 genotype with response to sertraline treatment of premature ejaculation.

Few studies have included the additional variance associated with rs25531 within the l allele (the 'trialellic genotype'). One study that did is the 12 week randomized controlled trial [20] which showed that low-expression alleles (s and l_G) predicted early appearance and overall greater side-effects of citalopram that led to early treatment discontinuation in patients with dementia and behavioural or psychotic symptoms.

A further limitation common to many pharmacogenetic studies is that they rarely acknowledge that additive and interactive effects of multiple genes are likely to contribute to pharmacogenomic associations with drug effects. One study that did shows additive effects of tryptophan hydroxylase-2 (TPH2) and 5-HTT on clinical response to citalopram [21]. Subjects carrying a combination of *TPH2* –703G and the HTTLPR l alleles were most likely to respond to citalopram.

The 5-HT_{1A} receptor acts as an autoreceptor on serotonergic neurons, where it imparts an inhibitory control over neuronal activity. It is also found postsynaptically in the hippocampus, cortex and basal ganglia. It is a particularly important site in understanding psychiatric drug action; it is the site of action of some anxiolytic drugs, while several newer antipsychotics have 5-HT_{1A} partial agonist activity, implicated in their action on negative symptoms of schizophrenia. However, its greatest relevance to pharmacotherapeutics is its proposed involvement in the delayed antidepressant mechanism of the SSRIs. Thus, the 5-HT_{1A} receptor gene (*HTR1A*) is a strong candidate to explain individual differences in response to antidepressants, anxiolytics and perhaps antipsychotics.

Of the many identified single nucleotide polymorphisms (SNPs) in *HTR1A*, only one has been studied to any great extent, namely –1019C/G (rs6295). This SNP, associated with depression and suicidality, occurs at a binding site for transcription factors; the G allele prevents the binding of inhibitory transcription factors, including the repressor Deaf-1, theoretically resulting in an increase in the expression of 5-HT_{1A} autoreceptors with a consequent reduction in 5-HT neuronal transmission [22]. In antidepressant pharmacogenetics, Lemonde *et al*. [23] and subsequently several other studies have, fairly consistently, demonstrated that the –1019G allele is associated with a poorer response to treatment with SSRIs and, in some studies, other antidepressant drugs (reviewed by Drago *et al*. [24]). The effect on SSRI response is not restricted to depression; our study on the initial response of panic disorder to SSRI treatment has also shown a beneficial effect of the C allele [25].

This *HTR1A* –1019C/G SNP is strongly associated with changes in both negative features and depressive symptoms after 3 months of initial treatment of first-episode psychosis [26]. The G allele was again associated with poorer response, a finding replicated in Asian [27] and European samples [28]. Thus, the strong functional effect of this SNP has influences that generalize across drug types.

The 5-HT_{1B} subtype is another presynaptic autoreceptor and thus a good candidate for antidepressant function. However, other than a few negative studies, the only notable pharmacogenetic finding is that of Xu *et al*. [29], who identified an association of two linked *HTR1B* coding region SNPs with antidepressant response, and an interaction with recent stressful events. While there is little evidence that these synonymous SNPs are functional, the authors mention that they are in linkage disequilibrium with (unstudied) functional promoter polymorphisms, which may therefore mediate an effect on receptor expression.

Perhaps the best studied of 5-HT receptors is 5-HT_{2A}, reflecting the common high affinity of all second-generation antipsychotic drugs for this site, and its postulated role in the clinical effects of these drugs. Antagonism of 5-HT_{2A} with antipsychotics may well contribute to a lower incidence of extrapyramidal motor side-effects. There is also some evidence for their role in antidepressant action; a common consequence of antidepressant drug administration is the downregulation of 5-HT_{2A} receptors. The most studied are the 102T/C, a synonymous coding region SNP, and –1438A/G, a promoter SNP that is in complete linkage with 102T/C and, reportedly, has functional effects on gene expression [30].

