A systematic meta-review of predictors of adverse effect development in response to antidepressant medications

Emily Snook, BSc[1*]; Kelly Perlman, BSc[2*]; Eleanor H. Brown, BSc[3]; Timothé Langlois-Therien, MPhil[4,5]; David Benrimoh, MD, CM, MSc[6]; Myriam Tanguay-Sela, BSc[6]; Colleen Rollins, BSc[7]; Eunice You, MD[8]; Marcelo T. Berlim, MD, MSc[2,6]

* E.S. and K.P. contributed equally to this work
[1] Department of Medicine, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, Ontario
[2] Douglas Mental Health Institute, McGill University, 6875 Boulevard LaSalle, Verdun, Quebec
[3] Department of Psychological & Brain Sciences, Boston University, 64 Cummington Mall, Room 149, Boston, Massachusetts, USA
[4] Department of History and Philosophy of Science, University of Cambridge, Free School Lane, Cambridge, UK
[5] Department of Medicine, University of Ottawa, Roger Guindon Hall, 451 Smyth Road, Ottawa, Ontario
[6] Department of Psychiatry, McGill University, Ludmer Research & Training Building, 1033 Pine Avenue West, Montreal, Quebec
[7] Department of Psychiatry, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences, Forvie Site, Robinson Way, Cambridge, UK
[8] Department of Ophthalmology and Otolaryngology, Laval University, 2325, rue de l'Université, Quebec City, Quebec

Abstract

The pharmacological antidepressant (AD) treatments currently available to treat major depressive disorder (MDD) are associated with numerous adverse events (AEs), including gastrointestinal disturbances, sexual dysfunction, and sleep difficulties. Intolerance of the AEs caused by ADs is cited as a main reason for treatment discontinuation, hindering the recovery process. Therefore, the ability to predict the profile of AEs that an individual patient is likely to experience would hold great clinical value. Here, we review the extant research identifying biological, clinical, and sociodemographic features that are predictive of the incidence and severity of AD-induced AEs. We searched Embase and MEDLINE electronic databases for relevant reviews of all types that discuss predictors of AEs of antidepressant treatment published through March 2018, using a combination of relevant search terms. This protocol, filtered through our inclusion and exclusion criteria, resulted in the inclusion of 29 reviews. Several genetic factors involved in convergent biological processes, including the serotonergic, glutamatergic, and noradrenergic systems, were identified as predictive factors of AE incidence and severity. Non-genetic factors such as age, sex, and pre-existing medical comorbidities were also shown to have predictive value in this context. We could not conclusively determine the directionality of each finding or assign formal levels of evidence; rather, we focused on the emerging patterns of predictive factors. In summary, we systematically curated factors predictive of AD-induced AEs and discussed biological mechanisms that may underlie their predictive value. Additionally, we highlighted the paucity of predictive biomarkers beyond genetics, and emphasized the import of differential prediction.

Introduction

Major Depressive Disorder (MDD) is characterized by a complex constellation of symptoms including feelings of low mood, hopelessness and guilt, as well as anhedonia, loss of energy, changes in sleep and appetite, and suicidality.[1] According to a 2017 report from the World Health Organization, MDD affects over 300 million people globally, making it the leading cause of disability worldwide.[2] MDD is a costly condition in terms of morbidity and mortality as well as lost productivity and healthcare service utilization. This is in part due to the long and arduous process of optimal treatment selection for depressed patients. Standard treatment guidelines (e.g., the Canadian Network for Mood and Anxiety Treatments [CANMAT] guidelines) can provide only general recommendations with regards to personalizing antidepressant (AD) medication selection based on population-level variables. Therefore, finding an optimal treatment plan for a given patient often relies on an educated trial-and-error approach, in which a clinician and a patient try different ADs until a suitable treatment regime is identified.[3] An important consideration in the selection of AD treatment is the risk of side effects and adverse events (AEs). Minimizing the incidence and severity of medication-induced AEs is a central component of personalizing care and ensuring the best possible outcomes and quality of life.[4] Given that

Corresponding Author:
Emily Snook
emily.snook@mail.utoronto.ca

ADs are known to be associated with a range of troublesome AEs – including gastrointestinal (GI) disturbance, sexual dysfunction, weight changes, sleep disturbances, cardiovascular risks, and even suicidal ideation – mitigating AEs is a priority. In the literature, certain AEs have been associated with specific types of ADs such as "serotonergic AEs" arising from selective serotonin reuptake inhibitor (SSRI) use including nausea, sexual dysfunction, and headaches.[5,6] Linking AEs to ADs is the first step in understanding how to prevent AEs; the next step is elucidating the relationship between AD AEs and potential predictors. Understanding and minimizing AEs is also key when looking to maximize compliance and tolerability. Up to 50% of patients discontinue their AD treatment due to significant AEs.[7] Thus, AE prediction is a valuable avenue for the new field of precision psychiatry.[8]

Predicting specific AEs in individual patients remains elusive, although a range of biological, demographic and social factors are known to affect the presentation and severity of AEs.[9] The aim of this meta-review is to survey the literature to highlight promising predictors of AEs that may be implemented into routine clinical practice to reduce their incidence and severity, and improve treatment adherence, tolerability, and safety. This work will provide an overview of the landscape of predictors of AD AEs across modalities, ADs, AEs, and patient populations which to this point has not been done. Previous reviews in the field of AD AE predictors have been limited to focusing on genetic predictors exclusively; specific genes as predictors; and/or specific populations, AEs, and ADs.[10,11,12,13] In this review we considered factors that can be measured either at baseline and/or early on in the treatment to predict the incidence and severity of AEs, with a view to using these as input features in a future machine learning model aimed at personalizing MDD treatment choice. The features examined in this review include genetic factors such as polymorphisms in genes for serotonin transporters and receptors, cytochrome P450 enzymes, glutamate receptors, and other functional proteins as well as non-genetic factors such as age, biological sex, marital status, and co-morbidities. It is important to distinguish between predictors of drug-related AEs and predictors of drug interactions/drug toxicity. While drug interactions are relevant considerations when selecting ADs, the focus of this review will be on predictors of AD AEs based on patient characteristics, not including their current or past medications. Finally, we provide potential biological mechanisms as to why the highlighted factors may confer benefit to a machine learning model representing the complex dynamics of AEs.

Materials and methods

Search strategy

We sought meta-analyses and reviews of the literature, systematic and non-systematic, containing information on predictors of AEs of antidepressant treatment in two major electronic databases (Embase and MEDLINE) with publication dates from inception until March 2018. The EMBASE search was conducted using the syntax (exp antidepressant agent OR antidepressant agent/ OR antidepress* OR anti-depress* OR anti depress*) AND (major depressive disorder or depress* OR MDD OR exp depression/) AND (side effect* OR side-effect* OR adverse effect* OR adverse outcome* OR tolera* OR intolera* OR exp adverse event/ OR safety) AND (predict OR exp prediction/).

The MEDLINE search was conducted using the syntax (exp Antidepressive Agents OR exp Antidepressive Agents/ OR antidepress* OR anti-depress* OR anti depress*) AND (exp Depressive Disorder, Major/ OR major depressive disorder OR depress* OR MDD) AND (side effect* OR side-effect* OR adverse effect* OR adverse-effect* OR tolerab* OR intoler* OR safety profile) AND predict*.

Inclusion and exclusion criteria

In order to be included, a priori criteria was determined where reviews had to (1) be written in English; (2) be a review with or without meta-analysis containing information about predictors of AE development or severity after AD treatment in MDD; (3) include studies of adult patients being treated for MDD as their primary diagnosis (though patients could have psychiatric and/or medical comorbidities); (4) include information about biological, sociodemographic and/or symptom-based predictors of antidepressant AE development and/or severity.

