INVITED REVIEW

Precision medicine in mood disorders

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Abstract

The choice of the most appropriate psychoactive medication for each of our patients is always a challenge. We can use more than 100 psychoactive drugs in the treatment of mood disorders, which can be prescribed either alone or in combination. Response and tolerability problems are common, and much trial and error is often needed before achieving a satisfactory outcome. Precision medicine is therefore needed for tailoring treatment to optimize outcome. Pharmacological, clinical, and demographic factors are important and informative, but biological factors may further inform and refine prediction. Twenty years after the first reports of gene variants modulating antidepressant response, we are now confronted with the prospect of routine clinical pharmacogenetic applications in the treatment of depression. The scientific community is divided into two camps: those who are enthusiastic and those who are skeptical. Although it appears clear that the benefit of existing tools is still not completely defined, at least in the case of central nervous system gene variants, this is not the case for metabolic gene variants, which is generally accepted. Cumulative scores encompassing many variants across the entire genome will soon predict psychiatric disorder liability and outcome. At present, precision medicine in mood disorders may be implemented using clinical and pharmacokinetic factors. In the near future, a genome-wide composite genetic score in conjunction with clinical factors within each patient is the most promising approach for developing a more effective way to target treatment for patients suffering from mood disorders.

KEYWORDS
antidepressants, depression, precision medicine, psychiatry, psychopharmacology

WHY WE NEED PRECISION MEDICINE IN MOOD DISORDERS

Choosing the most appropriate psychoactive medication for each of our patients is always a challenge. In a very brief period of time during the patient consultation, we must choose from a large number of compounds while taking into account a variety of factors such as the patient's symptomatology profile, previous efficacy, medical comorbidities, subject preferences, family history, and biological findings.

We can use more than 100 psychoactive drugs in the treatment of mood disorders, which can be prescribed either alone or in combination. Because of biological factors that are still largely unknown, the few drugs or combinations of drugs that are effective and tolerated for each individual patient are identified only after a long process. The standard clinical practice involves a trial-and-error procedure that may take months or even years to determine the most effective treatment for each individual patient in a given situation. A significant economic and societal burden results, which we should

seek to alleviate wherever possible. Following a thorough collection of anamnestic and biological features, clinicians may be able to improve the treatment process by selecting the most appropriate treatments from the very beginning of the interaction with the patient. This is referred to as precision medicine, and it is this that will be the focus of this review. The following sections concentrate on antidepressants, but the approach is the same for mood stabilizers and antipsychotics as for antidepressants.

CLINICAL PRECISION MEDICINE

Before we get into genetic precision medicine tools, we will take a quick look at how it is currently possible to optimize our treatments solely on the basis of clinical information. The first and most important thing to remember is that psychiatrists should use any and all of the medications that are available to them. To accomplish this, we must constantly review and update our knowledge of all of the compounds that are available in our nation. While it is understandable that general practitioners may be familiar with a small number of drugs and that they use those same few drugs on a consistent basis, this is not acceptable in the field of specialization. In fact, it is possible that a psychiatrist is only familiar with a few antidepressants, such as sertraline, mirtazapine, and venlafaxine. This hypothetical psychiatrist may decide to prescribe mirtazapine for subjects who suffer from insomnia, venlafaxine for subjects who suffer from depression and anxiety at the same time, and sertraline for elderly subjects. While this strategy is not inherently wrong, it does have significant limitations. As a result, many patients may receive suboptimal treatment because of a lack of coverage for all possible medications that may be prescribed. For example, venlafaxine has been shown to be effective in subjects suffering from depression and anxiety at the same time in the literature, but it is frequently associated with significant sexual side effects, and escitalopram, for example, could be preferred for some subjects.

This example demonstrates how a lack of familiarity with all available antidepressants can result in suboptimal treatment and an increase in societal and individual burden.

Clearly, comprehensive knowledge of the over 40 antidepressants and over 100 psychoactive medications that may be used to treat mood disorders necessitates considerable effort. In the future, it will almost certainly be possible to receive assistance from automatic decision-making tools that are currently under development.[1] A benefit of clinical decision support tools has already been demonstrated in this direction.[2]

International guidelines are intended to aid in the process of decision-making. Unfortunately, due to the large number of factors that must be considered and which are not usually addressed by recommendations, guidelines are often ineffective when it comes to selecting the most appropriate compound. In reality, guidelines typically recommend the use of antidepressant classes rather than specific medications, and differences between specific medications are rarely noted.[3–6]

Additionally, the majority of meta-analyses strongly support the absence of a clear superiority in terms of efficacy among antidepressants.[7] They mainly differ regarding their pharmacodynamic and tolerability profiles.

Due to a lack of specific recommendations and the absence of clearly more effective compounds, psychiatrists typically prescribe based on their own subjective prior experiences and personal opinions. This is diametrically opposed to evidence-based precision medicine and should be avoided.

Consequently, we should base our decisions on evidence-based standards rather than on subjective judgments. To begin with, past responses must be considered: if an individual has previously experienced positive results from an individual drug, this is the most compelling reason to prescribe that drug again. If this information is not available, we can rely on information from other members of the same family who have similar characteristics. Given the fact that first-degree relatives share 50% of their genetic background, a positive response to a specific compound in a first-degree relative of the patient is also a very strong indication for the use of the same compound in the patient, unless the use of the same compound is contraindicated for other reasons (e.g., pregnancy).[8]

In the case of concomitant treatments, it is critical to consider the pharmacokinetic and pharmacodynamic interactions that may occur.[9]

Previous paragraphs detailed the very first steps in the development of clinical personalized medicine in the treatment of mood disorders. The pharmacodynamic profile may then serve as a further guide for the development of specific symptomatology profiles. Drugs for treating depression have a wide range of pharmacodynamic profiles, which can be very different from one another. Because of this, it is critical to select the appropriate medication based on the specific profile of the compound versus the specific symptomatology of the patient.[10]

A patient suffering from anhedonia and lethargy may benefit from compounds that inhibit noradrenaline and dopamine transporters, for example, because these two neurotransmitters have been shown to have a more stimulating effect than other neurotransmitters. For patients who suffer from severe anxiety as well as insomnia, compounds with anticholinergic or serotonin 2c inhibiting properties may be more beneficial than others. However, despite the fact that this appears reasonable and that many practitioners employ algorithms similar to this in their practice, specific proof is still lacking, and research demonstrating the superiority of such algorithms over standard care would be extremely beneficial.

