Genetic Markers for the Diagnosis and Management of Treatment-Resistant Depression

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Abstract

The incidence of depression is increasing worldwide, yet its diagnosis and management remain difficult, particularly in the case of Treatment-Refractory Depression (TRD). Herein, we review recent advances in the diagnosis and treatment of TRD, with a focus on genetic biomarkers for diagnosis and N-Methyl-D-Aspartate (NMDA) receptor blockers for treatment. TRD may be difficult to diagnose because of comorbidity with other psychological disorders. Criteria proposed in the *International Classification of Diseases*, Tenth Revision (*ICD*-10) and the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) are currently used to diagnose depression, but the use of genetic biomarkers would make the diagnosis more objective. Improvements in technology have made genetic analysis faster and less expensive; however, to date, there is no established medically objective test for the diagnosis of depression. Various genomic analyses, such as Genome-Wide Association Studies (GWAS), studies of single-nucleotide polymorphisms, pharmaco genetic studies, epigenetic studies, and studies of micro Ribo Nucleic Acid (miRNA), have been performed. Although genetic differences related to depression have emerged from these types of studies, the importance and utility of the biomarkers identified remain unclear. Depression is generally treated with various antidepressants, with physicians switching their patients from one drug to another as needed. Antidepressants may be used concomitantly with atypical antipsychotics as well as lithium, thyroid hormone, dopamine agonists, and/or electroconvulsive therapy. New antidepressants affecting the glutamatergic system, such as ketamine (which blocks NMDA receptors), are currently under investigation. Genetic factors also play a role in the response to medication. Therefore, genetic testing holds promise for personalizing the patient's response to therapy. Therefore, objective genetic tests and new types of drugs may improve the outcomes of patients with TRD.

Keywords: Treatment-Refractory Depression; Ketamine; N-Methyl-D-Aspartate receptor blockers; Epigenetics; Hydroxy Methylation; miRNA

Abbreviation

TRD: Treatment-Refractory Depression; MDD: Major Depressive Disorder; COMT: Catechol-O-Methyl Transferase; SLC6A4: Serotonin Transporter Solute Carrier Family 6 Member 4; GRIK4: Glutamine Receptor Ionotropic Kainate 4 Protein; NMDA: N-Methyl-D-Aspartate; GWAS: Genome-Wide Association Studies; EWAS: Epigenome-Wide Association Studies; 5 mC: 5-Methyl Cytosine; 5hmC: 5-Hydroxy Methyl Cytosine; ICD-10: International Classification of Diseases: Tenth Revision; *DSM*-4-TR: *Diagnostic and Statistical Manual of Mental Disorders*: Fourth Edition; *DSM*-5: *Diagnostic and Statistical Manual of Mental Disorders*: Fifth Edition; miRNA: micro-Ribo Nucleic Acid; VNS: Vagus Nerve Stimulation; TMS: Transcranial Magnetic Stimulation; rTMS: repetitive Transcranial Magnetic Stimulation; TCAs: Tri Cyclic Antidepressants; MAOIs: Monoamine Oxidase Inhibitors

Introduction

Although people are most likely to suffer their first depressive episode at 30-40 years of age: there is a smaller peak at 50-60 years [1]. Current understanding of the causes of depression remains incomplete; proposed causes include psychological: psychosocial: hereditary: and biological factors. In contrast to other types of mental illness: depression may be cured. Depression is also known to recur easily; some cases become intractable soon after initial treatment. Numerous factors may cause depression to become intractable. Improvement in environmental factors (e.g.: stress) is considered

to be the most critical issue. The Sequenced Treatment Alternatives to Relieve Depression (STAR'D) study reported that the remission rate for depression is 67% [2,3]. The STAR'D study: funded by the U.S. National Institute of Mental Health (NIMH): was a large-scale: prospective study of more than 3000 outpatients with nonpsychotic Major Depressive Disorder (MDD). Results of the study showed that up to 35% of these patients may be considered to have Treatment-Refractory Depression (TRD) [4].

The diagnosis of psychological disorders is typically based on international criteria for clinical classification: such as those in the *International Statistical Classification of Disease and Related Health Problems* (*ICD*-10) and the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-IV: *DSM*-5) (Table 1a,1b). However: diagnosis is ultimately determined by the clinical experience and skill of the psychiatrist.

