Towards personalised antidepressive medicine based on "big data": an up-to-date review on robust factors affecting treatment response

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Prescribing antidepressant medication is currently the most effective way of treating major depression, but only very few patients achieve permanent improvement. Therefore, it is important to identify objectively measurable markers for effective, personalised therapy. The aim of this review article is to collect all the markers that are robustly predictive of the outcome of therapy. We searched for systematic review articles that have simultaneously investigated the effects of as many different markers as possible on the response to antidepressant therapy in major depressive patients. From these we extracted markers that have been found to be significant by at least two independent review studies and that have proven replicable also within each of these reviews. A separate search was performed for meta-analyses of pharmacogenetic genome-wide association studies. Based on our results, onset time, symptom severity, presence of anhedonia, early treatment response, comorbid anxiety, alcohol consumption, frontal EEG theta activity, hippocampal volume, activity of anterior cingulate cortex, as well as a peripheral marker, serum BDNF levels have proven replicable predictors of antidepressant response. Pharmacogenomic studies to date have not yielded replicable results. Predictors identified as robust by our study may provide a starting point for future machine learning models within a 'big data' database of major depressive patients.

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INTRODUCTION

Nowadays major depressive disorder (MDD) is a very common disorder with a wide range of symptoms, and its incidence is increasing in the general population. (1, 2) In 2008, the World Health Organization (WHO) ranked unipolar, or major depressive disorder, third in the world's list of the most debilitating diseases, and it is predicted to become the leading cause of disability by 2030. (1) Both the management and recognition of the disorder present a major challenge to clinicians, due to the many different manifestations and types of the disorder, the irregular course and

prognosis, and the different responses of patients to treatment in clinical practice. (1) As drug selection is currently based on a 'trial and error' approach, this contributes greatly to treatment failure, thus emphasising the importance of identifying the predictors of antidepressant treatment response. (3) The identification of objectively measurable markers and early predictors of treatment response would be really important, as it would allow clinicians to select effective, personalised drug therapy. (4) To this end, a predictive model would be most useful to analyse all the data available in the clinic from the available databases and to look for correlations between input variables (which would include all possible biomarkers with predictive value), the typical symptoms of the disease and the response to therapy. (4) This would include all the available clinical data to select the markers that best predict the treatment response among the many variables (and in the future it would be enough to measure these selected markers in patients, which would be very cost-effective). One promising method for this is artificial intelligence, including machine learning methods, which could provide a truly useful guide to the selection of an effective and well tolerated pharmacological treatment for each patient in the future, thus helping to alleviate the long-term symptoms of depression and helping patients achieve remission. (4) The aim of this review is to collect the most recent literature, meta-analyses and systematic reviews in order to describe predictive markers that could be useful in the selection of pharmacological treatment. These significant markers with predictive power could be incorporated into the machine learning model, thus contributing to the alleviation of long-term symptoms of depression and the patient's recovery process.

METHODS

In March 2021 we searched PubMed database for systematic review articles using the search terms "(antidepress*[Title/Abstract]) AND (treatment response[Title/Abstract])". The search was primarily limited to patients with a diagnosis of MDD as the primary cause of the underlying disease. This was limited to English-language systematic reviews including only those that simultaneously examined as many factors as possible in the background of treatment response. These criteria yielded 6 comprehensive studies for our present review: (3-9). In writing this article, our primary consideration was to select from the many markers examined, those that were investigated in more than one original study according to the review articles. From these, we selected those whose effects were found to be replicable by the review across multiple studies.

We also conducted a PubMed search specifically focused on pharmacogenomics results. In February 2021, we searched the terms "((("Genome-Wide Association Study"[Mesh]) AND "Pharmacogenetics"[Mesh]) AND "Antidepressive Agents"[Mesh]" and limited the results to meta-analyses, which resulted in 3 relevant papers: (10-12). Among the discussed genetic markers, we selected those that had either a genome-wide significance within the study or a replicable effect across studies.

RESULTS

Factors affecting the effectiveness of therapy in general

Among systematic reviews, Perlman et al, 2019 (4) provided the most thorough review on factors associated with treatment response, therefore we will focus on the factors that proved to have a replicable effect both within Perlman et al, 2019 (4) and within any of the other selected review papers. These factors are listed in **Table 1** and will be detailed in the following chapters in the following categories:

- symptom profile,
- early response to treatment,
- psychiatric comorbidities,
- electrophysiological markers,
- imaging test results,
- other biological and peripheral markers, which can be found in saliva, urine, spinal fluid, blood and lymph circulation
- genetic predictors (4)

Symptom profile; onset time, symptom severity of depressive episodes

This symptom profile category includes markers and variables that describe the characteristic symptoms of the illness, the severity of symptoms and some determinants of the patient's clinical history. Predictive factors based on the symptom profile are predominantly used in clinical practice, as these components are determined at the beginning of the anamnesis record and clinical interview in order to establish the diagnosis, prognosis and treatment. (4)

The onset of a depressive episode at a young age is a significant marker associated with high treatment

Table 1. Significant and replicable predictors of antidepressant treatment response in major depressive patients.
Markers are presented in the table if replicable both within Perlman et al, 2019 and any other systematic review paper, citing original studies different from each other. AD: antidepressant; ACC: anterior cingulate cortex; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor; NRI: norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant; BDNF: brain-derived neurotrophic factor.

