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Review Article

Pharmacogenetics of Fluoxetine; a Review of the Genetic Effects on Its Efficacy and Adverse Effects During Treatment of Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is one of the leading psychiatric disorders which has now emerged as an important public issue. It drastically affects one's quality of life and causes a substantial decline in social and occupational functioning. Environmental, social, and genetic factors are thought to be involved in the etiology of MDD. Different treatment options are available for the treatment of MDD. Treatment options include both pharmacological and psychological. Selective Serotonin Reuptake Inhibitors (SSRIs) are most commonly prescribed among different pharmacological options. Fluoxetine was the first SSRI to be approved in the USA for MDD, and since then, it has positively impacted treating MDD. Fluoxetine is considered effective without producing many adverse effects caused by other antidepressants. Despite the fact that fluoxetine is still associated with many side effects, many clinicians still prescribe it with the hope of additional antidepressant efficacy compared to other antidepressants. This review focuses on the epidemiology, risk factors, etiology, neurobiology, and treatment options of MDD, with special emphasis on the role of fluoxetine. Genetic variants linked with the clinical efficacy and side effects of fluoxetine are reviewed, and those with the potential to act as a clinical predictor of therapeutic response and/or side effects are discussed. Recommendations are made for the use of some of these genetic variants in clinical medicine.

Keywords: Depression, fluoxetine, genetic polymorphism, adverse effects, efficacy

Introduction

There is considerable impairment, co-morbidity, poor quality of life, and a high death rate associated with depressive disorders, making them one of the most critical public health challenges (Kupfer, Kuhl et al. 2013, Ahmed, Negash et al. 2020). It affects the capacity of people to participate in economic activities, education, social and cultural life, and the communities in which they live. (Ahmed, Negash et al. 2020) (Teh, Ngo et al. 2015). In young people, depression increases the likelihood of suicide and suicide attempts. A chronic illness known as Major depressive disorder (MDD) is characterized by the presence of at least one separate episode of depression that lasts for at least two weeks, as well as observable shifts in mood, interests, and joy, as well as cognitive alterations and somatic symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, MDD or, in simple words, depression can be defined as the existence of low mood or sad mood, anhedonia (loss of pleasure), lethargic feeling with decreased energy, inability to concentrate properly, with changes in sexual desire, changes in sleep and appetite with changes in weight for at least 14 days. Feeling of guilt, suicidal ideation, and suicide attempts are among the prominent symptoms of depression.

Among all these, at least 5 symptoms must persistently present for at least fourteen days, with at least one of these symptoms being either a depressed mood or a loss of pleasure (Regier, Kuhl et al. 2013). Compared to single-nucleotide polymorphism-based estimations from genome-wide association studies (GWAS), greater heritability has been discovered in family and twin studies. It is assumed that the hereditary component of MDD accounts for approximately 35 percent of the disease. Despite recent progress in our knowledge of MDD pathophysiology, no one pathway can account for all characteristics of the illness. In the treatment of MDD, combined psychotherapy and pharmacotherapy are useful. However, even after many therapy attempts, roughly 30% of people do not recover from MDD. After adolescent years, MDD is twice as likely to affect females as it does males. The estimated age for the beginning of MDD is approximately 25 years for both sexes, and the age range with the highest risk for the onset of MDD is from the mid-to-late teens to the early 40s (Filatova, Shadrina et al. 2021).

Epidemiology

According to Global Health Data Exchange 2002, around 251-310 million people have depression globally, which places the global prevalence of depression at 3.4. The prevalence of depression is 2.1% and 4.7% in males and females, respectively. Aged people, i.e., age 70 or above, have the highest risk of developing depression compared to any other age. 1 in every 15 adults experiences depression every year. Another study reveals that one in every six people experiences depression at least once during their lifetime. According to the data provided by World Health Organization (WHO), Ukraine has the highest prevalence of depression in the world (6.3%), followed by the United States, Estonia, and Australia, where the depression prevalence is about 5.9%. The Pacific Islands of Oceania are the places with least depression prevalence in the world. Solomon Island has the lowest prevalence of depression in the world (2.9%), followed by Papua New Guinea and Timor-Leste 3.0%. One reason for the high prevalence of depression in developed countries is that they have a proper and advanced healthcare system that helps more people report the disease. While according to WHO, lower- and middle-income countries lack good healthcare facilities for their population, which are required for treatment. Around 76-85% of people in these lower- and middle-income countries suffering from depression and other mental disorders do not have access to the necessary treatment. According to WHO, the prevalence of depression in Pakistan is 4.2%. The data provided by WHO states that there are somewhat 7.43 million (7436224) cases of depression in Pakistan. The prevalence of depression in India is about 4.5%. It is estimated that up to half of the 800,000 people who take their own lives every year do so while experiencing a depressive episode, and people who suffer from MDD have nearly 20 times the risk of dying by suicide as the general population does (Saloni Dattani 2021).

Major Risk Factors of MDD

Researchers assume that there are several reasons for depression. There are many things that can lead to depression, some of which are listed below.

- Hereditary and Genetics
- Gender
- Social factors
- Other chronic medical conditions
- Substance use
- Stress
- Environmental factors

An imbalance of neurotransmitters in the brain may contribute to causing depression. People having compromised physical health, like those suffering from diabetes, cancer, and other chronic diseases, are at an increased risk of developing depression. Family history is another risk factor that increases the chances of

someone developing depression (Grover, Dutt et al. 2010).

Stressful Life Events

Significant risk factors for depression include stressful life events. Various researchers conclude that the incidence of negative life experiences usually acts as a precursor for the onset of depression (Paykel 2001, Brigitta 2022). Some studies have also highlighted the influence of life experiences on disease prognosis and found that positive life events may prevent the onset of MDD and may also decrease the chances of relapse after onset (Paykel, Cooper et al. 1996, Brigitta 2022).

