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Review Article

Venlafaxine and Genetic Variation; Implications for Therapeutic Efficacy and Adverse Effects

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Abstract

Response to antidepressant drugs vary considerably and a significant portion of this variation stems from genetics. Venlafaxine (VEN) is one of the most prescribed antidepressant drugs in the world. There is substantial interindividual variation in therapeutic response and adverse effects to VEN. Several studies suggest the importance of single nucleotide polymorphisms (SNPs) in determining the therapeutic outcome of VEN. In this paper, we reviewed several studies showing significant associations with VEN therapeutic efficacy and/or adverse effects. We propose that pharmacogenetic knowledge should be incorporated in decisions regarding VEN treatment outcome and adverse effect management. However, we also recommend additional, larger pharmacogenetic studies with VEN to reproduce already produced data and to incorporate additional variables. The issue of personalized medicine could be a key driver for providing the highest possible quality of treatment to patients. Bringing pharmacogenomics profile of patients on depression therapy with VEN into consideration will help patients gain maximum benefits from available treatments in terms of safety, therapeutic optimization and minimizing adverse effects. .

Keywords: Depression, Venlafaxine, Genetic Variation, Single Nucleotide polymorphism, Pharmacogenetics

Introduction

Major depressive disorder (MDD or depression) is a serious mental illness presenting with depressed mood, anxiety, sleep disturbances, various somatic symptoms, and cognitive impairments (Kennedy 2008, Rock et al. 2014). Many people view depression primarily a neuroinflammatory condition. Stress increases inflammatory cytokines in the peripheral and central nervous systems (CNS) and stimulates microglia in the brain, as indicated by an increase in the cell surface marker ionized calcium-binding adapter molecule-1 (Iba-1)(Wang et al. 2018, Frank et al. 2007). Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) are inflammatory mediators that play important roles in cell communication. Neurotransmitter systems, cognitive function, and mood are all affected (Anisman and Merali 2003, Raison, Capuron, and Miller 2006, Miller, Maletic, and Raison 2009). Although many antidepressants acting on synaptic monoamine levels have been used as the first-line drug treatment for MDD, they are not effective in a substantial proportion of patients (Hamon and Blier 2013). The most serious problem with treating depression is that the therapeutic advantages of antidepressant medicines take a long time to manifest. Furthermore, these drugs frequently have a slew of negative side effects (Taylor et al. 2005).This justifies the development of new treatment strategies in terms of efficacy and tolerability for patients suffering from

MDD (Rush, Trivedi, Wisniewski, Nierenberg, et al. 2006).

Epidemiology of Depression

MDD is a chronic, recurrent, and disabling psychiatric condition that affects 15% to 20% of the world's population (Amidfar et al. 2018). Depressed mood, lack of interest in life, and unpleasant emotions are the main symptoms of MDD (Clair 2020, Gonda et al. 2019). South Asia accounts for around one-fifth of all mental disorder incidents (Bishwajit et al. 2017). The proportion of patients with MDD in South Asian countries was among the highest in the world (Ferrari et al. 2013). Symptoms of depression are highly prevalent in South Asian countries, such as Pakistan, Bhutan and Bangladesh (29% to 46%) (Muhammad Gadit and Mugford 2007, Pelzang 2012, Asghar et al. 2007). Because of its influence on individuals' daily lives and its link to psychosocial dysfunction, cognitive deficiencies, higher risk of suicidal behavior, and high mortality, MDD has emerged as a major public health issue (Bender and Farvolden 2008, Kessler et al. 2016). Identifying biomarkers that could predict therapeutic efficacy of antidepressant prior to their administration would be useful. Several recent studies have found that genetic variations are linked to treatment response (Tsai et al. 2010, Saito et al. 2017).

Pathophysiology of Depression

According to the monoamine hypothesis, depression is caused by a lack of monoamine neurotransmitters, particularly serotonin (5-hydroxytryptamine [5HT]) and norepinephrine (NE); the normal amount of these neurotransmitters could be depleted as a result of stress, illness, or drug use, resulting in depression (Castrén 2005). These neurotransmitters are necessary for transmission of information among neurons (Figure 1). The data in the brain is processed through and then stored in the complex interconnections of neurons in neural networks (Buzsáki 2004, Hua and Smith 2004). According to the neurotrophic hypothesis of depression, neuronal flexibility plays a significant role in the development of depressive episodes and the clinical response to antidepressants. The role of protein brain-derived neurotrophic factor (BDNF) is also critical (Troyan and Levada 2020). Plasma concentrations of BDNF are found to be lower in bipolar disorder, manic depression, and depressive individuals in human studies (Cunha et al. 2006, Palomino et al. 2006).