Categories	Predictors	Compound	Tested sample (age)	Moderators	References
Symptom profile	anhedonia	bupropion	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	depressed mood, somatic symptoms, anhedonia	SSRI versus venlafaxine	adolescents	-	Boylan K, et al. *Eur Child Adolesc Psychiatry* 2020; 29(4):433-443.
	higher symptom severity	Van de Carlo et al, 2016: fluoxetine, lithium, desipramine, escitalopram; Schmidt et al, 2016: ketamine, AD; Trivedi et al, 2001: citalopram, fluoxetine, lithium, buspirone	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	disorder severity	SSRI versus venlafaxin	adolescents	-	Goodyer IM & Wilkinson PO. *J Child Psychol Psychiatry* 2019; 60(3):232-243.
	youth depressive episode	AD/ nortriptyline	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	first episode	SSRI versus venlafaxine	adolescents	-	Goodyer IM & Wilkinson PO. *J Child Psychol Psychiatry* 2019; 60(3):232-243.
Early response	early treatment response (2 weeks)	Papakostas & Fava 2008: SSRI, TCA; Dupuy et al: SSRI, SNRI, NRI, lithium; Szegedi et al, 2009: mirtazapine	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	early treatment response (2 weeks)	SSRI versus venlafaxine	adolescents	-	Boylan K, et al. *Eur Child Adolesc Psychiatry* 2020; 29(4):433-443.
Psychiatric comorbidities	psychiatric comorbidities (anxiety)	venlafaxine/SSRI/fluoxetine/bupropion	adults	drug arm	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	comorbidities (anxiety)	duloxetine; fluoxetine	adults	treatment discontinuation	Berwian IM, et al. *Psychol Med* 2017; 47(3):426-437.
	cigarettes, alcohol consumption	fluoxetine	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	drugs and alcohol consumption	SSRI versus venlafaxine	adolescents	-	Boylan K, et al. *Eur Child Adolesc Psychiatry* 2020; 29(4):433-443.
Electrophysiological marker	frontal EEG theta activity before treatment and at the end of the first week of treatment	Papakostas & Fava 2008: SSRI, TCA; Dodd & Berk, 2004: TCA, SSRI, lithium; Iosifescu et al, 2011: SSRI, venlafaxine, TCA; Steiger & Kimura, 2010: SSRI, SNRI	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	frontal EEG theta activity before treatment	Bares et al: bupropion	adults	-	Voegeli G, et al. *Drugs* 2017; 77(18):1967-1986.
Neuroimaging marker	hippocampus volume	Chi et al, 2015: sertraline; El Hage et al, 2013: SSRI, SNRI, TCA; Leuchter et al, 2010: SSRI, SNRI; MacQuenn et al, 2009: fluoxetine	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	hippocampus volume	citalopram, fluoxetine, venlafaxine	adults	-	Voegeli G, et al. *Drugs* 2017; 77(18):1967-1986.
	ACC hyperactivity	SSRI, SNRI, NRI, bupropion, TCA	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	ACC volume and hyperactivity (emotion perception tasks, resting state, working memory, inhibitory control tasks)	Brockman et al, 2009: citalopram; Salvador et al, 2009: ketamine; Walsh et al, 2007: fluoxetine; Roy et al, 2010: citalopram; Samson et al, 2011: mirtazapine, venlafaxine; Chen et al, 2007: fluoxetine; Rizvi et al, 2013: fluoxetine, olanzapine	adults	-	Voegeli G, et al. *Drugs* 2017; 77(18):1967-1986.
Peripherial marker	Serum BDNF level	Young et al, 2016: escitalopram, nortriptyline	adults	-	Perlman K, et al. *J Affect Disord.* 2019; 243:503-15.
	Serum BDNF level	escitalopram, nortriptyline	adults	variability over time	Voegeli G, et al. *Drugs* 2017; 77(18):1967-1986.

resistance. (4, 6) MDD is one of the most common mental disorders among young adolescents aged 12-18 years, with a lifetime prevalence of up to 12%. (9) Its early formation can cause lifelong detrimental effects, significantly impairing an individual's quality of life and social belonging, which is why early treatment, and thus improving mental health, is a key concern for clinicians. (9)