Investigation of this genetic factor in relationship to response to treatment has been inconsistent and inconclusive, although from early days of pharmacogenetic studies *HTR2A* has been considered to be important in the variability in symptom response to antipsychotic drugs. While Lane *et al*. [31] reported that, in Chinese patients, the 102CC genotype is related to better clinical response to risperidone, particularly of negative symptoms, Joober *et al*. [32] suggested the 102CC genotype to be more frequent in patients with poor response to typical antipsychotic drugs. Arranz *et al*. [33] also showed that this genotype is more frequent among European clozapine nonresponders than responders. Perhaps a stronger indication that *HTR2A* variation may contribute to antipsychotic treatment response comes from the study of the CATIE cohort by Need *et al*. [34] reporting an intronic SNP in this gene to be one of 22 SNPs, taken from an investiga-

tion of 2769 in 118 genes, to associate significantly ($P < 0.01$) with improvement in Positive and Negative Syndrome Scale (PANSS) scores.

In the STAR*D study, McMahon *et al*. [35] showed –1438AA homozygotes to have an 18% reduction in absolute risk of having no response to citalopram treatment, compared with those homozygous for the G allele. But, as with the HTTLPR, there may be racial differences in outcomes of antidepressant treatment; Choi *et al*. [36] reported a better response to citalopram treatment associated with the GG genotype in Korean patients with major depressive disorder.

In addition to treatment response, the 5-HT_{2A} receptor is implicated in side-effects. The reciprocal effects of dopamine and serotonin indicate a role for the latter transmitter in motor function and dysfunction, particularly drug-induced EPS. A small study has shown association of undifferentiated EPS with both *HTR2A* and *HTR2C* SNPs [37]. Tardive dyskinesia (TD), the severe and chronic EPS which has limited the use of the first generation of antipsychotic drugs, has been found to be associated with the –1438A/G and 102C/T *HTR2A* polymorphisms, albeit with inconsistent results suggestive of a weak effect. In a large, multicentre study, Lerer *et al*. [38] found that the 102C/T genotype was significantly associated with TD in older patients and in those with non-orofacial symptoms, illustrating the multiplicity of factors, in addition to ethnicity, that may influence the relationship between genotype and this phenotype.

Genetic variation of the related 5-HT_{2C} receptor may also be weakly related to TD. Here a missense coding region SNP (ser23gly), common in Caucasians but not in Asian populations, is inconsistently reported to associate with occurrence of TD [39]. Interestingly, there are additive effects reported between SNPs in the dopamine receptor gene *DRD3* and *HTR2C* [40], illustrating at the level of genetic variation the close interaction between dopamine and serotonin systems in EPS.

Polymorphisms in the 5-HT_{2C} receptor gene are most associated with individual variability in metabolic side-effects, particularly antipsychotic drug-induced weight gain. Antagonism of this receptor is certainly implicated in the pharmacological mechanism of weight gain following treatment with some drugs [41], and it is the site of agonist action of a recently introduced anti-obesity drug, lorcaserin. An early study of a promoter region *HTR2C* SNP showed an association with weight gain after initial antipsychotic drug treatments [42], which has subsequently been replicated many times over (reviewed by Zhang *et al*. and Reynolds [39, 43]). The studied –759C/T polymorphism, along with other promoter region polymorphisms with which it is in linkage disequilibrium, appears to be functional in influencing gene expression [44]. Interestingly, the genetic association generalizes to different drugs, including those with both high (clozapine and olanzapine) and relatively low affinity (risperidone) for the 5-HT_{2C} receptor. Thus, the functional effects of the polymorphism may involve mechanisms other than solely mediating the direct effects of drugs at this receptor, perhaps in modifying the downstream physiological control of body weight, which is disrupted by drug action. One clue concerning the mechanism is the association of the –759C/T polymorphism with circulating levels of the hormone leptin, which is important in the control of body weight and also implicated in weight gain pharmacogenetics [45].

