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REVIEW

Investigational drugs for treating major depressive disorder

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ABSTRACT

Introduction: Treatment of patients suffering from major depression could be highly challenging for psychiatrists. Intractability as well as relapse is commonly seen among these patients, leading to functional impairment and poor quality of life. The present review discusses some of the novel investigational drugs that are under pre-clinical or clinical phases in the treatment of major depression.

Areas covered: Molecules belonging to different classes such as triple reuptake inhibitors, opioid receptors, ionotropic and metabotropic glutamate receptors, and neurotrophin in the treatment of major depression are covered in this article.

Expert opinion: Although the historical discovery of earlier antidepressant molecules (iproniazid and imipramine) is through serendipitous discovery, the present research focuses on discovering novel molecules based on our current pathophysiological knowledge of the disease condition. The fast-acting antidepressant property of N-methyl-D-aspartate (NMDA) receptor molecules, including ketamine is an exciting area of research. Other drug molecules such as amitriptyline (triple reuptake inhibitor), ALKS-5461 (kappa receptor antagonist and mu opioidergic receptor agonist), rapastinel (NMDA glutamatergic receptor modulator) are under Phase-III clinical trials and could be approved in the near future for the treatment of major depression.

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Major depression; preclinical and clinical studies; opioid receptors; glutamatergic receptors; neurotrophins; triple reuptake inhibitors

1. Introduction

Major depression is a common psychiatric disorder that is associated with high rates of mortality and morbidity [1,2]. A genetic make-up plays an important role in its pathophysiology, the difference in maturational white matter microstructures in mood regulatory pathways has been noticed in children who are predisposed to its outcome due to their parental history [3]. Major depression is generally comorbid with other disorders of the body, including anxiety [4], schizophrenia [5], diabetes [6], obesity [7], cancer [8], chronic obstructive pulmonary diseases [9], cardiovascular abnormalities [10], stroke [11], and many more. As per the findings from Singapore Mental Health Study, major depression is more prevalent in Indian men living in Singapore compared to other ethnicities such as China [12]. Further, women (7.2%) are more prone to depression disorder compared to men (4.3%), as per the report of Singapore Mental Health Study [12].

Stress is an important pathophysiological factor responsible for major depression. Continuous stress could lead to degenerative changes in different regions of the brain, including hippocampus and amygdala, and thus affect synaptic plasticity and cognitive decline [13]. Besides its effect on the cognitive abilities of the patient, depressed patients could have increased suicidal tendencies [14]. The symptoms of depression could be commonly seen in patients addicted to various psychotropic and the substance of abuse molecules, including

marijuana [15]. There is no clear-cut biomarker for major depression so that early intervention could be initiated [16].

Selective serotonin reuptake inhibitors (SSRIs) are the first choice of drugs for the treatment of major depression; however, around half of the depressed patients do not respond to the monotherapy and often requires a second line of treatment in order to achieve full remission [17]. Moreover, conventional antidepressants, including SSRIs takes 3–4 weeks in order to show their effectiveness [18]. Antidepressants that could enhance the neuroplasticity and neurogenesis mechanisms, for example agomelatine and novel molecules listed in this article, are of particular interest [19]. In present scenarios, researchers have been focusing on some rapidly acting antidepressants such as N-methyl-D-aspartate (NMDA) receptor blockers, including ketamine [18]. This article will discuss some of the important investigational drugs that are in pre-clinical or clinical stages of drug development. A particular emphasis has been given toward opioidergic receptor modulators, glutamatergic, triple reuptake inhibitors as well as neurotrophin class of molecules (Figure 1). The details of these molecules were searched on electronic database (Pubmed, Medline, clinicaltrial.gov, molecule originator's company sites, abstracts in various conferences) from the year of their inception until November, 2016. The combination of following text-words were used: major depression, novel molecules, clinical trials, neurotrophic factors, opioidergic receptors, triple reuptake inhibitors, glutamatergic receptor modulators, preclinical findings.