The recognition of MDD is problematic for clinicians because of the condition's heterogeneous nature: a lack of standardized definitions: and frequent concomitant comorbidities that confound the differential diagnosis [5,6]. Patients with TRD may have a tendency toward bipolar depression. Up to 35% of patients with TRD may have bipolar disorder and up to 80% show evidence of bipolarity [7]. Furthermore: MDD is not easily differentiated from other similar disorders and cannot be medically diagnosed with objective tests. However: to the best of our knowledge: an innovative auxiliary diagnostic method has not yet been established.

The existence of TRD is one of the factors making MDD intractable. In this article: we will present genetic biomarker studies that are being conducted globally as the latest approach to diagnose depression in reduce the factors that cause cases to be prolonged and become intractable.

Differentiating Depression from Other Disorders

Complications of other psychological disorders may exhibit early symptoms that are similar to those of MDD: and treatment may be started before symptoms indicative of MDD have been diagnosed. The onset of MDD occurs in various ways. The lack of a standardized definition and the numerous comorbidities that confuse differential diagnosis become problematic [5]. MDD is frequently complicated by anxiety disorder [8]. Unless other psychological disorders are identified and appropriate treatments are given: the primary disease may be exacerbated: thereby causing the diagnosis to be reconsidered. The diagnosis of psychological disorders is narrowed down primarily through medically subjective information based on the patient's complaint and information obtained from family members. Objective data from examinations: such as physiological tests: are also considered. Efforts to narrow the differential diagnosis also include a consideration of the time course of symptoms. However: there are many circumstances wherein the definitive diagnosis of MDD cannot be made from the initial examination: even if exclusion diagnosis is used. Bipolar disorder and double depression are depression disorders that are likely to be diagnosed as TRD [7].

When TRD is diagnosed: we must carefully exclude false TRDs. Patients with a diagnosis of TRD may have latent bipolar depression. Approximately 35% of patients who are diagnosed with TRD show signs of being bipolar: and 80% of these patients may exhibit bipolar disorder [7]. According to a study that examined 196 previous studies on TRD and bipolar disorder: patients with TRD had a greater

possibility of having latent bipolar disorder [9]. In *DSM*-5: the clinical diagnostic criteria delineated a clear boundary between bipolar disorder and MDD. In the clinical setting: however: after a patient is diagnosed with MDD: symptoms that meet the diagnostic criteria for bipolar disorder may appear: and the diagnosis may be modified over time. In particular: it is necessary to carefully differentiate bipolar disorder type II from mixed affective episodes with strong depressive symptoms. If hypomania is observed during the course of treatment with antidepressants: activation syndrome and serotonin syndrome may also be differentiated (based on the type of antidepressant used). However: it is necessary to consider the possibility of bipolar disorder and to promptly reconsider the diagnosis by initiating treatment with anti-manic agents within a few days.

Dysthymia is a disorder in which depressive symptoms are likely to become chronic. It is a representative differential disorder of MDD. It also is known to coexist with MDD: and this is termed as double depression [10]. Although dysthymia often develops during adolescence: it is often initially considered a personality problem rather than an illness. For this reason: it is rare that patients seek medical consultation for dysthymia alone. However: when MDD symptoms rapidly develop in patients with dysthymia: they often receive medical consultation for the first time as double depression. In such cases: it is difficult from the beginning to distinguish this condition from TRD. Even if patients recover from coexisting MDD: symptoms persist if underlying dysthymia is not effectively addressed. As described above: for the definitive diagnosis of MDD: it is necessary to collect accurate information from various aspects and to simultaneously and meticulously exclude other psychological disorders.

Although clinical diagnostic criteria are important: it is important to strive to thoroughly examine and diagnose the patient: even if the process is time consuming. The clinician must carefully listen to information such as the patient's feelings: upbringing: current environment: and relationship with others in order to firmly ascertain an overall picture of the patient's health. However: it is difficult to standardize the method of diagnosis: and the current situation is such that it is left up to each physician's skill. Psychiatrists are trained in these diagnostic procedures and may therefore establish a definitive diagnosis. Even so: it is a fact that there is a large variation in the speed of diagnosis depending on the physician. Therefore: a more standardized: objective test will be required to improve the diagnostic techniques for MDD.

