



Pharmacogenetics of antipsychotics: Clinical utility and implementation

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ABSTRACT

Decades of research have produced extensive evidence of the contribution of genetic factors to the efficacy and toxicity of antipsychotics. Numerous genetic variants in genes controlling drug availability or involved in antipsychotic processes have been linked to treatment variability. The complex mechanism of action and multitarget profile of most antipsychotic drugs hinder the identification of pharmacogenetic markers of clinical value. Nevertheless, the validity of associations between variants in *CYP1A2*, *CYP2D6*, *CYP2C19*, *ABCB1*, *DRD2*, *DRD3*, *HTR2A*, *HTR2C*, *BDNF*, *COMT*, *MC4R* genes and antipsychotic response has been confirmed in independent candidate gene studies. Genome wide pharmacogenomic studies have proven the role of the glutamatergic pathway in mediating antipsychotic activity and have reported novel associations with antipsychotic response. However, only a limited number of the findings, mainly functional variants of CYP metabolic enzymes, have been shown to be of clinical utility and translated into useful pharmacogenetic markers.

Based on the currently available information, actionable pharmacogenetics should be reduced to antipsychotics' dose adjustment according to the genetically predicted metabolic status (CYPs' profile) of the patient. Growing evidence suggests that such interventions will reduce antipsychotics' side-effects and increase treatment safety. Despite this evidence, the use of pharmacogenetics in psychiatric wards is minimal. Hopefully, further evidence on the clinical and economic benefits, the development of clinical protocols based on pharmacogenetic information, and improved and cheaper genetic testing will increase the implementation of pharmacogenetic guided prescription in clinical settings.

1. Introduction

Antipsychotic drugs are the mainstay treatment for Schizophrenia and are also used for the treatment of psychotic symptoms in other mental disorders. Over 1% of the population are prescribed antipsychotic medications [1]. However, 30–50 % of patients do not respond adequately to antipsychotic treatment and develop long-lasting and severe side-effects. Several reasons have been hypothesised for treatment failure including clinical (age of onset, severity, adherence, comorbidities), demographic (gender, living area), environmental (smoking, drug use, diet), and genetic factors. This review will summarise pharmacogenetic factors that impact on the clinical outcome of antipsychotic treatments.

The last decades have seen a surge in studies providing evidence on

the contribution of genetic factors to variability in antipsychotic response. Since the early investigations in the 1990s, candidate-gene (pharmacogenetic) studies and genome-wide (pharmacogenomic) investigations have revealed numerous associations between genetic variants in metabolic enzymes and in antipsychotic targets associated with different response phenotypes. However, only a limited number of genetic variants have been implemented for the improvement of antipsychotic response. A complex mechanism of action, differences in the definition and determination of clinical response, and heterogeneity of study cohorts among other reasons have hampered the identification of clinically usable pharmacogenetic markers of antipsychotic response. Nevertheless, pharmacogenetic tests are already commercially available and can be used as helpful prescription tools for the psychiatrist in the selection of drug dose and type. The following sections will focus on the

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genetic factors that have been reported in association with variability in the response to antipsychotic medications and on their applicability in clinical settings.

2. Pharmacogenetic studies

Candidate-gene pharmacogenetic studies investigate genes selected from the pharmacological and pharmacodynamic profile of antipsychotics. Table 1 lists the main metabolic pathways and pharmacodynamic targets of commonly used antipsychotics. Detailed information on antipsychotic pharmacokinetics and pharmacodynamics can be found elsewhere (i.e. www.pharmGKB.org & www.drugBank.ca). Although this strategy does not provide information on novel areas for antipsychotic intervention, it has succeeded in identifying several markers of clinical utility. Drug metabolising enzymes and neurotransmitter systems targeted by currently available antipsychotics have been thoroughly investigated for response-determining variants. Several polymorphisms in cytochrome P450 (CYP) genes have been repeatedly found associated with antipsychotic response and induced adverse reactions. Genetic variants in dopamine and serotonin receptors have also been associated with the clinical outcome of antipsychotic treatment, although with moderate or small effects. It is important to note that many pharmacogenetic studies investigate genetic associations with one or a few antipsychotics, whereas combination pharmacotherapy is often used in psychiatry. In many cases, drug-drug interactions that may significantly influence the clinical outcome have not been considered. Most interactions between antipsychotic drugs are caused by their CYP metabolism although pharmacodynamic interactions are also possible [2]. Detailed information on drug-drug interactions can be found elsewhere [2–5].

We conducted searches on the electronic PubMed and Web of Sciences databases using the terms (Pharmacogenetics OR Pharmacogenomics) and antipsychotics (166 results), (Genetic OR genomic) and association and antipsychotic (172 results), and (CYP OR cytochrome P450) and antipsychotics (162 results) to identify significant pharmacogenetic associations in the last 5 years. After manual screening of the results, studies with significant findings are summarised in the next two sections.