Article highlights

- Major depression is a severe mood disorder that requires immediate clinical investigation.
- Various conventional antidepressant molecules are available for the management of major depression; however, 30–40% of these patients do not respond to the monotherapy and therefore requires the addition of 2nd drug in their dosing regimen.
- There is a continuous effort from researchers exploring the novel drug targets as well as drugs for patients who do not respond to drug therapy
- Some of these investigational targets include, opioidergic system, ionotropic and metabotropic glutamatergic receptors, neurotrophins, triple reuptake inhibitors and many more.
- The investigational molecules discussed in this article include, ALKS 5461, CERC-501, rapastinel, dueteriated dextromethorphan, CERC-301, basimglurant, amitifadine, tedatioxetine and ansofaxine.
- Amitifadine, ALKS-5461 and rapastinel are in late clinical trials. These drugs may soon show up in the clinics for the treatment of major depression.

This box summarizes key points contained in the article.

2. Opioid receptor modulators

Opioid receptors, well known linked to the pathophysiological basis of pain, stress, and drug addiction plays an important role in mood disorders [20]. The opioidergic and/or NMDA receptor system is partly involved in the antidepressant-like effect of fluoxetine in animal model of physical stress [21]. Huang and colleagues have shown that the combination of LY2444296 (a κ -opioidergic receptor antagonist) and ADL5859 (a δ -opioidergic receptor agonist) produces synergistic antidepressant-like effect when tested in the mouse forced swim test [22].

The κ -opioidergic receptors (a subtype of opioid receptors) and its natural ligand dynorphin have a direct role in the reward and stress phenomenon and are upregulated during stress and chronic administration of drugs of abuse. Activation of κ -opioidergic receptors has been linked to the increase in dynorphin levels, which in turn blocks the release of glutamate. Glutamate is an important neurotransmitter that is involved in neuronal plasticity and, therefore, glutamate levels may result in impaired learning abilities resulting in learned helplessness. Activation of these receptors could also lead to a reduction in the levels of dopamine in different neurocircuitry pathways of the brain, and thus produce anhedonia, depression, and anxiety-like state. It is well known that the κ -opioidergic receptor antagonists have antidepressant-like effect in preclinical animal models. The action may be through modulating dopaminergic, serotonergic as well as an enhancing mRNA expression of brain-derived neurotrophic factor (BDNF) [23–26].

Buprenorphine is a partial agonist of μ receptors and opioid receptor-like (ORL-1) with κ -opioidergic receptor antagonistic properties. As an anti-nociceptive agent, it displays a bell-shape curve. At low doses, it acts on μ receptors, which is solely responsible for its anti-nociceptive activity. However, at higher concentrations, buprenorphine acts on ORL-1 receptors, resulting in counteracting its anti-nociceptive effect [27]. In contrast, the antidepressant effect of buprenorphine is

correlated to its antagonistic activity at κ -opioidergic receptors [28]. The κ -opioidergic receptor antagonists such as buprenorphine by blocking the release of dynorphin could increase glutamate to its physiological levels in the hippocampus area of the brain, thus resulting in the antidepressant effect. The κ -opioidergic knock-out mouse do not respond to the antidepressant effect of buprenorphine [28].

Buprenorphine, a κ -receptor antagonist, has been found to be effective as a rapid antidepressant agent in treatment-resistant depression when administered as an average dose of 0.4 mg/day among patients of 15–50 years of age [29]. Buprenorphine has shown antidepressant-like effect in certain, but not all strains of rats, when tested in the forced swim test [30]. The molecule did not show an antidepressant-like effect in Wistar or Sprague–Dawley strains of rats [30]. Some of the other κ -opioidergic receptor antagonists, such as JDTic and PF-4455242, although active in preclinical animal models of depression, have been declined for further clinical development due to their propensity to induce toxic side effects, for example, tachycardia associated with JDTic. In a very recent study, buprenorphine in ultra-low dose (0.1 mg once or twice daily) have been found to prevent suicidal tendencies in patients without substance abuse [31].