Diagnostic criteria for MDD

Generally: psychiatrists diagnose MDD based on diagnostic criteria. The diagnostic criteria of MDD are characterized by reduced activity: depressed mood: and loss of satisfaction was lasting for at least 2 weeks (American Psychiatric Association 2000). MDD has been typically diagnosed using criteria designated by ICD-10 and DSM-IV-TR (American Psychiatric Association: 2000; World Health Organization: 2010). DSM-IV-TR requires the fulfillment of at least five out of the nine specific symptoms: and ICD-10 requires the fulfillment of four out of the 10 symptoms. (American Psychiatric Association: 2000; World Health Organization 2010) Nonetheless: in the actual clinical setting: the diagnosis of MDD is not easy owing to the diversity of clinical symptoms. Thus: psychiatric clinicians make full use of various types of information: such as medical history: clinical course: and epidemiological approaches: to determine the diagnosis. However: because the diagnostic criteria were previously
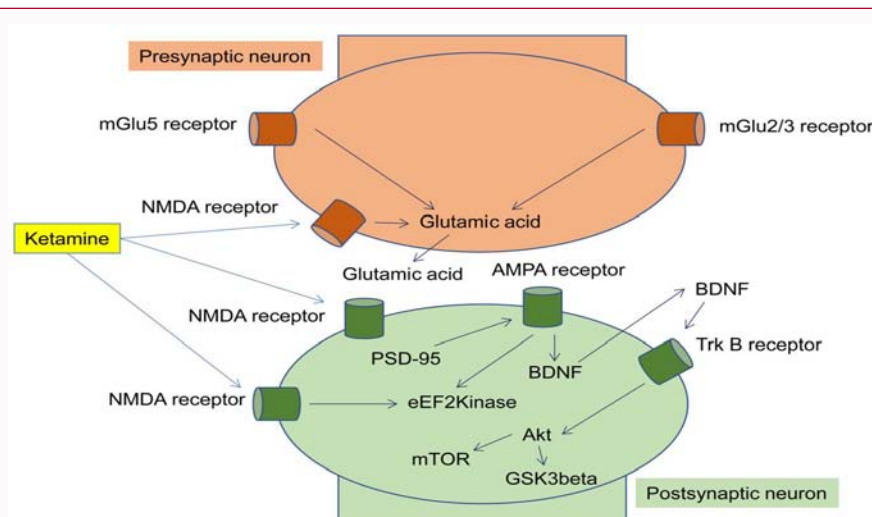
Figure 1: Ketamine binds to both open channel and allosteric parts. It is an N-Methyl-D-Aspartate (NMDA) receptor antagonist and selectively acts on the NMDA receptor in the postsynaptic film of the central nervous system and blocks excitatory neurotransmission.

concise: if the amount of information that could be obtained is limited: we base our findings on subjective psychological symptoms. For this reason: clinicians who are not experts in MDD may misdiagnose a patient who self-diagnosed him/herself as having MDD and may prescribe antidepressants to patients without MDD. This may lead to the primary disease becoming intractable. It is of course necessary to suspect MDD throughout the course of the disease; however: in the above case: it is desirable to first start treatment with non-drug therapy: such as medical psychotherapy and cognitive behavioral therapy. Currently: there are numerous studies that aim to diagnose MDD by measuring some biological markers through optical topography and blood collection.

DSM-IV-TR indicates five subtypes of MDD (melancholic depression: atypical depression: catatonic depression: postpartum depression: and seasonal affective disorder) (American Psychiatric Association 2000). Recently: there have been attempts to re-classify these subtypes to lead to better treatment; however: the studies did not reach a consensus [11,12].

Epigenetics of MDD

Multiple layers of epigenetic mechanisms are implicated in the fine-tuned regulation of gene expression. The most characterized epigenetic mechanisms involve chemical modifications of the DNA (e.g.: DNA methylation and hydroxy methylation) and of the histone proteins around which the DNA fiber is wrapped. This chromatin structuration regulates the accessibility of transcription factors and functionalizes the genome in a tissue and cell type specific manner. Dnmt1 and Dnmt3a are important DNA methyl transferases that are expressed in post mitotic neurons [13]. These are required for synaptic plasticity: learning: and memory through their overlapping roles in maintaining DNA methylation and modulating neuronal gene expression in adult CNS neurons [14]. Kleimann et al. [15] investigated the promoter methylation of the Brain-Derived Neurotrophic Factor (BDNF) using a sample after the ECT treatment of TRD and: as a result: patients with TRD remitting under ECT had significantly lower mean promoter methylation rates: particularly concerning the exon I promoter: compared with that of non-remitters [15]. Practically: although most tissues may be treated equally in GWAS: that is not the case in Epigenetic-Wide Association