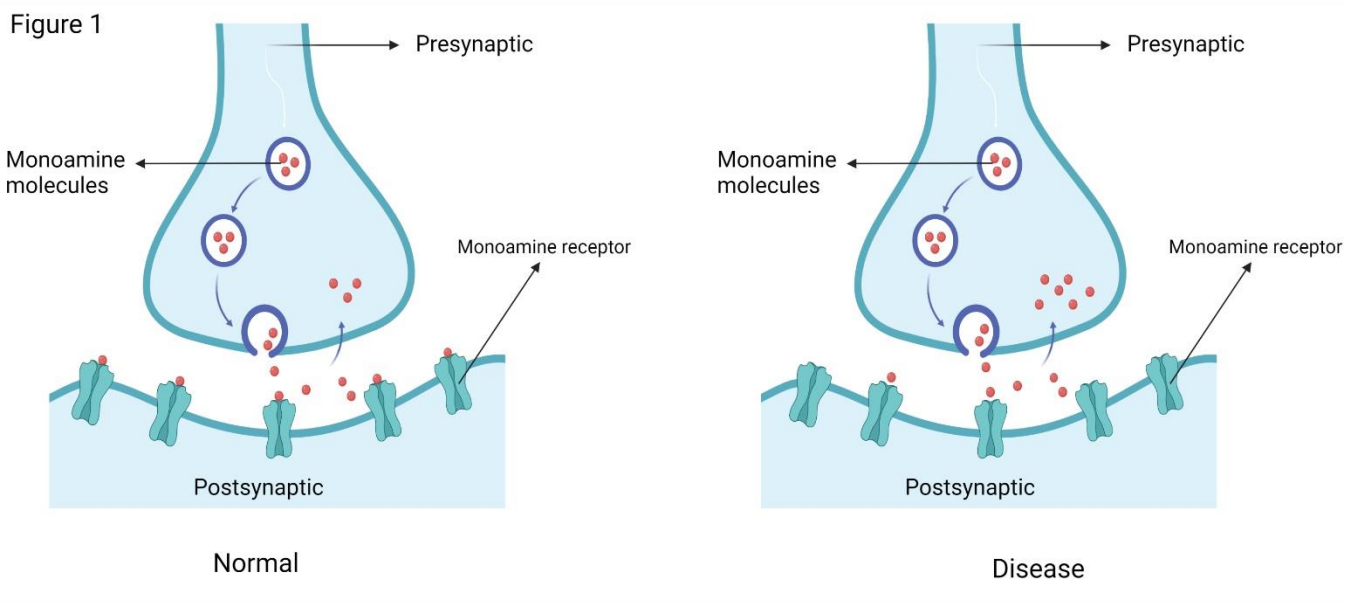

Figure 1. A decrease in the concentration of monoamines may cause depression.

Current Treatments

Tricyclic Antidepressants (TCAs)

TCAs were originally developed to treat MDD in 1959. TCAs are approved by the Food and Drug Administration (FDA) to treat a variety of illnesses, depending on the formulation. Amitriptyline, amoxapine, doxepin, desipramine, nortriptyline, protriptyline, imipramine, and trimipramine are

TCAs that have been approved by the FDA to treat MDD (Dopheide 2006, Stokes et al. 2020, Boafo et al. 2020). Their antidepressant effects are associated with increased levels of NE and serotonin in the synapses (32, 33). They also inhibit post-synaptic alpha cholinergic (α1and α2), muscarinic, and histaminergic receptors by acting as competitive antagonists.

Monoamine Oxidase Inhibitors (MAOIs)

Brain monoamine oxidase (MAO) is a presynaptically located enzyme that oxidatively deaminates a wide spectrum of monoamines, including monoamine neurotransmitters (NE, dopamine, serotonin) as well as monoamines found in food (tyramine, phenylethylamine) (McDaniel 1986). Most of the therapeutically available MAOIs bind to MOA in an irreversible manner. The persistence of activity following drug withdrawal is due to enzyme resynthesis, which is expected to occur in the brain with drugs that have a half-life of 10 to 12 days. Some newer MAOIs (competitive inhibitors) do not form covalent bonds with the enzyme and are thus reversible (Fowler and Ross 1984, Murphy, Sunderland, and Cohen 1984). Isocarboxazid, phenelzine, selegiline, tranylcypromine are important MAOIs drugs.