Pathophysiology of MDD

Over the course of the past few decades, numerous hypotheses pertaining to the neurobiology of depression have been put out by various researchers. Among these theories, the Monoamine theory is well-known and widely presented to explain the pathophysiology of depression (Palazidou 2012). A brief overview of pathophysiology is presented in the figure below:

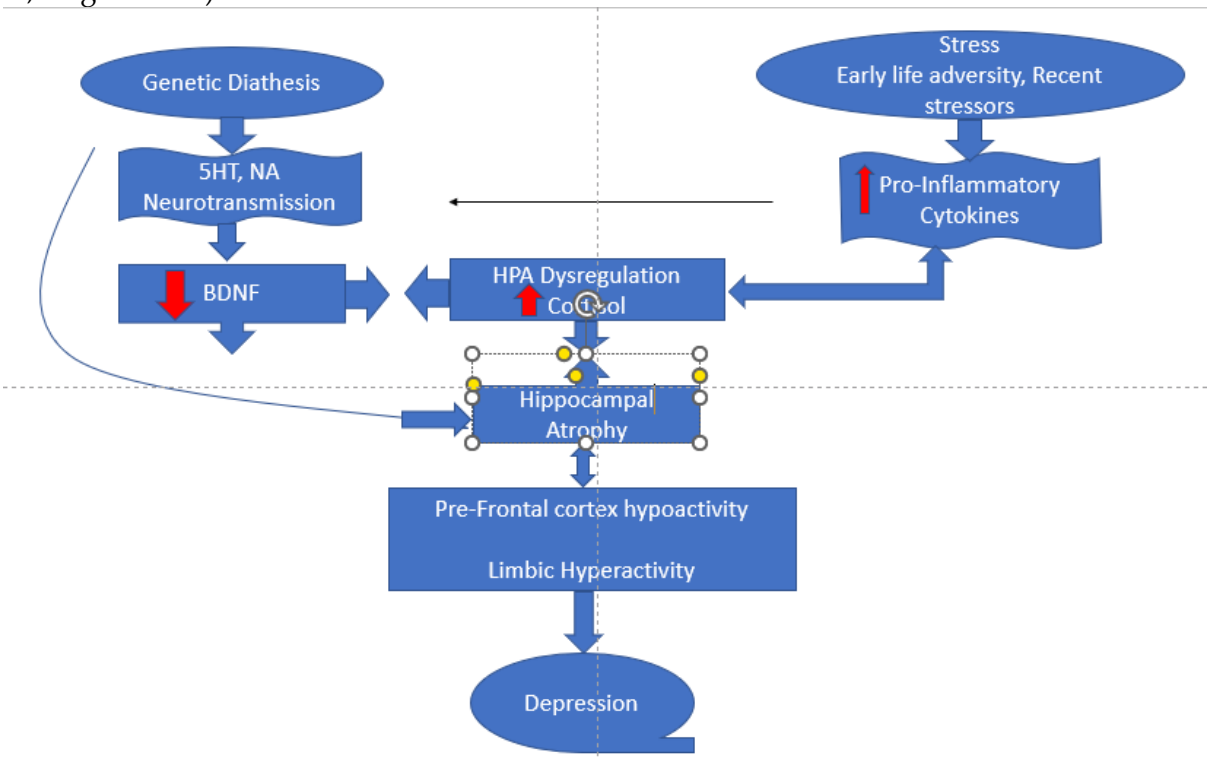

Figure 1 A diagrammatic illustration of the neuroscience behind depression

This schematic diagram shows the overall summary of how depression starts. It starts with causing factors like stress or genetic cause, which in turn causes some disturbances in the brain, most probably monoamines, which in turn causes depressive symptoms.

Monoamine Theory

Dopamine, norepinephrine (NE), and serotonin (5-HT) are called monoamines. According to this theory, the depletion of monoamines in the synaptic cleft leads to depression. This theory is established on the basis of different drugs which deplete monoamines like reserpine, which in turn produce depression-like symptoms in the animal models. Similarly, autopsy studies also reveal low monoamines in the brain of depressed patients (Krishnan and Nestler 2008). Iproniazid and imipramine are two

antidepressants structurally unrelated to one another and were initially developed for treating non-psychiatric disorders. However, both of these antidepressants showed significant antidepressant effects in human subjects and were subsequently shown to improve central 5-HT or NE transmission. Reserpine, an antihypertensive medication known to deplete monoamine reserves, was found to trigger depressive symptoms in certain people (Berton and Nestler 2006).

Neurotrophins and Neurogenesis

One other hypothesis which is thought to be involved in depression is a decrease in neurotrophic factors, which are neurodevelopmentally expressed growth factors that also control plasticity in adult brains. The involvement of brain-derived neurotrophic factor (BDNF), which is abundantly produced in adult limbic regions, has been the focus of these investigations. Significant preclinical literature supports this 'BDNF theory,' indicating that various kinds of stress impair the signaling in the hippocampus that is mediated by BDNF, whereas persistent antidepressant therapy improves BDNF-mediated signaling (Nestler, Barrot et al. 2002, Duman and Monteggia 2006). Post-mortem examination of the hippocampus of depressed patients has revealed changes that are comparable to those seen during life (Duman and Monteggia 2006), as well as in serum BDNF concentrations, the cause of which is still unknown. Figure 2 outlines the mechanisms and pathways involved in depression.

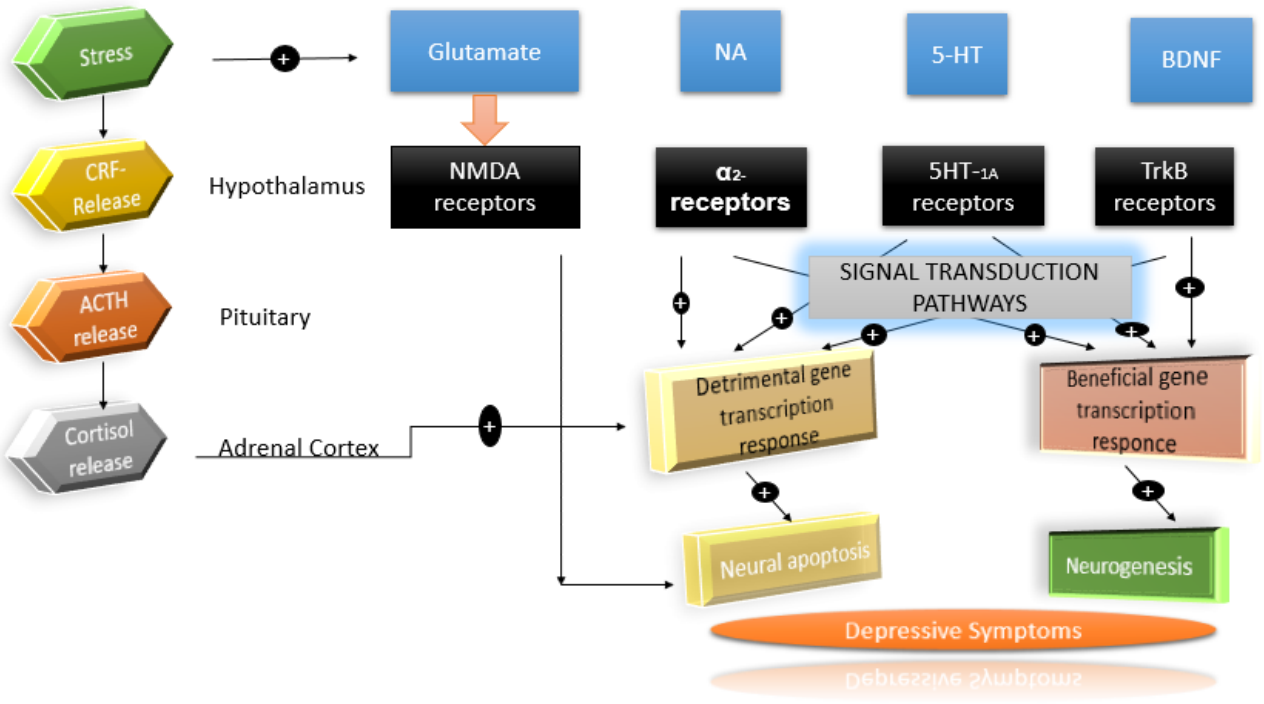

Figure 2 A simplified diagram depicting pathways that are thought to have a role in depression's etiology.