Reviews were excluded, based on a priori criteria, if (1) they were primarily concerned with individuals with bipolar affective disorder, though these were considered for inclusion if they compared predictors of AE occurrence between bipolar and unipolar depression treated with ADs; (2) MDD was explicitly described as being secondary to traumatic brain injury, stroke, tumour, heart attack, or other non-psychiatric illness; (3) only experimental or very recently approved antidepressants were considered (e.g., ketamine, scopolamine); or (4) their full text could not be accessed.

Data extraction procedure

This systematic meta-review is registered on the PROSPERO registry (https://www.crd.york.ac.uk/prospero/ - ID number 90532). PRISMA reporting guidelines were followed in the organization of this review. Title and abstract screening was conducted using the publicly available online tool Rayyan (https://rayyan.qcri.org/). Two of four authors (E.S., E.B., K.P., T.L-T.) read and extracted data from each review based on criteria listed in our standardized data extraction table template, which included the following categories: type of review (non-systematic, systematic, and/or meta-analysis), list of significant predictors, list of predictors with conflicting evidence, list of non-significant predictors, and reasons for review exclusion (if applicable). Any discrepancies in the content of the data extraction details from the two readers were resolved by group consensus. We defined a "predictor" inclusively to encompass mediators and moderators as described in Perlman et al., 2018, where a factor is considered a predictor if its presence, absence, or value before or early on in AD treatment was found to be significantly associated with the presence, absence, or severity of a specific AE or general AE burden.[14]

We looked for predictors of AEs across phenomenological data (e.g., sociodemographic and clinical data) and all biomarker categories (e.g., genomics, neuroimaging, and circulating factor data). Since there is no valid metric for level of evidence for evaluating multimodal prediction of any given parameter of AD treatment, we elected not to use any level of evidence metric.14 Any of the current level of evidence frameworks used can be misleading since they are not intended to compare findings of different predictor modalities with variable measurement and timing parameters. Additionally, it

Table 1. Summary table of the genetic predictors of AE incidence, type, or severity. Predictors followed by "+" indicate predictors which were described in systematic reviews. Predictors followed by "++" indicate predictors which were described in meta-analyses and systematic reviews. Other predictors were only described in non-systematic reviews. A detailed version of this table with the polymorphisms and their corresponding AE phenotypes can be found in the supplementary material (online)

Gene Symbol	Gene Name	Polymorphisms and/or site of polymorphisms
5-HTR2A	5-Hydroxytryptamine Receptor 2A	· 102 T/C SNP (rs6313) · -1438 G/A SNP (rs6311) + · G/A SNP (rs7997012) +
5-HTR2C	5-Hydroxytryptamine Receptor 2C	· G/T SNP (rs6644093) +
5-HTR3A	5-Hydroxytryptamine Receptor 3A	· 178 C/T SNP (rs1062613) +
5-HTR3B	5-Hydroxytryptamine Receptor 3B	· 100-102 AAG del + ·Tyr/Ser SNP (rs1176744) +
5-HTT/SLC6A4	5-Hydroxytryptamine Transporter	· 5-HTTLPR variants (promoter region; S/LA/G alleles) ++ · sTin2 (intron 2: 12/12, 10/10 repeat units of 17bp carriers) + · A/G SNP (rs25531)
ABCB1/MDR1	ATP Binding Cassette Subfamily B Member 1	· C/T SNP (rs1128503) + · G2677T SNP (rs2032582) + · A/G SNP (rs2235040) · G/T SNP (rs10245483) · C3435T SNP (rs1045642) + · A/G SNP (rs9282564)
ADRA2A	Alpha 2A Adrenergic Receptor	· C/A SNP (rs11195419) +
BDNF	Brain-Derived Neurotrophic Factor	· Val66Met (196G/A) SNP (rs6265) + · A/G SNP (rs962369) +
CREB1	CAMP Responsive Element Binding Protein 1	· C/T SNP (rs4675690)
CYP2C19	Cytochrome P450 2C19	· PM genotype *2/*2, *2/*3, *3/*3 +
CYP2D6	Cytochrome P450 2D6	· PM genotype *3, *4, *5, *6, *7, *8, *16, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62, *68, *92, *100, *101 ++
DRD2	Dopamine receptor D2	·Taq1A (A1 allele)
ELP3	Elongator Acetyltransferase Complex Subunit 3	· Unspecified +
EMID2	Collagen Alpha-1(XXVI) chain	· C/T SNP (rs17135437) +
FKBP5	FK506 Binding Protein 5	· Unspecified +
GDA	Guanine Deaminase	· A/C SNP (rs11143230) +
GRIA1	Glutamate Ionotropic Receptor AMPA Type Subunit 1	· G/C SNP (rs1994862) + · A/T SNP (rs10515697) + ·T/C SNP (rs1864205) +
GRIA3	Glutamate Ionotropic Receptor AMPA Type Subunit 3	· G/A SNP (rs2285127) + · G/A SNP (rs2269551) + · A/G SNP (rs550640) + · A/G SNP (rs4825476)
GRIK2	Glutamate Ionotropic Receptor Kainate Type Subunit 2	· A/C SNP (rs2518224) · rs51326+ · G/A or G/C SNP (rs9404130)+ · C/A SNP (rs2518302)+ · C/T SNP (rs2518244)+
GRIN3A	Glutamate Ionotropic Receptor NMDA Type Subunit 3A	· G/A SNP (rs1323427)+ · A/G SNP (rs1323423)+ · A/G SNP (rs2050641)+
IL28RA/IFNLR1	Interferon Lambda Receptor 1	· C/T SNP (rs10903034)+
KCNIP4	Potassium Voltage-Gated Channel Interacting Protein 4	· C/T SNP (rs358592)+
PAPLN	Papilin, Proteoglycan Like Sulfated Glycoprotein	· C/T SNP (rs11628713)+

is challenging to compare predictors from distinct modalities to any meaningful extent given the large disparity in sample sizes required to obtain appropriate statistical power, as well as the under-reporting of effect sizes.

Results

Our formal search initially identified 6,187 papers, and an additional 3 papers were hand-picked by the authors, which were identified by focused searches on classes of AEs. This included 4,153 unique papers after duplicates were removed. These papers were then screened by title and abstract. Based on our inclusion and exclusion criteria listed above, 4,062 papers were removed, such as papers that were not reviews, papers discussing animal studies, or papers in which depression was not the primary diagnosis. This left 91 full-text papers to be read. Two authors, out of E.S., E.B., K.P., and T.L-T., independently read each text and excluded 62 more papers that either did not mention AE predictors or were not review articles. At the end of this process, as outlined by the PRISMA flow chart in Figure 1,

29 papers discussing predictors of antidepressant AEs were included in our review consisting of 22 non-systematic reviews, 6 systematic reviews, and 1 meta-analysis. Supplemental Table 1 (online) provides a summary of the AE predictors identified.

Genetics

Genetic factors seem to be the most well studied predictors of antidepressant AEs. The most replicated findings relate to genes encoding serotonin receptors and transporters.