Of course, this is only one of many SNPs identified as risk factors for drug-induced weight gain and related metabolic pathology [43]. Although one might expect influences from other 5-HT-related genetic factors, there have been few consistent reports of associations with 5-HTT or other 5-HT receptor SNPs, except for some *HTR2A* findings [46]. However, another gene of relevance associated with metabolic side-effects is *ADRA2A*, as mentioned in the next section. The protein encoded by *ADRA2A*, the α_{2A}-adrenoceptor, is found as a heteroceptor on serotoninergic neurons; polymorphisms in this gene may thus influence the activity of those neurons in their control of body weight.

Of the other serotonin receptors, 5-HT_4, 5-HT_6 and 5-HT_7 have been particularly implicated in affective behaviour and/or cognitive function. Polymorphisms in each gene have been investigated for association with antidepressant and antipsychotic response, but no consistently reproduced results have been reported. However, a notable finding from the CATIE cohort indicated that SNPs in *HTR4* are associated with response to antipsychotic treatment of some symptoms, particularly cognitive measures [34], although the underlying functional relationship between these SNPs and treatment outcome is unclear. Finally, a GWAS identified a significant association of an *HTR7* SNP with alcohol dependence, which is an intriguing finding that deserves further investigation [47].

Catecholamine systems

For most of five decades, dopamine has been central to our understanding of the neurotransmitter pathology of schizophrenia, and it is well established that the primary mechanism of the antipsychotic drugs, in relieving the symptoms of both schizophrenia and mania, involves antagonist action at dopamine D_2-like receptors in the brain. Dopamine receptor and transporter genes are therefore strong candidates for investigating the association between genetic polymorphisms, antipsychotic drug treatment outcome and the extent of side-effects; however, associations have also been observed between polymorphisms in these genes and susceptibility to major depression, attention deficit hyperactivity disorder (ADHD) and anxiety disorders [48–50]. Polymorphisms have been reported in all five dopamine receptor genes

(*DRD1–DRD5*) and the dopamine transporter gene *SLC6A3*/*DAT1*. This has provided a set of potential variants for investigation of genetic associations with drug efficacy and side-effects.

The development of second-generation atypical antipsychotics has had a dramatic influence on the profile of side-effects seen in response to antipsychotic treatment. Extrapyramidal side-effects associated with typical antipsychotics (akathisia, dystonia and parkinsonism) are much less frequent with the newer 'atypical' drugs. However, other side-effects, such as hyperprolactinaemia and weight gain, are potential adverse consequences of current drugs, with both drug-to-drug and pharmacogenetic variability.

Inevitably, polymorphisms in the *DRD2* gene have been investigated for associations with treatment outcome in schizophrenic patients, with the majority of studies focusing on the Taq1A and –141 Ins/Del polymorphisms. The Taq1A polymorphism, originally believed to be located in the promoter region of the *DRD2* gene, but now identified as located in the coding region of the *ANKK1* gene, influences the expression of the *DRD2* gene; compared with noncarrier homozygotes, carriers of the A1 allele have reduced striatal *DRD2* receptor density [51], leading to reduced dopaminergic activity. This reduction in receptor density has been shown in imaging studies to have functional consequences, with the Taq1A polymorphism predicting response to reward [52]. The –141 Ins/Del polymorphism is located in the promoter region and represents a deletion or insertion of a cytosine base; the Del allele has been associated with lower expression levels of *DRD2 in vivo* and *in vitro* [53, 54]. Initial studies into associations of these two SNPs with antipsychotic treatment outcome were inconsistent [55–58]; however, a comprehensive meta-analysis [59] has shown that the Del allele is associated with a poor response to antipsychotic drugs compared with the Ins/Ins genotype, but the Taq1A allele shows no association. The Taq1A polymorphism, along with two others (rs6277 and rs1079598) in the *DRD2* gene, has been associated with increased susceptibility to weight gain [60, 61].