Serotonin and NE Reuptake Inhibitors (SNRIs)

The FDA approved the first SNRI in December 1993.(Sansone and Sansone 2014). SNRIs appear to alleviate depression by inhibiting serotonin and NE transporter proteins in the presynaptic area (Norris and Blier 2009, Chen et al. 2015). This delays the resorption of these neurotransmitters, affecting several homeostatic pathways and, as a result, boosting postsynaptic receptor activity. SNRIs' affinities for the serotonin and NE transporters vary. Although desvenlafaxine, duloxetine, and VEN are stronger serotonin reuptake blockers than NE reuptake inhibitors, levomilnacipran and milnacipran preferentially inhibit NE reuptake (Schatzberg and Nemeroff 2017, Nelson 2020, Asnis and Henderson 2015, Auclair et al. 2013).

Selective Serotonin Reuptake Inhibitors (SSRIS)

Antidepressants known as SSRIs are widely prescribed across the world due to their efficacy in treating a range of mental diseases (Gobin et al. 2014, Lin et al. 2017). SSRIs have can block serotonin presynaptic absorption in the central nervous system and prevent serotonin from flooding back in the neuron by blocking the serotonin reuptake transporter. (Slaton, Champion, and Palmore 2015). These medications are commonly used to treat depression, anxiety, obsessive-compulsive disorder, migraines, and other neuropathic pain issues (Yilmaz et al. 2010, Mosby 2005). SSRIs are considered to be safer and more widely accepted than previous classes of antidepressants (Von Wolff et al. 2013).

Atypical Antidepressants

As our understanding of brain neurophysiology has evolved, several atypical antidepressants have been identified (Horst and Preskorn 1998). Atypical antidepressants are commonly prescribed to those patients with severe depression who haven't responded well to SSRIs or are experiencing too many adverse effects (Rush, Trivedi, Wisniewski, Stewart, et al. 2006). Agomelatine, Bupropion, and Mirtazapine are atypical antidepressants.

Importance of VEN

VEN is an SNRI that is among the most often prescribed antidepressants for the management of MDD (Holliday and Benfield 1995). In fact it was the sixth most-prescribed antidepressant in the USA in 2017 (Guerra 2017). VEN has long been thought to be a therapeutically useful antidepressant medicine, although its therapeutic impact varies depending on ethnicity and genetic background (Hall et al. 2015). VEN is often used as an alternative drug in treatment of SSRIs–resistant depression being (Perahia et al. 2008, Magalhães et al. 2015). A significant improvement in symptoms of depression was observed in a 31-year-old patient when genetic variance in genes such as ANK3, MTHR, SLC6A4, COMT, 5HT2C was determined and her VEN dose was adjusted accordingly (Lawrence 2014). Clinical cases such as this one reflects the usefulness of VEN pharmacogenetics. Pharmacogenetics approaches can help improve therapeutic efficacy of VEN and help decrease its adverse effects (Figure 2). In this paper, we reviewed those studies which investigated various candidate genes for VEN pharmacogenetics, primarily for the treatment of MDD (Table 1).