Several polymorphisms of serotonin receptor genes including 5-HTR2A, 5-HTR2C, 5-HTR3A and 5-HTR3B have been associated with antidepressant AEs. Polymorphisms of the 5-HTR2A gene have been studied extensively. A C/C genotype of the 102 T/C polymorphism has been linked to GI and paroxetine associated AEs, and a general increased risk for AEs in European and Asian populations as well as geriatric patients.[15,16,17,18,19,20] Similarly, the G allele of the -1438 G/A polymorphism has been associated with increased AE risk and severity, particularly GI and sexual AEs.[19] Receptor polymorphisms 5-HT3A and 5-HT3B have been associated with increased vomiting and nausea with paroxetine treatment, including the rs1062613 SNP of 5-HTR3A, the 129 Tyr/Ser and rs1176744 polymorphisms and the 100-102 AAG deletion of 5-HTR3B.[15,21] Serotonin transporter gene (SLC6A) polymorphisms have also been reviewed extensively, particularly in the HTTLPR region. The S allele is associated with increased AEs and reduced tolerability of ADs in Caucasians, including AD-induced mania, GI effects, severe headaches, insomnia and agitation, higher suicidality and weight loss, while the L allele has been associated with decreased AEs.[10,15,19,20,22,23] This may be limited to Caucasian patients, as these results have not been replicated in Asian populations for whom the opposite effect has been found.[10,23]

Genes underlying the cytochrome P450 enzymes CYP2D6 and CYP2C19 have also been implicated in AD AE severity. Based on enzyme activity, patients can be categorized as poor metabolizers (PM), extensive (normal) metabolizers (EM), or ultra-rapid metabolizers (UM). The PM phenotype is often associated with increased AEs, although there have been some studies showing no association.[11,16,19,25,26] In particular, the CYP2D6 PM phenotype was not associated with AEs in geriatric patients treated with paroxetine or with sexual dysfunction during paroxetine treatment.[16,19,25] CYP2C19 PM status has also been associated with AEs.[10,27]

In a 2016 review, Bruckl & Uhr identified several ATP Binding Cassette Subfamily B Member 1 (ABCB1) polymorphisms associated with AEs.[11] A T/T genotype of rs1045642 predicted increased AE risk, especially postural hypotension with nortriptyline, while a T/T genotype of rs1128503 and rs2032582 predicted sexual dysfunction in females treated with SSRIs.[11] The minor alleles of SNPs rs2235040 and rs2032583 were predictive of a higher number of AEs, particularly sleep-related and serotonergic AEs, which include weight gain and GI issues.[11,28] Genotypes of polymorphisms rs2032582, rs2214102, and rs1045642 were associated with antidepressant treatment-emergent suicidal ideation (TESI).[11,28] By contrast, the A allele of rs2032582 and the minor allele of rs9282564 predicted reduced AEs, and the C allele of rs1882478 predicted reduced insomnia with escitalopram.[11]

Several glutamate receptor genes have been associated with the AEs of sexual dysfunction and TESI. Thomas and Ellingrod (2009) reported that a C/C genotype of the GRIK2 SNP rs2518224 and the G allele of the GRIA3 SNP rs4825476 were associated with citalopram TESI.[19] Additionally, several glutamate receptor genes were identified to predict sexual dysfunction with citalopram treatment in Caucasians. Orgasm difficulties and reduced libido were associated with polymorphisms in genes underlying the glutamate AMPA receptor genes GRIA1 (SNPs rs1994862, rs10515697, and rs1864205) and GRIA3 (SNPs rs2285127, rs2269551, and rs550640), respectively.[19] Additionally, reduced libido was associated with the glutamate kainate receptor gene GRIK2 (rs51326, rs9404130, rs2518302, and rs2518244).[19] Finally, erectile dysfunction in males has been associated with the glutamate NMDA receptor gene GRIN3A (rs1323427, rs1323423 and rs2050641).[19]

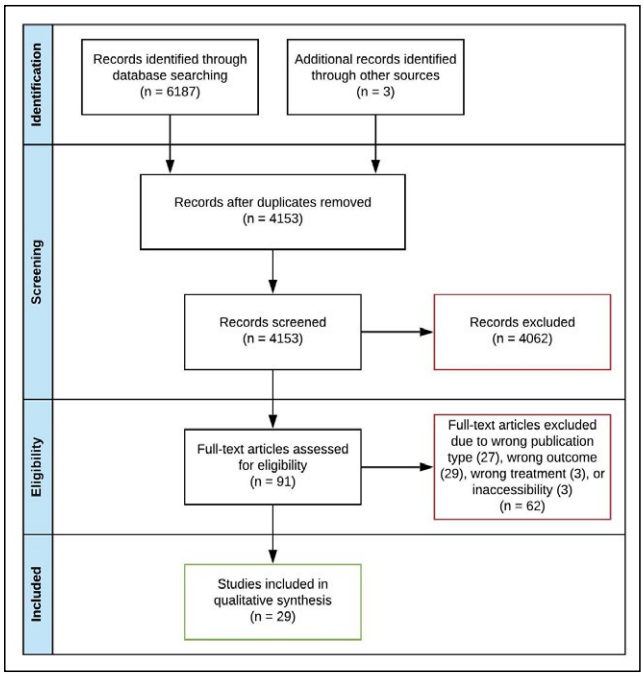

Figure 1. Prisma flow diagram depicting the review article selection process.

Genes involved in the CREB1-BDNF signaling pathway seem to be implicated in the development of TESI and sexual dysfunction as well. Specifically, variants of the CREB1 SNP rs4675690 were associated with TESI during the first three days of citalopram treatment.[19] The BDNF polymorphism rs962369 is also associated with TESI.[19] Additionally, Chinese patients with the Met allele of the BDNF Val66Met polymorphism were less likely to experience decreased sexual desire with fluoxetine treatment.[13]

Several other genes have been identified to predict various AEs. For example, Lett et al. (2016) identified the PAPLN polymorphism rs11628713 and the IL28RA polymorphism rs10903034 to be associated with citalopram TESI.[10] Similarly, FKBP5 variants were found to be associated with TESI.[10] Crisafulli and colleagues (2011) additionally pointed out associations between the ADRA2A polymorphism rs11195419 with TESI from nortriptyline treatment.[21] Additionally, variants of the hERG gene, which encodes for a potassium channel subunit, was found to be related to a longer QT interval induced by drugs such as tricyclic antidepressants (TCAs).[22]