Treatment options are determined largely by the severity of the symptoms of depression. Based on preliminary evidence of a moderately severe episode and with the approval of the US Food and Drug Administration (FDA), selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, citalopram) are the first choice in combination with psychotherapy, including cognitive behavioural therapy (CBT), for adolescents with MDD. (9) Unfortunately, just over half of affected adolescents respond to initial SSRI treatment. In general, more severe symptoms and higher comorbidity distributions are observed in young people with treatment-resistant MDD (TR-MDD). (9) The more severe form of major depression also significantly determines the risk of relapse, which is observed in 50-70% of successfully treated patients 1 year after treatment. (6) Therefore the more severe the major depressive episode is, when the symptoms are fewer but more severe, it is more unlikely that the patient will respond to the treatment. (4, 6)

However, in addition to the more severe form of the illness, the increased persistence of certain symptoms, such as anhedonia for most of the day, significantly prolongs the time needed to achieve symptom-free status in affected patients. (4, 9) Antidepressant treatment, especially a combination therapeutic approach, and adherence to therapy are important factors that reduce the risk of relapse. (7) As the prevention of relapse of a depressive episode is a top priority for treatment, it is important to identify a wide range of potential predictors of relapse risk. (7)

Early response to treatment

The question of early response, which can significantly predict the outcome of the therapy, is also a significant predictor and greatly assists healthcare professionals in the care of MDD. If individuals respond to the therapy within 2 weeks after initiation of treatment, it is generally observed that they do much better in the longer term and achieve a higher rate of symptom relief. (4, 9, 13) Early response as a potential predictor also has diagnostic value, as individuals in this group can be compared with others in controlled trials to identify and understand the mediators of treatment response, potential predictors, and the complexity of the MDD phenotype. (9) The existence of these variables may provide powerful information in connection with the predictors of treatment response, remission, and relapse in young people with TR-MDD. (9) As it is well known that the prevalence of TR-MDD is particularly high in 12-18 year old adolescents, there is a great need to develop a treatment strategy with an effective and targeted approach, especially for those in high-risk groups.

Psychiatric comorbidities

Co-existing psychiatric comorbidities are a very common feature of a major depressive episode, sometimes with diagnostic value, and can have a significant impact on the outcome of treatment. These effects have proven replicable in case of anxiety disorders and substance use disorders. (4) The higher baseline symptom levels of these comorbid psychiatric disorders, as well as the severity of depression result in poorer therapeutic outcomes when determining the treatment response profile to different antidepressants. (4) Co-existing anxiety disorders with MDD are associated with significant clinical suffering in most of the cases. Symptoms are persistent, sometimes associated with frightening autonomic syndromes, and their manifestations are often disproportionate to the sociocultural context and events. (14) Avoidant behaviour in affected patients is also common. (14) Anxiety symptoms may reduce the response to antidepressants. This finding was particularly significant for venlafaxine and SSRIs, especially fluoxetine. (4) However, there was some difference in response outcome between drug groups of anxious patients. Indeed, the positive therapeutic response to venlafaxine was more significant compared to fluoxetine, while the response profile of SSRIs was more effective compared to bupropion, although the validity of this was questioned. (4) Another study also measured a significant effect of anxiety on treatment non-reponse. High anxiety increased the risk of relapse, but this finding was significant only among those who stopped taking their medications, while in those who continued taking antidepressants there was no significant association. (7) Within anxiety disorders, generalised anxiety disorder was primarily considered as a possible predictor of non-response, while worse outcomes were also observed for obsessive-compulsive disorder. No significant correlation was found in the association of social

phobia and PTSD with the lack of response to antidepressants. (13)

Co-existing comorbid anxiety disorders therefore have a major impact on remission and increase treatment resistance, increasing the risk of relapse. Their prevention, accurate diagnosis and appropriate treatment strategy are key to the treatment of major depression. (7) Cognitive behavioural therapy is a long-term treatment option for mild comorbidities associated with MDD. In more severe cases, a combination of anti-anxiety drugs, benzodiazepines and SSRI antidepressants has been shown to be effective. (15) The Treatment of Resistant Depression in Adolescents (TORDIA) study has shown that CBT used alongside pharmacological treatment is more effective for those with comorbid conditions than monotherapy. (16) Transcranial magnetic stimulation (TMS), which was approved by the US Food and Drug Administration (FDA) in 2008 for treatment-resistant depression in comorbid depressed patients, has also been shown to be an effective method. (15) The TMS method works by inducing a magnetic field and then applying it to the surface of the skull to generate an action potential that alters cortical activity, making it effective in the treatment of major depression. (15) The response and remission rates, although different between subjects, were significant. Depressive symptoms as well as comorbid syndromes were also relieved by the treatment (39.5-70% of participants responded to antidepressant treatment, 16.6-76.9% achieved asymptomatic MDD, while nearly 50-84.6% of patients responded to TMS and pharmacological treatment and had alleviation of comorbid symptoms). (15)