Studies (EWAS); therefore: it is necessary to seriously consider which tissue to select. Furthermore: when an epigenetic change is used as a biomarker of a disease: it is necessary to detect the disease as accurately as possible in many patients: and thus: the biomarker must be able to accurately detect stable mutations. Although genetic mutations are not caused by illnesses: epigenetic changes are sensitive to the environment. Therefore: epigenetic changes may become predictors of a disease or markers to determine treatment effect rather than biomarkers of etiology. It is difficult to distinguish whether the changes in EWAS occurred before or after the onset of a disease. The existence of the modified nucleotides: 5-methyl Cytosine (5mC) and 5-hydroxy methyl Cytosine (5hmC) has long been known. Recently: the function of 5hmC has attracted attention owing to its localization: not in CpG islands but in a large region of a gene. DNA methylation (5mC) is involved in many cellular processes and emerges as an important epigenetic player in brain development and memory formation. The recent discovery that 5mC may be oxidized to 5hmC by Ten-Eleven-Translocation proteins provides novel insights into the dynamic character of 5mC in the brain [16]. 5hmC is involved in demethylation: and by regulating methylation: it may be a factor that changes gene expression.

miRNA markers for MDD

miRNAs are a new class of non-protein-coding small RNAs [17] that possibly act on mRNA to control the genes that produce protein. miRNAs that play a role in posttranscriptional regulation have been a focus in many studies in recent years: and their usefulness as biomarkers for diagnosing a disorder or for determining prognosis is anticipated. In the study that investigated the effect of treatment by ECT and Ketamine infusions for TRD and analyzed the expression of microRNA for each treatment of TRD (compared with controls): the baseline expression of the microRNA let-7b was lesser in patients with TRD than in controls. The baseline expression of let-7c was also lower in patients with TRD who received ECT [18]. In future studies: it is anticipated that the function of miRNAs will play a key role in the course of depression onset [19]. In a recent study: Fang et al. investigated miR-124 and miR-132: which are plasma neuro trophin-related miRNAs of the MDD patients. The plasma levels of BDNF and miR-124 increase with MDD and treatment by antidepressants. This study suggested the possibility that plasma MiR-132 is a status maker

Table 1a: Major Depressive Disorder (DSM-5; American Psychiatric association).

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
1, Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
2, Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3, Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4, Insomnia or hypersomnia nearly every day.
5, Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6, Fatigue or loss of energy nearly every day.
7, Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8, Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9, Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.

of depression [20]. Tavakolizadeh et al. [21] reported that exosomes: which function as biological nano carriers: become the biomarkers of depression [21]. mRNA and nucleic acid material including miRNA are contained in exosomes and are delivered to other cells (recipient cells). miRNA: a molecule transferred by exosomes: change the behavior of the recipient cells [22,23]. Alural et al. [24] thoroughly investigated a previous study reporting the association of miRNA in neuropsychiatric disorders and described it as a useful diagnostic aid as well as a useful factor for an index of the treatment response [24].

Genetic Biomarkers for TRD

Bio psychosocial models have been used routinely for research since the 1980s. Various molecular approaches have been used to identify genetic links: novel targets: and potential biomarkers for disease. At first: genetic studies for MDD were not conducted as actively as studies on psychological disorders that are more strongly genetically associated than depression: such as schizophrenia: bipolar disorder: and dementia. This may be because categorization becomes complex due to the difficulty in diagnosing MDD or that it is difficult to collect postmortem brain samples from patients with MDD. Although they are now distinguished in *Diagnostic and Statistical Manual of Mental Disorders*: Fifth Edition (*DSM*-5): previously: depression was often discussed in the same category as bipolar disorder and was considered simultaneously with genetic studies on bipolar disorder.

Although several candidate genes have been suggested as biomarkers of depression: there are still very few reports concerning this: but no notable results have been reported [25]. Some studies have included genetic relatives of patients with TRD. Catechol-O-methyl Transferase (COMT): BDNF: and Serotonin transporter (SLC6A4) have shown significant association with TRD. In addition: in a recent review using the PRISMA-P method: Menezes et al. [26] reported that BDNF could contribute to the improvement of differential diagnosis between BPD and MDD [26].