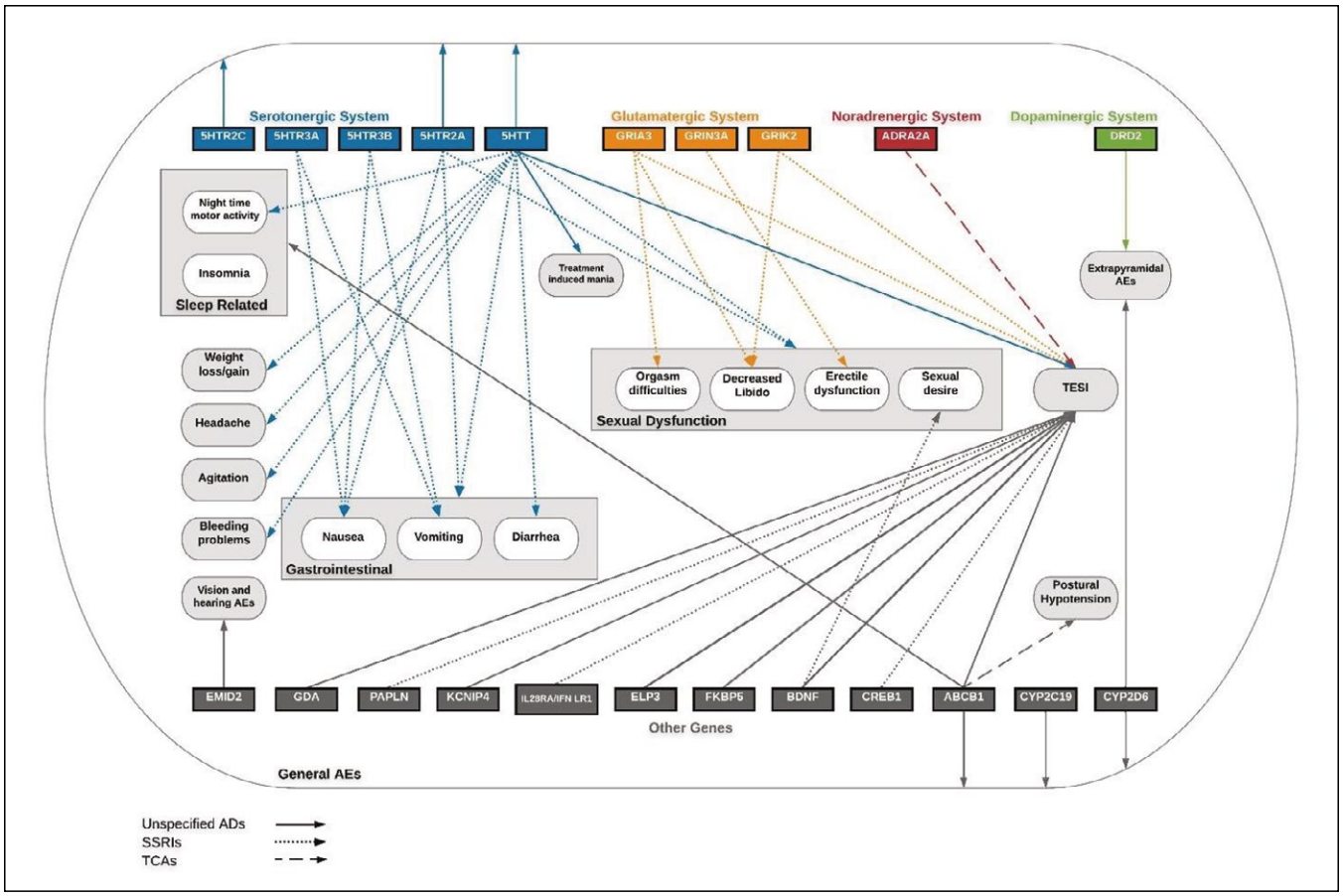

Figure 2. A graphical representation of the relationships between the genetic predictive finding with respect to AD-induced AEs. The border of the figure represents "General AEs", meaning the AEs associated with the genes linked to the border by arrows were not described within specified categories. Several patterns of note can be appreciated visually here in terms of both patterns of genes with respect to AEs and patterns of AEs with respect to genes:
1) The serotonergic system, ABCB1, and CYP gene variants are associated with "General AEs". The vast majority of "Other Genes" are associated only with TESI. Serotonergic system genes as a group display the most diverse AE associations, the 5-HTT gene in particular, and these associations have generally been shown with SSRI therapy. Glutamatergic system genes are associated with Sexual Dysfunction AEs and TESI, and these associations have been shown with SSRI therapy. 2) TESI is associated with genes from the serotonergic system, glutamatergic system, noradrenergic system, and nine genes from the "Other Gene" group, making it the AE with the most diverse genetic associations. Sexual Dysfunction AEs are associated mainly with serotonergic and glutamatergic system genes, as well as BDNF and ABCB1. GI AEs appear to be associated exclusively with serotonergic genes.

Non-genetic predictors

Sociodemographics

Sociodemographic predictors of antidepressant AEs include age, sex and marital status. These have been studied less extensively than genetic predictors but are important as they are often more easily accessible. Elderly patients are at a higher risk of hyponatremia with fluoxetine or paroxetine compared to other SSRIs and venlafaxine, and orthostatic hypotension with imipramine compared to reboxetine.[28,29] Patients younger than 40 years old are at a higher risk for TESI.[30] Younger patients are at risk of orgasm dysfunction during citalopram treatment, and patients with earlier onset of illness are at risk of decreased libido.[13,28] Female patients experience greater orgasmic inhibition and are more likely to develop sexual dysfunction with SSRIs, specifically paroxetine.[13,28] Being male and being married are associated with decreased libido and increased orgasm dysfunction with citalopram treatment.[13,28]

Comorbidities

Cumulative medical comorbidities in general have been associated with orgasm dysfunction during citalopram treatment,[13] but specific illnesses have been studied as well. For example, patients with pre-existing liver disease and patients who drink alcohol heavily have a higher risk of hepatotoxicity with duloxetine.[12] Additionally, an underlying central nervous system (CNS) pathology may increase a patient's risk for akathisia with fluoxetine treatment.[31]

Discussion

The results from our analysis give insight into potential predictors which could be measured at the beginning of treatment to help select the AD with the least AEs for a given patient. The literature appears to frequently report predictors of AEs without specification of the type or severity of an AE; "general AEs" was often the reported outcome. In order to highlight the patterns found, we will emphasize the plausible biological mechanisms and supportive evidence for the extracted predictors as well as discuss how these pathways and

systems may interact. Figure 2 illustrates the interactions between types of AEs, neurotransmitter systems, genetic constituents, and other relevant genes.

The multimodal nature of the extracted predictors and heterogeneity in methodologies and reporting restricted our ability to assign a level of evidence to predictors, but in Table 1 we have denoted predictors which were described in a systematic review with "+" and predictors which were described in a systematic review and a meta-analysis with "++" as a proxy for level of evidence. This is adapted from an approach by Kirk et al., 2012 based on the Canadian Best Practice Initiative Methodology Background Paper; we considered predictors identified through systematic reviews and/or meta-analyses to be suitable for developing effective clinical recommendations, compared to non-systematic reviews as suitable for developing promising clinical recommendations.[32,33]

Genetics

Serotonin transporter and receptor genes

We found a high volume of research on both serotonin transporter and receptor gene polymorphisms and their influence on AEs. Most often, these were linked to GI AEs and sexual AEs, particularly with respect to SSRIs. These findings have important implications for the prescription of ADs given that approximately 50% of patients treated with SSRIs report GI AEs such as nausea and vomiting, and 40-65% report sexual AEs, two of the most common reasons for discontinuation.[35,36,37]

5-HT2 receptors located in the spinal cord are involved in sexual arousal and are likely responsible for some SSRI-induced sexual dysfunction; antagonists to these receptors have been shown to be effective in relieving AD treatment-emergent sexual dysfunction, and mirtazapine and nefazodone, both agents with antagonistic action for 5-HT2 receptors, have shown no difference compared to placebo in terms of sexual dysfunction.[6,38] Another physiological mechanism proposed to mediate AD-induced sexual AEs is a reduction of dopamine in the mesolimbic system due to the inhibitory actions of 5-HT2Rs in the brain.[39,40] It has been suggested that the concordant administration of dopaminergic agents could counteract sexual AEs emerging from SSRI treatment with pro-sexual effects.[41,42]

Agents acting on the peripheral serotonergic system are known to affect gastric motility and sensory regulation, and agents acting on central serotonin receptors have been associated with nausea and vomiting.[43,44] Specifically, the 5-HT3 receptor subtype is concentrated in the dorsal vagal complex of the brainstem, an area involved in the initiation and coordination of the vomiting reflex. Variants of this gene are directly associated with GI AEs, and antagonists to this receptor have been shown to reduce nausea with AD and chemotherapy treatment.[45]

Another AE associated with serotonergic antidepressants is weight gain, which has been hypothesized to result from desensitization and downregulation of 5-HT2C receptors associated with appetite control.[46] The relationship between 5-HT2C receptors and drug-induced weight gain has been investigated with antipsychotic treatment, where polymorphisms within the 5-HT2C gene impact circulating leptin levels, and protective alleles against antipsychotic-induced weight gain in the promoter region lead to reduced activity.[47]

Cytochrome P450 genes

Genetic polymorphisms within the genes for CYP 2C19 and 2D6 predict general AEs with ADs. Stratification according to CYP metabolic function has already been proposed as a clinical tool to guide treatment with dosage reduction of ADs metabolized by these enzymes in PM phenotypes to avoid excess drug concentration and consequent AEs.[48,49]

