Trends in Pharmacological Sciences

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Feature Review

Pharmacogenomics in treatment of depression and psychosis: an update

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Genetic factors can, to a certain extent, successfully predict the therapeutic effects, metabolism, and adverse reactions of drugs. This research field, pharmacogenomics, is well developed in oncology and is currently expanding in psychiatry. Here, we summarize the latest development in pharmacogenomic psychiatry, where results of several recent large studies indicate a true benefit and cost-effectiveness of pre-emptive genotyping for more successful psychotherapy. However, it is apparent that we still lack knowledge of many additional heritable genetic factors of importance for explanation of the interindividual differences in response to psychiatric drugs. Thus, more effort to further develop pharmacogenomic psychiatry should be invested to achieve a broader clinical implementation.

Highlights

A review of recent scientific papers reporting data from large cohort studies and randomized clinical trials containing pharmacogenomic information reveals that more efficient and cost-effective drug treatment of depression and schizophrenia can be obtained by genotype-guided decisions on the prescription of psychiatric drugs as compared with treatment as usual.

Clinical implementation requires better prioritization using the best strategies for pharmacogenomically assisted drug treatment as well as improved and continuous education of psychiatrists.

Much scientific effort should be dedicated to identifying the currently missing heritable genetic factors, which should in turn be used as additional tools for more successful pre-emptive genotyping in psychiatry, thereby further optimizing antidepressant and antipsychotic drug treatment.

Pharmacogenomics in drug treatment of psychiatric disorders

Mental health is essential to personal well-being, interpersonal relationships, and the ability to contribute to society. Mental disorders cause problems that may reduce physical health, cause pain and disability, or lead to death. They are among the most common causes of disability and associated suicide and constitute the tenth leading cause of death in the United States.[i] Neuropsychiatric disorders account for 19% of all years of life lost to disability and premature mortality in the United States.[i] The major mental diseases include schizophrenia and depression, which together affect more than 300 million people worldwide [1].[ii–iv]

The drugs commonly used to treat psychiatric disorders are often ineffective, especially antidepressants. When compared with placebo in large **randomized clinical trials (RCTs)** (see Glossary), only a limited number of people with psychiatric disorders benefit. Particularly, for patients with **major depressive disorder**, which affects 163 million people, the drug response rate is estimated to be only 42–53% [2,3]. However, research on and development of new psychotropic drugs is near a standstill, and there is thus a great need to optimize treatment with the currently available drugs.

The reactions of patients to psychiatric drugs differ tremendously in both extent and manner. This difference is due to genetic, environmental, pathophysiological, and dietary factors. Among those, drug–drug interactions and differences in genetic constitution are most important. Genetic variants of importance for drug treatment can be used as **pharmacogenomic biomarkers**. These are listed by the FDA and form the basis of the pharmacogenomic information used by a physician in order to individualize drug treatment. Such biomarkers are commonly used in oncology but not yet in psychiatry.

The value of pharmacogenomic testing in psychiatry is disputed. However, results from recent large pharmacogenomic studies justify a reconsideration of genetic testing in antidepressant and antipsychotic treatment. In this Review, we consider the most recent developments in the

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field of psychiatric pharmacogenomics; discuss the relative value of pharmacogenomics versus **therapeutic drug monitoring (TDM)** as tools in psychiatry; emphasize the gap of knowledge between the observed and known genetic variation in kinetics of and response to psychiatric drugs; and consider the ethical, clinical, and cost–benefit aspects of using pharmacogenomic testing in psychiatry.

Recent developments in psychiatric pharmacogenomics

Overview of the genetic polymorphisms of relevance for neuropsychopharmacology

An effect of variant genes encoding the expression of drug-metabolizing enzymes on treatment efficacy would be expected to be accompanied by altered effective drug concentrations. Substantial effort in the past has been focused on the question of which genetic variants could be of importance for decisions regarding clinical treatment and dosing in psychiatric disorders. The research has been focused mainly on variants of (i) drug targets, such as *SLC6A4*, which encodes the serotonin reuptake transporter; the *HTR2A* and *HTR2C* genes encoding the serotonin 5-HT_{2A} and $5HT_{2C}$ receptors, respectively; and the dopamine D_2 receptor gene *DRD2*; (ii) transporter genes, mainly *ABCB1*, encoding P-glycoprotein that controls uptake of drugs into the brain, and *OCT1*, encoding the organic cation transporter mainly expressed in the liver; and (iii) genes such as *CYP2C19*, *CYP2D6*, and *COMT*, which encode drug-metabolizing enzymes (see Figure 1 for a summary). Indeed, during the past 6 years, more than 2000 reports focused on genetic **polymorphism**, depression/schizophrenia, and psychiatric drug metabolism have been published. The studies encompass a variable number of patients – often too few – under different dosing regimens (cf. [4–6]). However, it is now becoming possible to approach consensus regarding the significant impact of polymorphic genes, where *CYP2C19* and *CYP2D6,* encoding the corresponding cytochrome P450 (CYP) enzymes CYP2C19 and CYP2D6, are the only such genes that significantly influence the pharmacokinetics or effectiveness of relevant psychiatric drugs [7–11]. Consequently, we focus this presentation on the role of these two polymorphic genes in psychiatric drug treatment.

CYP2C19 and *CYP2D6* genotypes as predictive biomarkers of psychiatric drug exposure

The question whether optimal drug exposure translates into optimal efficacy and increased tolerability has been a topic of debate in psychiatry for a very long time. A recent meta-analysis quantified dose–response curves for risperidone treatment and found that doses between 3 and 5 mg/day of risperidone dose-equivalents provide the most favorable antipsychotic treatment outcome [4]. Similarly, dose-equivalents of 20 and 40 mg/day of fluoxetine provide the most favorable antidepressant treatment outcome [12]. In addition, evidence-based therapeutic ranges are also available [13]. Therefore, to obtain optimal exposure to antipsychotics and antidepressants for each patient, **pre-emptive** CYP **genotyping** could be used for precision dosing during treatment initiation, which is the critical point for symptom improvement in psychiatric diseases. To detect important genetic variants, all currently commercially available pharmacogenetic tools intended to support drug selection and dosing decisions in psychiatry search for major CYP gene polymorphisms and rely on *CYP* genotypes [14]. Thus, dosing guidelines from the FDA[v], the Clinical Pharmacogenetics Implementation Consortium, [15,16], and the Dutch Pharmacogenetics Working Group include pharmacogenomic recommendations that are based on CYP genotypes [17]. Dosing instructions in relation to genetic variation are also written in the product characteristics summary for many psychiatric drugs, focused on specific instructions concerning the *CYP2C19* and *CYP2D6* genotypes [18,19]. However, recommendations and instructions differ between sources and require harmonization [20], and the extent to which these pharmacogenomic drug labels are used in the psychiatric clinics can be expanded.