Having medical comorbidities is another important factor to consider when looking at how the aging population will affect treatment modalities. There are a number of substances that may be contraindicated in the case of certain medical conditions. Several other sources of detailed information on tailored treatment for patients with specific medical problems can be found.[5] As an example, we should avoid administering drugs with a long half-life to patients with hepatic impairment or compounds that reduce respiratory function in patients with chronic respiratory disorders.

The tolerability profile of a given medication, on the other hand, should be examined not only in patients with concomitant medical disorders, but also in patients who do not have medical comorbidities, to promote compliance. As a matter of fact, it has been observed that compliance in outpatient settings can be as low as 50% due to patients' inability to tolerate minor but bothersome side effects such as weight gain, sexual dysfunction, gastrointestinal issues, or sleepiness.

The range of side effects caused by different medications is quite variable, and it is arguably the most important factor to consider when determining the most appropriate medication for each individual patient. For clinically based precision medicine, tolerability is one of the most important principles to keep in mind when selecting treatments. Unfortunately, there is no antidepressant that is completely free of side effects. We have seen that the efficacy criterion does not provide useful information for the selection of pharmaceutical compounds. Due to these considerations, selecting the tolerability profile that will work best for each individual patient is arguably the most important aspect of precision medicine that we can implement in clinical practice at this time. Though generally well tolerated, antidepressants are associated with a variety of side effects, ranging from minor ones that may impair our patients' compliance to more serious ones that can be life-threatening. A detailed knowledge of each drug profile is therefore important. Many psychiatric diseases, particularly depression, are associated with sleep disturbances, as is the case with many other medical conditions. Antidepressants, on the other hand, have a variety of effects on sleep, with nearly all of them having some effect. This feature is extremely beneficial in terms of the individualization of the treatment. Unfortunately, labels and current recommendations are not very helpful when it comes to selecting a substance based on its sleep effects, as many compounds have been reported to cause both insomnia and somnolence in the same individual. In addition, the therapeutic experience varies greatly from person to person. In an unpublished Italian survey, 1000 psychiatrists were polled on a list of antidepressants, and they were asked whether they thought each one was primarily sedating or activating. The results were astonishing. The results revealed wide variations in the psychiatrists' opinions, to the point where some compounds were rated as sedative by half of the psychiatrists and as stimulant by the other half. This shows that evidence-based data are needed otherwise subjective opinions may lead to suboptimal treatment in many subjects.

A number of meta-analyses have been conducted to provide evidence-based data that could be used to guide appropriate prescriptions. This information is extremely useful, despite the fact that it is scattered throughout the literature and may be difficult to find for psychiatrists who spend the majority of their time in clinical practice. The following section contains a few examples of this type of information, but a more detailed list of steps for the selection of the most appropriate treatment has already been published, and the reader is encouraged to consult it for additional information.[11]

It is common for people to experience sexual dysfunction while they are depressed or as a side effect of many treatments for depression, making it particularly bothersome for them and potentially leading to treatment discontinuation. In fact, sexual dysfunction is so common during depressive episodes that it has been included in rating systems as an indicator of the overall severity of the depression. However, many psychiatric medications, including antidepressants, have the side effect of sexual dysfunction as a result of their administration. The result is that treating patients who suffer from treatment-induced sexual dysfunction is particularly difficult: patients are expected to improve their sexual functioning while also improving their depression; however, treatment may actually counteract this progress by causing treatment-induced sexual dysfunction. As has been documented numerous times in clinical practice, this time course may result in a lack of compliance or a false impression that depression is still present. Because of this, patients must be given a thorough explanation of the phenomenon, but having evidence-based knowledge about the degree of sexual dysfunction caused by each available medication is also beneficial. As a result, we discovered a wide range of effects in our first meta-analysis. For example, some compounds (venlafaxine, fluoxetine, paroxetine, sertraline, and citalopram) were associated with treatment-induced sexual dysfunction in more than 80% of the subjects, while others (escitalopram, duloxetine, and fluvoxamine) were associated with mild sexual dysfunction.[12]

Sexual dysfunction is not the only possible side effect. Another relevant one is insomnia or diurnal somnolence. We ranked antidepressant drugs based on their ability to induce diurnal somnolence or insomnia in a recent meta-analysis;[13] this evidence based ranking is another clear example of possible guidance for clinical practice.