ABCB1 gene

The ABCB1 gene (also known as MDR1) encodes P-glycoprotein, a transporter expressed throughout the body including tissues in the liver, intestines, and blood-brain barrier.[50] Polymorphisms affecting the activity of this gene may influence the intracerebral concentrations of AD substrates and therefore their efficacy or potential for AEs. More specifically, ABCB1 polymorphisms have been associated with female sexual dysfunction, TESI, and sleep related AEs, all of which are related to cognition.[11,35,51]

Glutamate receptor genes

Our review suggests two main AEs associated with glutamate receptor gene polymorphisms: sexual dysfunction and TESI. While the main hypothesis for sexual dysfunction triggered by AD therapy revolves around serotonergic pathways, the association between treatment-emergent sexual dysfunction and genes encoding glutamate receptor subunits deserves to be explored further.[39,40] Glutamatergic neurotransmission plays a role in normal mammalian sexual function and there is evidence that monoaminergic-based ADs alter the function of the glutamatergic system with the observation of reduced glutamine concentrations in cerebrospinal fluid and reduced glutamate in serum and plasma associated with AD treatment.[52,53,54] It may be that some ADs modulate glutamatergic transmission through serotonin receptors to cause sexual dysfunction.[55]

Gene variants of receptors involved in the glutamatergic system have been linked to TESI; specifically GRIK2 and GRIA3.[56,57] The involvement of the glutamatergic system with suicidal ideation has been demonstrated through investigations of the efficacy of ketamine, an NMDA receptor antagonist, in the acute treatment of suicidality.[58,59,60,61] As further support for the relationship between variants of glutamate receptor genes and TESI, differential expression of GRIA3 has been observed to be significantly down-regulated in the prefrontal cortex of individuals with and without MDD who died by suicide.[62]

BDNF-CREB1 Pathway genes

The BDNF-NTRK2-CREB1 signaling pathway has been implicated in the pathophysiology of MDD and response to AD treatment.[63,64,65,66] CREB1 is a transcription factor; one of its target genes is the BDNF gene, encoding a neurotrophin involved in the regulation of neural circuit development and synaptic function and plasticity.[67] Data from animal and human studies suggest that acute stress decreases BDNF expression in the hippocampus and prefrontal cortex, mediated by decreased CREB1 signaling, and the use of ADs has been associated with reversing this decrease in BDNF expression and CREB activity.[64,66,68,69] In terms of AEs, there is evidence to suggest that overexpression or upregulation of the CREB1-BDNF signaling pathway in regions outside of the prefrontal cortex and hippocampus, such as the ventral tegmental area and nucleus accumbens, is associated with an MDD-like phenotype.[66]

Thus, a potential mechanism for AD TESI and reduced sexual desire could involve increased BDNF-CREB1 pathway activity in regions of the brain that were functioning normally pre-treatment.

Other genes

Several other genes have been associated with AEs of ADs. In particular, the FKBP5 gene linked to TESI encodes a co-chaperone for glucocorticoid receptor folding with the ability to modulate the glucocorticoid-mediated stress response.[10,70,71]

The link between TESI and FKBP5 variants that decrease the sensitivity of the glucocorticoid receptor may be explained by the relationship between suicidal ideation and insensitivity of the hypothalamic-pituitary-adrenal (HPA) axis to negative feedback, resulting in chronically increased cortisol secretion.[72] Anacker and colleagues (2012) hypothesized that antidepressant modulation of the glucocorticoid receptor at least partially involves restoration of glucocorticoid sensitivity in the brain and negative feedback signals to the HPA axis.[73] The glucocorticoid receptor modulated by FKBP5 has been shown to regulate BDNF expression, also connected with TESI.[74]

A variant in the ADRA2A gene has been associated with an increased risk for TESI during nortriptyline treatment, particularly in males.[65] The ADRA2A gene encodes the alpha-2A adrenergic receptor concentrated in the prefrontal cortex - interestingly, upregulation, increased expression and increased sensitivity of this receptor in this brain region has been observed in individuals who have died by suicide compared to those who have not.[75,76] Variants within this gene may have promise for differential prediction of treatment-induced AEs, as ADRA2A polymorphisms specifically affect the adrenergic system targeted directly by SNRIs.[77]

Non-genetic predictors

Sociodemographic factors which were reported to associate with AD AEs include age, sex and marital status. Patients who develop TESI are more likely to be younger than 30 years old, and those who develop suicidal behavior after initiation of AD treatment tend to be younger than 40 years old.[30,78] It may be that ADs increase suicide risk in younger individuals through induction of a state of agitation or restlessness, or that AD treatment first addresses symptoms of depression such as anhedonia before mood which leads to an increased ability to act without alleviation of mood symptoms.[72,79,80]

Overall sexual dysfunction during SSRI treatment has been generally reported to affect males more than females, although specific aspects of sexual dysfunction may appear more frequently among women. Notably, women are said to experience higher rates of arousal dysfunction, which may be related to greater dependence on cognitive compared to physiological aspects of arousal.[28] While this trend is interesting, it is important to consider it in concert with factors which may affect its validity. Firstly, sexual dysfunction AEs are notoriously underreported.[28,39] Furthermore, women may be more likely to report arousal dysfunction and men more likely to report overall sexual dysfunction, decreased libido, and orgasm dysfunction.

Finally, medical comorbidities are associated with significant AD-linked AEs. Severity of general medical comorbidity is associated with erectile dysfunction and difficulty with orgasm during AD treatment and in general without AD treatment.[81,82,83] CNS pathology has been proposed as a risk factor for fluoxetine-induced akathisia, a movement disorder of restlessness and an inability to remain still, which is hypothesized to result from reduced dopaminergic neurotransmission secondary to AD treatment.[84] Fluoxetine-induced akathisia may result from drug accumulation due to its long half-life and increased serotonergic inhibition of dopaminergic neurons through its affinity for 5-HT2C receptors, and CNS pathologies may affect dopaminergic transmission at baseline, predisposing patients to this AE.[84,85,86] These comorbidities with predictive value for AD-induced AEs may be explained in a "multiple-hit" fashion, where both AD treatment and medical comorbidities individually increase the risk for a given symptom or AE and result in an additive effect when both are present.

An unexpected finding of this systematic meta-review was the relative lack of sociodemographic predictors compared to genetic predictors. Our previous work reported a plethora of multimodal predictors for AD treatment response, including dimensions of genetics, neuroimaging, sociodemographics and peripheral markers.[14] In the case of AD AE predictors, there is a striking dominance of genetic predictors, a paucity of sociodemographic predictors and an absence of any other dimensions such as peripheral markers or neuroimaging. This discordance between research into predictors of AD treatment response versus AD-induced AEs is relevant in and of itself, as it appears that these other modalities have not yet been explored to a great extent despite the importance of AEs in treatment adherence and success. Thus, while the genetic predictors discussed here certainly hold value in their relationship to AD AEs, more research into other modalities is needed.

Relevance for clinical decision support systems

The patient features discussed may hold some value independently for prediction of optimal therapy for a given patient but are more likely to be of use when integrated into a comprehensive panel as part of a clinical decision support system (CDSS). While the predictors reported here have not been assessed using a quality of evidence metric, the identification of these features was intended to provide a maximal pool of features from which a machine learning model could parse and assign weight to features which hold relevant predictive value for AD AEs. In this sphere of research and development, breadth and diversity of predictors is paramount for a model to build its predictions to assist in clinical decision making rather than depth and detail of predictor relationships with outcomes in group analyses.[14] Our discussion here provides plausible biological bases for the identified predictors of AD AEs, and this information may be helpful in confirming or questioning features identified through a machine learning approach which may hold predictive value for AD AEs. A CDSS could help identify and refine optimal treatments by considering personalized patient factors influencing AEs and treatment response. Indeed, recent trials have shown the utility of using genetic information to help select ADs. Iniesta and colleagues (2018) have demonstrated the feasibility of using genetic information as part of machine learning model aimed at predicting remission.[87]

A confound in AD AE studies is related to the difficulty in disentangling AEs which arise solely as a result of the pharmacotherapeutic agents from changes in heterogeneous disease symptomatology. Consistent reporting of timing, medication dosage changes and adherence, symptom scales, and AEs scales would help to better establish causal relationships between AD use and reported

AEs. Overall, tracking these variables through a clinical support system paired with a patient digital health reporting platform would allow for higher resolution information such as dose-dependency and timing of AE development and provide optimized data for future studies.