Glossary

Absorption, distribution, metabolism, and excretion (ADME): refers to all biological processes in the organism that occur from the moment when a drug is released from its dosing formulation until it is eliminated from the organism.

h^2SNP: the sum of all genetic effects detected by SNPs related to the phenotypic variance within a defined population. It is an indicator of the degree of heritability of a trait and theoretically ranges between 0 and 1. An h^2SNP value of 1 indicates complete heritability.

Hamilton Anxiety Rating Scale (HAM-A): measures the severity of anxiety symptoms. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).

Hamilton Depression Rating Scale (HAM-D): a multiple-item questionnaire used to provide an indication of depression and as a guide to evaluate recovery. The patient is rated by a clinician on 17 to 29 items.

Haplotype and diplotype: a haplotype is a physical grouping of genomic variants (or polymorphisms) that tend to be inherited together. A specific haplotype typically reflects a unique combination of variants that reside near each other on a chromosome. The diplotype is the combination of two alleles, one from the mother and one from the father.

Major depressive disorder: also known as clinical depression, is a mental disorder characterized by at least 2 weeks of pervasive low mood, low self-esteem, and loss of interest or pleasure in normally enjoyable activities.

Pharmacogenomic biomarkers: genetic biomarkers indicative of altered functionality of a gene related to the action of a drug. Biomarkers can contain one distinct variant allele or a composite set of allelic variants and are often presented in the product information of the drug.

Phenoconversion: any phenomenon, e.g., drug–drug interactions, that converts genotypic extensive metabolizers (EMs) into phenotypic poor metabolizers (PMs), intermediate metabolizers (IMs), or ultrarapid metabolizers (UMs) of drugs.

Numerous different genetic variants for *CYP2C19* and *CYP2D6* have been described, and the information is continuously updated by the PharmVar organization.[vi] To facilitate the clinical use of this information, patients carrying different genetic variants are stratified into metabolizer categories based on their *CYP2C19* and *CYP2D6* gene variants (see Box 1): (i) normal metabolizers (NMs) carry gene variants which encode 'normal' CYP2C19 or CYP2D6 enzyme capacity; (ii) poor metabolizers (PMs) lack the functional CYP gene in question, having no enzyme activity; (iii) intermediate metabolizers (IMs) carry partially defective combinations of CYP alleles and have reduced enzyme activity; and (iv) ultrarapid metabolizers (UMs) exhibit higher-than-normal metabolic capacity, sometimes due to gene duplications. The metabolic phenotype is related to the success of drug treatment. Monitoring of groups of patients receiving antidepressant or antipsychotic treatment reveals that drug switching is much more common among PMs and UMs than among patients with a normal rate of drug metabolism. This indicates that adjusting the dose according to genotype would benefit the drug treatment outcome for millions of people (Figure 2).

To what extent does pre-emptive genotyping of *CYP2D6* and *CYP2C19* improve psychiatric drug treatment?

We recently pooled together all representative studies that dealt with associations between individual genes and drug exposure, and we collected sufficient data to conduct 14 individual meta-analyses for specific gene–drug interactions [21]. We concluded that clinically relevant 48%, 36%, and 68% differences in aripiprazole, risperidone, and haloperidol exposure, respectively, are detected between CYP2D6 metabolizer categories. Similarly relevant 2.6- and 2.7-fold differences in escitalopram and sertraline exposure, respectively, were observed between CYP2C19 metabolizer categories. In addition, clinically relevant 2.2-, 1.5-, 3.3-, 3.5-, and 1.3-fold increased exposures were detected in CYP2D6 PMs and IMs for fluoxetine, fluvoxamine, mirtazapine, nortriptyline, and paroxetine, respectively, compared with CYPD6 NMs. Among CYP2C19 PMs and IMs, 2.9- and 2.1-fold increased exposures, respectively, were observed for fluoxetine and venlafaxine, respectively, as compared with NMs. However, some of these observations are based on an insufficient number of patients; to obtain more reliable data, we think that further validation studies are needed. In this context, a recently initiated European Union Horizon 2020–supported *PSY-PGx* project (2021–2025) encompassing 12 different countries including the United States and Israel[vii], is evaluating the effects of aripiprazole, escitalopram, risperidone, and sertraline personalized dosing based on pre-emptive *CYP2C19* and *CYP2D6* genotyping. The aim is to provide best quality of care, thereby reducing the personal suffering and societal and financial burden caused by psychiatric disorders. The results are expected in 2025. In conclusion, recent development in genetic research allows adequate metabolizer categorization [22,23], and clinical relevance for several CYP gene–drug associations has been confirmed.

To what extent can attention to the dose variations caused by interindividual differences in the *CYP2C19* and *CYP2D6* genes translate into improved clinical effects?

For evaluation of this issue, it is evident that RCTs reduce interpretation biases. In total, we found 15 different RCTs focused on the role played by polymorphisms in drug-metabolizing genes in the effects of drug treatment of depression [24–38]. The major sources of bias in these studies are the generally very small number of participants and differences in study designs. If one focuses on the largest studies, such as those shown in Table 1, it is apparent that pharmacogenomic information can improve the treatment outcome, but firm conclusions would require additional large prospective studies. Currently, four ongoing RTCs are being conducted on this topic [39–42][viii], and these are likely to provide more conclusive data in due time.

Patient Health Questionnaire-9 (PHQ-9) scale: a depression module that scores each of the nine DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria) as '0' (not at all) to '3' (nearly every day). It has been validated for use in primary care. It is not a screening tool for depression, but it is used to monitor the severity of depression and response to treatment.

Polymorphism: the occurrence of two or more clearly different morphs or forms, also referred to as 'alternative phenotypes,' in the population of a species. In pharmacology, 'common polymorphism' or the adjective 'polymorphic' usually means that the frequency of a genetic variant is >1%. Genetic variants occurring at a frequency <1% are called 'rare.'

Pre-emptive genotyping: the clinical intervention in which a genetic biomarker is genotyped; this intervention precedes treatment initiation and guides the clinician's decision related to the choice of medication and dose.

Quick Inventory of Depressive Symptomatology (QIDS): scores range from 0 to 27, with scores of 5 or less indicative of no depression, scores from 6 to 10 indicating mild depression, scores of 11 to 15 indicating moderate depression, scores of 16 to 20 reflecting severe depression, and total scores greater than 21 indicating very severe depression. QIDS-SR is the self-reported variant.

Randomized clinical trial (RCT): a study in which the participants are divided by chance into separate groups for comparison of different treatments or other interventions.