The accumulation of body fat is another important and common side effect of antidepressants and the vast majority of psychiatric medications. Patients are frequently concerned about gaining weight, which is a common source of noncompliance, not to mention the metabolic consequences. A ranking of available compounds for this common side effect was also conducted, and we found that there was significant variability, particularly in the long term, with mirtazapine and paroxetine both causing weight gain of approximately 2–3 kg, while others are more neutral, and bupropion caused weight loss on average, likely due to its dopaminergic profile.[14]

Following the findings of those studies, and others available in literature, it is possible to implement a precision medicine strategy that is based on clinical information. Meanwhile, as we await the development of more complex algorithms that incorporate biological or genetic measures, we can improve our current prescription practices by incorporating all available clinical evidence-based information. Despite the fact that guidelines are useful, in this section we outlined some of the processes that should be followed to arrive at a treatment that is tailored to our patient's clinical characteristics, while taking into consideration everything that is known about the over 40 drugs that can be used to treat depression, including the possible use of psychotherapies, which are not detailed in the present review but the reader may find more information on these in the literature.[15] In conclusion of this section, it is clear that there is no such thing as a "good" or "bad" medication; any side effect may be problematic in some cases while being advantageous in others. Patients who have

lost a significant amount of weight as a result of a disease, for example, may find it beneficial to gain some weight. Despite the fact that consultation time is always limited, and the amount of readily available information about compounds is vast and constantly changing, we should strive to optimize our prescribing method to obtain an evidence-based precision medicine prescription as much as is reasonably possible in each case.

GENETIC PRECISION MEDICINE

We have seen in the previous section how a detailed clinical and pharmacological selection process can be of significant assistance. However, it is possible that this will not be sufficient. We know that approximately one-third of depressed subjects do not respond to first-line treatments, and it is difficult to predict in advance who will develop treatment resistance at this point in time.[16,17] Precision medicine in the treatment of mood disorders will, as a result, be complemented by biological considerations. Aspects of biology include laboratory and genetic findings, which can provide information about potential treatment resistance as well as the selection of specific compounds for each patient. The knowledge of potential resistance is valuable in itself because it allows us to begin treatment with greater intensity from the beginning, avoiding the time-consuming process of trial and error.[18] We recently detailed this[19] and also in a step-by-step approach.[20]

The first and most straightforward step is the measurement of drug plasma levels, which is commonly referred to as therapeutic drug monitoring (TDM). Plasma level is routinely used for mood stabilizers and clozapine, but it is not used nearly as much for antidepressants, with the exception of the old tricyclic drugs.[21] This is based on the assumption that for new antidepressants the plasma level is not relevant for response. The contrary is true, as accumulating evidence indicates that not only do low plasma levels reduce efficacy, but that excessively high plasma levels are also harmful, as they are associated with a higher incidence of side effects and reduced efficacy as well.[22–24]

TDM should therefore be performed in clinical practice at least in those cases where there is no response or severe side effects. However we should also be aware of the genetic metabolizing background of the patient. Cytochrome P450 superfamily enzymes (CYP450) variants in fact may inform on the potential metabolizing status also in the absence of TDM.

The following metabolic phenotypes are distinguished based on genetic variations: ultra-rapid metabolizers (UM; increased conversion into metabolites, higher risk of treatment failure), normal (extensive) metabolizers (NM; average risk of side effects and therapeutic failure), intermediate metabolizers (IM; slower elimination and higher risk of side effects), and poor metabolizers (PM; slower elimination and higher risk of side effects). The polymorphic variations that are clinically actionable are mainly found in the CYP2C19 and CYP2D6 genes, which encode enzymes that are heavily involved in the metabolism of antidepressants.

Due to the convincing evidence of their association with antidepressant response and side effects, these metabolizing groups have been included in guidelines as biomarkers useful for guiding antidepressant prescription, to the point that, according to the Food and Drug Administration, the number of psychoactive compounds with a suggestion of performing CYP genetic analysis[25] in the label is second only to oncology.[26] The reader may refer to international guidelines for details for each specific drug.[27] Citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine are all recommended with a moderate or strong level of evidence. Accordingly, the largest meta-analysis available confirms that PM subjects report a higher level of side effects.[28] Oral doses should be then adjusted on the basis of the metabolizing status of the subject.

So far we have listed laboratory and genetic variants that are indeed supported by guidelines and should be used in routine clinical practice, at least in those patients who show poor response or a high level of side effects. However, the largest part of the genetic variation that modulates drug efficacy and tolerability is the one relative to brain expressed genes. It has been demonstrated that about 50% of the variance of the effects of antidepressants is linked to genetic variations[8,29] and that those variations are modulating interindividual brain function differences.

Early studies focused on single genetic variants expressed in the brain. The working hypothesis that served as the foundation for this first study was extremely sound, given that we know that serotonergic antidepressants block the serotonin transporter (HTT) in the brain within a few hours of ingestion, and that this is the starting point for the entire antidepressant efficacy. As a result, patients with different functional serotonin transporters might have a reduced response to antidepressant medications. That hypothesis could be tested at the time because it had only been a few years since the discovery of the possibility of investigating genetic variants within the HTT and that a gene variant located in the promoter (5-HTTLPR) had a functional effect by altering the amount of HTT available in the brains of patients.[30] Initial findings were interesting,[31–35] but after over 20 years, replication has occurred in some samples, while replication has not occurred in other samples, and replication has occurred in a few other samples but in the opposite direction of the original results.[36] Also the investigation of a number of other possible genes influencing antidepressant outcome, belonging to the serotonin system, glutamatergic system, neurodevelopment, intracellular signalling, and so on, yielded mixed results.[37,38] At present we may not therefore support variations within the 5-HTTLPR as a strong and unequivocal factor modulating antidepressant response and tolerability, probably due to the fact that a number of complementary and alternative pathways interact together with environmental factors, with 5-HTTLPR obscuring possible effects.[39,40]

Despite these unstable results coming from single candidate gene analyses, at present a number of commercially available genetic testing kits are routinely used. The spread of such kits reached the general press and a few years ago the international press reported a case who apparently benefited from pharmacogenetic analysis.[41] This was the case of a woman suffering from treatment-resistant

depression who did not respond to a large number of antidepressants. Genetic testing was performed, amitriptyline was suggested, and the woman improved. This news sparked general interest and a number of pharmaceutical companies developed pharmacogenetic kits, each one differing from the other. Later in this review these kits will be critically evaluated, and the reader may also find detailed information in specific papers.[42]

The failure to provide relevant information from the analysis of single gene variants prompted researchers to investigate the whole genome.