Limitations

While this topic is of significant relevance to the improvement of MDD treatment, there are several limitations of this review. First, we did not consider grey literature (e.g., doctoral theses, unpublished materials) which may contain important information in a field with ongoing research.[88] Given the widespread scope of relevant literature, the decision was made to consider only extant reviews, as these were arguably most likely to capture the most widely reproduced results.

We elected to include non-systematic reviews (e.g. narrative reviews and scoping reviews) in our search, in addition to systematic reviews and meta-analyses, in order to provide a broader overview of the predictor landscape in terms of predictor modalities, AEs, ADs, and patient populations. In contrast to a meta-analysis, which would have allowed us to assign some level of evidence to the various predictors, we were limited in the conclusions we could draw from the selected reviews. While our broad approach aligns with our rationale of determining the state of research in the AD AE prediction field and ensuring maximal identification of predictors, we are aware that the tradeoff with a modality- and methodology-inclusive approach is a loss of granularity in the description of our findings and an inability to assign quality of evidence metrics to our results. This is particularly relevant with genome-wide association studies (GWAS) where sample sizes, effect sizes, and methodology provide important insight into the quality of results.[89] Thus, our synthesis focused on extracting overall trends of predictors of AD-induced AEs and delving into the biological evidence supporting these predictors. We believe that explaining the relationship between a predictor, AD treatment, and AEs within a reasonable biological framework can add to the overall credibility of such a predictor. However, this cannot be the sole dimension used to determine a predictor's level of evidence, and we recognize that an objective and comprehensive quantification of the potential predictors' relevance and validity remains to be explored.

Currently, mixed results have been reported regarding many of the genetic predictors of AD-related AEs and it is difficult to determine whether negative results are, for example, due to the lack of statistical power in the primary studies. The data captured in this review is the result of studies which mainly (but not exclusively) recruited Western Caucasians, which may limit the generalizability of these trends to other populations and overlook relevant patterns of ethnicity-specific predictors of AD-induced AEs.

An innate limitation to the field of AD AE research is the lack of a standard metric to measure AE type, severity, and burden with AD treatment. Several scales exist to evaluate a patient's AD AEs including the Toronto Side Effects Scale (TSES), the Antidepressant Side Effect Checklist (ASEC), and the Frequency, Intensity, and Burden of Side Effects Rating Scale (FIBSER), although AEs were often reported in the literature as "general AEs" without description of the specific type of AE.[90,91,92] Further, scales such as the Arizona Sexual Experience Scale (ASEX) have been used to characterize categories of AD AEs such as sexual dysfunction. This heterogeneity in methodology further limited our ability to effectively compare predictors.[93] We recommend development and consensus on a standardized and detailed AE metric or equivalence system specifically for AD treatment to be used consistently in future research, and we emphasize the importance of reporting specific types of AEs rather than aggregating AE burden into a single metric.

A critical limitation of the interpretation of our results is the lack of insight we have into the details of predictors reported to be associated with "general AEs". While certain classes of predictors such as variants within the CYP enzyme family might be expected to produce systemic AEs, many others are directly associated with a specific biological system, and in these cases researchers should investigate and report on specific types of AEs related to that system rather than a general score of AE burden.[94]

Conclusions

From this systematic meta-review, it is evident that genetic information is the most explored biomarker in the context of AD AE profile prediction. This research has generated promising findings, and therefore it would be a worthwhile investment to continue to make pharmacogenomic technology more accessible, encourage its adoption into routine clinical use, and promote basic and clinical studies in this area. More recent research in transcriptomics, epigenomics and microbiomics may lead to even more useful indicators of AE development, burden, specificity and/or timing given that they might be able to capture more dynamic processes that have been shown to be involved in AD AEs.[95]

Acknowledgements

We would like to thank Jingla-Fri Tunteng and Marina Wakid for their helpful feedback.

Declaration of Authors' Competing Interests

K.P., D.B., E.S., E.H.B., T.L.-T., M.T.-S., C.R., are all either shareholders, contractors, or volunteers at Aifred Health, medical technology company that uses deep learning to improve treatment selection in psychiatry. E.Y. and M.T.B. declare no conflict of interest.

References

1. Diagnostic and statistical manual of mental disorders : DSM-5 [Internet]. Fifth edition. Arlington, VA : American Psychiatric Publishing, 2013. Available from: https://search.library.wisc.edu/catalog/9911111397702121
2. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. JAMA. 2017 Apr 18;317(15):1517. https://doi.org/10.1001/jama.2017.382610.1176/foc.6.1.foc69
3. Lam RW, Milev R, Rotzinger S, Andreazza AC, Blier P, Brenner C, et al. Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. BMC Psychiatry. 2016 Apr 16;16(1):105. https://doi.org/10.1186/s12888-016-0785-x
4. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. Dialogues in Clinical Neuroscience. 2008 Dec;10(4):409–18
5. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context [Internet]. 2015 Oct 8 [cited 2020 Nov 9];4. Available from: 10.7573/dic.212290
6. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. 1998 Dec 1;51(3):215–35. https://doi.org/10.1016/S0165-0327(98)00221-3
7. Rheker J, Winkler A, Doering BK, Rief W. Learning to experience side effects after antidepressant intake - results from a randomized, controlled, double-blind study. Psychopharmacology. 2017;234(3):329–38. https://doi.org/10.1007/s00213-016-4466-8
8. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry.' BMC Medicine. 2017 Apr 13;15(1):80. https://doi.org/10.1186/s12916-017-0849-x