2.1. Pharmacogenetic studies on drug metabolic enzymes and transporters

Cytochrome P450 s (CYPs) enzymes, a major phase I enzyme family, are involved in the metabolism of more than 85 % of drugs. The isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are the main metabolic pathways of currently used antipsychotic drugs [6]. Numerous

Table 1
Main targets and metabolic pathways of commonly used antipsychotics.

Antipsychotic	Pharmacodynamic profile	Main metabolic pathways
Amisulpride	D2, D3	Kidney excretion
Aripiprazole	D2, 5-HT1, 5-HT2A	CYP2D6, CYP3A4
Chlorpromazine	D1, D3, D4, 5-HT1A, 5-HT2A, ADR1A, ADR1B, H1	CYP2D6, CYP1A2, CYP3A4
Clozapine	5-HT2A, 5-HT2C, 5-HT6, D2, D4, H1, M1, ADR1A	CYP1A2, CYP2C19, CYP3A4, CYP2D6
Haloperidol	D2, D3, D4	CYP2D6, CYP3A4
Olanzapine	5-HT2A, 5-HT2C, 5-HT6, D2, D3, D4, H1, M1, ADR1A	CYP1A2, CYP2D6
Pimozide	D2, D3, 5-HT2, ADR	CYP1A2, CYP3A4, CYP2D6
Quetiapine	5-HT1A, 5-HT2A, D1, D2, H1, ADR1A	CYP3A4, CYP2D6
Risperidone	5-HT2A, 5-HT2C, 5-HT1A, 5-HT1C, D2, D3, D4, H1	CYP2D6, CYP3A4
Ziprasidone	D2, D3, D4, 5-HT2, ADR	CYP2D6, CYP3A4

Abbreviations: D= dopamine receptor, 5-HT= serotonin receptor, ADR= adrenergic receptor, H= histaminic receptor, CYP: cytochrome P450 enzyme.

functional polymorphisms that render CYP enzymes inactive or slow (Poor Metabolizers or PM) or that induce high metabolic rates (Ultrarapid metabolizers or UM) have been described.

Pharmacogenetic research has provided evidence of the importance of CYP functional polymorphisms in psychiatric treatment, with numerous studies associating their presence with the variability observed in treatment response. Recent evidence confirms the relevance of the findings. Table 2 summarizes the most relevant pharmacogenetic findings regarding antipsychotic metabolism and availability published during the last five years. Variants in the *CYP1A1* and *CYP2C9* genes has been linked with higher incidence of somnolence and neurological events when evaluating the use of quetiapine in healthy volunteers [7]. Additionally, *CYP1A2* genetic variants are associated with higher serum concentrations and better response to olanzapine [8]. Antipsychotics' side-effects such as tardive dyskinesia (TD) have also been linked to the presence of functional variants in *CYP1A2* and *CYP2D6* genes [8–10]. The enzyme CYP2D6 has a critical impact in the efficacy and adverse events of antipsychotics, as previously known. Recent studies have shown a higher incidence of switching from risperidone to another antipsychotic when administrated to CYP2D6 poor or ultrarapid metabolizers [11]. Children who are CYP2D6 poor or intermediate metabolizers have higher risk of side effects when using risperidone [12]. Other adverse effects, such as hyperprolactinemia, have been observed in patients treated for schizophrenia with CYP2D6 functional variants [13]. CYP2D6 metabolic activity correlates with duration of

Table 2
Summary of pharmacogenetic findings in genes involved in antipsychotic metabolism and availability during the last 5 years.

GENE	ASSOCIATION	N	REFERENCE
CYP1A1	Several polymorphisms associated to somnolence and neurological events after quetiapine dose	79	Cabaleiro et al. (2015) [7]
	*1D & *1 F carriers show better response.	98	Czerwensky et al. (2015) [8]
CYP1A2	rs762551-C allele associated to TD in smoker patients	319	Ivanova et al. (2015) [10]
	*1 F associated with TD	353	Ivanova et al. (2016) [9]
	*4/*4 genotype associated with TD	353	Ivanova et al. (2016)[9].
CYP2D6	PM & UM higher rate of medication switches	2632	Jukic et al. (2019) [11]
	Children with PM or IM phenotypes are at greater risk for risperidone induced adverse events.	257	Oshikoya et al. (2019) [12]
	Presence of *3, *4, *5, *6, *1XN variants associated with longer periods of hospital stays	226	Kurylev et al. (2018) [14]
CYP2C9	*4 & *3 alleles associated with high risk of adverse events in pediatric patients.	81	Grădinaru et al. (2019) [103]
	Functional variants associated with treatment resistance	9	Thümmler et al. (2018) [15]
	rs3892097 associated with hyperprolactinemia.	128	Fedorenko et al. [13]
CYP2C19	Several polymorphisms Associated to higher somnolence related to quetiapine	79	Cabaleiro et al. (2015) [7]
	*2 carriers have higher risk of metabolic syndrome when treated with clozapine. *17 allele protects against metabolic complications of clozapine treatment and is associated with better clinical response.	60	Vasudev et al. [18]
UGT1A4	rs2011425-G allele linked to decreased olanzapine side effects	91	Hattori et al. (2020) [19]
	rs10808071 associated with modulation of QT(c).	77	Corponi et al. (2019) [21]
ABCB1	Carriers of rs1045642-T allele showed a considerable increase in BMI after treatment with clozapine	137	Piatkov et al. (2017)
ABCC1	rs212090-A allele with increase in BMI after clozapine treatment	137	Piatkov et al. (2017) [20]