Almatroudi and colleagues have discussed the beneficial effect of combining buprenorphine (a partial μ -receptor agonist with κ -receptor antagonistic properties) and naltrexone (a μ -receptor antagonist) in the forced swim test and novelty induced hypophagia tasks [32]. By combining these two molecules, one can achieve the antidepressant property resulting from the blockage of κ -opioidergic receptors without activating μ receptors. In this manner, the addiction potential that is associated with the activation of μ receptors could be easily prevented. The combination was found to be neither rewarding nor aversive in the conditioned place preference paradigm [32].

ATPM-ET, (–)-3-*N*-ethylaminothiazolo [5,4-*b*]-*N*-cyclopropylmethylmorphinan hydrochloride, is a novel κ -agonist and μ -opioid receptor partial agonist that has shown both anxiolytic as well as an antidepressant activity when tested in the forced swim, tail suspension, open field as well as elevated plus-maze tests [33]. This is in contradiction to the common hypothesis that κ -receptor antagonists have antidepressant effect, given the fact that ATPM-ET is a κ -receptor agonist and still shows antidepressant activity. The authors have discussed that the agonists of κ receptors may produce both depressant as well as antidepressant activity, depending on the animal behavioral model studied, while κ -receptor antagonists demonstrates the consistent antidepressant effect in all the animal models of depression [33]. Some of the important investigational molecules that are in clinical trials and belong to this class are discussed in the following.

2.1. ALKS 5461

It is a combination of buprenorphine (a κ -opioid receptor antagonist with partial μ -receptor agonist property) and samidorphan (a μ -opioid receptor antagonist). ALKS 5461 is being developed as sublingual tablets by Alkermes plc for the treatment-resistant depression [34]. Buprenorphine was launched

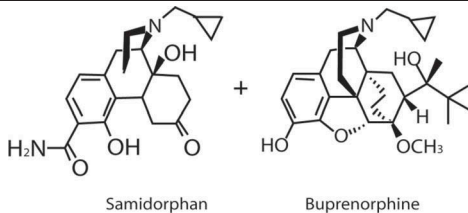
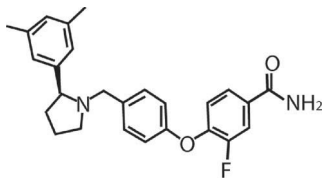
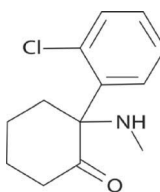
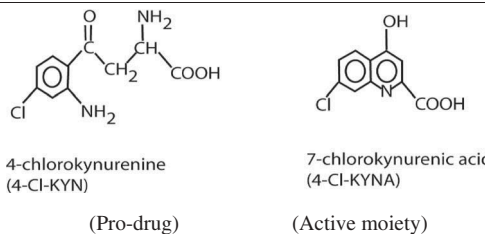
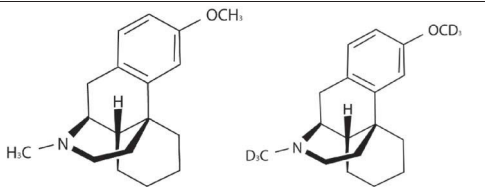
Name of the Investigational Molecule	Molecular mechanism and clinical phase	Structure
ALKS 5461 (combination of samidorphan and buprenorphine)	κ -opioid receptor antagonist	 Samidorphan Buprenorphine
CERC-501	selective κ opioid receptor antagonist	
Ketamine	NMDA receptor antagonist	
AV-101 (4-Cl-KYN)	NMDA receptor glycine-binding site antagonist	 4-chlorokynurenine (4-Cl-KYN) 7-chlorokynurenine acid (4-Cl-KYNA) (Pro-drug) (Active moiety)
Dextromethorphan and deuterated dextromethorphan (AVP-786)	NMDA receptor antagonist; Sigma-1 receptor agonist	 Dextromethorphan (present in Nudexta®) Deuterated Dextromethorphan (present in AVP786)

Figure 1. Structures of some investigational antidepressant molecules discussed in this article.

in the United Kingdom in year 1978 for the treatment of pain; however, samidorphan has been discovered recently in the laboratory of Mark Wentland at Rensselaer Polytechnic Institute (RPI) New York, USA. In order to achieve the antidepressant effect without any addiction potential, ALKS 5461 has been designed to combine the properties of opioid receptor agonist as well as antagonist effect.