The introduction of chip-based microarray technology, which is capable of interrogating thousands of polymorphisms throughout the genome, has given new life to genetic association studies and heralded the arrival of new design studies, such as genome-wide association studies (GWAS). Because of these advancements, a new term, pharmacogenomics, has emerged to reflect the shift from single genes to virtually the entire genome, accurately genotyping 500,000 to more than 7,000,000 SNPs in a cost-effective manner, and identifying novel therapeutic targets. GWAS do not necessitate the development of an a priori hypothesis to overcome the problem that the mechanisms of psychotropic drug action are not fully understood.

Furthermore, noncoding sequence polymorphisms outside exons were found to be the most significantly associated polymorphisms in behavioral GWAS,[43] and the disruption in a gene or pathway function is caused by the cumulative effect of multiple variants. We will see in the following sections how this concept has the potential for a much more informative support in clinical routine practice. The effect size for each single polymorphism is expected to be very small in comparison to that found for rare disorders because common disorders are influenced by genetic variations that are also common in the general population. Because of this assumption and the heritability of common disorders, it is reasonable to assume that multiple common alleles influence disease susceptibility at the same time.

During the last decade, many GWAS have been performed targeting antidepressant response and tolerability,[44,45] including the most recent and large meta-analysis.[46] Results, however, have so far failed to yield strong findings, and at present results from GWAS are not used in clinical routine activity and need further clarification. In fact the variance explained is in the range of 1%, much less than the 50% that we know is due to genetic factors from heritability studies. The remaining information may then be found in variants not included in GWAS studies. GWAS include only less than 0.1% of the genome, approximately one base in every 1000. Therefore studies are now including all the variants in the genome, both common and rare variants. These studies are exome sequencing, which sequence the whole exomes, and whole-genome sequencing, which sequence the complete genome. Whole-genome sequencing analyses are at present quite expensive and also difficult to manage in terms of analysis considering that for each subject seven billion variants are available.[47]

Thus, the first exome sequencing studies on antidepressant response were performed.[48] The results were highly encouraging. When compared to responders, TRD patients associated genetic variants were located within genes and pathways that modulated cell survival and proliferation, neurodegeneration, and immune response, to name a few examples, pathways that are known to be part of antidepressant action.[49] There was also a significant prediction of TRD versus response using genetic models, and these models were improved by the addition of clinical predictors. Many variations across the genome may be summarized in the so-called polygenic risk scores (PRS for GWAS).

The combination of clinical and cumulative genetic predictors such as PRS is therefore a clear pathway for future routine applications. We have already shown the importance of clinical predictors, but an in-depth analysis of depressed patients showed the details needed are more than few clinical variables, they include personality dimensions, temperament, psychological defense mechanisms, self-esteem, intelligence, and social adjustment to mention just some of them.[50] Indeed, for other medical disorders it has been suggested that the variability due to biological and environmental factors is strong to the point that in the future clinical trials may be performed at an individual basis.[51]

We may therefore hypothesize that in the near future all patients will be described by a composite score summarizing all clinical and genetic factors which may contribute, in a nonlinear way, to treatment response and tolerability. We detailed this method in a recent paper[52] and it has the potential to be included in individual health records to produce a support tool for prescribing clinicians.

A very recent example suggests the possibility that PRS may even inform about the specific compound to use in a given patient. Indeed depressed subjects with high PRS of schizophrenia (but not affected by schizophrenia) show a better response when treated with second-generation antipsychotics combined with antidepressants, while depressed patients with low schizophrenia PRS show little or no benefit from the combination.[53] Others similarly reported that high PRS for schizophrenia may also predict poor lithium response in bipolar patients.[54] It has therefore been hypothesized that a composite score for all the major psychoses may be informative for profiling a precision treatment for every patient.[55]

PRECISION MEDICINE IN CLINICAL PRACTICE

At the moment, there is a vigorous and ongoing debate within the scientific community about the advantages of the commercial tools that are currently available that include 5-HTTLPR gene variants. According to the International Society of Psychiatric Genetics, only a careful use of pharmacokinetic CYP variants should be used in clinical routine, but not other brain expressed variants such as 5-HTTLPR.[56] Concerns have also been raised by other scientists.[57] On the other hand, a number of researchers in the field are confident that existing tools, including pharmacodynamic genes, will be beneficial for routine clinical activity.[58]

In any case, the use of available tools is uncommon in current routine clinical practice due to their high cost, clinicians' lack of

knowledge, and lack of stakeholder support. Within this still-uncertain landscape, the Food and Drug Administration recently approved the use of pharmacogenetic tests directly available to consumers, a move that sparked considerable debate.[59,60] Warnings for an inappropriate use of direct to consumer genetic tests.[61] Indeed, it is a common occurrence for us and clinicians working in this field to receive patients presenting with results obtained independently and requesting endorsement and targeted prescription. Clinicians should be aware, however, that extreme caution should be exercised when interpreting current findings, except for the CYP pharmacokinetic ones, which may also result in incorrect conclusions for specific patients.[62]

We recently evaluated commercially available pharmacogenetic kits and concluded that they may be useful in some cases, particularly for pharmacokinetic variants, but that concerns about pharmacodynamic variants remain, as does the fact that the algorithm underlying each tool is not available for independent testing in academic trials.[42]

Candidates' gene studies have yielded over 50 commercial tests so far, but the lack of experimental validation, insufficient evidence of effectiveness, and the high cost/utility of these tests have been the primary obstacles to their routine application in clinical settings.[42] Only a few of the commercial tests have been subjected to rigorous clinical testing.