hospital stays, with poor and ultrarapid metabolizers staying for longer periods [14]. Furthermore, functional anomalies in CYP2D6 were present in 50 % of pharmacoresistant children with severe mental disorders [15]. A previous study had also found that CYP2D6 functional status influenced risperidone response in ASD children [16]. The *CYP2C19**17 allele, associated with ultrarapid metabolism, may confer protection against metabolic complications of clozapine and produce better clinical results [17]. On the other hand, the presence of the *CYP2C19**2 allele, associated with poor metabolic rates, may confer a higher risk of metabolic syndrome in patients treated with clozapine [18]. There is growing evidence of the contribution to antipsychotic response of genetic variants in phase II enzymes. A recent study showed a *UGT1A4* rs2011425 polymorphisms associated with olanzapine tolerability [19]. Patients with the rs2011425-G allele presented less side effects and nervous system dysfunction when treated with the drug.

Genetic variants in transporter genes regulating brain drug availability may also play an important role in modulating antipsychotic response. Polymorphisms in *ABCB1* and *ABCC1* transporter genes have significant influence on weight gain after treatment with clozapine, with a higher impact in males [20]. The *ABCB1* rs10808071 polymorphism was linked with QTc prolongation during antipsychotic treatment [21]. Finally, a trend towards association between *ABCB1* polymorphisms and clozapine induced agranulocytosis was observed [22].

In summary, genetic variants in genes controlling drug availability have been consistently associated with the efficacy and tolerability of antipsychotic drugs. Of note, genetic associations with antipsychotic induced side effects tend to be of a higher magnitude than the associations with the level of response, suggesting a higher clinical value as predictors of adverse events. Finally, several recent case reports illustrate the clinical utility of using pharmacogenetic information in *CYPs* and other kinetic genes to improve response to antipsychotic treatments [23,24].

2.2. Pharmacogenetic studies in pharmacodynamic areas

The precise mechanism of action of antipsychotics is still partially unclear. Antipsychotic drugs interact as agonists or antagonists with several neurotransmitter pathways which have been the focus of numerous pharmacogenetic studies. Table 3 summarises reports of association between genes involved in pharmacodynamic processes and response phenotypes published during the last five years.

All currently available antipsychotics display variable affinities for the dopamine type 2 receptor (D2). However, excessive D2 blockade leads to side effects and even clinical deterioration in some patients [25]. Dopamine type 3 and type 4 receptors (D3 and D4, respectively) are also important antipsychotic targets. Genetic variants in dopamine receptors have been thoroughly investigated for their possible influence on clinical outcome. In the last five years, several studies have confirmed the association between variants in dopamine receptors genes (*DRD2* and *DRD3*) and treatment response and side effects, particularly movement disorders [26–30]. These findings together with previous reports confirm the contribution of *DRD2* and *DRD3* genetic variation to the efficacy and safety of antipsychotic treatments.

Genes coding for serotonin receptors, strongly targeted by second generation antipsychotics (SGA) and involved in the regulation of mood and social behaviour, also harbour genetic variants associated with response. Variants in serotonin (5-HT) type 2A, 2C and 6 receptor genes (*HTR2A*, *HTR2C*, and *HTR6*, respectively) have been associated with response to SGA [31–33]. Dysfunction of the glutamatergic system has been hypothesised as a major cause of schizophrenia and mental illness. Although the contribution of glutamatergic receptors to the efficacy of currently available antipsychotics is not clear, several studies suggest that mutations in glutamatergic genes may contribute to antipsychotic efficacy [34–36]. Several genes previously associated with mental disorders have also been associated with treatment resistance, including *BDNF*, *COMT*, *NRG1*, *RELN*, *SLC6A2* [26,27,34,37–39]. Two genes

Table 3

Summary of pharmacogenetic findings in genes involved in antipsychotic processes during the last 5 years.