Stress activates the hypothalamic–pituitary–adrenal axis, which in turn promotes the excitotoxic effect of glutamate, mediated by NMDA receptors, and activates genes that cause neuronal death in the hippocampus and prefrontal cortex. BDNF operates on a G protein-coupled receptor (GPCR) and on a kinase-linked receptor (TrkB) to activate genes that protect neurons from apoptosis and also promote neurogenesis, whereas NA and 5-

hydroxytryptamine (5-HT) act on G protein-coupled receptors. ACTH, adrenocorticotrophic hormone; CRF, corticotrophin-releasing factor.

Pathophysiology of Depression: Hypothalamic-Pituitary-Adrenal Axis

Early clinical trials in depression found tiny but repeatable increases in serum glucocorticoid concentrations. A significant amount of study has been motivated by the hypothesis that an imbalance in the hypothalamic–pituitary–adrenal axis contributes to the pathophysiology of depression. Physical or psychological stress raises glucocorticoid levels in the blood, and persistent glucocorticoid administration can cause depression-like symptoms in rodents (Palazidou 2012).

Current Treatment Options

Both psychological therapy and medication are commonly used as initial treatments for MDD. There is widespread consensus among the many guidelines that the treatment of moderate-to-severe depressive episodes should involve the use of medication alone or a combination of medication and psychotherapy (Khan 2016, Otte, Gold et al. 2016, McLachlan 2018). On the other hand, a brief bout of depression may respond well to treatment consisting only of psychotherapy at first. On the other hand, the patient's preferences, as well as their treatment history, should always be taken into consideration. Watchful waiting as an initial technique in the absence of therapy is also a realistic option for patients experiencing moderate depressive episodes (Härter, Klesse et al. 2010).

Psychotherapy

Psychotherapy for MDD can take a variety of forms, the most popular of which is explained below. These varied paradigms are based on a wide variety of conceptual models and prescribed techniques that are distinct from one another in terms of the issues they prioritize and the approaches they take (Cuijpers, Van Straten et al. 2008, Cuijpers, Berking et al. 2013).

Cognitive–Behavioral Therapy

Patients with MDD can benefit from cognitive–behavioral therapy, which teaches them how to identify and combat the distorted thinking patterns that contribute to depression, as well as how to challenge and test their negative beliefs in order to swap them with more appropriate positive ones (Cuijpers, Berking et al. 2013).

Behavioral Activation Therapy

Psychotherapy with an emphasis on encouraging patients to engage in more pleasurable and self-satisfying behaviors is at the heart of the behavioral activation treatment approach. A frequent focus of this treatment is recognizing avoidance habits and developing strategies to overcome them (Veale 2008).

Psychodynamic Therapy

In psychodynamic therapy, the therapist works with the patient to help them investigate and comprehend how past experiences, thoughts, and feelings have led to the patient's current difficulties. Acknowledging these traits can help a person deal with them and make changes in how they behave in response to them (Kudler, Blank Jr et al. 2000).

Problem-Solving Therapy

Patients who participate in problem-solving therapy receive an organized set of abilities that may be used for coming up with creative solutions to problems, recognizing and resolving potential obstacles on the path to accomplishing goals, and making good decisions (D'Zurilla and Nezu 2010).

Interpersonal Therapy

Interpersonal therapy aims to assist individuals in recognizing and addressing problems that arise within their relationships and social roles. These issues may include interpersonal conflicts,

role transitions, and worsened or impoverished relationships (Markowitz 2005).

Mindfulness-Based Therapy

The practice of mindfulness has its origins in meditative traditions, most notably Buddhism. It entails a regular meditation practice in which one cultivates the ability to pay attention to one's thoughts, feelings, and feelings without passing judgment on them. This helps one learn to embrace things as they are without trying to change them (Otte, Gold et al. 2016, Segal, Williams et al. 2018).

Pharmacotherapy

Different pharmacological options are available for the treatment of depression, which are discussed below;

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have an immediate impact on the 5-HT transporter that is extremely selective (SERT). SSRIs block the transporter allosterically, binding at a location different than serotonin. They have minor inhibitory or blocking effects on the NE transporter and adrenergic and cholinergic receptors. SSRIs include sertraline, fluoxetine, escitalopram, citalopram, paroxetine, and fluvoxamine (Tripathi 2013).

Serotonin Norepinephrine Reuptake inhibitors (SNRI)

SNRIs bind to 5-HT and NE transporters, potentially increasing the effects of both neurotransmitters. This group includes venlafaxine, desvenlafaxine, milnacipran, duloxetine etc. Venlafaxine's affinity for the NE transporter is lower than that of desvenlafaxine or duloxetine. SNRIs do not block peripheral receptors strongly, such as histamine H1, muscarinic, or -adrenergic receptors (Rang, Dale et al. 2011, Tripathi 2013).

Tricyclic Antidepressants (TCA)

TCAs immediately inhibit the reuptake transporters involved in the termination of both NE and 5-HT synaptic activities in the brain. Their neurotransmitter activities at synaptic receptors are probably potentiated as a result of this. It includes clomipramine, imipramine, amitriptyline, doxepin, amoxapine, desipramine, and maprotiline (Trevor, Katzung et al. 2009, Rang, Dale et al. 2011).

Serotonin 5-HT2 Receptor Antagonists

Blocking the 5-HT2A receptor, a G-protein-coupled receptor found in multiple central nervous system (CNS) areas, including the neocortex, appears to be the main antidepressant activity of nefazodone and trazodone. The anti-anxiety and antidepressant effects of these medicines are linked to the antagonistic activity of this receptor (Trevor, Katzung et al. 2009, Tripathi 2013).

Other Heterocyclic Antidepressants

Mirtazapine works by antagonizing presynaptic 2 adrenoceptors, which are involved in feedback inhibition, to enhance amine release from nerve terminals. The medication is also a serotonin 5-HT2 receptor antagonist. Bupropion's antidepressant mechanism is uncertain; the medication has no impact on 5-HT or NE receptors or on amine transporters (Tripathi 2013).

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs raise brain amine levels by interfering with their metabolism in nerve terminals, resulting in an increase in NE and 5-HT vesicular storage. Increased levels of amines are produced when neural activity discharges the vesicles, probably boosting the activities of these neurotransmitters. This class includes drugs such as iproniazide, moclobemide, toloxatone, and selegiline (Trevor, Katzung et al. 2009, Rang, Dale et al. 2011, Tripathi 2013).