Therapeutic drug monitoring (TDM): the concept of measuring drug concentrations in plasma, serum, or blood at a certain dose and relating them to a target therapeutic or reference range. The drug concentration is determined by the dose and pharmacokinetic processes.

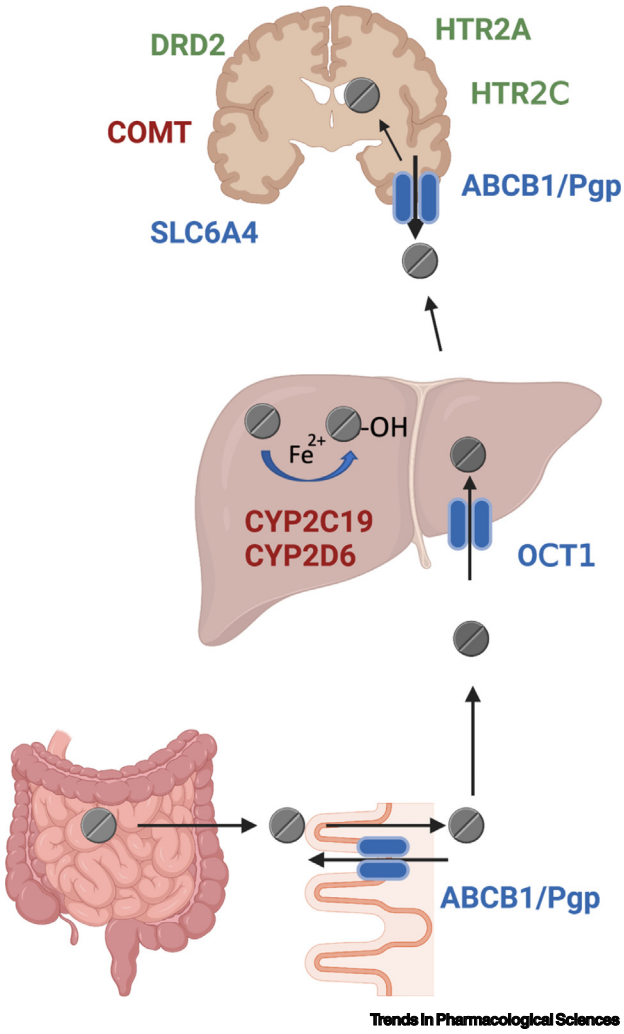

Figure 1. Studies of genetic variants and efficacy of antidepressant and antipsychotic drug treatment. The studies have included examination of genetic polymorphism of (i) metabolizing enzymes such as CYP2C19, CYP2D6, and COMT (red); (ii) the SLC6A4 (serotonin transporter SERT), ABCB1 (Pgp), and OCT1 transporters (blue); and (iii) the serotonin receptors HTR2A and HTR2C and dopamine receptor DRD2 (green). Genes in green letters have been found to explain interindividual variations in drug efficacy, whereas genes in red letters provide hitherto no important information regarding pre-emptive genotyping of psychiatric patients. Figure made in part with BioRender.com.

CYP pharmacogenomics and TDM as instruments in psychiatric drug treatment

As mentioned earlier, besides genetic factors, also drug–drug interactions, dietary, pathophysiological, and environmental factors contribute to interindividual variability in drug response. Such variability occurs (i) during polypharmacy when other drugs taken concomitantly inhibit or induce the activity of the enzyme important for the primary drug, which may cause **phenoconversion** of, for example, normal metabolism to UM, IM, or PM status; (ii) when kidney or liver function is impaired, in which case drug exposure increases due to tissue failure that retards drug elimination; and (iii) when dietary habits influence drug exposure by changing drug bioavailability via changes in the rate of drug metabolism or transport due to interactions between the drug and dietary components. In such cases, TDM of drug blood levels can be used to capture all sources contributing the pharmacokinetic variability. After initial pre-emptive genotyping, TDM can be used routinely in the clinic as an effective tool to fine-tune drug dosage for a few weeks after the start of treatment. Indeed, this is already recommended for some drugs with narrow therapeutic ranges or severe adverse drug reactions (see Figure 3A, Key figure and Box 2) [43].

Box 1. Polymorphic CYP catalyzed metabolism of antipsychotics and antidepressants

The polymorphic cytochrome P450 enzymes are very important for the metabolism of drugs used in the treatment of central nervous system (CNS)-related disorders, and their activity differs between individuals, largely because of genetic inheritance.

The relative activity of known variants of the *CYP2C19* and *CYP2D6* genes allows stratification of individuals into different apparent phenotypes: PMs carry null alleles and are devoid of the drug-metabolizing activity in question; IMs carry defective **diplotype** combinations resulting in decreased drug metabolism; NMs carry fully active alleles; and UMs metabolize drugs at an increased rate, often because of gene duplications. The basis for the phenotypes is given in Table I.

Table I. Functional variant *CYP2C19* and *CYP2D6* allele frequency worldwide and metabolizer categorization. Whereas the interindividual differences in rate of drug metabolism are relatively small among carriers of null alleles (PMs), these differences are substantial among IMs and NMs, most likely due to additional genetic factors controlling the expression and activity of the CYP2C19 and CYP2D6 products responsible for drug metabolism[a]

Allele[b]	Europe	Africa	East Asia	South Asia	America	Haplotype	Diplotype	Metabolizer category
*CYP2C19*2*	18.3%	18.1%	31.0%	34.0%	10.1%	CYP2C19 Nonf	Nonf/Nonf	PM
*CYP2C19*3*	<1%	<1%	6.7%	<1%	<1%		Nonf/Norm Nonf/Incr	IM IM
CYP2C19Norm	59%	58%	61%	48%	78%	CYP2C19 Norm	Norm/Norm	NM
*CYP2C19*17*	22.4%	23.5%	1.5%	13.6%	12.0%	CYP2C19 Incr	Norm/Incr Incr/Incr	UM (NM) UM
*CYP2D6*3*	4.1%	<1%	<1%	<1%	<1%	CYP2D6 Nonf	Nonf/Nonf	PM
*CYP2D6*4*	15.5%	11.9%	<1%	11.6%	15.7%		Nonf/Decr	IM
*CYP2D6*5*	3.0%	4.0%	6.5%	2.0%	3.0%		Nonf/Incr	NM (IM)
*CYP2D6*6*	2.2%	<1%	<1%	<1%	<1%			
*CYP2D6*9*	1.6%	<1%	<1%	<1%	1.3%	CYP2D6 Decr	Decr/Decr	IM (NM)
*CYP2D6*10*	<1%	3.2%	58.7%	6.5%	<1%		Nonf/Norm	IM (NM)
*CYP2D6*17*	<1%	19.7%	<1%	<1%	1.0%		Nonf/Decr	NM (IM)
*CYP2D6*29*	<1%	9.2%	<1%	<1%	<1%		Decr/Incr	NM
*CYP2D6*41*	3.0%	3.0%	3.0%	13.5%	3.5%			
CYP2D6Norm	68%	40%	30%	65%	74%	CYP2D6 Norm	Norm/Norm	NM
CYP2D6xN	2.3	9.3	2.0%	1.5%	1.0%	CYP2D6 Incr	Norm/Incr Incr/Incr	UM

[a]Abbreviations: Decr, decreased function allele; IM, intermediate metabolizer; Incr, increased function allele; NM, normal metabolizer; Nonf, nonfunctional allele; Norm, normal (reference) function allele; PM, poor metabolizer; UM, ultrarapid metabolizer.
[b]Allele frequency data from Zhou *et al*. [67].