GENE	ASSOCIATION	N	REFERENCES
ABL1	antipsychotic induced EPS	356	Boloc et al. (2020) [61]
ACAD10	Nuclear encoded mitochondrial genes associated with AIWG	168	Mittal et al. (2017) [48]
ADCY2	Incomplete response to antipsychotics	742	Jajodia et al. (2016) [34]
ANKS1B	Improvement with amisulpride	174	Kang et al. (2017) [104]
ATM	BMI during antipsychotic treatment	53	Garfunkel et al. (2019) [105]
BDNF	196-G/A polymorphism associated with insulin resistance	89	Sukasem et al. (2018) [60]
CCL2	Incomplete response to antipsychotics	742	Jajodia et al. (2016) [34]
CHRM2	rs1824024-G/G genotype less frequent in TD patients	472	Boiko et al. (2020) [55]
CLPB	Nuclear encoded mitochondrial genes associated with AIWG	168	Mittal et al. (2017) [48]
	Val158Met Met/Met genotype carriers have higher PANSS improvement with aripiprazole	40	Kaneko et al. (2018) [37]
COMT	Val158Met polymorphism associated with treatment resistance	318	Escamilla et al. (2018) [26]
	Several polymorphisms associated with risperidone response	690	Han et al. (2017) [27]
DISC1	Gene variants marginal association with TD	193	Lu et al. (2018) [56]
	241-A/G polymorphism associated with treatment resistance	318	Escamilla et al. (2018) [26]
	Several polymorphisms associated with risperidone response	690	Han et al. (2017) [27]
DRD2	rs2514218 associated with response to clozapine	208	Huang et al. (2016) [28]
	rs2514218 associated with antipsychotic response	100	Zhang et al. (2015) [29]
	rs324026 & rs12610827 polymorphisms associated with olanzapine response	238	Zhou et al. (2019) [30]
DRD3	Ser9Gly associated with treatment resistance	318	Escamilla et al. (2018) [26]
DTNBP1	Haplotype associated with TD	152	Maes et al. (k202) [57]
ERBB4	rs839523-C/C genotype associated with risk for TD	153	Zai et al. (2019) [58]
FKBP5	rs1360780 associated with clozapine response	591	Mitjans et al. (2015) [40]
FTO	rs7185735-G & rs9939609-A carriers develop higher AIWG	350	Schroder et al. (2019) [45]
GHRL	rs696217-G/G genotype associated with increase in BMI	84	Ryu et al. (2016) [46]
GRIA4	Incomplete response to antipsychotics	742	Jajodia et al. (2016) [34]
GRM3	rs6465084 polymorphism associated with antipsychotic response	61	Bishop et al. (2015) [106]
GRM7	Several polymorphisms associated with response to antipsychotics	2413	Liang et al. (2020) [36]
HCRTR2	Several SNPs nominally associated with AIWG	122	Tiwari et al. (2016) [107]
HSPG2	rs2445142-G allele associated with TD	278	Zai et al. (2018) [108]
	rs6313-T alleles associated with higher response to risperidone & olanzapine	221	Maffioletti et al. (2020) [31]
HTR2A	rs1928040 associated with TD in females	449	Pozhidaev et al. (2020) [51]
	Cys23Ser associated with response	171	Li et al. (2019) [32]
	rs1801412 associated with TD in females	449	Pozhidaev et al. (2020) [51]
HTR2C	rs6318 associated with hyperprolactinemia	128	Fedorenko et al. (2017) [13]
	-3008-C/G genotype associated with BMI during clozapine treatment	60	Vasudev et al. (2017) [18]

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Table 3 (continued)

GENE	ASSOCIATION	N	REFERENCES
	-759-T/T or C/T genotypes associated with less AIWG	48	Daray et al. (2017) [42]
HTR6	rs6699866 associated with risperidone response	201	Zhou et al. (2018) [33]
LEP	-2548-G/A associated with BMI during clozapine treatment	60	Vasudev et al. (2017) [18]
LEPR	688-A/G associated with BMI during clozapine treatment	60	Vasudev et al. (2017) [18]
LSMAP	rs938112 associated with antipsychotic induced extra pyramidal side effects	356	Boloc et al. (2020) [61]
MTHFR	C677 T associated with AIWG	135	Misiak et al. (2017) [50]
NEUROD2	4 SNPs associated with antipsychotic response	167	Spellmann et al. (2017) [109]
NOS1AP	rs12029454 associated with QTc prolongation	71	Corponi et al. (2019) [21]
NRG1	Incomplete response to antipsychotics	742	Jajodia et al. (2016) [34]
NTRK2	rs1778929 & rs10465180 associated with clozapine response	591	Mitjans et al. (2015) [40]
OCT1	Associated with BMI during antipsychotic treatment in ASD patients	53	Garfunkel et al. (2019) [105]
PARL	associated with AIWG	168	Mittal et al. (2017) [48]
PTPRD	rs73398242 associated with AIWG	201	Maciukiewicz et al. (2019) [47]
RABEP1	rs1000940-A/C associated with fasting glucose levels	497	Delacretaz et al. (2017) [49]
RELN	rs155333 & rs6465938 associated with antipsychotic response	260	Xu et al. (2020) [38]
SCN5A	H558R associated with QTc prolongation	199	Spellman et al. (2018) [59]
SH2B1	rs38881906-C/A associated with LDL levels	497	Delacretaz et al. (2017) [49]
SLC6A2	rs3785143 associated with response in autistic individuals	60	Shindler et al. (2020) [39]
SNAP25	rs6039769 associated with response	2128	Guan et al. (2020) [41]
SREBF1	rs11654081-T allele associated with metabolic syndrome during treatment with olanzapine, clozapine or risperidone	722	Yang et al. (2016) [110]

involved in immunological processes and immune response (*CCL2* & *FKBP5*) have been related to incomplete response and poor response to clozapine treatment [34,40]. Other single reports with response phenotypes require further investigation [41].