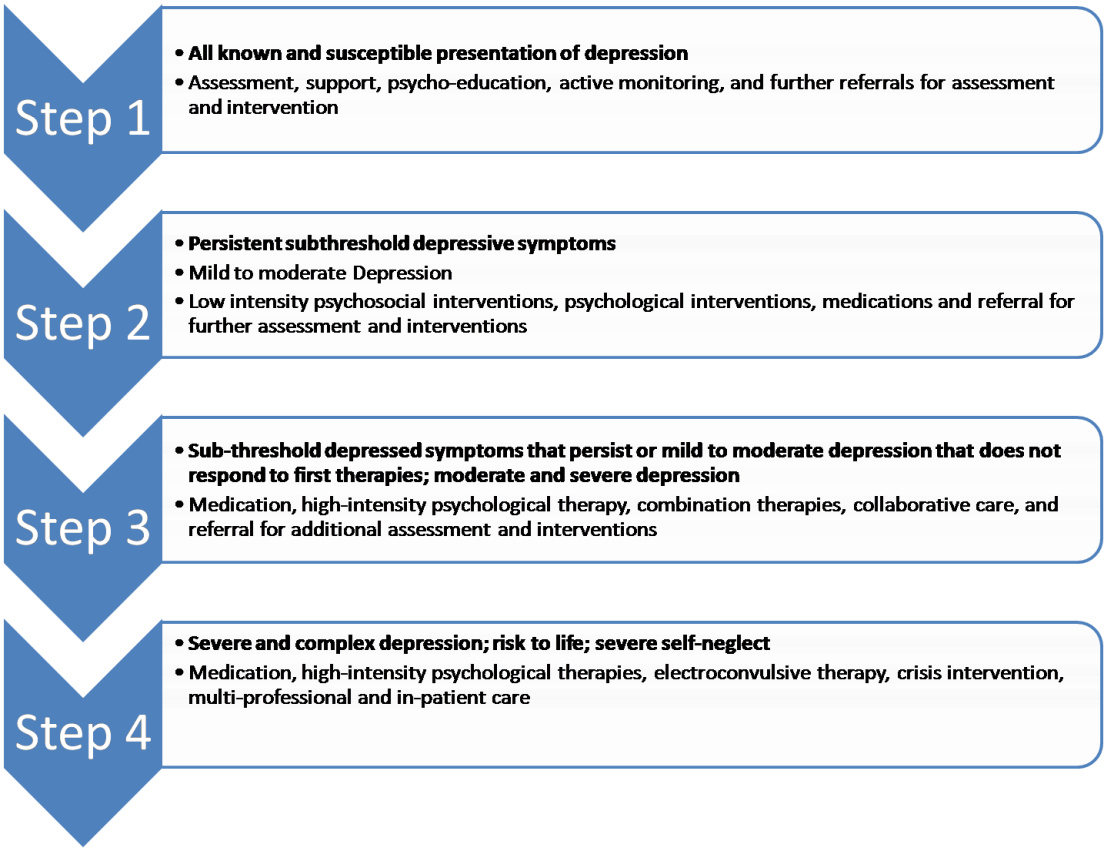

Figure 3 Model of stepped care for the treatment of Depression

First, the least invasive and most effective intervention should be offered. A suitable intervention from the above phase should be presented if the original intervention fails or if the subject rejects it. If repeated therapies fail to alleviate the symptoms of complex depression, or if psychotic symptoms exacerbate the condition, then the condition is said to be "complex."

Combined Pharmacotherapy and Psychotherapy

It has been shown in a number of studies that beginning treatment with a combination of psychotherapy and pharmacotherapy produces significantly better results than beginning treatment with either therapy solo. Adding psychotherapy or antidepressant drugs to the treatment not received can help raise response rates when monotherapy fails to give adequate results (Schatzberg, Rush et al. 2005, Cuijpers, van Straten et al. 2009).

Other Non-Chemical Novel Therapies

Several other therapies, which are considered novel therapies, are also used in the management of depression. Sleep deprivation (total: full night; partial: second half), Light treatment, Electroconvulsive therapy, Magnetic stimulation, Vagus nerve stimulation, and Deep brain stimulation are key therapies (Otte, Gold et al. 2016).

Challenges with Current Treatment Options

Despite several well-delivered therapies, about one-third of those suffering from a severe depressive episode will not achieve long-term remission. These people go through a lot of pain.

These patients are generally termed as difficult to treat (DTD) patients (Rush, Sackeim et al. 2022). After four phases of treatment, remission was maintained by just two-thirds of patients in the Sequenced Therapy Alternatives to Relieve Depression (STAR*D) research. Also, the rate of relapse one year after remission was between 35% and 70%, and the number of acute treatment trials needed to achieve remission was growing (Rush, Trivedi et al. 2006). Despite the advances achieved by the pharmaceutical industry in recent decades, no antidepressant treatment can presently be deemed suited to the majority of individuals who require medication to treat MDD. When it comes to certain patients, the potential benefits far outweigh the possible risks, which puts them at risk for developing a tolerance to the medication and developing a psychological addiction to it as a result of their drug abuse, but for others, the hazards may lead to noncompliance (even if they have a single moderate side effect that is viewed as important). Adding to these factors many factors like antidepressant specific side effects like mirtazapine causes sleep which may be good for those who have insomnia, compared to those who don't have this problem which in turn will cause non-compliance in the latter group. Similarly, another antidepressant, venlafaxine may cause dose-related hypertension in about nine percent of depressive patients. Also, types of depression like Treatment-resistant depression, depression with the psychotic feature, atypical depression etc. have a great impact and pose a challenge in treating depression (Popa-Velea, Gheorghe et al. 2015). The current and latest research also shows positive relation of epigenetic and genetic causes in the failure or ineffectiveness of depression treatment (Schroeder, Krebs et al. 2010).