Novel TDM methods: metabolite profiling by high-resolution mass spectrometry

The recent introduction of the Orbitrap MS device (high-resolution accurate mass spectrometry; Thermo Fisher Scientific) has increased the value of TDM substantially. Higher resolution and higher mass accuracy allow us to discriminate between analytes with identical masses. The method has a higher sensitivity and specificity and can generate and store full-scan data, making it possible to perform retrospective data analysis of the patients' samples. The current TDM concept as applied to antidepressants and antipsychotics is to prevent dose-dependent side effects and ensure satisfactory drug concentrations for optimal clinical effect. However, the most serious side effects are often not dose-dependent but are mediated by secondary metabolites whose concentrations are not correlated with those of the parent compounds. A typical example is clozapine, where agranulocytosis is a potentially fatal side effect that is not mediated by the parent compounds but probably by toxic metabolite(s) triggering an immune response resulting in granulocyte depletion [44]. By using chromatographic methods linked to high-resolution mass spectrometry detectors, comprehensive metabolic spectra can be analyzed [45], which could make it possible to identify and monitor such metabolites as part of TDM as well.

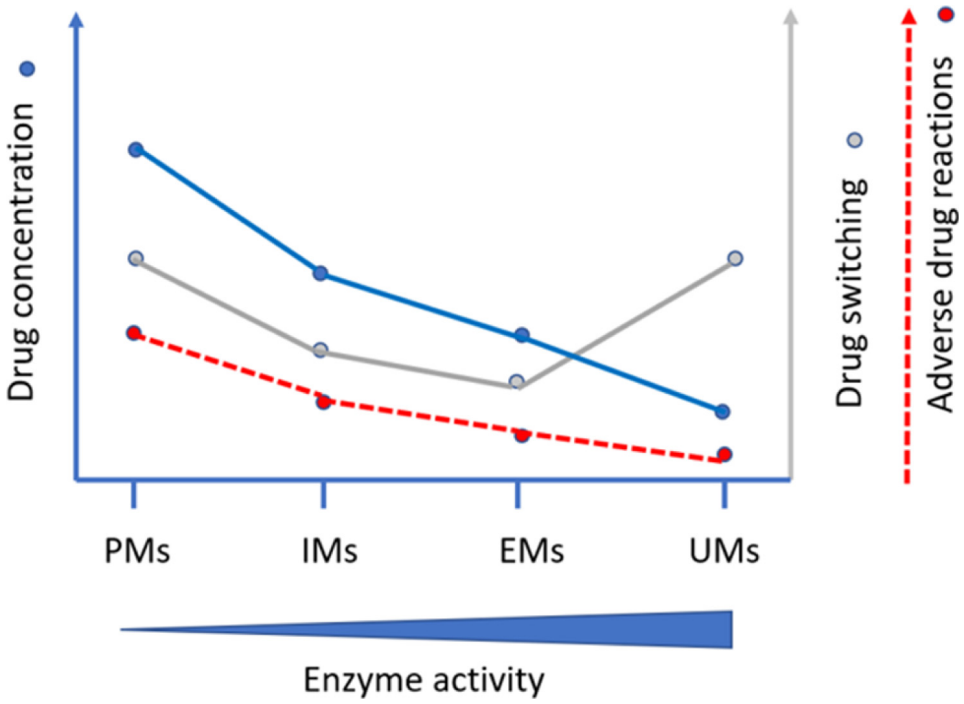

Figure 2. Effects of CYP2C19 and CYP2D6 phenotypes on drug metabolism. Patients lacking active enzymes (PMs) or having excessive enzyme activity (UMs) will obtain too high or too low levels of the drugs that are substrates for the enzyme to be effective. Three studies have examined the relationship between drug concentrations and the likelihood of switching medications among patients receiving escitalopram (substrate for CYP2C19) or risperidone or vortioxetine (substrates for CYP2D6). As seen, drug switching is more common among PMs and UMs, likely because too high and too low concentrations of the drugs are obtained, respectively. Increased capacity for drug metabolism during standard dosing causes lower drug concentrations and lower risk for side effects among UMs and vice versa among PMs. Data from [50,51,71]. Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizers; UM, ultrarapid metabolizers.

Altogether, the use of pre-emptive *CYP2C19* and/or *CYP2D6* genotyping to predict individual dose requirements during initiation of psychiatric drug treatment with follow-up by TDM is currently the best attainable way to ascertain the optimal drug exposure for every patient and subsequently to improve treatment outcome (see Figure 3). It is anticipated that such an approach will become dominant among good psychiatric clinical practices worldwide in the foreseeable future.

Genetic prediction of drug pharmacokinetic parameters: the missing heritability

Whereas the effect of known common *CYP2C19* and *CYP2D6* allelic variants on pharmacokinetic parameters is of very high clinical relevance and concerns large subpopulations, other currently unknown genetic factors can strongly influence drug pharmacokinetics. Twin studies have been very informative in evaluation of the genetic contribution to interindividual differences in drug metabolism (Figure 4) [46]. With respect to the inheritance of CYP-mediated drug metabolism, such studies revealed that pharmacokinetic parameters for the CYP2D6 substrate metoprolol and the CYP2C9 substrate torsemide are highly heritable, with correlation coefficients of 0.9–0.95 among monozygotic twins and 0.3–0.4 among dizygotic twins [47], providing $\mathbf{h^2_{SNP}}$ >0.8. A similar analysis of the pharmacokinetics of midazolam, a CYP3A4 substrate, revealed much higher impact of environmental factors [48], whereas recent analyses for clearance of

Table 1. Large randomized clinical trials that compared pharmacogenomically guided treatment and treatment as usual for depression[a]