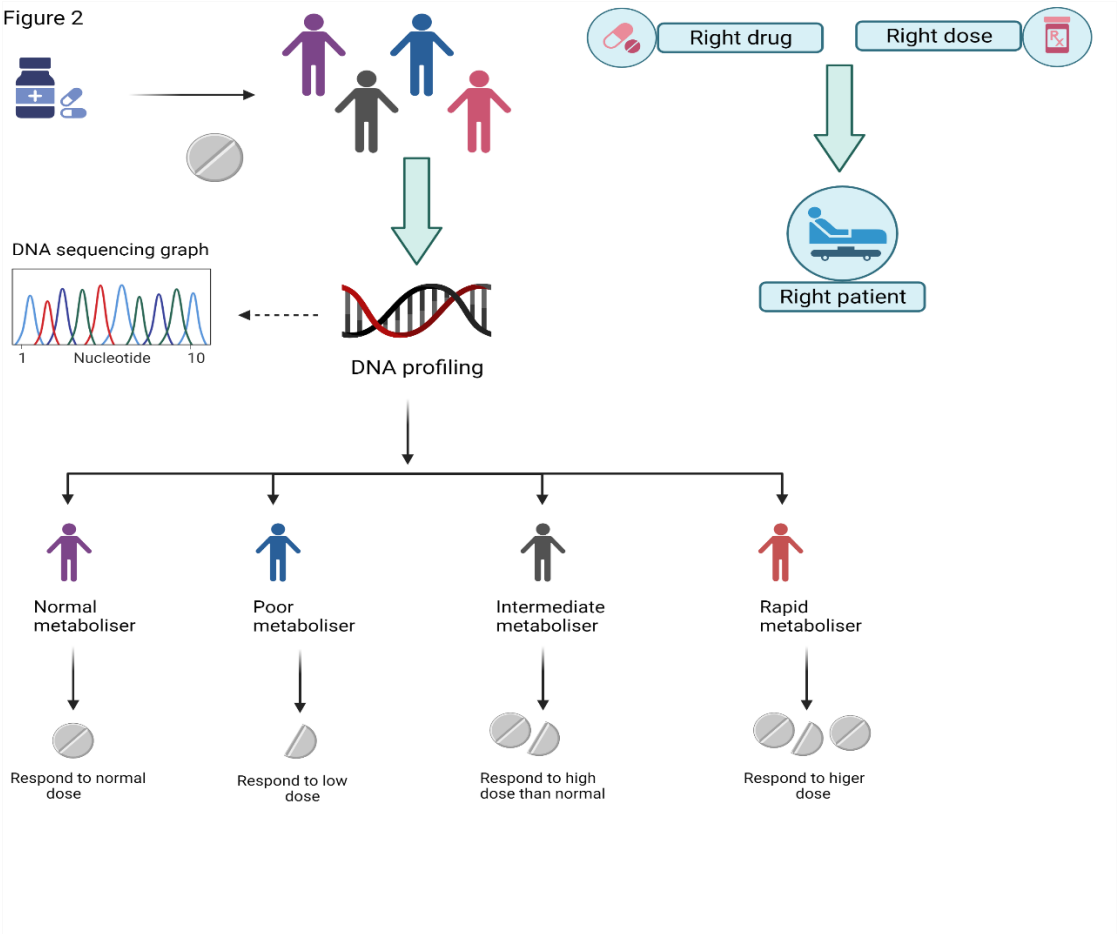

Figure 2. Pharmacogenetics can improve treatment outcome by helping in select the right drug for the right patient in right dose at the right time.

Pharmacogenetics of VEN

Nuclear Receptor Subfamily 3 Group C Member 2 (NR3C2)

NR3C2 gene encodes for mineralocorticoid receptor protein. This protein aids in the regulation of sodium levels in the body. Blood pressure and fluid balance are also affected by sodium management (https://medlineplus.gov/genetics/gene/nr3c2/). In an investigation in which 195 Chinese Han patients with MDD were randomized and given a 6-week VEN medication, the genotype frequency of the rs1512325 locus in the NR3C2 gene was found to be considerably different between the responder and non-responder groups (p 0.05). In the responder group, the frequency of the rs1512325 C-allele was considerably low (p 0.05). Levels of thyroid stimulating hormone increased considerably following VEN medication (p 0.05) in the responder group. These results suggest that in Chinese Han MDD patients, rs1512325 variant in the NR3C2 gene is associated with the therapeutic efficacy of VEN treatment (Yuan et al. 2020).

Solute Carrier Family 17 Member 7 (SLC17A7)

SLC17A7 mediates glutamate absorption into synaptic vesicles in excitatory neural cell presynaptic nerve terminals and is also involved in the inorganic phosphate transport (https://www.uniprot.org/uniprot/Q9P2U7). In a recent clinical investigation, several SNPs of SLC17A7 gene were studied to find out any correlation with the therapeutic efficiency of VEN. Their analysis of the data suggests that one of the investigated SNP of SLC17A7 (rs1578944) showed a significant association (P = 0.022) with VEN response after 6 weeks of therapy (Liu et al. 2021a) indicating its possible role in predicting therapeutic outcome after VEN administration.