Another significant association was measured for cigarette, alcohol and drug use. Cigarette smoking has been associated with a reduced response to antidepressant (AD) treatment, and current alcohol consumption has been shown to predict fluoxetine nonresponse. (4) On the other hand, lower levels of drug use, smoking and drinking alcohol resulted in an improvement in symptoms 72 weeks after treatment. (9)

Electrophysiological markers; Theta wave activity

One group of measurable markers that has been evaluated for objective prediction of pharmacological treatment is the brain's electrophysiological parameters. Electroencephalography (EEG) is essentially a method and technique for measuring electrical activity that is non-invasive, easy to access, and at the same time helps to determine the therapeutic response to the antidepressants. (17) Another, more recent type is quantitative or qEEG, which now includes computer spectral evaluation of EEG signals to obtain more specific information. (4) Although there are a few inconsistent results as well, the most significant finding was an increase in theta (slow-wave phase) activity in the frontal cortex before treatment, which was associated with a positive therapeutic outcome. (3, 4) However, in addition to baseline values, markers measured during the initial phase of therapy were also predictive. Namely, a decrease in frontal activity in the theta domain of EEG at the end of the first week of treatment correlated with a greater therapeutic response after 4-10 weeks of treatment. (4, 17) This indicator is essentially calculated from electrodes placed on the scalp and the absolute and relative power measurements of EEG spectra. It has also been observed that even acute changes in EEG (changes in neurophysiological function of the frontal brain region) in the theta range, which in qEEG measurements focus primarily on abnormalities in brain perfusion and metabolism, can discriminate between subjects responding to pharmacological treatment and non-responders up to 2 hours after the first AD administration, and their application is therefore worth a further extensive investigation. (4)

Neuroimaging markers

Recent improvement in neuroscience has opened up the possibility of shedding new light on the interpretation of individual patient responses to antidepressant treatment, as the information provided by imaging techniques may grant the most effective approach in the future. Structural, functional and neurochemical brain disorders are primarily associated with cortico-limbic regions. Functional magnetic resonance imaging (fMRI) is the first choice for the assessment of functional disorders, which assesses changes in neural activity based on the blood-oxygen level-dependent (BOLD) signal. (4) Other technical approaches include single-photon emission computed tomography (SPECT), positron emission tomography (PET-SCAN), and magnetic resonance spectroscopy (MRS), which can also be used to monitor changes in metabolite levels within the skull. (4) Within the cortico-limbic brain regions, the anterior cingulate cortex (ACC), as well as the hippocampal area, showed replicable effects of sufficient magnitude. (3)

A comparison of hippocampal size before and after

antidepressant treatment showed that the smaller hippocampal size before therapy results in worse treatment outcome. (3, 4) This finding is thought to be due to the impairment of glucocorticoid receptor function and hyperactivation of the hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in a reduction of serotonin levels and hippocampal volume. (12) In more detail, a collective feature of subjects with MDD is a reduced or lost sensitivity to glucocorticoids, which greatly reduces negative feedback, hence increasing the duration of HPA axis activation and also leading to a stress-sensitive immune response, inflammation. (3)

Besides this, the structure and activity of the ACC were also examined and it was replicated and concluded that hyperactivation of the ACC at baseline, mainly in the rostral (rACC), pregenual (pgACC) and ventral cortex (vACC), was the biomarker with the highest predictive value of antidepressant treatment response in various cognitive tasks, such as emotion perception tasks, working memory tasks, or resting state. (3, 4, 18) This has been tested and confirmed for a number of drugs (SSRI, SNRI, TCA, bupropion). In the rACC, it has been shown that elevated resting glucose metabolism predicts a better treatment response, while impaired rACC activity predicts the opposite. (4, 17)

Similar abnormal activity was also detected within several fronto-temporal and limbic brain regions, in which increased functional connectivity was also associated with the drug treatment response. However, amygdala activity during emotion perception tasks showed inconsistent association with response rate between the two review papers (3, 4). The altered connectivity between different brain regions, as well as changes in the volume of each brain area, could serve as potential markers for future studies. However, there are few longitudinal studies on the time course of volume changes and the biochemical and morphological background of these changes remains unclear. (17)

Peripheral markers

As it is well known, a large group of biomarkers can be detected in urine, saliva, blood and cerebrospinal fluid (CSF), so they are among the variables that can be measured and collected relatively quickly and efficiently. Since their application in clinical practice is feasible and practicable, it is worthwhile to focus in the future on the broad investigation of this category. (4) Most of the results are closely related to immune function, as a correlation between the pathophysiology of MDD and the background of immune dysfunction is hypothesised. However, only the predictive effect of brain-derived neurotrophic factor (BDNF) can be replicated across review studies. The role of BDNF in serum is to promote cell differentiation. Therefore, elevated levels in the early treatment phase are a good predictor of the subsequent therapeutic response. (4) If the serum level does not rise after two weeks, this is likely to reflect a failure to achieve remission or an increased risk of relapse. Peripheral markers are measured before starting treatment or in the early course. (4) Elevated levels of BDNF were associated with treatment response in another study, but here it was important to note that they had a predictive value only when the time variability of the peripheral marker was taken into consideration. (3) However, BDNF levels measured after treatment should not be forgotten, because they have predictive value for relapse.