Author	Arms	PGx tool	Setting	Design	Results
Greden *et al.,* 2019 [24]	TAU (n=607) vs. PGx guided (*n*=560)	GeneSight test based on Jablonski 2018 [72] and personalization algorithm from Hall-Flavin 2012 [73] were used	Outpatients with MDD with previous therapeutic failure during the current episode	24-week, patient-blinded randomized trial	Significantly better symptom improvement and remission rates were found in CYP guided group (**QIDS** and QIDS-SR scales) at week 8
Perlis *et al.,* 2020 [25]	TAU (n=150) vs. PGx guided (*n*=146)	Genecept Assay (version 2.0) for seven pharmacokinetic and 11 pharmacodynamic genes was used	Outpatients with MDD with previous therapeutic failure during the current episode	8-week follow-up, randomized double-blind trial	Symptom improvement and remission rates were not significantly different between test arms (as monitored with **HAM-D** and QIDS scales)
Bradley *et al.,* 2018 [26]	TAU (n=121) vs. PGx guided (*n*=140)	NeuroIDgenetix test for 10 genes (*CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A, MTHFR*) and IDgenetix personalization algorithm were used	Outpatients with MDD and/or anxiety with previous therapeutic failure during the current episode or new to the pharmacological therapy	12-week follow-up, randomized double-blind trial	Guided arm experienced better symptom reduction and response rate (measured with HAM-D scale) and anxiety symptom improvement (measured with **HAM-A scale**)
Perez *et al.,* 2017 [27]	TAU (n=161) vs. PGx guided (*n*=155)	Neuropharmagen test based on FDA, CPIC, or KNMP guidelines was used	Outpatients with MDD with previous drug change or new to the pharmacological therapy	12-week follow-up, randomized double-blind trial	No differences in sustained response were found between arms, but response rate was marginally higher in guided arm at week 12. Odds of achieving better tolerability were significantly higher in guided arm at week 12
Oslin *et al.,* 2022 [28]	TAU (*n*=826) vs. PGx guided (*n*=842)	GeneSight test based on Jablonski 2018 [72] and personalization algorithm from Hall-Flavin 2012 [73] were used	Primary care outpatients with MDD with previous drug change or new to the pharmacological therapy	8-week follow-up, randomized single-blind trial	Patients were followed up every 4 weeks for 24 weeks total. Pharmacogenetic guided arm had superior response and remission rates (measured with **PHQ-9 scale**) during week 8 and week 12 visits, but not at weeks 4, 18, and 24

[a]Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; GAD, generalized anxiety disorder; HAM-D, Hamilton Depression Scale; KNMP, Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie; MDD, major depressive disorder; PGx, pharmacogenomics-guided treatment; TAU, treatment as usual.

other drugs such as clopidogrel, gentamicin, tacrolimus, and cyclosporine showed inheritance h^2_{SNP} correlation coefficients of 0.41–0.48 [49]. Importantly, only 30–40% of the inherited variability could be explained by known genetic polymorphisms in genes encoding enzymes for drug **absorption, distribution, metabolism, and excretion (ADME)**, thus indicating that an important amount of heritability remains unexplained. This is discussed in detail below and graphically summarized in Figure 4A. The same phenomenon is specifically seen for metabolism of antidepressants and antipsychotics, where the lack of full understanding of the genetic basis for interindividual variation in CYP2C19 and CYP2D6 enzyme activity is illustrated in Figure 4B. The metabolism of escitalopram and risperidone is widely distributed within the

Key figure

Principle for individualized pharmacogenomically guided and therapeutic drug monitoring (TDM)-guided drug dosing in psychiatry

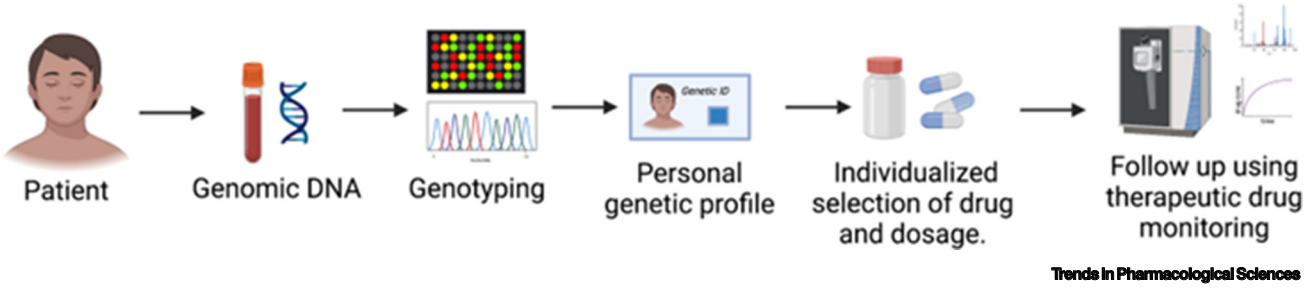

Figure 3. Initially, pre-emptive genotyping is carried out using a platform determining the relevant genetic variations in *CYP2C19* and/or *CYP2D6*. This gives the patient information of lifelong benefit for future drug treatment. Drug therapy is started in compliance with the results obtained, and drug and metabolite levels are followed up using TDM. Figure made in part with BioRender.com.

phenotypically defined NM, IM, and PM groups, with less relative variation in the PM groups [50,51]. This indicates that despite these firm phenotype classifications, there are additional genetic factors of importance determining the actual metabolism in the specific patient (see Figure 5). Putative factors of importance for explaining the missing pharmacogenomic information in studies of drug pharmacokinetics include (i) the contribution of rare variants, (ii) incomplete next-generation sequencing in genetically complex loci that require long-read sequencing or special bioinformatic tools, (iii) the occurrence of functionally different **haplotypes** of alleles all harboring a genetic variant specifically classified in the allelic nomenclature, (iv) the fact that one given enzyme variant has an altered specificity for different substrates as compared with the normal variant, (v) the global inheritance of genetic variants indirectly affecting the level of enzyme expression, and (vi) the direct regulation of ADME genes by polymorphic nuclear factors such as nuclear factor IB (NFIB). Below we explain further the situation in relation to prediction of psychiatric drug response, starting with the rare genetic variants.