Table 1: Genes and their variants reviewed in this present study

Genes	Sample Size	Location	Drug	Association/ Correlation	Reference
NR3C2	195	China	Venlafaxine	associated with the therapeutic efficacy	(Yuan et al. 2020)
SLC17A7	175	China	Venlafaxine	Associated with the positive outcome in efficacy	(Liu et al. 2021b)
CYP1A2	175	China	Venlafaxine	Associated with improving symptoms of depression	(Zhu et al. 2019)
CYP2D6 (PM)	175	Chinese	Venlafaxine	Raises the likelihood of frequent adverse events	(Shams et al. 2006)
CYP2D6	75		Venlafaxine	Carrier group showing lower ODV/VEN ratios	(Komahashi-Sasaki et al. 2021a)
CYP2C19	55	Afro-Indian	Venlafaxine	No association	(Montané Jaime et al. 2018)
CYP2D6 & CYP2C19	94	Sweden	Venlafaxine	Both genes associated with VEN metabolites	(Karlsson et al. 2015)
5-HTTLPR & HTR2A	156	USA	Venlafaxine	Associated with responsiveness to VEN	(Lohoff, Narasimhan, and Rickels 2013)
5-HTTVNTR & HTTLPR	84	Korean	Venlafaxine	no link with 5-HTTVNTR but 5-HTTLPR gene was associated with VEN treatment response	(Lee et al. 2010)
5-HTTLPR	84	Germany	Venlafaxine	Low-expressing alleles of 5-HTTLPR are associated with favorable treatment outcomes	(Proft et al. 2014)
GRIK4 & GRM7	193	China	Venlafaxine	GRIK4 and GRM7 are linked to VEN treatment response	(Sun et al. 2019)
ABCB1	52	Turkey	Venlafaxine	Polymorphisms in ABCB1 are more likely to develop akathisia	(Sun et al. 2019)
HTR2A	156	USA	Venlafaxine	HTR2A gene associated with treatment outcome	(Lohoff et al. 2013)
SLC6A2	161	China	Venlafaxine	Remission incidences were influenced by SLC6A2 variations.	(Yeh et al. 2015)

Cytochrome P450 1A2 (CYP1A2)

A member of the cytochrome P450 mixed-function oxidase system, CYP1A2 is involved in the metabolism of xenobiotics in the human body (Nelson et al. 2004). In a recent clinical trial, 175 Han Chinese depressive patients were enlisted to participate in a 6-week VEN therapy. Three SNPs in the CYP1A2 gene were investigated. There findings showed that rs2470890 in the CYP1A2 gene is associated with improving symptoms of depression following VEN therapy in MDD patients (Zhu et al. 2019).

Cytochrome P450 2D6 (CYP2D6)

CYP2D6, which belongs to the cytochrome P450 mixed-function oxidase system, is responsible for addition or removal of certain functional groups of approximately 25% of clinically utilized medications (Wang et al. 2009). In a recent study, serum concentrations of VEN, O-desmethylvenlafaxin (ODV), and *N*-desmethylvenlafaxine (NDV), as well as the ratios of concentrations ODV/VEN (as a marker of O-demethylation) were measured in 100 individuals treated with VEN. The Clinical Global Impressions Scale (CGI) was used to track clinical therapeutic effects, while the Udvalg för Kliniske Undersogelser Side Effect Rating Scale (UKU) was used to track side effects. VEN's O-demethylation phenotype was highly influenced by CYP2D6 genotype. The study also demonstrated that CYP2D6 poor metabolizer (PM) phenotype having SNPs (rs3892097, rs5030655) raises

the likelihood of frequent adverse events (Shams et al. 2006). Another investigation examined the link between VEN dose, CYP2D6 and CYP2C19 genotypes, and VEN and ODV serum concentrations in a clinical setting. Their findings suggest that common CYP2D6 and CYP2C19 gene variations can have a major influence on VEN pharmacokinetics. Their data indicates that allelic variations in both genes should be taken into account while prescribing VEN and dosage adjustments should be made accordingly (McAlpine et al. 2011). In another study consisting of Japanese MMD patients, there was a significant difference in the ODV/VEN ratio between CYP2D6 -mutated allele carriers (rs1065852) and noncarriers, with the carrier group showing lower ODV/VEN ratios. The ODV/VEN ratio appears to be affected by the CYP2D6 polymorphism (Komahashi-Sasaki et al. 2021b).

In a previous study in which 55 patients were genotyped, with 47 completing the 8-week VEN therapy, the majority of patients exhibited metabolic ratios for VEN and activity ratings that predicted phenotype from genotype. There were no connections with CYP2C19 genotype (Montané Jaime et al. 2018).