Hyperprolactinaemia following antagonism of dopamine receptors in the pituitary gland is a serious side-effect of antipsychotics that increases the risk of amenorrhoea, galactorrhoea, sexual dysfunction, breast cancer and osteoporosis [62]. Several studies have indicated a dopamine receptor genotype effect on the severity of these side-effects [63–65]; however, the results are somewhat inconsistent. A study of healthy volunteers given one dose of antipsychotic showed that plasma prolactin increase was modulated by drug, sex and Taq1A polymorphism, with higher levels of prolactin secretion being associated with women, risperidone (in contrast to olanzapine and quetiapine) and the 1A allele [66].

A functional polymorphism in the *DRD3* gene (rs6280) results in a coding region substitution of Gly for Ser; *in vitro* studies have shown increased binding affinity of dopamine for the receptor with the Gly allele [67]. The Gly allele has been associated with improved treatment response to clozapine and risperidone [68, 69], although other studies have failed to replicate these findings [70, 71]. The functional effect of this polymorphism may also explain an association with risk of TD. A number of early studies indicated this [72–74], but recent meta-analyses are conflicting. Bakker *et al*. [75] considered 11 studies between 1976 and 2005 covering 1610 patients, and reported an increased risk of TD associated with the Gly allele. Tsai *et al*. [76] considered 13 studies between 1997 and 2008 and concluded that there was little or no association between the rs6280 polymorphism and TD. The authors of both papers consider publication bias as an explanation for these findings. In each analysis, an effect of publication date is seen, with earlier studies reporting an association, and later studies seeing a weaker or nonsignificant effect. As observed by Tsai *et al*. [76], this is a common pattern seen in pharmocogenetic studies, where positive findings are reported from early, small studies in discrete groups, followed by larger studies in heterogeneous populations that fail to confirm the initial findings. In the case of TD, there is an additional treatment effect; earlier studies were much more likely to include patients who had been treated with first-generation antipsychotics, with the associated higher risk of TD, whilst treatment protocols used in later studies show a clear bias towards the use of atypical antipsychotics, which are associated with a much lower risk of TD. This theory is supported by results from the CATIE trial in 710 patients [77], which did not find an effect of rs6280; in this trial, the majority of patients were on second-generation antipsychotics. Therefore, it can be concluded that the Gly allele of the rs6280 polymorphism may contribute to increased risk of TD, but this association is predominately seen in patients treated with typical antipsychotics and is less relevant in patients treated with atypical drugs.

The neuronal dopamine transporter (DAT) contributes to the control of synaptic dopamine. A VNTR polymorphism in the 3′ region of the gene that codes for DAT, *SLC6A3*/*DAT1*, gives rise to two to 11 tandem repeats of a 40 bp sequence, with nine or 10 repeats being the most common alleles. There is conflicting evidence of differences in DAT binding associated with the number of repeats, with some studies reporting increased binding associated with the 10-repeat allele, and others associating increased binding with the nine-repeat allele [78]. Methylphenidate, the most commonly prescribed medication for ADHD, binds to *DAT1* and reduces the reuptake of dopamine, thereby increasing synaptic dopamine. A number of studies have demonstrated the association of the 10-repeat allele with poorer treatment outcome [79, 80]; however, a recent meta-analysis failed to confirm this finding [81].

Other studies have investigated the effect of the DAT 9/10 repeat on treatment response in schizophrenia and depression; in schizophrenics, an association with clozapine response is reported [82], but no association with response to risperidone [83]. In major depressive disorder (MDD), Kirchheiner *et al*. [84] observed a reduced response to SSRIs associated with the nine-repeat allele.

The noradrenergic synapse has long been considered an important target for antidepressant drugs and, although SSRIs have focused attention on serotonin systems, the noradrenaline transporter and certain adrenergic receptors remain important sites of action of some effective antidepressants. Furthermore, several antipsychotics bind to α-adrenergic receptors, and the antagonism of α_2-adrenoceptors by clozapine has been suggested to underlie some of the unique properties of this drug.