From a scientific standpoint, this picture reflects the uncertainty surrounding which genetic variants are the most important to consider and which combination of genetic variants is the most effective in terms of predicting clinical outcomes, and this is still unknown. The tests that are currently available use various combinations of variants, but the model that was used to predict the outcome is never disclosed by the companies that produce them. Moreover, different models may produce results that are difficult to compare. When looking at the relevant literature, there is no definitive answer to these questions at this time. Following recommendations in clinical guidelines and drug labels, the only conclusively demonstrated effects are those of CYP2D6 and CYP2C19 on the pharmacokinetics of antidepressants and on the clinical outcomes of at least some of these medications. Those gene variants are almost always included in the tests, but their interpretation is not always disclosed. However, some meta-analyses are presenting positive outcomes.[63] Real-time, more extensive analyses covering the whole genome are in principle possible using portable devices, but they are still under development.[64]

Researchers, clinicians, stakeholders, and, most significantly, patients with depression are disoriented in this uncertain landscape. As such, we are presenting a possible viewpoint. Decades of genetic research in psychiatry have demonstrated unequivocally that each individual variant effect is small, variable across patients, and not present in all patients.[65]

Perhaps it is necessary to return to the beginning: we are dealing with a highly complicated phenomenon, antidepressant treatment outcome. This means that a patient develops a complex disease whose cause and pathophysiology are unknown, a patient who is surrounded by a plethora of socio-demographic factors,

comorbidities, and a history of previous episodes, among other things. Within this complexity, it is highly improbable that a single gene variant would provide enough information for a straightforward clinical application, unless the effect is extremely relevant, as is the case with liver CYP enzyme variants. Additionally, clinical factors on their own have some potential for outcome prediction, but only in the context of a complex interaction.[11] For instance, a patient may present with a severe clinical picture of depression, but other favorable clinical and demographic factors may compensate for this negative predictor, resulting in a better outcome, as opposed to another patient who presents with a milder clinical picture of depression but is burdened by negative factors resulting in a final worse outcome, as we previously clearly demonstrated.[50]

Thus, this is the context in which we should view the modulatory effect of genetic variants: as a complex interaction, a complex interaction that is exceedingly difficult to understand using a linear model. While we know that antidepressants inhibit the serotonin transporter within a few hours of administration, the antidepressant effect does not manifest clinically until days or weeks after administration. During this lag, a highly complex cascade of events occurs, of which we only have a partial understanding. As a result, it is likely that at any point in this cascade of events following antidepressant intake there will be factors that facilitate or impair the final antidepressant action. As a simple example, consider a patient whose serotonergic system is less plastic than that of other patients, but this impairment in flexibility can be compensated for by the plasticity of collateral pathways. The range of possible alternatives is nearly impossible to model. Thus, only a flexible statistical genetic liability model is capable of reliably accounting for all the factors that influence antidepressant outcome; additionally, the complex interaction of genetic factors must be combined with the modulating effects of clinical variables.[48,66]

Recent advances in the field of psychiatric genetics may hold the key. The Psychiatric Genetic Consortium is a massive global effort aimed at collecting genome-wide data on patients. In recent years, all major psychiatric diseases have been investigated, with samples approaching one million patients. In this way, and for the first time in psychiatric genetic research, genetic liability factors for psychiatric disorders have been identified.[67–70] Two very interesting aspects of this unprecedented effort are as follows. First, for the first time, the genetic liability identified within the Psychiatric Genetic Consortium has been confirmed and replicated in all newly added samples, which has never occurred previously when replications failed to confirm original findings. This strengthens and validates the finding. However, and perhaps more importantly for the purposes of this discussion, the second point is that the liability factor is not due to a single variant or gene, but to a combination of signals from a large number of genes, hundreds of genes. For each patient, the score we previously mentioned, PRS, is calculated. This score represents the average genetic loading that a single patient has regardless of where or which single variants are located, in a similar way to the example reported above from our studies. This very clearly explains the hypothesized heterogeneity that we previously described, and it makes a lot of sense

in light of current knowledge about how our brain functions in normal and abnormal conditions. A system malfunction may be compensated for by other compensatory pathways that maintain the system's stability. It is also consistent with the heterogeneity observed at the clinical level, where impairments to proper recovery may result from a variety of clinical or environmental factors.

This revolution is currently taking place across the board of medicine. For instance, PRS are clinically relevant in stroke, and some institutions are beginning to incorporate them into clinical practice.[71]

PRS have the potential for clinical application in psychiatry,[72,73] and recent studies suggest that, at least for extreme scores, the effect size may be clinically relevant and equivalent to the risk conferred by monogenic mutations.[74] With the use of larger biobanks our knowledge of genetic effects will be more and more clear/We have already investigated the large UK Biobank[75] and soon the even larger US Biobank will be available.[76]

Research on biologic factors which may guide precision medicine includes a range of potential biomarkers that are still under development at present and do not have direct clinical application. They include multi-omic biological potential biomarkers, such as proteomics, metabolomics, and epigenetics, but also brain imaging and the potentially very large information coming from the increased use of wearable devices.[77–79]

The final impediment to implementing routine care is the ease with which this combined biologic and clinical score information is available. With the increasing use of electronic health records, this information may become readily available in the patient record profile following a single genome-wide analysis or sequencing, providing a real-time indication to the treating physician or psychiatrist for the time ahead. Additional interpretation of the genetic background gleaned from research can be added to the algorithm within the electronic health record on a periodic basis, resulting in an ever-increasing degree of precision in the clinical indication for a targeted prescription. Several consortia are currently working in this direction, concentrating on the definition of a digital tool capable of incorporating all genetic and clinical data for routine clinical use.[1,80]

In conclusion, precision medicine in mood disorders is needed. At present we may make use of clinical predictors and the pharmacologic profile of the available drugs in a much more detailed way compared to what is currently done in the clinical routine by a large part of psychiatrists. Biological factors such as TDM and genetic metabolizing profile should be used at least for those patients not responding to a carefully selected first-line treatment. In the near future more complex genetic scores will further improve precision medicine (Table 1).