Importance of Fluoxetine

Fluoxetine was the first big advancement in depression treatment since the discovery of TCAs and MAOIs roughly 30 years ago. It outperformed TCAs and MAOIs as the first SSRI approved by the US Food and Drug Administration (FDA) for both effectiveness and side effects. Even if there is an ongoing discussion on the precise mechanism by which fluoxetine demonstrates its therapeutic efficacy, the importance of fluoxetine and other similar SSRIs in the field cannot be denied (Wenthur, Bennett et al. 2014). Fluoxetine is licensed to treat MDD in adults and children, obsessive-compulsive disorder in adults and children, acute depressive episodes in Bipolar I patients, premenstrual syndrome, panic disorder, bulimia nervosa, and bulimia nervosa dysphoria (Wenthur, Bennett et al. 2014). For antidepressants to be marketed were TCAs, then MAOIs. But both have unwanted and fatal side effects, which patients with suicidal tendencies sometimes misuse. There were no SSRIs available in the United States prior to Fluoxetine becoming licensed for use there, and it revolutionized not just depression therapy but also the way people thought about depression. Webster's dictionary defines Fluoxetine as Prozac. All of this publicity has helped to raise awareness of depression and remove the stigma attached to it, lowering the barriers that prevent many depressed persons from seeking therapy. Recent research shows that only one-third of depressive patients are able to achieve remission with typical SSRIs and that the commencement of action can take up to three to six weeks, but the influence of fluoxetine is unquestionable (Rush, Trivedi et al. 2006). In the realm of 5-HT research, this chemical has been a driving force and inspired a new therapeutic landscape for severe depression, influencing how society views and responds to depression (Wisniewski, Rush et al. 2007). Both the efficacy and safety of fluoxetine is subject alteration as a result of genetic variations as listed below

Table 1: Genetic factors affecting adverse effects and efficacy of fluoxetine in MDD.

Genes	Variant	Size	Location	Drug	Association/Correlation	Reference
ABCB1	*rs2032582*	83	Barcelona	Fluoxetine	Associated with clinical efficacy	(P Gasso et al. 2014)
ABCB1	*rs4148739*	261	Europe	Fluoxetine and other SSRI, SNRI and TCA	Associated with clinical efficacy	(Manfred Uhr et al. 2007)
ABCB1	*rs28401781*	290	China	SSRI	Associated with clinical efficacy	(Xiaoye Huange et al. 2013)
ACE	*rs1799752*	126	Iran	Fluoxetine and Sertraline	Associated with clinical efficacy	(Bahramali Ehsan et al. 2016)
BDNF	*rs61888800*	536	USA	Antidepressants and Fluoxetine	No association	(Licinio Julio et al. 2009)
CRHRI	*rs242941*	127	China	Fluoxetine	Associated with clinical efficacy	(Liu Zhongchun et al. 2007)
CYP2D6	Various SNPs	83,,64	Europe	Fluoxetine	Associated with clinical efficacy	(Lerena Adrián et al. 2004)
FKBP5	*rs4713916*	2852	Multiple locations	Fluoxetine	Associated with clinical efficacy	(Zou Yan-Feng et al. 2010)
GSK3B	*rs334558*	168	China	Fluoxetine & Sertraline	Associated with clinical efficacy	(Tsai S-J et al. 2008)
HTR1A	*rs6295*	224	Taiwan	Fluoxetine	Associated with clinical efficacy	(2006. Hong C-J et al.
HTR1B	*rs9361233*	84	Barcelona	Fluoxetine	Associated with clinical efficacy	(Gassó Patricia et al. 2007)
REEP5	*rs153549*	387	China	SSRI	Associated with clinical efficacy	(Yang Zhenxing et al. 2012)
REEP5	*rs153560*	165	China	SSRI	Associated with clinical efficacy	(Yang Zhenxing et al. 2012)
SERPINE1	*rs1799889*	140	China	Fluoxetine	Associated with clinical efficacy	(Tsai Shih-Jen et al. 2008)
SERPINE1	*rs2227631*	140	China	Fluoxetine	Associated with clinical efficacy	(Tsai Shih-Jen et al. 2008)
SLC6A4	*rs57098334*	372	Korea	Fluoxetine	Associated with clinical efficacy	(Kim D K et al. 2000)
SLC6A4	Several SNPs	36	Europe	Fluoxetine	Associated with adverse effects	(Perlis Roy H et al. 2003)
SLC6A4	Several SNPs	224	Taiwan	Fluoxetine	Associated with clinical efficacy	(Hong C-J et al. 2006)
SRP19	*rs495794*	165	China	Fluoxetine	Associated with clinical efficacy	(Yang Zhenxing et al. 2012)
BDNF	*rs6265*	305	China	Fluoxetine	No association with side effects	(Zou Yan-Feng et al. 2010)
SLC6A4	*rs25531*	96	Europe	Fluoxetine	No association with efficacy	(Kraft Jeffrey B et al. 2005)
TPH1	*rs1800532*	159	Spain	Fluoxetine and Citalopram	Associated with clinical efficacy	(Arias Bárbara et al. 2013)

TPH1 Gene (Tryptophan Hydroxylase 1)

This gene encodes for the enzyme TPH. Many enzymes like MAO play an important role in regulating serotonin in the brain, including TPH. TPH helps synthesize 5-HT and controls how it works in the brain (Arias, Fabbri et al. 2013).

A study done in the Spanish city of Barcelona included 159 people who met the DSM-IV criteria for a diagnosis of MDD. The findings

suggested that TPHl *rsl800532* may have a selective influence on citalopram responsiveness in MDD patients with psychotic and melancholy symptoms, while the other polymorphisms had no significant effect. If confirmed findings are confirmed, they may guide therapy decisions in individuals with severe MDD subtypes (Arias, Fabbri et al. 2013).

ABCB1 Gene (ATP binding cassette subfamily B member 1)

The *ABCB1* gene codes for an adenosine triphosphate-binding transporter protein. Numerous ATP-binding cassette (ABC) genes are found in all kingdoms of life that play a crucial role in maintaining cellular homeostasis, one of which is *ABCB1* (Rosenberg, Callaghan et al. 1997, Jones, George et al. 2004). There may be an impact on plasma concentrations and pharmacological response to the transportation of fluoxetine. Drugs such as antidepressants can be ***transported*** across theblood–brain barrier by P-glycoprotein (P-gp), a plasma membrane transporter (Uhr, Grauer et al. 2003, Uhr and Grauer 2003, Uhr, Grauer et al. 2007). There have only been a handful of researches that have investigated the effect that *ABCB1* polymorphisms have on fluoxetine responsiveness, and none of these studies have investigated the effects in children and adolescents (Menu, Gressier et al. 2010).

In one specific study conducted in Barcelona, 83 MDD-diagnosed patients were included. Despite the fact that the *ABCB1* genotype was not linked to fluoxetine plasma levels, it did appear to have an impact on clinical medication response. The non-synonymous polymorphism of *G2677TABCB1* was linked to clinical improvement following fluoxetine therapy in this research. Because the link was detected in the majority of the scales tested, these findings were solid. The *2677T* allele was associated with reduced levels of depressive symptoms, anxiety, and obsessive-compulsive symptoms, as well as a better clinical impression overall (Gassó, Rodríguez et al. 2014).

In yet another research in China, patients with MDD were given fluoxetine to see whether the *ABCB1* gene polymorphism influenced their response to the drug. For this purpose, around 290 patients of depression were recruited and genotyped. A total of nine single nucleotide polymorphisms (SNPs) were targeted in *ABCB1, ABCB6,* and *ABCG1*. The *rs28401781* and *rs4148739* allele frequencies in *A*BCB1 indicated a significant disparity between those who responded and those who did not respond. The *ABCB6* and *ABCG1* genes were found to have no significant correlations. The findings show that *ABCB1* polymorphisms in the Chinese Han population may be linked to SSRI treatment response (Huang, Yu et al. 2013).