In another study a total of 94 postmortem cases were included, all of which tested positive for VEN during toxicological screening. The ODV/VEN (P=0.003), DDV/NDV (P=0.010), and DDV/ODV (P=0.034) ratios were shown to be substantially affected by the CYP2D6 genotype. The CYP2C19 genotype had a substantial impact on the DDV/ODV (P=0.013) and DDV/VEN (P=0.021) ratios. Both CYP2D6 SNPs (rs35742686, rs3892097, rs5030655) and CYP2C19 genotypes had a substantial impact on VEN S/R ratios. PMs of CYP2D6 exhibited lower VEN ratios, while CYP2C19 PMs had high S/R VEN ratios. Study findings reveal that the CYP2D6 genotype affects VEN and its metabolites' O-demethylation, whereas CYP2C19 affects VEN and its metabolites' N-demethylation (Karlsson et al. 2015).

5HT Receptor 1B (HTR1B) and Serotonin-Transporter-linked Promoter region (5HTTLPR)

HTR1B is a G-protein coupled receptor that mediates inhibitory neurotransmission and regulates the release of serotonin, dopamine, and acetylcholine in the brain by activating a second messenger cascade (Guimarães et al. 2009) while SLC6A4, the gene that codes for the serotonin transporter, has a degenerate repeat polymorphism region called (5-HTTLPR) (Heils et al. 1995, Heils et al. 1996). Genetic variations in both have been implicated in adverse effects such as impaired bone formation after VEN treatment. Serum indicators of bone formation procollagen type I N pro-peptide (P1NP) and resorption serum cross-linked C-telopeptide of type I collagen (CTX) were measured before and after therapy in 69 patients who took part in a 12-week open-label study of the VEN for serious depression. In subjects with the high-expressing 5HTTLPR (rs25531) genotype and those with the low-expressing HTR1B genotype, VEN dramatically impaired bone formation. This was more common in patients who had both the high-expressing 5HTTLPR genotype and the low-expressing HTR1B genotype (Garfield et al. 2014).

Therapeutic response to VEN is also affected by variations in these genes A study in which 156 patients were evaluated for therapy response in generalized anxiety disease (GAD), findings showed that genotyping the 5-HTTLPR/rs25531 haplotype as well as the HTR2A SNP rs7997012 might be useful in predicting treatment responsiveness to VEN (Lohoff, Narasimhan, and Rickels 2013). Another study comprised 84 Korean individuals with severe depressive illness. The Hamilton Depression Rating Scale (HDRS), Montgomery-sberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), and Beck Anxiety Inventory (BAI) were used to assess all patients at baseline and week four. However, there was no link between 5-HTTVNTR and VEN therapy response. The genotype of the 5-HTTLPR gene has been linked to VEN treatment responses (Lee et al. 2010). In another study in which 56 inpatients with depressive episodes in the context of either MDD or bipolar affective disorder were investigated in a clinical setting. After four weeks of therapy, the response to VEN was measured and linked with blood concentrations and functional variations in the NE (SLC6A2; rs28386840) and serotonin transporter genes (SLC6A4; [5-HTTLPR], rs25531). There was no association discovered between treatment response, VEN serum levels (active moiety), and rs28386840. A poor response to VEN was identified more frequently among carriers of high-expressing SLC6A4 genotype (lAlA-). This study shows that low-expressing alleles of 5-HTTLPR are associated with favorable treatment outcomes (Proft et al. 2014).

Glutamate Ionotropic Receptor Kainate Type Subunit 4 (GRIK4) and Glutamate Metabotropic Receptor 7 (GRM7)

GRIK4 is a member of the glutamate-gated ionic channel family of proteins. Glutamate activates ligand-gated ion channels and G protein-coupled membrane receptors in the central nervous system. With the subunits expressed by related gene family members, the protein encoded by this gene forms functional heteromeric kainate-preferring ionic channels (GRIK). In the mammalian central nervous system, GRM7 is a key presynaptic regulator of neurotransmission.(Peterlik et al. 2014). A study recruited 193 unrelated people (ages 18–65) who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for MDD. Results revealed that, rs6589847 and rs56275759 in GRIK4 and rs9870680 in GRM7 may be linked to VEN treatment responses in Chinese MDD patients.(Sun et al. 2019).