CONFLICT OF INTERESTS

Dr. Serretti is or has been consultant/speaker for Abbott, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier, Taliaz.

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The ethics statement for this article is not applicable.

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TABLE 1 Present and future steps for precision medicine in mood disorder

Summary of steps for precision medicine in mood disorders
• Careful and extensive clinical assessment
• Knowledge of the pharmacokinetic and pharmacodynamic profile of psychotropic drugs
• Match clinical data with the most appropriate psychotropic drug following assessment data, guidelines, and available evidence
• In case of lack of response or poor tolerability to first-line treatment, perform genetic analysis of CYP enzymes, using existing commercial tools, and therapeutic drug monitoring
In the near future:
• Use polygenic risk scores to refine diagnosis and guide treatment
• Use a wide range of biologic and wearable measuring tools, currently under development
• Apply machine learning algorithms to combine all data for a more precise prescription

REFERENCES

1. Maron E, Baldwin DS, Balõtšev R, Fabbri C, Gaur V, Hidalgo-Mazzei D, et al. Manifesto for an international digital mental health network. Digit Psychiatry. 2019;2(1):14–24.
2. Sebastian A, Carroll JC, Oldfield LE, Mighton C, Shickh S, Uleryk E, et al. Effect of genetics clinical decision support tools on health-care providers' decision making: a mixed-methods systematic review. Genet Med. 2021;Apr 23(4):593–602.
3. Guideline Development Panel for the Treatment of Depressive Disorders (GDPFTT of Deppresive Disorders). APA Clinical Practice Guideline for the treatment of depression across three age cohorts [Internet]. PsycEXTRA Dataset. 2019. Available from: https://doi.org/10.1037/e505892019-001. Accessed 9 Nov 2021.
4. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. Can J Psychiatry. 2016;Sep 61(9):540–60.
5. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in psychiatry. Newark: John Wiley & Sons; 2018. p. 872.
6. NICE. Depression-NICE Pathways [Internet]. [cited 2021 Aug 17]. Available from: http://pathways.nice.org.uk/pathways/depression
7. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of

21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. FOCUS. 2018;16(4):420–9.

8. Serretti A, Franchini L, Gasperini M, Rampoldi R, Smeraldi E. Mode of inheritance in mood disorders families according to fluvoxamine response. Acta Psychiatr Scand. 1998;98(6):443–50.

9. Porcelli S, Fabbri C, Spina E, Serretti A, De Ronchi D. Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert Opin Drug Metab Toxicol. 2011;Sep 7(9): 1101–15.

10. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge, United Kingdom: Cambridge University Press; 2021. p. 624.

11. Serretti A. The present and future of precision medicine in psychiatry: focus on clinical psychopharmacology of antidepressants. Clin Psychopharmacol Neurosci. 2018;Feb 28;16(1):1–6.

12. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009; Jun 29(3):259–66.

13. Alberti S, Chiesa A, Andrisano C, Serretti A. Insomnia and somnolence associated with second-generation antidepressants during the treatment of major depression: a meta-analysis. J Clin Psychopharmacol. 2015;Jun 35(3):296–303.

14. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry. 2010;Oct 71(10):1259–72.

15. Calati R. Psychological interventions in suicide. In: Courtet P, editor. Understanding suicide: from diagnosis to personalized treatment. Cham: Springer International Publishing; 2016. p. 329–48.

16. Drago A, Serretti A. Sociodemographic features predict antidepressant trajectories of response in diverse antidepressant pharmacotreatment environments: a comparison between the STAR*D study and an independent trial. J Clin Psychopharmacol. 2011;31: 345–8.

17. Balestri M, Calati R, Souery D, Kautzky A, Kasper S, Montgomery S, et al. Socio-demographic and clinical predictors of treatment resistant depression: a prospective European multicenter study. J Affect Disord. 2016;189:224–32.

18. Fabbri C, Kasper S, Zohar J, Souery D, Montgomery S, Albani D, et al. Cost-effectiveness of genetic and clinical predictors for choosing combined psychotherapy and pharmacotherapy in major depression. J Affect Disord. 2021;Jan 15;279:722–9.

19. Zanardi R, Prestifilippo D, Fabbri C, Colombo C, Maron E, Serretti A. Precision psychiatry in clinical practice. Int J Psychiatry Clin Pract. 2020;Aug 27:1–9.

20. Fabbri C, Serretti A. How to utilize clinical and genetic information for personalized treatment of major depressive disorder: step by step strategic approach. Clin Psychopharmacol Neurosci. 2020;Nov 30;18(4):484–92.

21. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018; Jan 51(1–2):9–62.

22. Florio V, Porcelli S, Saria A, Serretti A, Conca A. Escitalopram plasma levels and antidepressant response. Eur Neuropsychopharmacol. 2017;Sep 27(9):940–4.

23. De Donatis D, Florio V, Porcelli S, Saria A, Mercolini L, Serretti A, et al. Duloxetine plasma level and antidepressant response. Prog Neuropsychopharmacol Biol Psychiatry. 2019;Jun 8;92:127–32.