Pharmacogenetic studies on dynamic genes have also focused on antipsychotic induced weight gain (AIWG) and movement disorders such as TD, two common and severe side-effects frequently present during antipsychotic treatment. Clear associations have been found between serotonin polymorphisms and AIWG. Genetic variants in the 5-HT_{2C} receptor, involved in control of appetite and digestion, have been associated with antipsychotic AIWG and changes in BMI [18,42]. In particular, the *HTR2C* rs759-T allele is associated with less AIWG as confirmed by several studies [42–44]. Variants in the gene *FTO*, previously associated with obesity in the general population, were also reported in association with AIWG [45]. Genetic variants in the leptin (*LEP*) and leptin receptor (*LEPR*) genes, involved in the regulation of homeostasis and previously associated with obesity and diabetes mellitus, were associated with changes in BMI during clozapine treatment [18]. Genetic variants in the ghrelin gene (*GHRL*), involved in the regulation of appetite, were associated with weight change during antipsychotic treatment [46]. Maciukiewicz and collaborators [47] replicated a previous finding of association between genetic variants in the *PTPRD* gene and AIWG, although different variants may contribute to weight gain in different ethnic groups. Additional associations were reported between mitochondrial genes (*ACAD10*, *CLPB* and *PARL*) and

AIWG [48]. There are several other single reports of genetic associations with AIWG and lipid and glucose metabolism that require further confirmation [49,50], given the moderate magnitude of the association and/or the sample size. Despite these novel associations, only a few genes have been confirmed in independent studies. A meta-analysis of 72 articles combining a large sample (N = 6700) showed that *ADRA2A*, *DRD2*, *HTR2C* and *MC4R* polymorphisms were the most significantly associated with AIWG [44]. Although these associations seem to be robust, further studies evaluating their value as markers of AIWG are required. Nevertheless, the genotyping of variants in these genes is already included in several pharmacogenetic tests.

Serotonin polymorphisms, *HTR2A* rs1928040 and *HTR2C* rs1801412, have been recently associated with TD in female patients [51] confirming previous reports of the contribution of this pathway to movement disorders [6,52–54]. As in the case of AIWG, other single reports of genetic associations with antipsychotic induced TD [55–58], long QTc [21,59], insulin resistance [60] and extra pyramidal side effects [61] require further study. A review of pharmacogenetic studies revealed that serotonin and dopamine receptors genes have been consistently associated with TD [62].

One downside of these findings is that most pharmacodynamic markers have small or moderate effects (odds ratios no greater than 2) and therefore are of limited clinical value. This is not surprising given the multitarget profile of most antipsychotics. Algorithmic combinations of several genetic variants that better reflect their complex mechanism of action have been attempted to improve their predictive value. In a previous study we reported a combination of polymorphisms in serotonergic, dopaminergic, adrenergic and histaminic genes for the prediction of clozapine response [63]. An algorithm comprising four polymorphisms in *DRD1*, *DRD3*, *HTR1A* and *HTR3B* genes predicted response to antipsychotic monotherapy with a 73.6 % accuracy [64]. A computational algorithm with different combinations (13 or 25) of single nucleotide polymorphisms (SNPs) and 53 baseline variables was used in the CATIE study to predict response [65]. A panel of 15 genes was used to retrospectively predict efficacy (p < 0.001) although it did not predict the tolerability of antipsychotics [66]. A combination of polymorphisms in genes belonging to the mTOR pathway (*AKT1*, *FCHSD1*, *Raptor* and *DDIT4*) resulted in an accurate prediction of extra pyramidal side effects (EPS) risk [67]. However, these algorithms have not been replicated in independent cohorts. Differences in ethnicity, severity, clinical response determination and sample size between studies may account for this low replicability [68]. Nevertheless, it is quite unlikely that pharmacodynamic information alone can be used to accurately predict response. Pharmacokinetic and environmental factors (metabolism, diet, smoking habits, concomitant treatment) play a highly significant role in antipsychotic efficacy and toxicity and must be included in prediction algorithms.