ACE Gene (Angiotensin-converting enzyme)

Studies have demonstrated that brain angiotensin II (Ang II), the primary ACE product, promotes norepinephrine release both *in vivo* and *in vitro*, indicating that ACE is widely distributed in the CNS (Phillips 1987, Gard 2002, Saavedra and Benicky 2007). In addition, it has been shown that exposure to environmental stimuli causes an increase in both the circulation and the concentrations of renin and Ang II in the brain (Peng and Phillips 2001). An increased level of RAAS activity in the brain is believed to raise the likelihood of developing depression by elevating the sensitivity of Ang II receptor type 1 (AT1) to Ang II (Saab, Gard et al. 2007). In addition, ACE is the enzyme responsible for the degradation of several neuropeptides, including substance P, (SP) (Skidgel and Erdös 2004). The involvement of SP and ACE in pathophysiology and depression mitigation has been proposed, given the possible antidepressant benefits of SP antagonists (Yang, Yu et al. 2014).

The frequencies of ACE insertion/deletion (I/D), *rs4291*, and *rs4343* polymorphisms in extracted DNA were investigated in this research of 200

newly diagnosed depressed individuals. Patients were placed in one of 2 categories according to a random assignment for a period of 12 weeks: one received fluoxetine, and the other received sertraline. This study enlightens that genetic variables are one of the most important predictors of therapeutic response. Sertraline was shown to be more effective than fluoxetine in this research because of the ACE gene's *D* allele and the ACE I/D polymorphism's *DD* genotype (Bahramali, Firouzabadi et al. 2016).

BDNF Gene (Brain-Derived Neurotrophic Factor)

A neurotrophin that is generated in high quantities and to a significant extent in the CNS is called BDNF (Connor and Dragunow 1998, Murer, Yan et al. 2001). In the last ten years, BDNF has established itself as a pivotal factor in complex behavioural patterns in the developing central nervous system that are associated to illness. BDNF affects gene transcription in the long run via modulating signalling pathways that alter local synaptic function (Tyler, Alonso et al. 2002, Bramham and Messaoudi 2005). Prosurvival *BCL2* gene expression is influenced by cyclic AMP (cAMP)-response element transcription factor in the peripheral and central nervous systems, enhancing neuronal survival (Schinder and Poo 2000). In addition to these functions, it plays a role in the transmission and plasticity of excitatory synapses, the processing and storage of memories, as well as the onset of temporal lobe epilepsy and kindling. Because of its importance to critical CNS activities, it has sparked research into its role in neurological and psychiatric conditions and psychiatric diseases (Tyler, Alonso et al. 2002, Lähteinen, Pitkänen et al. 2003, He, Kotloski et al. 2004).

A total of 536 individuals were included in the research conducted at the University of California, Los Angeles, which comprised 264 healthy controls and 272 people who had been clinically diagnosed with MDD using the DSM-IV manual. In the course of the research, 83 novel SNPs were discovered. In association studies of patients with MDD and controls, there was a significant correlation between six SNPs (*rs12273539*, *rs11030103*, *rs6265*, *rs28722151*, *rs41282918*, *and rs11030101*) and two haplotypes in distinct blocks (one having Val66, and the other around exon *VIIIhOne* of the observed SNPs in the 5 untranslated regions, *rs61888800*, was connected to antidepressant response including fluoxetine. This was the case even after taking into account factors such as age, sex, medication, and the baseline score on the 21-item Hamilton Depression Rating Scale (Licinio, Dong et al. 2009).

Related to BDNF polymorphism linkage to fluoxetine response in MDD patients, a study was conducted in China, where 305 Chinese depressed patients were genotyped. The study findings suggest that there was no link among Chinese individuals with MDD between depression severity and the BDNF Val66Met polymorphism. The BDNF Val66Met polymorphism may considerably impact the effectiveness and side effects of SSRIs in Chinese patients diagnosed with MDD (Zou, Wang et al. 2010).

CRHRI Gene (Corticotropin-Releasing Hormone Receptor1 gene)

One of the most prevalent findings in individuals diagnosed with MDD is a malfunction in the hypothalamic-pituitary-adrenal axis (up to 70 percent) (Holsboer 2000). In addition, people who commit suicide have decreased CRH binding sites in their frontal cortex and greater levels of CRH expression in their hypothalamic paraventricular nucleus. These findings suggest that changes in CRH function may play a role in the development of depression (Nemeroff, Widerlöv et al. 1984, Liu, Zhu et al. 2007). In addition, it has been shown that a reduction in CRH neuron activity accompanies some SSRIs' therapeutic impact. Consequently, it has been suggested that

inhibiting CRH activity is the last and most typical phase of antidepressant action necessary for the maintenance of MDD remission over the long term (Holsboer and Barden 1996). Two primary receptor subtypes are found in the CNS, and these are CRHR1 and CRHR2. It is believed that CRHR1 plays a significant part in the process of regulating the effects that CRH triggers in patients suffering from depression and anxiety (Wong, Licinio et al. 1994, Holsboer and Barden 1996).

In a study conducted on the Chinese population, about 127 MDD patients were involved after fulfilling the criteria of depression according to DSM-IV. In this research, SNPs in three locations in the CRHR1 gene (*rs1876828, rs242939, and rs242941*) were linked to the antidepressant efficacy of fluoxetine for six weeks. Researchers found a relationship between treatment responsiveness to fluoxetine in MDD patients and the *rs242941G/G* genotype and homozygous genotype *GAG* haplotype of the three SNPs. The findings back up the theory that the *CRHR1* gene is important in the antidepressant response in MDD patients. A link between MDD and the *CRHR1* gene has also been discovered. As a consequence of these results, the *CRHR1* gene can be investigated further as a candidate gene in the field of antidepressant pharmacogenetics (Liu, Zhu et al. 2007).

CYP2D6 gene (Cytochrome P450 2D6)

The cytochrome P450 mixed-function oxidase system, which includes CYP2D6, is responsible for adding or removing specific functional groups in roughly 25% of clinically used drugs (Wang, Yang et al. 2009). Fluoxetine and norfluoxetine plasma concentrations differ substantially amongst people when the same dosage of medication is administered. The disparities in CYP2D6 activity, one of the enzymes involved in drug metabolism, might account for some of this. It has been shown that CYP2D6 is involved in the conversion of fluoxetine to norfluoxetine after a single dose in both laboratory settings and in healthy volunteers (von Moltke, Greenblatt et al. 1997, Lundmark, Reis et al. 2001, Wang, Yang et al. 2009). The *CYP2D6* genotype has been connected to plasma concentrations of fluoxetine and norfluoxetine in people.