Rare functional variants in ADME genes

Unlike the common variants, rare variants have mostly not been considered among clinical pharmacokinetic studies, even though the role of rare variants has been shown to be more important than originally anticipated. Thus, rare genetic variants are significant for genetic polymorphism in about 50% of genes encoding important enzymes and transporters [52]. Analysis of genetic variants in 208 pharmacogenes from 60 706 individuals revealed that each individual harbored, on average, a total of 40.6 putatively functional variants, rare variants accounting for 10.8% of these, with about half of them seen only in one individual. Analysis of the data from 487 409 participants in the UK Biobank revealed that among eight ADME genes, 6.1% of subjects carried at least one deleterious variant [53]. Therefore, it can be assumed that rare variants alone can explain 6–10% of the missing heritability in ADME gene pharmacogenomics. Specifically, for *CYP2C19* and *CYP2D6,* 12% and 7% of the interindividual variability in enzyme function, respectively, can apparently be attributed to rare genetic variants [54]. To ascertain the best attainable treatment personalization with respect to rare variant contribution, a pharmacogenomically based prediction tool would therefore need to

Box 2. Use of TDM in psychiatry

There are typically four main indications for TDM of antidepressants and antipsychotics:

(i) Dose titration
(ii) Troubleshooting, that is, suspected nonadherence, side effects, or treatment resistance
(iii) Polypharmacy and drug interactions
(iv) Organ failure

Although items (ii–iv) are more or less universal indications, dose titration is primarily recommended for drugs with a narrow therapeutic window. Lithium, which is used in the treatment of bipolar disorder, is viewed by all as having a narrow therapeutic window, with a factor of 2 between the upper and lower boundaries of the target concentration range (0.5–1.0 nmol/l) [13]. Thus, TDM is routinely used to titrate lithium dosing. The same is true for clozapine, where there is a 1.7-fold range (1.07–1.83 nmol/l) between the upper and lower levels of the recommended concentrations [67]. For most other psychiatric drugs, though, the term 'narrow therapeutic window' is rarely used. This may reflect a lack of studies investigating this issue [68,69]. Furthermore, in many instances, TDM provides a good follow-up method for dose titration based on pre-emptive genotyping in psychiatric drug therapy, as summarized in Figure 3 in main text.

Guidance for the use of TDM in psychiatry is provided by Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie [70]. This was found to be very valuable for the use of TDM for antidepressants and antipsychotics in terms of standard recommendations. The recommendations follow a four-grade system as follows:

Level 1. 'Strongly recommended' for dose titration and for special indications
Level 2. 'Recommended' for dose titration and for special indications
Level 3. 'Useful' for special indications or problem solving
Level 4. 'Potentially useful' for special indications or problem solving

In the guidelines, a total of five antidepressants and eight antipsychotics are defined as Level 1 drugs, whereas 15 antidepressants and ten antipsychotics are defined as Level 2 drugs, respectively (Table I). Among antidepressants, tricyclic antidepressants and citalopram are classified as Level 1 drugs, whereas clozapine and olanzapine are the atypical antipsychotics assigned as Level 1 drugs.

Table I. Antidepressants and antipsychotics where TDM is strongly recommended (Level 1) or 'recommended (Level 2)' for dose titration in Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie guidelines [70]

Drug class	TDM strongly recommended (Level 1)	TDM recommended (Level 2)
Antidepressants	Amitriptyline, citalopram, clomipramine, imipramine, nortriptyline	Bupropion, desipramine, dothiepin, doxepin, duloxetine, escitalopram, fluvoxamine, maprotiline, milnacipran, mirtazapine, sertraline, trazodone, trimipramine, vortioxetine
Antipsychotics	Amisulpride, clozapine, fluphenazine, haloperidol, olanzapine, perazine, perphenazine, thioridazine	Aripiprazole, bromperidol, chlorpromazine, flupentixol, paliperidone, quetiapine, risperidone, sertindole, thioridazine, ziprasidone

include extensive sequencing of all ADME genes; however, this is not feasible for routine clinical use [55] and should be done only in special clinical cases.

Unknown genetic variations within the established ADME variant alleles

The prediction of genetically influenced drug pharmacokinetics today is based mainly on the distribution of the established genetic variants as presented, e.g., in PharmVar[vi] and PharmGKB.[ix] However, a defined *CYP* allele might also be in linkage disequilibrium with genetic variants in the vicinity of the gene locus, causing alterations in gene expression. Thus, a *CYP2C* haplotype harboring the wild-type *CYP2C19*1* allele but carrying *rs2860840(T)>C* and lacking *rs11188059G>A* mutations in the neighboring *CYP2C18* gene was recently found to associate with ultrarapid metabolism of escitalopram, at least as substantial as the commonly established ultrarapid *CYP2C19*17* allele [56]. It is thus likely that genetic variants remote from the ADME