Despite this, no link has been shown between polymorphisms in these genes and antipsychotic treatment efficacy [85]. Associations have been shown between polymorphisms in α-adrenergic receptor genes and metabolic syndrome abnormalities [86, 87], but there is limited evidence that variants in these genes confer a risk for antipsychotic drug-induced weight gain. Saiz *et al*. [88] found a marginal association between the –4884 A/A genotype in the *ADRA1A* promoter region and higher body mass index scores in patients treated with a range of antipsychotic regimens, while others [89] found a significant association between a bank of SNPs in the regulatory regions of the same gene and body mass index in a similar set of patients. Wang *et al*. [90] investigated the –1291 C/G promoter polymorphism in the *ADRA2A* gene and saw an association of the G allele with greater weight gain after clozapine treatment. This finding was contradicted [91] in a study showing that carriers of the C allele had more olanzapine-/clozapine-associated weight gain. Finally, De Luca *et al*. [92] concluded that –1291 C/G SNP only conferred a risk in a multiplicative model with the u-VNTR promoter polymorphism in the *MAOA* gene.

In contrast, several ADHD studies have linked methylphenidate response and *ADRA2A* gene variants [93–97]; however, this association was not found in adults [98], which may reflect differences in response to amphetamine analogues between adults and children.

The antidepressant serotonin–noradrenaline reuptake inhibitors (SNRIs) in contrast to SSRIs, bind to the noradrenaline transporter (NET), as well as to HTT. Polymorphisms in both *ADRA1A* and *ADRA2A* genes and *SLC6A2* (the NET gene) are associated with SNRI treatment outcome, with the *SLC6A2* SNPs interacting with childhood trauma to influence antidepressant response [29, 99, 100]. Wakeno *et al*. [101] demonstrated that C allele carriers of the *ADRA2A* –1291 polymorphism had improved response to the SNRI milnacipran compared with subjects who were GG homozygotes. Polymorphisms in *SLC6A2* have been shown to be associated with antidepressant response [99]; the –1287 G/A polymorphism was associated with response to milnacipran.

Glutamate and GABA systems

Monoamine systems have classically provided candidate genes for the pharmacogenetic study of treatment response in severe mental illness; typically, dopamine for antipsychotics and serotonin for antidepressants. Naturally, this reflected the major pharmacological mechanisms of these drugs, but also addressed the key theories of neurotransmitter pathology in the respective diseases. However, over the past two decades or so, increasing recognition has been given to the roles of glutamate and GABA neurotransmission in the pathology of these disorders, resulting in these transmitter systems being targets for novel treatments for both schizophrenia and affective disorders [102, 103]. This, in turn, has encouraged the investigation of glutamate and GABA neuronal transporter and receptor genes in psychiatric pharmacogenetics.

Glutamate and GABA are fast neurotransmitters, with effects that are more rapid and transient than the typical synaptic activity of the monoamine transmitters. Essential to this is a rapid removal mechanism as provided by the reuptake transporters; of the excitatory amino acid transporters (EAATs), EAAT3 is primarily found on neurons while EAAT2 is a glial transporter responsible for most glutamate removal from the synapse. Single nucleotide polymorphisms within the EAAT genes have mainly been studied in the context of neurological disorders. However, given the central role of EAAT2 in the control of synaptic glutamate and the importance of this neurotransmitter in psychiatric pathogenesis, it is perhaps surprising that its gene, *SLC1A2*, has been so little studied.

A functional SNP (rs4354668) –181 bp from the *SLC1A2* transcription start site affects transporter expression, with the variant allele inducing a reduction in promoter activity and resulting in an elevation of plasma glutamate [104]. In one of the very few pharmacogenetic studies, this EAAT2 functional polymorphism was shown to have a significant influence on recurrence rate in bipolar disorder, with T homozygotes being associated with fewer episodes as well as improved outcome of lithium treatment [105].