In summary, recent candidate-gene pharmacogenetic studies have confirmed previous findings regarding the important role played by functional polymorphisms in metabolic enzymes in determining variability in antipsychotic response. Additionally, the clinical validity of findings of association between genetic variants in the dopaminergic and serotonergic systems to antipsychotic response has also been confirmed. Other findings regarding genes involved in adrenergic, muscarinic and glutamate neurotransmission, transporters, genes associated with risk of mental disorders and other novel associations require further study to confirm their validity.

3. Pharmacogenomic studies

Although successful in the identification of several genetic markers of clinical use, candidate-gene pharmacogenetic studies are restricted to the current knowledge on the mechanism of action of antipsychotics. Recent years have seen limited progress in the identification of novel response biomarkers. However, genomic, transcriptomic and epigenomic studies are opening the field to other candidate areas that may

provide useful information for improved or novel treatments.

3.1. Genomic studies

Table 4 summarises the findings of genome-wide association studies (GWAS) and Whole Exome Sequencing (WES) studies performed in the last five years. A GWAS performed by Corftsen and collaborators [69] in 765 individuals found two genes previously related with susceptibility to obesity in the general population, *PPARG* and *PCSK1*, associated with AIWG. Ter Hark and collaborators [70] found an intragenic variant, rs73810016, associated with response to amisulpride in a GWAS performed on 339 patients, whereas Yu and collaborators [71] found two SNPs in the gene coding for *PTPRD*, involved in neurite growth, and 1 SNP in the *MTRR* gene, involved in cellular methylation, associated with AIWG in a total cohort of 1090 patients. A GWAS study in a combined sample of 3792 Chinese patients found several genes involved in neurotransmission and schizophrenia risk associated with treatment response [72]. A study of polymorphisms in 1204 selected genes identified a polymorphism in *ERBB4* associated with paliperidone response [73]. This same gene was later found associated with antipsychotic induced TD in a candidate gene study [58]. Finally, other GWAS and WES studies [74–78] found variants in genes of unclear association with response phenotypes. However, these studies were conducted in relatively small sample sizes for genomic analyses and require confirmation in independent cohorts. Nevertheless, a recent review of genome-wide association studies (GWAS) on antipsychotics revealed 7 genome-wide significant loci (*CNTNAP5*, *GRMT*, *TNIK*, *PCDH7*, *GRID2*, *KCNK9* and *SLCIA1*) which were identified in more than one study [79]. Interestingly, four of these loci are involved in glutamatergic pathways [79]. Furthermore, a whole exome sequencing study (WES) revealed variants in genes involved in glutamatergic and NMDA transmission associated with short-term response to antipsychotic treatment [80]. These results support the involvement of the glutamatergic pathway in psychosis and antipsychotic treatment.

3.2. Transcriptomic and proteomic studies

Although technically more demanding, the study of gene and protein expression levels may give a more accurate illustration of gene x environment interactions. The last decade has seen a surge of transcriptomic and proteomic studies which are likely to produce useful biomarkers of antipsychotic response and to unravel their mechanism of action. While there are numerous studies *in vitro* and *in vivo*, the number of transcriptomic studies in antipsychotic treated patients is relatively modest. Although transcriptomic studies in cells from peripheral blood may not reflect exactly brain expression, a promising study revealed that the basal expression of 4 genes (*HMOX1*, *SLC9A3*, *SLC22A16*, and *LOC284581*) could be used for the prediction of response to

Table 4
Summary of pharmacogenomic studies on antipsychotic phenotypes during the last five years.

STUDY TYPE	GENES & GENETIC VARIANTS	N	ASSOCIATION WITH	REFERENCE
GWAS	Rs73810016	339	Amisulpride response	Ter Hark et al. (2020) [70]
GWAS	PPARG & PCSK1 variants	765	AIWG	Corftsen et al. (2020) [69]
GWAS	MEGF10, SLC1A1, PCDH7	2413 & 1379	Antipsychotic response	Yu et al. (2018) [72]
GWAS	MANBA, COL9A2, NFKB1	103	Poor response	Ovenden et al. (2017) [74]
GWAS	ADCK1	1390	Paliperidone response	Li et al. (2017) [77]
GWAS	Several intergenic polymorphisms	189 & 86	AIWG	Brandt et al. (2016) [75]
GWAS	PTPRD, & GFPT2	543 & 547	AIWG	Yu et al. (2016) [71]
WES	Genes involved in glutamatergic and NMDA transmission	316 & 1920 Chinese patients	Short-term efficacy	Wang et al. (2018) [80]
WES	MYO7B & MTRR	11 extreme response phenotypes + 103 & 87	Treatment response	Drogemoller et al. (2016) [76]
WES	RIMS2	82 + 140	TD	Alkelai et al. (2019) [78]
Gene panel (1204 genes)	ERBB4	684 + 2856	Paliperidone response	Wang et al. (2015) [73]

antipsychotic medications [81]. Furthermore, the expression of *ADAMTS*, a gene directly related with dopaminergic signalling, is downregulated in responders to antipsychotic treatment [82]. A recent study has identified a panel of proteins that could potentially be used to predict response to risperidone and olanzapine [83]. In this study, enrichment analyses revealed differential expression between responders and non-responders in proteins involved in immune system processes. If confirmed, transcriptomic and proteomic data may give accurate predictions of antipsychotic response, as they are affected by clinical and environmental factors that contribute to variability in the response to antipsychotic treatment.