In general, knowledge of the pharmacokinetic and pharmacodynamic interactions may also be relevant for the choice of antidepressant drug, since interference with the function of CYP enzymes may alter the plasma levels of another agent taken concomitantly with the drug or of the drug itself by raising or drastically lowering them to toxic levels, not to mention the resulting consequences, which may be severe in some cases. (19)

Genetic markers

Recent improvement in science has given rise to the proliferation of genome-wide association studies (GWAS), which are used to analyse a wide range of single nucleotide polymorphisms (SNPs) using high-throughput genotyping technology across the entire human genome. SNPs can be used to determine the contribution of genes to drug efficiency in clinical association studies. (11) This is supported by indirect evidence that the combined effects of SNPs contribute about 50% or more to antidepressant response. GWAS studies differ from the candidate-gene approach in that they do not rely on a prior hypothesis about the relevant genes. (11) If the target of GWAS analyses is treatment response, it is called a pharmacogenomics study. A GWAS study is usually composed of four parts, which include the selection of participants involving a control group; DNA isolation and genotyping; statistical analysis of the association between each SNP and the outcome variable; replication studies of the identified associations,

and testing whether the SNPs in question survived genome-wide correction for multiple testing. (11) The approach faces a number of challenges, such as the issue of multiple comparisons, and dealing with deviations due to ethnicity as reflected in different allele frequencies. (11) In the present review, we focus only on pharmacogenomics results that either could be replicated or survived correction for multiple testing. However, there are no consistently reproducible results from GWAS studies on the effectiveness of antidepressants. One possible reason for this is that if the response to antidepressants is a polygenic inherited phenotype, individual studies may not be able to detect all most significant effects. (10) However, limited sample size, heterogeneity of the sample and limited coverage of genetic variants may also be reasons for the failure of these studies. (12)

In contrast, we found several genomic results that fulfilled the other criterion, namely survived correction for multiple testing. They are listed in **Table 2** and discussed in detail in the following chapter.

Pharmacogenomic results for drug efficacy and side effects in the three most comprehensive studies

The three most comprehensive pharmacogenetic studies are the Genome-Based Therapeutic Drugs for Depression (GENDEP), (20) the Munich Antidepressant Treatment Response (MARS) project, (21) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which focus on the effectiveness of antidepressants in depression. (22)

The common inclusion criteria in the meta-analysis of these comprehensive studies (GENDEP, MARS, STAR*D) were a Caucasian/white European ancestry to maintain homogeneity of the samples, and a diagnosis of unipolar depression, as well as (except in the GENDEP project) a minimum Hamilton Depression Rating Scale (HAM-D) score of 14. (10) Two larger analyses were conducted across the three comprehensive studies, first testing the role of common genetic variants in the treatment response with different antidepressants. (10) This was followed by a more specific study looking at the contribution of genetic variations within the antidepressant group of SSRIs. Percentage improvement in depression and remission was assessed over 12 weeks of treatment in the patients in the study. (10) In addition, two secondary outcomes (early percentage change in depression severity and early 25% improvement) were defined during the first 2 weeks of pharmacological treatment to analyse the genetic effects involved in early changes. (10) In addition to univariate tests, polygenic scores were determined to test the combined effect of weak associations in the genome. In the primary analyses conducted over 12 weeks of treatment, no individual SNP association reached the statistical significance threshold for the whole genome. (10) Analysis of STAR*D, as well as GENDEP limited to 1354 patients treated with SSRIs, however, identified an intergenic region on chromosome 5 that was associated with early improvement in the first two weeks of treatment. (10) Although not reliable, objective markers of pharmacological treatment outcome have been identified, indirect evidence is provided that these common genetic variants contribute to individual differences in treatment response. (10)