A 64-person research was done in a white European community. The patients were on fluoxetine as their only antidepressant. In order to determine the genotypes of CYP2D6 and CYP2C9, procedures that are particular to the polymerase chain reaction were used. This research aimed to investigate the relationship between the *CYP2D6* and *CYP2C9* genotypes and the steady-state concentrations of fluoxetine and norfluoxetine in the plasma of individuals suffering from mental illness. The study findings suggest that fluoxetine plasma concentration in patients is influenced by *CYP2D6* and maybe by *CYP2C9* genotypes under steady-state circumstances (LLerena, Dorado et al. 2004).

Another study comprising 83 individuals who, according to DSM-IV, had been diagnosed with MDD was conducted in Barcelona (Spain). The research results showed a negative correlation between CYP2D6 and fluoxetine steady-state plasma concentration and clinical response (Gassó, Rodríguez et al. 2014).

FKBP5 Gene (FKBP prolyl isomerase 5)

A variety of single nucleotide polymorphisms may be found in the *FKBP5* gene, located on chromosome 6p21, a region of the genome associated with both psychosis and bipolar disorder. Numerous studies have investigated whether or not there is a correlation between *FKBP5* gene variations and how well persons with mood disorders respond to treatment; however, the findings haven't always been consistent (Binder, Salyakina et al. 2004, Kirchheiner, Lorch et al. 2008, Lekman, Laje et al. 2008).

Here we will discuss a meta-analysis. This meta-analysis was conducted to determine whether

there is a connection between *FKBP5* gene polymorphisms and therapeutic responsiveness in people who suffer from mood disorders. There were eight independent studies found, using data from 2199 people. Three *FKBP5* gene polymorphisms were subjected to a meta-analysis (*rs1360780, rs3800373, and rs4713916*). A substantial link between the FKBP5 gene rs4713916 polymorphism and response rate was discovered in individuals with mood disorders. However, no link was found between the *rs1360780* and *rs3800373* polymorphisms in the *FKBP5* gene and therapy responsiveness in individuals with mood disorders. This meta-analysis shows that the *rs4713916* polymorphism in the *FKBP5* gene, but not the *rs1360780* and *rs3800373* polymorphisms, is linked to therapy response in individuals with mood disorders (Zou, Wang et al. 2010).

GSK3B Gene (glycogen synthase kinase-3β)

It is a serine/threonine protein kinase (GSK3) that is distributed throughout the human body. In mammals, GSK3α (GSK3A) and GSK3β (GSK3B) are two closely related isoforms of GSK3. Although a separate gene expresses each isoform, their kinase domains are substantially similar. It was first discovered that GSK3 was a negative regulator of glycogen synthesis in cells. It was only recently discovered that it is a very influential enzyme that controls a broad variety of cellular processes, such as the expression of genes, the formation of cellular structures, and the process of apoptosis. The activity of GSK3 is tightly regulated via a variety of different approaches (Jope and Johnson 2004). *GSK3B* is the most highly expressed *GSK3* isoform in brain tissue, where it is regulated throughout the development process. *GSK3B* may be implicated in the pathophysiology of MDD, as shown by many lines of evidence, and lowering *GSK3B* expression may help antidepressants work better, according to some researchers (Li, Zhu et al. 2004).

A total of 230 psychiatric outpatients from southern Taiwan who met the DSM-IV criteria for MDD were included in the research that was carried out in Taiwan. For the purpose of the SSRIs pharmacogenetic study, participants received daily doses of fluoxetine or citalopram beginning at 20 mg per day; the researcher may increase the dosage to 40 mg per day depending on the clinical response. The patients in the two therapy groups had similar treatment histories in the past. Four *GSK3B* SNPs were examined in this research. The findings support the concept that medications that regulate *GSK3B* activity might be a novel therapeutic strategy for MDD, mainly due to the fact that they demonstrate for the first time that *GSK3B* genetic variants have a role in the therapeutic response to SSRI antidepressants (Tsai, Liou et al. 2008).

HTR1A Gene (5-hydroxytryptamine 1A)

Depressive disorder is thought to be caused by abnormalities in the central serotonergic system, according to several studies. GWAS for major depression now often include genes encoding proteins involved in regulating serotonergic neurotransmission. According to the most recent genetic studies in animals and humans, depression is associated with a reduction in the number of serotonin type 1A (HTR1A) receptors and serotonin transporters. *SERTPR* isn't the only genetic variation associated with SSRI treatment response (Neumeister, Young et al. 2004).

In order to study the association of *HTRA1* gene polymorphism with fluoxetine efficacy a study was conducted in Taiwan comprised of 224 patients fulfilling DSM-IV criteria. According to the results of the research, individuals who had the polymorphisms *HTR1A 1019C/C* and *SERTPR l/l* reacted favorably to fluoxetine. However, other polymorphisms were not shown to be connected with the therapeutic response to fluoxetine (Hong, Chen et al. 2006).

HTR1B Gene (5-hydroxytryptamine 1B)

5-HT1B receptors are found in both pre-and post-synaptic regions throughout the brain. 5-HT production and release are controlled by autoreceptors, which are located on serotonergic axons, whereas other synaptic processes are influenced by heteroreceptors, which are found in post-synaptic locations (Castro, Pascual et al. 1998, Sari and Reviews 2004). The *HTR1B* knockout mice display a variety of behavioral changes, one of which is a decreased level of anxiety. Additionally, some of the impacts of SSRI drugs are not present in these animals *HTR1B* seems to be an important player in the treatment of depression, as shown by research (Zhuang, Gross et al. 1999, Ruf and Bhagwagar 2009). *HTR1B* genetic variations have been linked to antidepressant responsiveness and certain behavioral features following antidepressant therapy (Perroud, Bondolfi et al. 2011, Lenze, Dixon et al. 2013).

In order to investigate the relationship of *HTR1B* gene with the antidepressant effect, a study was conducted in Barcelona where 83 MDD patients receiving fluoxetine as first-time treatment were included. Two of these, *rs9361233* and *rs9361235*, were shown to be strongly linked with clinical improvement following fluoxetine therapy. The examination of heterozygous genotype combinations revealed a negative connection with clinical improvement. The patients who exhibited the least recovery were those who were heterozygous for all three SNPs. Clinical improvement was shown to be unrelated to the average level of methylation in the *HTR1B* promoter. Epigenetic and genetic factors have an important role in modifying *HTR1B* expression in the pharmacological response to antidepressants, as these data further demonstrate (Gassó, Rodríguez et al. 2017).

REEP5 Gene (The receptor accessory protein)

Near the APC locus on chromosome 5q21-22, the REEP5 gene belongs to the DP1/Yop1p protein family, which plays a role in the formation of endoplasmic reticulum (ER) tubules (Voeltz, Prinz et al. 2006). In prior genome association studies, researchers found a relationship between ADHD in adults and the REEP5 gene. These issues are connected to a greater risk of mental co-morbidity, such as depression and drug use disorder, as well as a failure to adapt psychosocially, as stated in the previous sentence (Lesch, Timmesfeld et al. 2008).