9. Simon GE, Perlis RH. Personalized medicine for depression: can we match patients with treatments? Am J Psychiatry. 2010 Dec;167(12):1445–55. https://doi.org/10.1176/appi.ajp.2010.09111680
10. Lett TA, Walter H, Brandl EJ, l EJ. Pharmacogenetics and imaging-pharmacogenetics of antidepressant response: towards translational strategies. CNS Drugs. 2016 Dec;30(12):1169–89
11. Bruckl TM, Uhr M. ABCB1 genotyping in the treatment of depression. Pharmacogenomics. 2016;17(18):2039–69
12. DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Annals of Pharmacotherapy. 2007 Jul;41(7):1201–1.
13. Osis L, Bishop JR. Pharmacogenetics of SSRIs and Sexual Dysfunction. Pharmaceuticals (Basel). 2010 Dec 15;3(12):3614–28. https://doi.org/10.3390/ph3123614
14. Perlman K, Benrimoh D, Israel S, Rollins C, Brown E, Tunteng J-F, et al. A systematic meta-review of predictors of antidepressant treatment outcome in major depressive disorder. J Affect Disord. 2019 Jan 15;243:503–15. https://doi.org/10.1016/j.jad.2018.09.067
15. Helton SG, Lohoff FW. Serotonin pathway polymorphisms and the treatment of major depressive disorder and anxiety disorders. Pharmacogenomics. 2015;16(5):541–53
16. Rasmussen-Torvik LJ, McAlpine DD. Genetic screening for SSRI drug response among those with major depression: Great promise and unseen perils. Depression and Anxiety. 2007;24(5):350–7
17. Schatzberg AF, DeBattista C, Lazzeroni LC, Etkin A, Murphy Jr GM, Williams LM. ABCB-1: Antidepressant response in geriatric depression and chronic depression. Biological Psychiatry. 2015;1:23S
18. Serretti A, Artioli P. The pharmacogenomics of selective serotonin reuptake inhibitors. The Pharmacogenomics Journal. 2004 Aug;4(4):233–44. https://doi.org/10.1038/sj.tpj.6500250
19. Thomas KLH, Ellingrod VL. Pharmacogenetics of selective serotonin reuptake inhibitors and associated adverse drug reactions. Pharmacotherapy. 2009 Jul;29(7):822–31
20. Zobel A, Maier W. Pharmacogenetics of antidepressive treatment. European Archives of Psychiatry & Clinical Neuroscience. 2010 Aug;260(5):407–17
21. Crisafulli C, Fabbri C, Porcelli S, Drago A, Spina E, De Ronchi D, et al. Pharmacogenetics of antidepressants. Frontiers in Pharmacology. 2011;2:6. https://doi.org/10.3389/fphar.2011.00006
22. Kirchheiner J, Nickchen K, Bauer M, Wong M-L, Licinio J, Roots I, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry. 2004 May; 9(5):442–73. https://doi.org/10.1038/sj.mp.4001494
23. Zhu J, Klein-Fedyshin M, Stevenson JM. Serotonin Transporter Gene Polymorphisms and Selective Serotonin Reuptake Inhibitor Tolerability: Review of Pharmacogenetic Evidence. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2017 Sep;37(9):1089–104
24. Bondy B. Pharmacogenomics in depression and antidepressants. Dialogues in Clinical Neuroscience. 2005 Sep;7(3):223–30
25. Malhotra AK, Murphy Jr GM, Kennedy JL. Pharmacogenetics of psychotropic drug response. American Journal of Psychiatry. 2004 May;161(5):780–96
26. Vandel P, el P. Antidepressant drugs in the elderly–role of the cytochrome P450 2D6. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2003;4(2):74–80
27. Ramos M, Berrogain C, Concha J, Lomba L, García CB, Ribate MP. Pharmacogenetic studies: a tool to improve antidepressant therapy. Drug Metabolism and Personalized Therapy. 2016 Dec 1;31(4):197–204
28. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. Primary Care Companion to the Journal of Clinical Psychiatry. 2001 Feb;3(1):22–7
29. Montgomery SA. Predicting response: noradrenaline reuptake inhibition. International Clinical Psychopharmacology. 1999 May;14(Suppl 1):S21-6
30. Moller HJ. Antidepressants: controversies about their efficacy in depression, their effect on suicidality and their place in a complex psychiatric treatment approach. World Journal of Biological Psychiatry. 2009;10(3):180–95
31. Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. Journal of Clinical Psychopharmacology. 1997 Oct;17(5):377–89
32. Kirk SFL, Penney TL, McHugh T-L, Sharma AM. Effective weight management practice: a review of the lifestyle intervention evidence. International Journal of Obesity. 2012 Feb;36(2):178–85
33. Ward MC, White DT, Druss BG. A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness. J Clin Psychiatry. 2015 Apr 1;76(4):e477-86
34. Kemp DE, Malhotra S, Franco KN, Tesar G, Bronson DL. Heart disease and depression: Don't ignore the relationship. Cleveland Clinic Journal of Medicine. 2003 Sep;70(9):745–61
35. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom. 2016;85(5):270–88. https://doi.org/10.1159/000447034
36. Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Ment Health Clin. 2016 Jun 29;6(4):191–6. https://doi.org/10.9740/mhc.2016.07.191
37. Sugai T, Suzuki Y, Sawamura K, Fukui N, Inoue Y, Someya T. The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. The Pharmacogenomics Journal. 2006 Sep;6(5):351–6.. https://doi.org/10.1038/sj.tpj.6500382
38. Zajecka J. Strategies for the treatment of antidepressant-related sexual dysfunction. J Clin Psychiatry. 2001;62 Suppl 3:35–43
39. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009 Jun;29(3):259–66. https://doi.org/10.1097/JCP.0b013e3181a5233f
40. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. Perspect Psychiatr Care. 2002 Sep;38(3):111–6
41. Alcántara AG. A possible dopaminergic mechanism in the serotonergic antidepressant-induced sexual dysfunctions. Journal of Sex & Marital Therapy. 1999 Apr;25(2):125–9. https://doi.org/10.1080/00926239908403985
42. Demyttenaere K, Jaspers L. Review: Bupropion and SSRI-induced side effects. Journal of Psychopharmacology. 2008 Sep;22(7):792–804. https://doi.org/10.1177/0269881107083798
43. Janssen P, Vos R, Tack J. The influence of citalopram on interdigestive gastrointestinal motility in man. Aliment Pharmacol Ther. 2010 Jul;32(2):289–95. https://doi.org/10.1111/j.1365-2036.2010.04351.x
44. Mawe GM, Hoffman JM. Serotonin Signaling in the Gastrointestinal Tract: Nat Rev Gastroenterol Hepatol. 2013 Aug;10(8):473–86. https://doi.org/10.1038/nrgastro.2013.105
45. Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology. 1999 Aug 1;38(8):1083–152. https://doi.org/10.1016/S0028-3908(99)00010-6
46. Khawam EA, Laurencic G, Malone DA. Side effects of antidepressants: an overview. Cleveland Clinic Journal of Medicine. 2006 Apr 1;73(4):351–3.. https://doi.org/10.3949/ccjm.73.4.351
47. Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychoticinduced weight gain - mechanisms and genetics. J Psychopharmacol (Oxford). 2006 Jul;20(4 Suppl):15–8. https://doi.org/10.1177/1359786806066040
48. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics. 2006 Jan 1;47(1):75–85. https://doi.org/10.1176/appi.psy.47.1.75
49. Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants. Clinical Pharmacology & Therapeutics. 2013;93(5):402–8. https://doi.org/10.1038/clpt.2013.2
50. Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR. Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. J Histochem Cytochem. 1990 Sep 1;38(9):1277–87. https://doi.org/10.1177/38.9.1974900
51. Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. Journal of Affective Disorders. 2006 Mar 1;91(1):27–32. https://doi.org/10.1016/j.jad.2005.12.007
52. Hull EM, Dominguez JM. Getting his act together: roles of glutamate, nitric oxide, and dopamine in the medial preoptic area. Brain Res. 2006 Dec 18;1126(1):66–75. https://doi.org/10.1016/j.brainres.2006.08.031
53. Georgescu M, Pfaus JG. Role of glutamate receptors in the ventromedial hypothalamus in the regulation of female rat sexual behaviors. II. Behavioral effects of selective glutamate receptor antagonists AP-5, CNQX, and DNQX. Pharmacol Biochem Behav. 2006 Feb;83(2):333–41. https://doi.org/10.1016/j.pbb.2006.02.019
54. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Exp Clin Psychopharmacol. 2015 Feb;23(1):1–21.. https://doi.org/10.1037/a0038550
55. Pehrson AL, Sanchez C. Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction. CNS Spectr. 2014 Apr;19(2):121–33. https://doi.org/10.1017/S1092852913000540
56. Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. FOC. 2008 Jan 1;6(1):69–79
57. Menke A, Lucae S, Kloiber S, Horstmann S, Bettecken T, Uhr M, et al. Genetic markers within glutamate receptors associated with antidepressant treatment-emergent suicidal ideation. AJP. 2008 Jul 1;165(7):917–8. https://doi.org/10.1176/appi.ajp.2008.08020274
58. Zorumski CF, Izumi Y, Mennerick S. Ketamine: NMDA receptors and beyond. J Neurosci. 2016 Nov 2;36(44):11158–64. https://doi.org/10.1523/JNEUROSCI.1547-16.2016
59. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014 Apr;31(4):335–43
60. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. - PubMed - NCBI. Biological Psychiatry. 2000;47(4):351–4