24. De Donatis D, Porcelli S, Zernig G, Mercolini L, Giupponi G, Serretti A, et al. Venlafaxine and O-desmethylvenlafaxine serum levels are positively associated with antidepressant response in elder depressed out-patients. World J Biol Psychiatry. 2021;Jun 22:1–8.

25. PharmGKB Drug label annotations. [Internet]. [cited 2021 Aug 12]. Available from: https://www.pharmgkb.org/labelAnnotations

26. Center for Drug Evaluation, Research. Table of pharmacogenomic biomarkers [Internet]. 2021 [cited 2021 Aug 12]. Available from: https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

27. Bank PCD, Caudle KE, Swen JJ, Gammal RS, Whirl-Carrillo M, Klein TE, et al. Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. Clin Pharmacol Ther. 2018;Apr 103(4): 599–618.

28. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: meta-analysis of data from genome-wide association studies. Eur Neuropsychopharmacol. 2018;Aug 1;28(8):945–54.

29. O'Reilly RL, Bogue L, Singh SM. Pharmacogenetic response to antidepressants in a multicase family with affective disorder. Biol Psychiatry. 1994;36(7):467–71.

30. Heils A, Mossner R, Lesch KP. The human serotonin transporter gene polymorphism–basic research and clinical implications. J Neural Transm. 1997;104(10):1005–14.

31. Smeraldi E, Zanardi R, Benedetti F, Dibella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry. 1998;3(6):508–11.

32. Serretti A, Cusin C, Rausch JL, Bondy B, Smeraldi E. Pooling pharmacogenetic studies on the serotonin transporter: a mega-analysis. Psychiatry Res. 2006;145(1):61–5.

33. Mandelli L, Marino E, Pirovano A, Calati R, Zanardi R, Colombo C, et al. Interaction between SERTPR and stressful life events on response to antidepressant treatment. Eur Neuropsychopharmacol. 2009;Jan 19(1):64–7.

34. Serretti A, Zanardi R, Rossini D, Cusin C, Lilli R, Smeraldi E. Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. Mol Psychiatry. 2001;Sep 6(5): 586–92.

35. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry. 2007;Mar 12(3):247–57.

36. Zhu J, Klein-Fedyshin M, Stevenson JM. Serotonin transporter gene polymorphisms and selective serotonin reuptake inhibitor tolerability: review of pharmacogenetic evidence [Internet]. Pharmacotherapy. 2017;37:1089–104. https://doi.org/10.1002/phar.1978

37. Fabbri C, Di Girolamo G, Serretti A. Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. Am J Med Genet B Neuropsychiatr Genet. 2013;Sep 162B(6):487–520.

38. Fabbri C, Serretti A. Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications. Curr Psychiatry Rep. 2015;Jul 17(7):50.

39. Culverhouse RC, Saccone NL, Horton AC, Ma Y, Anstey KJ, Banaschewski T, et al. Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol Psychiatry. 2018;Jan 23(1):133–42.

40. Vaht M, Merenäkk L, Mäestu J, Veidebaum T, Harro J. Serotonin transporter gene promoter polymorphism (5-HTTLPR) and alcohol use in general population: interaction effect with birth cohort [Internet]. Psychopharmacology. 2014;231:2587–94. https://doi.org/10.1007/s00213-013-3427-8

41. Charles S, Dunn L. Finding the right medication: gene test may help treat depression [Internet]. NBC News. 2017 [cited 2021 Aug 12]. Available from: https://www.nbcnews.com/health/mental-health/finding-right-medication-gene-test-may-help-treat-depression-n782781

42. Fabbri C, Zohar J, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: comparison of the available testing kits and clinical trials. Prog Neuropsychopharmacol Biol Psychiatry. 2018; Aug 30;86:36–44.

43. Quinn JP, Savage AL, Bubb VJ. Non-coding genetic variation shaping mental health. Curr Opin Psychol. 2019;Jun 27:18–24.

44. Fabbri C, Kasper S, Kautzky A, Bartova L, Dold M, Zohar J, et al. Genome-wide association study of treatment-resistance in depression and meta-analysis of three independent samples. Br J Psychiatry. 2019;Jan 214(1):36–41.

45. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. New insights into the pharmacogenomics of antidepressant response from the GENDEP and STAR*D studies: rare variant analysis and high-density imputation. Pharmacogenomics J. 2018; May 22;18(3):413–21.

46. Pain O, Hodgson K, Trubetskoy V, Ripke S, Marshe VS, Adams MJ, et al. Antidepressant response in major depressive disorder: a genome-wide association study. medRxiv. 2020;Dec 15. https://doi.org/10.1101/2020.12.11.20245035

47. Natarajan P, Peloso GM, Zekavat SM, Montasser M, Ganna A, Chaffin M, et al. Deep-coverage whole genome sequences and blood lipids among 16,324 individuals. Nat Commun. 2018;Aug 23; 9(1):3391.

48. Fabbri C, Kasper S, Kautzky A, Zohar J, Souery D, Montgomery S, et al. A polygenic predictor of treatment-resistant depression using whole exome sequencing and genome-wide genotyping. Transl Psychiatry. 2020;Feb 3;10(1):50.

49. Casarotto PC, Girych M, Fred SM, Kovaleva V, Moliner R, Enkavi G, et al. Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell. 2021;Mar 4;184(5):1299–313.e19.

50. Serretti A, Calati R, Oasi O, De Ronchi D, Colombo C. Dissecting the determinants of depressive disorders outcome: an in depth analysis of two clinical cases. Ann Gen Psychiatry. 2007;6:5.

51. Schork NJ. Personalized medicine: time for one-person trials. Nature. 2015;Apr 30;520(7549):609–11.

52. Serretti A, Fabbri C. The search for personalized antidepressant treatments: what have we learned and where are we going. Pharmacogenomics. 2020;Oct 21(15):1095–100.