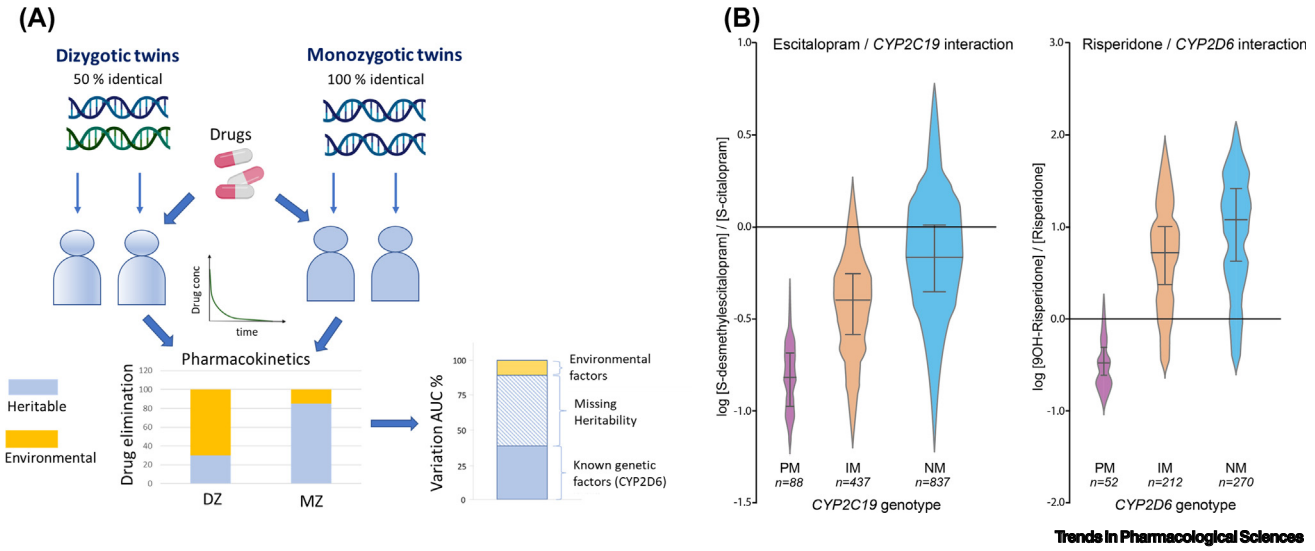

Figure 4. Missing heritability in drug metabolism. (A) Genetic heritability of drug metabolism by CYP2D6. The role of inheritance for interindividual variation in CYP2D6 activity was studied in monozygotic (MZ) and dizygotic (DZ) twins. By comparing the correlation coefficients between the pharmacokinetics of the CYP2D6 substrate metoprolol in MZ and DZ twins, the relative roles of genetic variation and environmental effects could be calculated. The heritability was found to be high, 82%, but only 40% of this genetic variation could be explained by known genetic *CYP2D6* variants. Data from [47]. (B) Rate of metabolism of the antidepressant drug escitalopram and the antipsychotic drug risperidone, determined by the metabolic ratio between metabolite and substrate in relation to the genetically classified phenotypes of CYP2C19 and CYP2D6, respectively. The interindividual variation in drug metabolite to substrate ratio is comparatively small in the poor metabolizer (PM) group devoid of enzyme activity but very extensive in the other phenotypic groups – intermediate metabolizers (IM) and normal metabolizers (NM) – who have active CYP genes. Data from [50,51].

gene in question – variants that are not currently known – contribute to the interindividual variation in ADME gene expression.

Among the ADME genes, several, such as *CYP2A6, CYP2B6, CYP2D6, UGT2B15, UGT2B17*, and *SULT1A1*, are located in complex regions of the genome, where, e.g., sequentially similar pseudogenes complicate high-resolution sequencing [57]. For such genes, it is important to apply PCR-based long-read sequencing using, for example, PacBio or Oxford Nanopore or synthetic long-read sequencing or special bioinformatic tools for correct sequencing analyses [58]. A recent investigation found that the predictability of CYP2D6-mediated metabolism of tamoxifen to endoxifen was increased from R^2 of 0.54 to R^2 of 0.79 by use of long-read sequencing [59]. This fact makes it of dubious value to determine pharmacogenomic variation only by using, for instance, next-generation sequencing in the whole-genome application; a reliable analysis must be accompanied in such cases by use of long-read-based methodology on the complex loci.

Substrate specificity for the influence of ADME variant alleles

The effects of the genetic ADME variants can include altered expression levels or altered enzyme functionality caused by amino acid exchanges, resulting in substrate-specific consequences. This applies, e.g., to the *CYP2D6*2, CYP2D6*10*, and *CYP2D6*17* alleles [60,61]. The establishment of universal algorithms for the prediction of drug pharmacokinetics then fails to accurately predict substrate-specific effects. For example, algorithms based on long-read PCR sequencing of *CYP2D6* differed substantially in their capacity to predict CYP2D6-dependent metabolism, depending on whether tamoxifen or venlafaxine was used as a substrate [59]. In summary, more research focused on substrate specificity of variant ADME alleles is needed to avoid prediction errors of pharmacogenetic tests; ideally, an individual predictive algorithm should be developed for each drug, based on its unique metabolic profile.

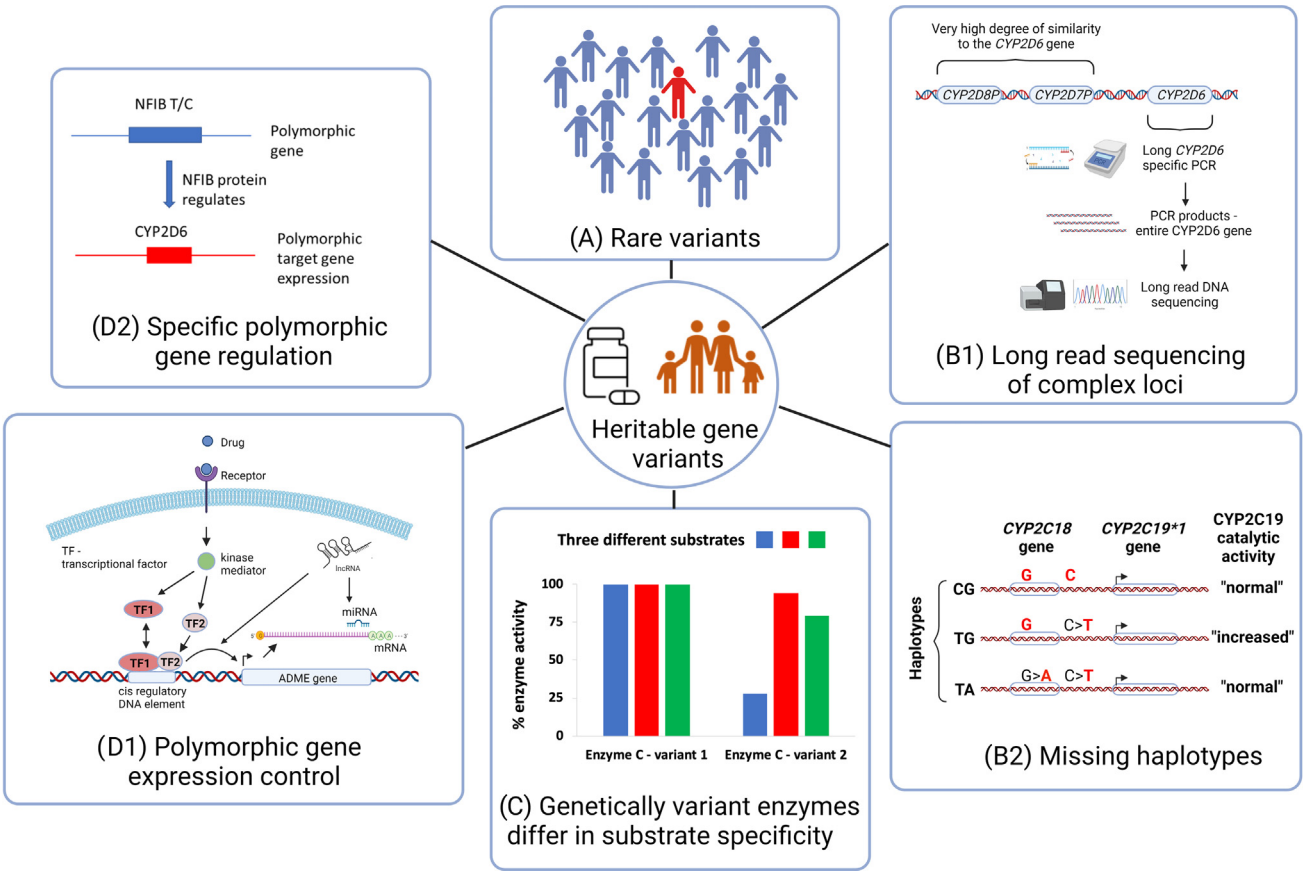

Figure 5. Factors of putative importance for explaining the missing heritability in pharmacogenomics. The observed heritability causing interindividual variation in drug metabolism and transport is in many cases much higher than what can be explained by known genetic variants of the genes of importance. Putative contributing factors are (A) rare genetic variants; (B) (1) the incomplete gene sequence obtained following next-generation sequencing in genetically complex loci that require long-read-based sequencing or special bioinformatic tools; (2) the occurrence of functionally different haplotypes of alleles harboring a common genetic variant traditionally used for a specific metabolic phenotype, here illustrated by the action of the CYP2C:TG allele [56]; (C) the fact that one given enzyme variant has an altered specificity for different substrates as compared with the normal variant; and (D) (1) genetic polymorphism in other classes of genes controlling the expression of genes encoding transporters or enzymes, where (2) illustrates the direct regulation of absorption, distribution, metabolism, and excretion (ADME) genes by polymorphic nuclear factors such as NFIB. Figure made in part by BioRender.com.