Genetic variation in the EAAT3 gene (*SLC1A1*) has been associated with obsessive–compulsive disorder in several studies [106], so perhaps it is unsurprising that it is also associated with obsessive–compulsive disorder symptoms occurring as a side-effect of antipsychotic drug treatment [107].

Despite the identification of the neuronal GABA transporter-1 as a potential drug target and the identification of functional polymorphisms in its gene (*SLC6A1*) [108], there appears to be very little work indicating that they have any association with psychiatric drug treatment.

Glutamate receptors are widely expressed in the central nervous system and are involved in synaptic plasticity, learning and memory processes. The best studied are the ionotropic glutamate receptors, the NMDA, kainate and AMPA receptors, which have *GRIN*, *GRIK* and *GRIA* genes, respectively, encoding their protein subunits.

There is certainly evidence for a fairly consistent, if weak, involvement of a genetic variability in a kainate receptor subunit in antidepressant response. In the STAR*D study of citalopram treatment [109], the effect of rs1954787, a *GRIK4* SNP, was found to be predictive of treatment outcome. While this effect alone was fairly modest, the G allele was associated with a greater response to treatment when combined with the *HTR2A* genotype. A subsequent study of 82 *GRIK4* SNPs in another sample identified a polymorphism with a stronger effect, also enhanced in its effect when combined with *HTR2A* [110]. While a multicentre study [111] was unable to replicate an effect of this gene on antidepressant response, the Chinese study of Pu *et al*. [112] also found a significant effect of rs1954787 in *GRIK4* on the outcome of antidepressant treatment.

This study by Pu *et al*. [112] also identified significant individual effects of several GABA receptor genes (*GABRP*, *GABRQ* and *GABRA6*), as well as some gene–gene interactions between other GABA receptors and glutamic acid decarboxylase, its synthesizing enzyme, on antidepressant response, providing strong support for pharmacogenetic associations of the GABA system with treatment of depression.

Other glutamate receptor genes have been associated with symptom response to antipsychotic drug treatment, although with little consistency and replication. *GRIA4* was one of six genes emerging from a GWAS with a significant association with iloperidone response [113]. Although the same results were not obtained for ziprasidone [114], *GRIA4* was significantly associated with risperidone response [115].

The broad candidate gene analysis of the CATIE sample identified significant associations of seven SNPs in glutamate receptor genes with improvement in total PANSS scores, although it should be noted that glutamate receptors were represented by over 1000 of the 2769 SNPs studied [34]. They did not include *GRIA4*; these were primarily metabotropic glutamate receptor genes, several of which appeared to have fairly specific effects on negative and cognitive symptoms, including *GRM7* and *GRM3*. This latter gene is of particular interest because it codes for a novel target for the treatment of schizophrenia [116], and others have also shown association of functional or potentially functional *GRM3* SNPs with antipsychotic response [117, 118], particularly of negative symptoms [119].

Another gene associated with antipsychotic-induced improvement of negative symptoms in schizophrenia is *GRIA2* [120]. Furthermore, an association of response to lithium with SNPs spanning this gene was one of several positive findings in a large GWAS of treatment in bipolar disorder [121].

Investigation of the possible role of genetic variability in GABA receptors in lithium response has proved negative (e.g. [122]). However, recognition of the importance of GABA systems in motor disorders, particularly dyskinesias, has yielded preliminary positive results for the association of tardive dyskinesia with genes for $GABA_A$ receptor subunits and a GABA transporter, *SLC6A11* [123].

In the absence of strong hypotheses for a primary involvement of glutamatergic dysfunction in adverse effects, few candidate gene studies have investigated amino acid receptor or transporter genes in the side-effects of antipsychotic and antidepressant drugs. One study that did found that the glycine transporter *SLC6A5* was associated with dyskinesias and EPS following haloperidol treatment, a finding replicated in further samples [124].