In one recent study: Milanesi [27] investigated the association of glutamine receptor-related genetic marker GRIK4 in patients with TRD under treatment with antidepressants. Researchers found that psychotic symptoms were associated with rs11218030

Table 1b: Major Depressive Disorder (DSM-5; American Psychiatric association). Coding and Recording Procedures

Severity / course specifier	Single episode	Recurrent episode*
Mild	296.21 (F32.0)	296.31 (F33.0)
Moderate	296.22 (F32.1)	296.32 (F33.1)
Severe	296.23 (F32.2)	296.33 (F33.2)
With psychotic features**	296.24 (F32.3)	296.34 (F32.3)
In partial remission	296.25 (F32.4)	296.35 (F33.41)
In full remission	296.26 (F32.5)	296.36 (F33.42)
Unspecified	296.20 (F32.9)	296.30 (F33.9)

*For an episode to be considered recurrent there must be an interval of at least 2 consecutive months between separate episodes in which criteria are not met for a major depressive episode. The definitions of Specifiers are found on the indicated pages.

**If psychotic features are present, code the "with psychotic features" specifier irrespective of episode severity.

In recording the name of a diagnosis, terms should be listed in the following order: major depressive disorder, single or recurrent episode, severity/psychotic/remission specifiers,

Followed by as many of the following specifiers without codes that apply to the current episode.

Specify: With anxious distress
       With mixed features
       With melancholic features
       With atypical features
       With mood-congruent psychotic features
       With mood-incongruent psychotic features
       With catatonia
       With peripartum onset
       With seasonal pattern (recurrent episode only)

and rs11218030 [27]. Kautzky et al. [28] investigated a sample of the Study of Resistant Depression (GSRD) and reported when the patients having the allelic combination of GG-GG-TT for rs6265: rs7430: and rs6313 of the BDNF: PPP3CC: and HTR2A genes showed a decrease of HAM-D [28]. However: two recently published studies: which boasted a large sample size: failed to identify genetic markers for TRD [29,30]. Consequently: these latest technologies have become more accessible: and Genome-Wide Association Studies (GWAS) began to dominate subsequent genetic studies. Therefore: association analysis of MDD and normal subjects became the standard. Moreover: associations with previously reported candidate

genes were subjected to re-examination. In three large-scale studies [STAR'D: Munich Antidepressant Response Signature: and The Genome Based Therapeutic Drugs for Depression study (GENDEP)] that investigated the association between response to treatment with antidepressant and genes using GWAS: statistical significance was shown only between the response to treatment with nortriptyline and the gene coding for uronyl 2-sulfotransferase. Moreover: this finding was reported by the GENDEP study but not confirmed by the other two [31]. Nonetheless: it has been recently suggested that polymorphisms in *catechol O-methyltransferase* and sodium-dependent dopamine transporter genes are correlated with MDD [32]. Furthermore: GWAS of chromosome 3(3p25-26) gene showed an association with serious recurrent depression [33].

Treatment of TRD

It may be difficult to diagnose TRD in patients who have been diagnosed with MDD but who do not achieve remission and who have prolonged disease that becomes intractable even after drug therapy has started. Therefore: objective diagnostic tools are urgently needed. Another issue is the difficulty in treating TRD. TRD symptoms are known to improve in approximately 15% of patients: even if they are treated with ≥ 2 antidepressants with different mechanisms of action [34]. In cases of depression that do become intractable with prolonged treatment: efforts must be made to correct relevant environmental factors. It has been reported that for the treatment of TRD: the addition of cognitive behavioral therapy to drug therapy with antidepressants is effective [35]. Clinicians anticipate the development of antidepressants that may be used safely with minimal side effects. Requirements for fewer doses will improve adherence to a medication regimen. Novel drugs should have a faster onset of action and address the symptoms of those with TRD. It has been indicated that 50% to 70% of patients with MDD do not respond to drug treatment [4].

Although Souery et al. [36] found that switching to a different class of antidepressant was not associated with improved response to treatment or rate of remission [36]: switching to a different drug class is usually advisable. If one drug is ineffective: other drugs with the same mechanism of action are likely to be ineffective [37]. When mono therapy with antidepressants fails: augmentation is performed. Augmentation is defined as the addition of a non-antidepressant to the current treatment. ECT: lithium augmentation: and thyroid augmentation has been recommended as treatment options. The first choice for augmentation is lithium. Other options include triiodothyronine: pindol: buspirone: and atypical antipsychotics [38]. The atypical antipsychotic aripiprazole has also been approved in Japan as an add-on treatment for adults who continue to experience MDD symptoms after at least 6 weeks of antidepressant therapy. Tri Cyclic Antidepressants (TCAs) and Mono Amine Oxidase Inhibitors (MAOIs) may also be considered after two or more failed attempts of pharmacologic therapy [39].