ATP Binding Cassette Subfamily B Member 1 (ABCB1)

ABCB1 is one of numerous ubiquitous adenosine triphosphate (ATP)-binding cassette (ABC) genes crucial for cellular homeostasis found in all kingdoms of life.(Jones and George 2004, Rosenberg et al. 1997, Croop 1993) . A study was carried out in which 52 outpatients who satisfied the (DSM-IV) criteria for MDD were recruited and 17-item Hamilton Rating Scale for Depression (HDRS17) was used to determine the degree of depression, and tolerance was determined by asking about side effects for six weeks. The findings imply that those who have the TT-TT/TA genotype for the C3435T-G2677T/A polymorphisms in ABCB1 are more likely to develop akathisia (Ozbey et al. 2017).

Hydroxy-Tryptamine Receptor 2A (HTR2A)

HTR2A, is a key regulator of prenatal brain development and adult cognitive performance (Gao et al. 2020). Gene for this protein has been investigated for its effect on therapeutic response to VEN. In a study in which GAD patients treated with VEN, it was found that genetic variant rs7997012 in the HTR2A gene predicts treatment outcome. This was a 6-month open-label clinical study in which 156 individuals were evaluated for treatment response to VEN. The HAM-A was reduced at 6 months in the primary study. At 6 months, the Clinical Global Impression of Improvement (CGI-I) score was used as a secondary end measure. Contingency analysis was used to compare genotype and allele frequencies between groups. Using the HAM-A scale as an outcome measure, the frequency of the G-allele differed substantially between responders (70%) and non-responders (56%) at 6 months (P=0.05). The G-allele was also significantly related with improvement (P=0.01) when the CGI-I was used as the endpoint. Assuming that the G-allele has a dominating influence, there was a significant difference in improvement across groups (P=0.001, odds ratio=4.72) (Lohoff et al. 2013).

Solute Carrier Family 6 Member 2 (SLC6A2)

The SLC6A2 gene encodes a NE transporter that regulates NE homeostasis and is responsible for NE reuptake into presynaptic nerve terminals (Kim et al. 2006). In a previous study in which 243 Han Chinese patients with MDD were recruited, an 8-week naturalistic therapy trial using VEN was conducted. Patients were tested for seven *SLC6A2* gene SNPs. The 8-week therapy was completed by 161 of the registered individuals. From baseline through endpoint, each subject's depression symptoms were assessed using HDRS. Significant variations in genotype frequencies were found between remitters and non-remitters in five of the SLC6A2 variants studied (rs28386840, rs1532701, rs40434, rs13333066, rs187714). In the SLC6A2 gene, the GCG haplotype (rs40434-rs13333066-rs187714) was linked to non-remission. Remission incidence throughout the 8-week therapy course is highly influenced by SLC6A2 variations, according to a Cox regression analysis (rs28386840, rs40434, and rs187714) (Yeh et al. 2015).

Future Directions

About two third depressed patients do not achieve full remission while adequate response is not exhibited by a little over one third of the patients with depression. Furthermore, about half to nine tenth of patients experience adverse effects that are treatment related which can lead to withdrawal symptoms and compromise their quality of life (Reyes-Barron et al. 2016, Kato and Serretti 2010). VE is one of the most prescribed drugs in the world and among the top 10 drugs prescribed in USA in 2017 (Guerra 2017). Therefore, improvement in the treatment efficacy and

improving its adverse effects profile would help a significant number of patients. We have found in this review that genetic variation affects VEN therapeutic efficacy as well as adverse effects. This knowledge should be utilized to improve VEN treatment outcomes both in terms of efficacy and safety. Pharmacogenetic testing could help implement this knowledge in improving VEN pharmacotherapy thus improving quality of patient life. However, large clinical trials should be conducted while considering the drug concentration measurements, as well as ethnic differences, to establish guidelines that are evidence based. Physicians should be properly trained how to use these guidelines and patients properly counselled so that they are comfortable with pharmacogenetic testing. This would ensure the proper use of simple, reliable, and cost-effective tests to improve medical care in patients taking VEN.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval

Not applicable.

Consent forms

Not applicable.

Authors contribution

AU conceptualized the review, AU, HA, and KL did the literature search and collected relevant studies, AA, II, and AM wrote the initial manuscript, AU wrote the final manuscript. All the authors have read and approved the final version of the manuscript.

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