61. Rajkumar R, Fam J, Yeo EYM, Dawe GS. Ketamine and suicidal ideation in depression: Jumping the gun? Pharmacological Research. 2015 Sep 1;99:23–35. https://doi.org/10.1016/j.phrs.2015.05.003
62. Sequeira A, Mamdani F, Ernst C, Vawter MP, Bunney WE, Lebel V, et al. Global brain gene expression analysis links glutamatergic and gabaergic alterations to suicide and major depression. PLOS ONE. 2009 Aug 11;4(8):e6585. https://doi.org/10.1371/journal.pone.0006585
63. Lee B-H, Kim Y-K. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. Psychiatry Investig. 2010 Dec;7(4):231–5. https://doi.org/10.4306/pi.2010.7.4.231
64. Juhasz G, Dunham JS, McKie S, Thomas E, Downey D, Chase D, et al. The CREB1-BDNF-NTRK2 pathway in depression: multiple gene-cognition-environment interactions. Biol Psychiatry. 2011 Apr 15;69(8):762–71. https://doi.org/10.1016/j.biopsych.2010.11.019
65. Perroud N, Aitchison KJ, Uher R, Smith R, Huezo-Diaz P, Marusic A, et al. Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. Neuropsychopharmacology. 2009 Nov;34(12):2517–28. https://doi.org/10.1038/npp.2009.81
66. Nair A, Vaidya VA. Cyclic AMP response element binding protein and brain-derived neurotrophic factor: Molecules that modulate our mood? J Biosci. 2006 Sep;31(3):423–4
67. Park H, Poo M. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci. 2013 Jan;14(1):7–23. https://doi.org/10.1038/nrn3379
68. Carlezon WA, Duman RS, Nestler EJ. The many faces of CREB. Trends in Neurosciences. 2005 Aug 1;28(8):436–45. https://doi.org/10.1016/j.tins.2005.06.005
69. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002 Mar 28;34(1):13–25. https://doi.org/10.1016/S0896-6273(02)00653-0
70. Brent D, Melhem N, Ferrell R, Emslie G, Wagner KD, Ryan N, et al. Association of FKBP5 polymorphisms with suicidal events in the treatment of resistant depression in adolescents (TORDIA) study. AJP. 2010 Feb 1;167(2):190–7. https://doi.org/10.1176/appi.ajp.2009.09040576
71. Scammell JG, Hubler TR, Denny WB, Valentine DL. Organization of the human FK506-binding immunophilin FKBP52 protein gene (FKBP4). Genomics. 2003 Jun;81(6):640–3
72. Mann JJ, Currier D. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. Arch Suicide Res. 2007;11(1):3–16. https://doi.org/10.1080/13811110600993124
73. Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology. 2011 Apr;36(3):415–25. https://doi.org/10.1016/j.psyneuen.2010.03.007
74. Sousa N, Cerqueira JJ, Almeida OFX. Corticosteroid receptors and neuroplasticity. Brain Res Rev. 2008 Mar;57(2):561–70. https://doi.org/10.1016/j.brainresrev.2007.06.007
75. Escribá PV, Ozaita A, García-Sevilla JA. Increased mRNA Expression of α2A-adrenoceptors, serotonin receptors and μ-opioid receptors in the brains of suicide victims. Neuropsychopharmacology. 2004 Aug;29(8):1512–21. https://doi.org/10.1038/sj.npp.1300459
76. García-Sevilla JA, Escribá PV, Ozaita A, Harpe RL, Walzer C, Eytan A, et al. Up-regulation of immunolabeled α2A-adrenoceptors, Gi coupling proteins, and regulatory receptor kinases in the prefrontal cortex of depressed suicides. Journal of Neurochemistry. 1999;72(1):282–91. https://doi.org/10.1046/j.1471-4159.1999.0720282.x
77. Wakeno M, Kato M, Okugawa G, Fukuda T, Hosoi Y, Takekita Y, et al. The alpha 2A-adrenergic receptor gene polymorphism modifies antidepressant responses to milnacipran. J Clin Psychopharmacol. 2008 Oct;28(5):518–24. https://doi.org/10.1097/JCP.0b013e31818455fc
78. Moller HJ. Outcomes in major depressive disorder: The evolving concept of remission and its implications for treatment. World Journal of Biological Psychiatry. 2008;9(2):102–14
79. Healy D, Whitaker C. Antidepressants and suicide: risk-benefit conundrums. J Psychiatry Neurosci. 2003 Sep;28(5):331–7
80. Mann JJ, Emslie G, Baldessarini RJ, Beardslee W, Fawcett JA, Goodwin FK, et al. ACNP task force report on SSRIs and suicidal behavior in youth. Neuropsychopharmacology. 2006 Mar;31(3):473–92. https://doi.org/10.1038/sj.npp.1300958
81. El-Sakka AI. Association of risk factors and medical comorbidities with male sexual dysfunctions. J Sex Med. 2007 Nov;4(6):1691–700. https://doi.org/10.1111/j.1743-6109.2006.00342.x
82. Hackett G. The burden and extent of comorbid conditions in patients with erectile dysfunction. Int J Clin Pract. 2009 Aug;63(8):1205–13. https://doi.org/10.1111/j.1742-1241.2009.02088.x
83. Perlis RH, Laje G, Smoller JW, Fava M, Rush AJ, McMahon FJ. Genetic and clinical predictors of sexual dysfunction in citalopram-treated depressed patients. Neuropsychopharmacology. 2009 Jun;34(7):1819–28. https://doi.org/10.1038/npp.2009.4
84. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. J Psychopharmacol. 1998 Mar 1;12(2):192–214. https://doi.org/10.1177/026988119801200212
85. Dutta BK, Saha A, Nagesh IV. Extrapyramidal symptoms after fluoxetine. Med J Armed Forces India. 2015 Jul;71(Suppl 1):S99–100. https://doi.org/10.1016/j.mjafi.2013.05.002
86. Lipinski JF, Mallya G, Zimmerman P, Pope HG. Fluoxetine-induced akathisia: clinical and theoretical implications. J Clin Psychiatry. 1989 Sep;50(9):339–42
87. Iniesta R, Hodgson K, Stahl D, Malki K, Maier W, Rietschel M, et al. Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. Sci Rep. 2018 Apr 3;8(1):5530. https://doi.org/10.1038/s41598-018-23584-z
88. Farace, J. Schöpfel. Grey literature in library and information studies. Berlin: Dr Gryuter Saur; 2010
89. Tam V, Patel N, Turcotte M, et al. Benefits and limitations of genome-wide association studies. Nature Reviews Genetics. 2019 Aug;20(8):467–84
90. Vanderkooy JD, Kennedy SH, Bagby RM. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. Can J Psychiatry. 2002 Mar;47(2):174–80
91. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. The British Journal of Psychiatry. 2009 Sep;195(3):202–10
92. Wisniewski SR, Rush AJ, Balasubramani GK, et al. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract. 2006 Mar;12(2):71–9
93. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): Reliability and Validity. Journal of Sex & Marital Therapy. 2000 Jan 1;26(1):25–40
94. Stahl SM. Selecting an antidepressant by using mechanism of action to enhance efficacy and avoid side effects. Journal of Clinical Psychiatry. 1998;59:23–9
95. Alessandrini M, Chaudrhy M, Dodgen TM, et al. Pharmacogenomics and global precision medicine in the context of adverse drug reactions: top 10 opportunities and challenges for the next decade. OMICS A Journal of Integrative Biology. 2016 Oct;20(10):593–603