Epigenetics and gene–environment interactions

Variations in the genomic DNA sequence are unlikely to explain fully all the individual differences in the response to, and side-effects of, psychiatric drug treatments. It is now well established that environmental factors can influence the outcome of such treatments. Traumatic events in early life have particularly been studied in this respect; notably, early childhood trauma appears to be a factor predictive of poorer response to the drug treatment of depression in adulthood [125]. Such stressful life events can affect response to SSRIs by interacting with functional *SLC6A4* polymorphisms [126, 127] and with SNPs on other serotoninergic genes, including *HTR1B* and *TPH2* [29].

The biological mechanisms underlying these interactions remain obscure. Early life stress can affect synaptic maturation and neuronal development through an influence on the hypothalamic–pituitary–adrenal axis [128]. However, epigenetic mechanisms may also be important. There is steadily accumulating evidence that DNA methylation may underlie the influence of early life stress on depression and its response to treatment. For example, expression of the serotonin transporter is related to the extent of DNA methylation in the promoter region of the gene, interacting with the HTTLPR [129]. This DNA methylation is greater in subjects reporting child abuse [130], and *SLC6A4* methylation relates to the severity of psychopathology [131]. Inhibitors of DNA methylation have been reported to have an antidepressant effect [132], although few specific genes associated with antidepressant response have been investigated for their methylation status. The same is true of antipsychotic response, although again DNA methylation appears to be influenced by drug treatment [133].

It is clear that there is still much to learn here. The study of DNA methylation and other epigenetic influences is still very much in its infancy, but it seems that pharmacoepigenetics is likely to be an important future addition to the pharmacogenomic influences on response to treatment of severe mental illness.

Conclusions

As we have indicated, this review has been restricted to consideration of the pharmacogenetics of neurotransmitter receptors and transporters, a fairly arbitrary restriction within the many and various influences on the activity of synaptic neurotransmission, in the treatment of psychiatric disorders. Even within these limitations, it has not been comprehensive; the focus has been primarily on the response to treatment of severe mental illness (depression, bipolar illness and schizophrenia), with some mention of the better-studied side-effects. We have selected, again in a fairly arbitrary manner, mainly positive association studies of known functional polymorphisms; these often underline known pharmacotherapeutic mechanisms in psychiatry, but occasionally can point to new and potential mechanisms of drug action.

There remain many unexplained inconsistencies between studies; perhaps those of greatest concern come from well-replicated candidate gene associations that do not emerge in findings from GWAS. There are always differences between samples in these studies; sample power, ethnicity, sex, extent of prior treatment and drug differences are all likely to contribute, although it is worth noting that despite some suggestions to the contrary, there is so far little evidence for truly drug-specific genetic associations. In addition, the clinical response phenotypes measured may often be complex and multifactorial, comprising several physiological responses under different genetic influences. Furthermore, adherence to drug treatment is notoriously poor in psychiatry and thus any factor that might influence this, such as side-effects or extent of social support, will also be important in determining response.

Nevertheless, we do see some convergence that, where different genes are associated with the same effects, may go unrecognized. Thus, it is notable that functional variants in each of *SLC6A4, HTR1A* and *HTR2A* may be associated with antidepressant response, with these gene products mediating synaptic serotonin activity and neurotransmission. There are other examples mentioned above of genetic variability in both a transporter and a postsynaptic receptor having a common influence on psychiatric drug actions; however, more needs to be done to address additive and interactive effects between genes, even in an exploratory manner, if there are sample size constraints that compromise statistical power.

The rapid progress in epigenetics should also help us to explain more of the variance in the individual response to drug treatments. As these new findings converge with more consistent GWAS and candidate gene findings, they will eventually provide us with opportunities for predictive genetic testing, once their scientific validity and clinical utility are established.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work, except for GPR who acts as advisor to Optimal Medicine Ltd.

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