An investigation on the *REEP5* gene polymorphism's link to depression and treatment outcomes with antidepressants was undertaken in the Chinese population. The research included a total of 397 patients suffering from MDD as well as 473 controls. The results showed that patients might have a different clinical response to antidepressant medication depending on genetic variants in the APC and REEP5 genes. In a study that lasted for six weeks and was conducted on a Han Chinese population, researchers looked into the relationship between polymorphisms in the APC and REEP5 genes and MDD and the effect of SNPs in both genes over the course of time. The result of the study revealed that three SNPs in the REEP5 gene (rs495794, rs153549, and rs153560) demonstrated statistically considerable discrepancies between those who responded and those who did not. Polymorphisms in the REEP5 gene may have an effect on how well the antidepressant medication works in patients with MDD (Yang, Ma et al. 2012).

SERPINE1 Gene (Plasminogen Activator Inhibitor Type 1 Gene)

There are many natural defense mechanisms against intravascular thrombosis, and one of them is the tPA-plasminogen proteolytic cascade (tPA-plasminogen). According to the findings of recent research, tPA and plasminogen are both highly expressed in the central nervous system and play important roles, both physiologically and pathologically, in a variety of processes, including learning and

memory, stress response, neuronal degeneration, and addiction. BDNF, a member of the neurotrophic family known to regulate neuronal plasticity and survival, may play a key role in the pathogenesis of MDD and, as a result, in the mechanisms underlying antidepressant therapeutic action. This evidence comes from studies conducted in recent years on both animals and humans. Similar to the majority of other secreted proteins, BDNF is first produced as a proBDNF precursor, which is then converted into the mature form of the protein by a proteolytic processing step (Collen and haemostasis 1999, Melchor, Pawlak et al. 2003, Melchor, Strickland et al. 2005). tPA–plasminogen involvement in MDD development is conceivable, given the role of BDNF in MDD pathogenesis and the efficacy of antidepressant therapy (Tsai 2006, Martinowich, Manji et al. 2007). Because PAI-1 is an important tPA inhibitor, it may be involved in the pathogenesis of MDD by disrupting the tPA–plasminogen system and the cleavage of proBDNF (Yamamoto, Takeshita et al. 2002). Animal tests that were subjected to restraint stress showed a considerable rise in plasma PAI-1 antigen as well as tissue *PAI-1* mRNA (with the biggest elevation occurring in adipose tissues), which suggests that *PAI-1* is a gene that is controlled by stress (Pawlak, Magarinos et al. 2003). Another research using mice indicated that the presence of tPA in the brain is essential for the maturation of behaviors that are triggered by stress. PAI-1 levels were shown to be higher in women with MDD compared to healthy controls in clinical studies (Eskandari, Mistry et al. 2005).

A study was carried out in China with the purpose of providing evidence of a link between the *SERPINE1* gene polymorphism and MDD, as well as the responsiveness to antidepressant medication. The research consisted of around one hundred forty participants who used either fluoxetine or citalopram. They were genotyped for six *SERPINE1* SNPs (*rs2227631*, *rs1799889*), as well as for *rs6092*, *rs6090*, *rs2227684*, and rs7242. According to the results of this research, genetic differences in the *SERPINE1* gene may have a role in both the susceptibility to MDD and the initial therapeutic response to SSRI antidepressants. (Tsai, Hong et al. 2008).

SLC6A4 Gene (Solute Carrier Family 6 Member 4)

The *SLC6A4* gene encodes the 5-HT transporter. It is hypothesized that this protein is responsible for the beginning of the antidepressant activity of SSRIs. SSRIs are drugs that combat depression by inhibiting the absorption of serotonin by presynaptic serotonergic neurons (Serretti and Artioli 2004). On chromosome *17q11.2*, *SLC6A4* encompasses 37.8 kilobases (kb) of the genomic sequence, has an open reading frame consisting of 630 amino acids and a total of 15 exons, two of which are considered to be noncoding and are designated as *1A* and *1B*. Many researchers have looked for a link between 5-HT transporter deoxyribonucleic acid (DNA) variations and SSRI responsiveness (Bradley and Blakely 1997, Glatt, DeYoung et al. 2001).

In one study conducted in Europe, some 96 MDD-diagnosed patients were included. *SLC6A4* was re-sequenced in persons with severe depression to examine whether it was associated with SSRI response. The researchers discovered 27 *SLC6A4* variations, 21 of which were previously unknown. Three of the five exonic variations were found on each of the seventeen chromosomes. Researchers found that one polymorphism near the *HTTLPR* was linked to treatment response, and biochemical experiments showed that this polymorphism changed nuclear extract binding to a consensus sequence for the activator protein 2 transcription factors, which is thought to be a key regulator of neural gene expression in mammals. These results provide evidence in support of the hypothesis that SSRI responsiveness is associated with a DNA variant located within the serotonin transporter locus. In addition to

this, a possible physiological mechanism that may be responsible for mediating the impact of this relationship was found, as well as a possibly important functional variation that adds to this connection (Kraft, Slager et al. 2005).

Recommendations

Although medicine is frequently a matter of therapeutic procedure, when treating a complicated condition like depression, the physician should evaluate all circumstances that might impede the pharmacological impact and make appropriate judgments. Older medications can also be used if they suit better in the therapeutic setting of the patient. Overall, there are no new and old medications in the treatment of depression; instead, we should consider employing molecules that address diverse demands. The availability of medical information and its impact on patients should be evaluated. Overall, a comprehensive clinical assessment of each case should not be replaced by generic procedures but should be employed on a frequent basis as an essential and powerful method in treating every depressed patient. As elucidated in this review, genetic factors are important factors in predicting an antidepressant response and side effects, so efforts are needed to develop genetic testing which is lower in cost, which may help the clinicians in selecting a drug for a patient of MDD, and it will save both time and quality of life of a patient.

Future directions

Some genes, such as *BDNF* and *SLC6A4*, as well as many others, have been shown to have no influence on the effectiveness or side effects of fluoxetine when administered to individuals suffering from MDD. This area of research offers a tremendous amount of untapped potential, notably in the field of psychiatry, due to the scarcity of physiologically-based therapeutic suggestions. There is a great deal of optimism that genetic profiles may, in the not-too-distant future, make it possible for us to personalize mental health treatments. For this purpose, a large sample with diverse population data is required, which may play a pivotal role in defining personalized treatment care in MDD patients.

Conflict of Interest

The authors declare that they have no competing interests.

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IK conceptualized the study and wrote the final manuscript, SS, SMAH, IK, and KUD reviewed literature, SMAH supervised the whole project.

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