Because of this initial failure, the samples from the STAR*D and GENDEP studies were re-examined in a subsequent meta-analysis. Possible reasons for the unsuccessful initial analyses included limited genome coverage, small sample sizes, treatment heterogeneity, and therefore this new meta-analysis attempted to overcome these previous limitations. (12) The coverage of genetic variables was addressed by exome genotyping and dense imputation. The association with response to pharmacological treatment was investigated at the levels of SNPs, genes and pathways. (12) Heterogeneity was resolved by administration of matching antidepressants. During the whole study, patients were given citalopram, escitalopram and nortriptyline. Two other replication samples were also used for the analysis, where the replicability of potential variables was investigated: the Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) and the Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS). (12) The primary outcome was improvement in depressive symptoms and remission after 12 weeks of antidepressant treatment. Partial replication was achieved only for the rs116692768 SNP, which showed a strong association with symptom improvement from baseline. (12) However, this result was only replicated in the PGRN-AMPS sample and not in NEWMEDS. This SNP is located within the intron region of a gene called *ITGA9*, integrin a9. Involvement of these integrins in antidepressant effect is suspected, but further studies are needed to clarify their exact role. (12) Besides *ITGA9* rs116692768, another SNP survived correction for the 12-week treatment response in this study: rs76191705 of neurexin 3 gene *NRXN3*, but this result could not be replicated at all

(12). At the level of genes, only *OR4K2* gene, encoding olfactory receptor family 4 subfamily K member 2, survived correction, especially for symptom improvement. However, its rare alleles had opposite effects compared to common alleles between the two subsamples used for meta-analysis, and the effect of this gene was not tested for replication. (12) At the level of gene sets, three hits emerged, but only the steroid hormone receptor signalling pathway could be replicated and in only one of the two independent samples. (12)

The results described above investigated genetic markers associated with drug efficacy of ADs in patients with major depression. However, there are also GWAS studies in which potential candidate markers were analysed in relation to the side effects of antidepressant drugs. (11) Several genome-wide significant results were obtained in the STAR*D study. Drug-related side effects were grouped in the study, four of which were highlighted including general adverse events, burden of sexual side effects, dizziness, and adverse symptoms related to vision or hearing. (11) The first significant result associated with bupropion-induced sexual side effects was 10 SNPs in the *SACM1L* gene. (11, 23) Besides this gene, another genome-wide significant result was the rs7136572 SNP (*USP44* gene), which was found to be significant in relation to early sexual side effects. (11) Adverse symptoms related to vision and hearing caused by citalopram were associated with rs17135437 SNP in the *COL26A1* gene, a member of the collagen protein family. (11, 24) A genome-wide significant result for general adverse events was rs16965962 SNP located in an intergenic region on chromosome 13. Rs13432159 SNP (mapped to *LINC01812* and *AC007422.1* genes in 2p14) was also significant for general adverse events. (11, 24) Perhaps the most notable and noteworthy of the aforementioned side effects is the development of suicidal ideation. Although medication is used primarily to avoid the most tragic outcome of major depression, which is a completed suicide, unfortunately some medications can still induce such ideation. This effect has been observed particularly with SSRIs. (11) In the STAR*D study, an investigation was conducted to identify SNPs that enhance the development of suicidal ideation during citalopram treatment. The GWAS study identified a genome-wide significant association with citalopram treatment, rs11628713 SNP located in the *PAPLN* gene. In another GWAS, rs11143230 located in the *GDA* gene, was associated with suicidal ideation during treatment. (11, 25)

Although the results were significant at the genome level, they could not be replicated, which calls into question the validity of these associations. Furthermore, the small sample size does not justify confident conclusions. (11) As monitoring of serum levels was not ensured, this could lead to further biases. Furthermore, investigations were only conducted in relation to specific antidepressants and therefore no general conclusions can be drawn. In addition, for the results related to AD side effects, gene variants that showed a relatively significant effect were of rare allele frequency. (11) The potential for gene-gene or gene-environment interactions was also not assessed. In the future, more extensive exploration of SNP genotypes could help both patients and physicians to make more informed and personalised decisions. Currently, pharmacogenetic tests are available in the US with FDA approval and in several other countries, which are performed on patients before prescribing medication. (11) The so-called PGx tests, which have received approval, detect differences in the genes encoding enzymes involved in drug metabolism and make dose adjustments on a personalised basis. (26) A good example is the case of the antidepressant nortriptyline, whose plasma levels can vary by a factor of up to 10 depending on the number of functional *CYP2D6* alleles. Although there is not yet solid evidence, it is suspected that *CYP2D6* polymorphisms have significant clinical consequences in nortriptyline response. (26) If these tests were more widely used and genetic data were taught in a niche way, the method could be effectively applied in future global primary care. It would also represent an improvement and would increase the predictive power of the model if the coverage of genetic variations was much deeper in GWASes for response or intolerance to a single compound. (11) It is also essential to establish a candidate gene set that can be well replicated as an indicator of AD response in the future. At this point, several selection criteria should be considered for the selection of candidate pharmacogenetic genes/SNPs. (11) Examples include dense genotyping and independent replication, where correlations are verified by the choice of a multistep method. Other relevant aspects that, although independent of SNP selection, are worth discussing are methodological factors such as the sampling source (blood, saliva, bucca), diagnostic factors and other environmental influences (family status, education, health status, etc.). (11) Whole exome as well as whole genome sequencing is required to detect rare allele variants. As far as the analysis of gene-

Table 2. Pharmacogenomic results of meta-analyses on antidepressant treatment response or side effects, which are significant at a genome-wide corrected level.