In patients with MDD: results indicating abnormalities in glutamic acid neurologic function have been reported. The increase in levels of glutamic acid in the blood of MDD patients treated with antidepressants was found: and an increase in glutamic acid levels in plasma reflects the severity of MDD. A placebo-controlled double-blind study that included 18 patients was designed to study the effects of ketamine in patients with TRD [40]. In addition: ketamine is effective in treating TRD that does not respond to ECT [3,41,42]. Single dose as well as consecutive doses of ketamine have been tested [43,44]. When researchers observed that the effects of treatment with ketamine persisted for hours after the initial administration: they postulated an effect of consecutive doses of ketamine [45-47]. Ketamine shows a persistent antidepressant effect with an immediate effect at a lower dose than that required for anesthesia [48-50]. Increasing numbers of studies have been designed to investigate the intranasal administration of s-ketamine: which is an enantiomer of ketamine [51]. S-ketamine has higher affinity to the glutamate NMDA receptor than R-ketamine: and esketamine has fewer side effects: such as elevated blood pressure: than IV infusion ketamine: and the effect of dose continuation of several weeks is expected by repeating nasal cavity administration.

A recent study by Collo et al. [52] reports that the anti parkinsoinian agents ropini role and pramipexole may assist in the treatment of TRD [52]. One study including patients with depression reported higher blood levels of inflammatory markers such as Tumor Necrosis Factor (TNF): soluble TNF Receptor 2 (sTNF-R2): and interleukin (IL) -6 in patients who exhibited a poor response to antidepressant treatment [53].

Our present focus is on antidepressants that modulate the glutamatergic system that have been recently discussed extensively as a class of drugs for treating TRD [54]. The antidepressant effects due to N-Methyl-D-Aspartate (NMDA) receptor blockade have attracted attention because an NMDA receptor blocker showed antidepressant effects in a forced swimming test by Trullas et al. [55,56]. Berman et al. [57] of Yale University first demonstrated the antidepressant effect of the NMDA receptor blocker ketamine in humans in 2000 [57-71] (Figure 1). In clinical trials conducted at NIMH: it was confirmed that ketamine shows rapid antidepressant effects that were maintained for a week [40].

The immediacy of the effect observed in patients with TRD is attributed to NMDA receptor blockade. However: its clinical use remains a challenge because NMDA receptor blockers have side effects: such as psychiatric symptoms: cognitive dysfunction: and movement disorders.

Non-pharmacological strategies that may be used alone or in conjunction with pharmacological therapy generally include psychotherapy: ECT: phototherapy: VNS (Vagus nerve stimulation): TMS (Transcranial Magnetic Stimulation) or rTMS (repetitive Transcranial Magnetic Stimulation): and deep brain stimulation.

Conclusion

In the present study: we reviewed the necessity of genetic diagnosis as an auxiliary diagnostic tool in the treatment of patients with TRD. In addition: we reviewed recent findings in particularly problematic cases that do not reach remission and become prolonged and intractable. We hope that this information adds to the store of knowledge about TRD: so as to ultimately improve the cure rate for this condition. We also reviewed important study findings related to the prevalence of TRD: common difficulties in treating this disorder: and NMDA receptor antagonists that are anticipated to be effective in treating TRD.

Environmental factors are considered to play a more important role than genetic factors in the etiology of TRD. Therefore: it is difficult to diagnose TRD using currently available genetic tests at the present time. The comorbidity of other psychological disorders and/or insufficient drug therapy may result in persistent symptoms.

Current research efforts should contribute to the development of antidepressants that treat TRD more effectively: with a faster onset of action. In this review: we have highlighted the potential of antidepressants that act through the glutamatergic system. Since ketamine was first reported to be effective in treating depression in 2000: there have been other reports of its efficacy in treating TRD.

Currently: research on the genetic basis for a diagnosis of depression is in progress. The sample sizes included in such studies continue to increase. Furthermore: advances in genetic technology should lead to the development of tests that may be performed more rapidly at lower cost: for ease of application in the clinical setting.

Because depression involves unique psychosocial problems specific to a given individual: there are substantial differences among individuals in the pattern of onset.

To improve the efficacy of personalized medicine: technological advancements related to diagnosis and treatment will be necessary.

Acknowledgment

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