4. Pharmacogenetic prediction of antipsychotic response

In addition to improving our knowledge on the mechanism of action of antipsychotics, pharmacogenetic studies provide information for the personalisation of antipsychotic treatment. Pharmacogenetic data may help to choose the most adequate drug for each patient according to their pharmacogenetic profile. While most candidate-gene studies have been conducted in relatively moderate sample sizes, several results have been replicated in independent studies and have been shown to be of clinical utility. By contrast, pharmacogenomic studies have not produced clinically applicable results yet. Further studies and technology improvements may be required before genomic strategies (i.e. polygenic risk scores or transcriptomic data) can be implemented in clinical settings. **Table 5** summarises a list of genes that have been consistently associated with antipsychotic response phenotypes and the drugs influenced by their genetic variants.

Table 5

List of confirmed pharmacogenetic associations and the antipsychotic drugs affected.

GENE	ANTIPSYCHOTIC DRUGS AFFECTED
ABCB1	All antipsychotics
COMT	Haloperidol
CYP1A2	Chlorpromazine, Clozapine, Olanzapine , Trifluoperazine
CYP2D6	Aripiprazole, Clozapine, Haloperidol, Paliperidone, Pimozide¹, Risperidone, Quetiapine
CYP2C19	Clozapine
DRD2	All antipsychotics
DRD3	Clozapine, Quetiapine
HTR2A	SGAs
HTR2C	SGAs
MC4R	SGAs

In bold genetic associations deemed actionable by international medicine associations (FDA, EMA, Swissmedic, PMDA and/or HCSC).

¹ Genotyping of CYP2D6 required by FDA when considering Pimozide as treatment.

SGA: second generation antipsychotics.

As described before, the association between functional polymorphisms in CYP metabolic enzymes and antipsychotic toxicity is well documented, although the influence of these polymorphisms on treatment efficacy is not so clear [6,84]. Pre-treatment genotyping of functional CYP variants can be used to determine the right dose or to select an alternative antipsychotic not metabolised by the affected pathway. It has been estimated that the pre-treatment genotyping of CYP polymorphisms may result in a 10–20 % increase in efficacy and tolerability [85]. Recent studies have proven the clinical utility of using functional CYP polymorphisms to inform of the adequate dose of antipsychotic. In a previous study, we developed a protocol including pharmacogenetic testing using a then commercially available array to determine functional variants in CYP1A2, CYP2D6, CYP2C19, CYP3A4 and CYP3A5 enzymes and a table of antipsychotic dose adjustments according to the genetic results. This intervention resulted in lower antipsychotic induced toxicity, specially of those antipsychotics metabolised by one major pathway [86]. Pharmacogenetic reports including genetic information in CYP2D6 and CYP2C19 enzymes helped to improve the side effect profile in 80 patients treated with antipsychotics and antidepressants [87]. CYPs metabolic enzymes play a prominent role in controlling drug availability and are responsible for the metabolism of about 80 % of the currently available drugs. Thus, the genotyping of functional CYP polymorphisms is also useful for the adjustment of the clinical dose of other psychotropics and of drugs used in other medical areas.

To date, it is not sufficiently established the clinical utility of pharmacodynamic variants. While the translational value of functional CYP metabolic polymorphisms is well documented, little is known on the actionability of variants in neurotransmitter systems and in other genes involved in psychotropic processes. Despite this lack of validation, polymorphisms in *BDNF*, *COMT*, *DRD2*, *DRD3*, *DRD4*, *HLA*, *HTR2A*, *HTR2C*, *ABCB1* and other genes have been included in several pharmacogenetic tests [88]. The benefits of using information on genes coding for the serotonin transporter (5-HTT) and 5-HT_{2A} receptor, together with genetic information in CYP enzymes, to personalise antidepressant treatment has been validated in several studies [89,90]. However, no clear evidence on the translational value of polymorphisms in antipsychotic targets has been produced yet. The complex mechanism of action and multitarget profile of antipsychotics hinder the identification of pharmacodynamic biomarkers of clinical utility. The clinical utility of genotyping dopamine and serotonin variants is limited by the moderate genetic effects observed and their modest impact on response. Additionally, as most currently available antipsychotics target both neurotransmitter systems in varying degrees, selection of antipsychotic based on the presence of mutations in dopamine or serotonin systems may prove difficult. Similar problems of limited discriminating power diminish the clinical value of other pharmacodynamic variants. More investigations in large cohorts of patients on antipsychotic monotherapy with detailed clinical and environmental data are required to determine the translational value of these variants.