None of them could be fully replicated. Genome-wide significant results were found either at SNP level or pathway level. It has to be noted that GO: 0030518 pathway is only very close to corrected significance threshold (p=0.055). SNP: single-nucleotide polymorphism; GO: Gene Ontology; SSRI: selective serotonin reuptake inhibitor; PGRN-AMPS: Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study; NEWMEDS: Novel Methods leading to New Medications in Depression and Schizophrenia; GENDEP: Genome-Based Therapeutic Drugs for Depression; STAR*D: Sequenced Treatment Alternatives to Relieve Depression.

SNP	Gene(s) mapped to significant SNP(s) / significant gene or pathway	Effect/Side effect	Active ingredient	Sample size	Replicated in	References
rs12054895	*PURPL, AC093300.1* genes in 5p14.1	early improvement (continuous outcome)	2 weeks of SSRI treatment (citalopram, escitalopram)	1354	not	GENDEP Investigators, MARS Investigators, STAR*D Investigators, 2013; Am J Psychiatry 170(2): 207-217.
rs116692768	*ITGA9* gene in 3p22.2	depressive symptom improvement	12 weeks of SSRI treatment (citalopram, escitalopram)	1828	replicated in PGRN-AMPS (n=492, treated with citalopram or escitalopram), but not in NEWMEDS	Fabbri C et al, 2018; Pharmacogenomics J 18(3): 413-421.
rs76191705	*NRXN3* gene in 14q31.1	depressive symptom improvement	12 weeks of SSRI treatment (citalopram, escitalopram)	1828	not	Fabbri C et al, 2018; Pharmacogenomics J 18(3): 413-421.
	GO: 0005694 chromosomal pathway (main genes: *UPF1, HMGB1, FOXC1, PAM*)	depressive symptom improvement	12 weeks of antidepressant treatment (citalopram, escitalopram, nortriptyline)	1739	not	Fabbri C et al, 2018; Pharmacogenomics J 18(3): 413-421.
	GO: 0044427 chromosome fragment (main genes: *UPF1, FOXC1, PAM*)	depressive symptom improvement	12 weeks of antidepressant treatment (citalopram, escitalopram, nortriptyline)	1739	not	Fabbri C et al, 2018; Pharmacogenomics J 18(3): 413-421.
	GO: 0030518 Steroid hormone receptor signalling pathway (major gene: *YWHAH*)	remission	12 weeks of antidepressant treatment (citalopram, escitalopram)	1422	replicated in NEWMEDS (n=370, treated with citalopram or escitalopram) but not in PGRN-AMPS	Fabbri C et al, 2018; Pharmacogenomics J 18(3): 413-421.
rs2742417, rs2251954, rs2742421, rs2742423, rs1969624, rs2673057, rs2742431, rs2742435, rs2245705, rs2742390	*SACM1L* gene	sexual side effects	12 weeks of antidepressant treatment (bupropion)	1439	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs7136572	*USP44* gene	early sexual side effects	12 weeks of antidepressant treatment (bupropion)	1439	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs17135437	*COL26A1* gene	vision/hearing side effects	12 weeks of SSRI treatment (citalopram)	1762	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs16965962	*RPL7P45, AL138954.1* genes in 13q33.2	general side effect burden	12 weeks of SSRI treatment (citalopram)	1762	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs13432159	*LINC01812, AC007422.1* genes in 2p14	general side effect burden	12 weeks of antidepressant treatment (sertraline)	1439	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs11628713	*PAPLN* gene	suicidal thoughts during treatment	14 weeks of SSRI treatment (citalopram)	180	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.
rs11143230	*GDA* gene in 9q21.13	increasing suicidal tendency	12 weeks of anti-depressant treatment (escitalopram, nortriptyline)	706	not	Lin E & Lane HY, 2015; Pharmacogenomics 16(5): 555-566.

gene and gene-environment interactions is concerned, machine learning techniques, which are part of artificial intelligence, could also offer an effective aid and an acceptable method for predicting drug efficacy. Further research and independent replication patterns are needed in the future to validate the role of SNPs in GWAS studies. (11)

DISCUSSION

The results discussed in the present review article, which is based on the most recent literature, summarise the potential predictive factors that influence the effectiveness of antidepressant treatments in depression. (4) We discussed only the markers that have shown replicable effects between at least two former systematic review papers and also within each of these review papers. Moreover, we discussed genome-wide significant pharmacogenomics results from former meta-analyses. With our stringent selection criteria for markers we aimed to align the most robust predictors across different conditions and different moderators of antidepressant response.