Regulation of pharmacokinetic properties by non-ADME polymorphic regulatory genes

To explain the high heritability of drug metabolism by, for example, CYP2D6, additional hitherto unknown non-ADME polymorphic genes must be considered. These are expected to influence ADME gene expression on the genetic level or post-transcriptional level. Several of the ADME gene products are regulated by miRNAs, lncRNAs, and post-translational events such as activation through phosphorylation or different rates of degradation through the endoplasmic reticulum ubiquitin complex or via the autophagosomal–lysosomal pathway. Indeed, the field of pharmacogenomics has hitherto not considered these aspects. Taken together, it is likely that inherited differences in all these control levels, including a myriad of different regulatory RNAs and proteins, can contribute to the missing heritability identified by the twin studies.

One example of such an external regulatory factor, which was only recently discovered, is the *NFIB* gene, involved in the control of tumor growth and embryonic development. The role of

NFIB rs28379954 T>C (*NFIB_TC*) polymorphism was initially discovered by a genome-wide association study where NFIB_TC carriers had an almost 40% lower dose-adjusted serum concentration of clozapine [62]. Using a liver spheroid model, it was found that NFIB controlled CYP2D6 expression, which had important clinical consequences regarding risperidone metabolism, where CYP2D6 NMs carrying the NFIB_TC polymorphism exhibited an UM phenotype [63]. Therefore, this report demonstrated that polymorphisms not even on the same chromosome 22 as the *CYP2D6* locus can affect CYP2D6 metabolism, and it is anticipated that more such examples will be presented in the near future and will explain a substantial amount of missing heritability.

Practical challenges and ethical considerations

As mentioned earlier, the routine use of psychiatric pharmacogenomics in the clinics is currently not very common. Major challenges for the implementation of pharmacogenomic biomarkers in the psychiatric clinic are clinicians' reluctance to change their treatment routines and their lack of knowledge related to new developments in pharmacogenomic research. This emphasizes the need for pharmacogenomic education of physicians and nurses but also the importance of effective dissemination of recent findings in pharmacogenomics in a manner that can motivate clinicians to consider pre-emptive genotyping.

Due to national differences in the cost of both laboratory pharmacogenetic testing and health care writ large, it is difficult to estimate the cost-effectiveness of pre-emptive genotyping in psychiatry. Karamperis *et al.* [64] recently reviewed this area and found that 16 of 18 studies (89%) showed results in favor of pharmacogenomics-guided treatment testing, of which nine genome-guided interventions were cost-effective and seven were not more costly than standard treatment. The best supportive evidence was, as expected, for the *CYP2D6* and *CYP2C19* drug–gene associations. Using an economic model of the cost utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care, Sluiter *et al.* indicated that screening for *CYP2D6* is cost-effective, but this hypothesis still requires further validation [65]. There is thus growing evidence supporting the cost-effectiveness of genome-guided interventions in psychiatry, and more studies are expected to confirm this conclusion.

Regarding ethical considerations, pharmacogenomically based treatment individualization is of benefit for the patient and of no primary ethical concern, because the analyses exclusively target variants of relevance for drug treatment. Although whole-genome sequencing can sometimes lead to incidental findings of, for example, risk genes for particular diseases, this is seldom an issue when using the predefined commercial pharmacogenomic genotyping tools. However, in contrast to the guidelines for handling incidental findings developed for whole-exome or whole-genome sequencing, no such guidelines have been developed for clinical laboratories performing pharmacogenomic analyses [66]. It is therefore important to educate patients and providers to minimize any fears related to incidental findings and their potential negative consequences.

Concluding remarks and future perspectives

Genotype-guided psychiatric drug treatment is not yet extensively used in psychiatry. However, several recently published high-power RCTs studies suggest that treatment outcome can be improved if genotype-guided decisions on prescribing psychiatric drugs replace the traditional, treatment-as-usual approach while also being cost-effective. Better understanding of the origin of the inherited pharmacokinetic variability of psychiatric drugs is required to formulate even more appropriate decision support tools and dosing recommendations; currently, we are not able to explain more than 50% of the genetic factors that determine interindividual differences

Outstanding questions

Which of the current pharmacogenomic biomarkers in psychiatry should be routinely used in clinics?

What are the genetic bases for the missing heritability in the interindividual variability regarding pharmacokinetics of antidepressants and antipsychotics?

What are the socioeconomic advantages of pre-emptive genotyping in psychiatry?

To what extent can genetic screening based on genome-wide association studies and whole-genome sequencing improve the value of pharmacogenomics in psychiatry?

Will the use of therapeutic drug modeling increase understanding of dose–efficacy relationships in psychiatry?

in pharmacokinetic parameters. Furthermore, implementation of pharmacogenomics into psychiatry needs well-educated and motivated clinicians, as well as support from patient organizations. We believe that a broader use of genetically based psychiatric drug therapy is realistic in the foreseeable future and will further contribute to improving psychiatric treatment outcomes, with reduced costs for psychiatric drug treatment and improved mental health in the population (see Outstanding questions).

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Declaration of interests

M.I.-S. is a cofounder and co-owner of HepaPredict AB. The other authors declare no conflicts of interest.

Resources

[i]https://www.healthypeople.gov/2020/topics-objectives/topic/mental-health-and-mental-disorders

[ii]https://www.who.int/news-room/fact-sheets/detail/schizophrenia

[iii]https://www.who.int/news-room/fact-sheets/detail/depression

[iv]www.who.int/news-room/fact-sheets/detail/depression

[v]www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

[vi]www.pharmvar.org/

[vii]www.psy-pgx.org/PSY-PGx

[viii]www.cochranelibrary.com/central/doi/10.1002/central/CN-02376282/full

[ix]www.pharmgkb.org/

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