5. Clinical implementation of pharmacogenetics in clinical settings

Despite the growing evidence, the implementation of pharmacogenetics in psychiatric wards is minimal. There are major barriers to the integration of pharmacogenetics interventions in clinical practice [91, 92]. Lack of facilities to perform genetic testing, lack of information on the clinical and economic benefits of actionable pharmacogenetic tests, lack of clinical intervention protocols, length of delivery time of results and cost of tests are several reasons that hinder the implementation of pharmacogenetics.

The lack of appropriate testing to perform accurate and rapid genotyping within hospitals may be compensated by commercially available pharmacogenetic tests. There are currently more than 20 commercially available tests that interrogate genes involved in the

metabolism or mechanism of action of psychotropics [93]. Most pharmacogenetic tests cover functional metabolic polymorphisms, particularly in CYP2D6 and CYP2C19 enzymes, although there is no consensus on the polymorphisms and the number investigated [88]. Additionally, the genotyping methods and the manner the results are conveyed to the client vary greatly between pharmacogenetic tests. The long time to deliver results from a pharmacogenetic test, which can be longer than two weeks, and their cost further limits their implementation. Nevertheless, several clinical trials have proven the clinical utility and the cost-effectiveness of commercial tests for the improvement of response to antidepressant treatments [94–96], although their clinical utility for the personalisation of antipsychotic treatment is not yet proven.

Most health professionals are unaware of the benefits of pharmacogenetic tests although several countries are introducing pharmacogenetics as a subject during clinical training. Furthermore, there is inexperience in the interpretation and clinical application of pharmacogenetic results. While pharmacogenetic test reports summarise to various extents the clinical implications of results, most tests require the clinician to be knowledgeable in the use of pharmacogenetic information. Guidance on the required clinical changes based on pharmacogenetic data is needed. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have published several extremely useful guidelines informing of the required dose adjustment for TCA and SSRI antidepressants based on the patients' CYP2D6 and CYP2C19 variants [97–99]. However, antipsychotics are sparsely covered by these guidelines. Apart from dose adjustment recommendations for Aripiprazole and Pimozide issued by the DPWG and the Food and Drug Agency (FDA), respectively, no other clinical guidelines have been published. In absence of specific guidelines, several papers offer recommendations on the dose adjustment required for antipsychotics according to functional CYP polymorphisms [86,100].

Finally, there are several advantages and disadvantages of pharmacogenetic tests when comparing them with other prescription tools. As explained before, all available pharmacogenetic tests give information on the metabolic status of the patients regarding CYP enzyme substrates. However, unless this information is provided before the start of the treatment or during its first days, more precise information on drug availability can be obtained by measuring the plasma levels of the antipsychotic used and its metabolites. Delay in delivering pharmacogenetic results is one of the major drawbacks of pharmacogenetic testing. By contrast, rapid or pre-emptive pharmacogenetic testing may facilitate drug and dose selection, resulting in improved efficacy and safety [101,102]. Thus, early knowledge of the patient's pharmacokinetic and pharmacodynamic profile can be one of the major advantages of genetic testing. Secondly, pharmacogenetic testing needs to be performed only once, as the genetic code does not change during a lifetime, while measurements of drug plasma levels or gene expression need to be obtained whenever a new treatment is started to provide useful information. The development of accurate and rapid assays for key pharmacogenetic markers in hospital laboratories will increase the clinical benefits of an early intervention and will lower the costs. Pharmacogenetic reports including evidence based clinical recommendations and support teams helping in the interpretation of results will aid the clinician to personalise antipsychotic treatment. In a recent study we showed that a strategy of pharmacogenetic interventions using rapid on-site genotyping methods and personalised reports improved the response to psychotropic medications, including antipsychotics, in treatments resistant ASD children (data submitted for publication). However, several areas require further research. Current pharmacogenetic data has limited validity for the prediction of efficacy levels of antipsychotic medications, and algorithms combining information in pharmacokinetic and pharmacodynamic genes, clinical and environmental data should be developed. Furthermore, in addition to genetic information, pharmacogenetic interventions should consider possible drug-drug interactions to improve their accuracy and clinical utility.

6. Conclusions

Based on currently available information, actionable pharmacogenetics should be reduced to antipsychotics' dose adjustment according to the genetically predicted metabolic status (CYPs' profile) of the patient. Growing evidence suggests that such interventions will reduce antipsychotics' side-effects and increase treatment safety. Although several pharmacodynamic variants have been associated with response, their clinical validity and utility are still to be proven. Hopefully, with further evidence on the clinical and economic benefits, improved clinical guidelines, lowering costs and shorter delivery times pharmacogenetic interventions will become routine in psychiatric clinical practice.

Author statement

This is to certify that the authors are not consulting for any company that may have influenced the content of the manuscript and have no conflict of interests.

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