Although many studies have been devoted to the identification of these markers, despite much effort, few predictive factors are actually incorporated into clinical practice. Despite the recent focus on genetic and other peripheral markers, there is still no established evidence-based approach to personalised treatment. (4) Due to cost and resource constraints, only those markers that prove to be the most cost-effective can be introduced into clinical practice. Drugs are also primarily targeted at patients who are most likely to benefit from the effectiveness of the therapy. (4) Psychological tests (questionnaires) are considered to be the most cost-effective method in this case, as they provide a preferred and already known predictor and because they are the easiest way for clinicians to measure and evaluate. With advances in science and cost reduction, it is assumed that it would be possible to include biomarkers. (4) From these markers, especially the qEEG measurements have a significant discriminatory value. The relatively low cost and high predictive power of this method make it attractive for incorporation into clinical practice. (4) In the near future, these routine tests could have a robust impact in determining the probable therapeutic response to antidepressants in patients with major depression. (4)

In the future, the best solution would be to set up a predictive model that takes into account the patient's predominant symptoms, medical history and available biomarkers that influence his or her therapy. (4) The predictive value would consist of a combination of several aspects, with each factor being weighted according to its effect size. One way to develop a model to describe the predictive factors of antidepressant response and to explore the differential effects of each predictor is to apply machine learning. (4) Using machine learning models, datasets from clinical trials and clinical registries, as well as from different research areas, could be pooled. The results of the studies would be validated by a program that would be able to detect relationships between different variables, validate the attributes and assign appropriate weights to them. (4) The model would also be able to learn which properties predict different responses and for different drugs. There is a pressing need for the widespread development of this method in the near future to provide truly evidence-based, personalised and effective treatment for people with major depression. (4) The search for a solution is also urgent because the prevalence of this disorder is increasing in the world population, to which the current pandemic-induced situation is a major contributory factor.

It is important to note however, that effective, personalised and evidence-based pharmacological treatment alone is not enough. (4) In addition, lifestyle counselling, regular check-ups and psychotherapeutic treatments are needed. This is an important aspect, as effective controlled therapy contributes to the recovery process, helps to achieve remission and reduces mortality.(4)

Another important limitation of our current approach is that we focused on the most robust predictors of antidepressant response. Although this set of robust predictors can be useful for an initial inclusion of markers into machine learning models, further sets of markers should also be identified later. These further sets of markers exert their effects on treatment response only in the presence of certain moderator conditions (such as age, sex, socio-economic status or active ingredient of the drug). It would also be crucial to identify moderator variables that consistently modify the effect of these different sets of predictors on treatment response.

To conclude, our present results intended to provide a list of general and robust markers of antidepressant response in major depression, which markers can be utilised by a start of further empirical studies with machine learning methods on “big data” of patients.

Conflicts of interest:
The authors declare no conflict of interest.

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A nagy adatbázisokon alapuló személyre-szabott antidepresszív kezelések felé: a legfrissebb szakirodalmi áttekintés a terápiás választ robusztusan befolyásoló faktorokról

Az antidepresszáns gyógyszerek felírása jelenleg a major depresszió kezelésének leghatékonyabb módja, ennek ellenére rendkívül alacsony számban érünk el végleges javulást. Emiatt fontos, hogy objektíven mérhető markereket azonosítsunk a hatékony, személyre szabott terápia szempontjából. Ezen összefoglaló cikk célja, hogy összegyűjtse mindazon markereket, amelyek robusztusan prediktívek a terápia kimenetele szempontjából. Egyszerre a lehető legtöbb féle marker hatását vizsgáló, szisztematikus áttekintő tanulmányokat kerestünk az antidepresszív terápiára adott válaszról major depressziósok körében, és ezekből kigyűjtöttük azokat a markereket, amelyeket minimum két áttekintő tanulmány szignifikánsnak talált, és amelyek egyúttal az adott áttekintő tanulmányon belül is replikálhatónak bizonyultak. Külön keresést végeztünk a farmakogenetikai teljes genom asszociációs vizsgálatok meta-elemzéseiről. Eredményeink alapján replikálható prediktornak bizonyultak a betegségkezdet időpontja, a tüneti súlyosság, az anhedónia tünet jelenléte, a korai terápiás válasz, a komorbid szorongás, az alkoholfogyasztás, a frontális EEG theta aktivitás, a hippocampus térfogata, az anterior cingularis kéreg aktivitása, illetve egy perifériás marker, a szérum BDNF szintje. Az eddigi farmakogenomikai kutatások nem hoztak replikálható eredményt. Robusztusnak azonosított prediktoraink kiindulási alapot jelenthetnek a jövőbeli, major depressziós betegek „big data" adatbázisán dolgozó, gépi tanulásos modellekhez.

Kulcsszavak: major depresszió, terápiás válasz, precíziós medicina, anhedónia, qEEG, hippocampus, ACC, BDNF