53. Fanelli G, Benedetti F, Kasper S, Zohar J, Souery D, Montgomery S, et al. Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2020;Nov 10;108: 110170.

54. International Consortium on Lithium Genetics, Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, et al. Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: a genome-wide association study. JAMA Psychiatry. 2018;75(1):65–74.

55. Ikeda M, Saito T, Kanazawa T, Iwata N. Polygenic risk score as clinical utility in psychiatry: a clinical viewpoint. J Hum Genet. 2021; Jan 66(1):53–60.

56. International Society of Psychiatric Genetics (ISPG). Genetic Testing Statement | [Internet]. [cited 2019 Jun 20]. Available from: https://ispg.net/genetic-testing-statement/

57. Robbins R, Begley S, Robert Weisman—Boston Globe, Joseph A, Piller C. Can genetic tests gauge how well antidepressants will work? [Internet]. 2018 [cited 2021 Aug 12]. Available from: https://www.statnews.com/2018/09/28/genetic-test-antidepressants/

58. Bousman CA, Zierhut H, Müller DJ. Navigating the labyrinth of pharmacogenetic testing: a guide to test selection [Internet]. Clin Pharmcol Ther. 2019;106:309–12. https://doi.org/10.1002/cpt.1432

59. Zagorski N. FDA clears first direct-to-consumer pharmacogenetic test [Internet]. Psychiatr News. 2018;53:221–6. https://doi.org/10.1176/appi.pn.2018.12b19

60. Abbasi J. Companies tout psychiatric pharmacogenomic testing, but is it ready for a store near you? JAMA. 2018;Oct 23;320(16):1627–9.

61. Roberts C. Read this before you buy a genetic testing kit [Internet]. Consumer Reports. 2021 [cited 2021;Aug 12]. Available from: https://www.consumerreports.org/genetic-testing/genetic-testing-kit-read-this-before-you-buy/

62. Rahman T, Ash DM, Lauriello J, Rawlani R. Misleading guidance from pharmacogenomic testing. Am J Psychiatry. 2017;Oct 1;174(10):922–4.

63. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials [Internet]. Pharmacogenomics. 2019;20:37–47. Available from https://doi.org/10.2217/pgs-2018-0142

64. Oliva M, Milicchio F, King K, Benson G, Boucher C, Prosperi M. Portable nanopore analytics: are we there yet? Bioinformatics. 2020; Apr 11;36(16):4399–405.

65. Border R, Johnson EC, Evans LM, Smolen A, Berley N, Sullivan PF, et al. No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples [Internet]. Am J Psychiatry. 2019;176:376–87. https://doi.org/10.1176/appi.ajp.2018.18070881

66. Chang B, Choi Y, Jeon M, Lee J, Han K-M, Kim A, et al. ARPNet: antidepressant response prediction network for major depressive disorder. Genes [Internet]. 2019;Nov 7;10(11). https://doi.org/10.3390/genes10110907

67. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell. 2018;Jun 14; 173(7):1705–15.e16.

68. Coleman J, Breen G, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. The genetics of the mood disorder spectrum: genome-wide association analyses of over 185,000 cases and 439,000 controls [Internet]. Biol Psychiatry. 2020;Jul 15;88(2):169–84. https://doi.org/10.1101/383331

69. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet. 2019;May 51(5):793–803.

70. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;May 50(5):668–81.

71. Dichgans M, Pulit SL, Rosand J. Stroke genetics: discovery, biology, and clinical applications. Lancet Neurol. 2019;Jun 18(6):587–99.

72. Goldman D. Polygenic risk scores in psychiatry. Biol Psychiatry. 2017;Nov 15;82(10):698–9.

73. Halldorsdottir T, Piechaczek C, Soares de Matos AP, Czamara D, Pehl V, Wagenbuechler P, et al. Polygenic risk: predicting depression outcomes in clinical and epidemiological cohorts of youths. Am J Psychiatry. 2019;Aug 1;176(8):615–25. https://doi.org/10.1176/appi.ajp.2019.18091014

74. The Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke S, Walters JTR, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia [Internet]. medRxiv. 2020;Sep 13. Available from: https://doi.org/10.1101/2020.09.12.20192922

75. Fabbri C, Hagenaars SP, John C, Williams AT, Shrine N, Moles L, et al. Genetic and clinical characteristics of treatment-resistant depression using primary care records in two UK cohorts. Mol Psychiatry [Internet]. 2021;Mar 22;26:3363–73. https://doi.org/10.1038/s41380-021-01062-9

76. Dyer O. "All of Us" study begins to sequence and follow a million Americans. BMJ [Internet]. 2018;May 3361. [cited 2021 Aug 12]. Available from: https://www.bmj.com/content/361/bmj.k2001.abstract

77. Sverdlov O, Curcic J, Hannesdottir K, Gou L, De Luca V, Ambrosetti F, et al. A study of novel exploratory tools, digital technologies, and central nervous system biomarkers to characterize unipolar depression. Front Psychiatry. 2021;May 6;12:640741.

78. Goldstein-Piekarski AN, Staveland BR, Ball TM, Yesavage J, Korgaonkar MS, Williams LM. Intrinsic functional connectivity predicts remission on antidepressants: a randomized controlled trial to identify clinically applicable imaging biomarkers. Transl Psychiatry. 2018;Mar 6;8(1):57.

79. Klengel T, Binder EB. Epigenetics of stress-related psychiatric disorders and gene × environment interactions. Neuron. 2015;Jun 17;86(6):1343–57.

80. Chekroud AM, Bondar J, Delgadillo J, Doherty G, Wasil A, Fokkema M, et al. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry. 2021;Jun 20(2):154–70.