In a multicenter, randomized, double-blind, placebo-controlled phase-II clinical trial, the 2/2 mg doses of samidorphan and buprenorphine provided a significant improvement in three of the depressions measuring outcome scales,

Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impressions severity scale (CGI-S). The authors also find improvement in 8/8 mg doses, but it did not achieve statistically significant results compared to the placebo treatment [34]. The study enrolled those patients who were non-responsive with the use of standard antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) or dual reuptake inhibitors of serotonin and norepinephrine (SNRIs). Although the combination is safe to be administered, however, the incidence of treatment emergent

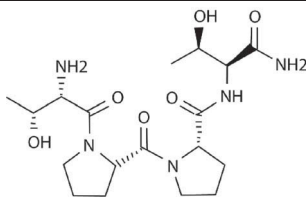
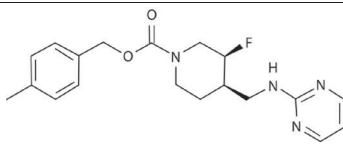
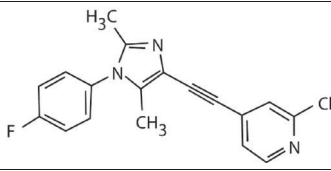
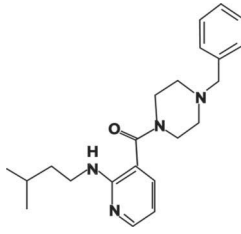
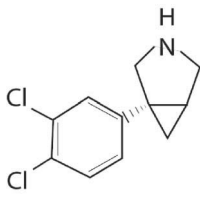
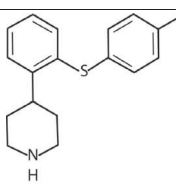
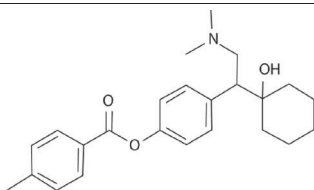
Rapastinel (GLYX-13)	Selective, weak partial agonist (mixed antagonist/agonist) of an allosteric site of the glycine site of the NMDA receptor	
CERC-301	NR2B-specific NMDA antagonist	
Basimglurant	Negative allosteric modulator of the mGlu5 receptor	
NS-189	Neurotrophin; enhance the expression of brain-derived neurotrophic factor (BDNF)	
Amitifadine	Triple reuptake inhibitor	
Tedatioxetine	Multimodal antidepressant	
Ansofaxine	Triple reuptake inhibitor	

Figure 1. (continued)

adverse effects was 85.8%, the most common being gastrointestinal (52.5%) and neurological (46.8%). These adverse effects included, nausea, vomiting, dizziness, and headache [34]. Some of the rare adverse effects reported were acute opioid withdrawal, intraocular melanoma and attempt to suicide [34].

In two phase III studies (also known as Forward-3 and Forward-4), ALKS-5461 or placebo was administered to patients as an adjunctive therapy to SSRIs or SNRIs. Forward-3

was designed as a double blind placebo lead and followed a 6-week treatment period (2/2 mg of buprenorphine/samidorphan) while Forward-4 was a parallel design study where the effect of ALKS 5461 (2/2 or 0.5/0.5 mg) was studied against the placebo-control group [35]. In a Forward-4 study, which comprises of 385 subjects, the 2/2 mg group resulted in improvement in the MADRS scale, but the results could not reach statistically significant. However, the authors mentioned that upon additional analysis at different time points of ALKS 5461

administration, they found a clinically meaningful result. The authors did not find any beneficial effect of ALKS-5461 over placebo in the Forward-3 study. The results may probably due to higher significant positive response that was observed in the placebo-control group. It has been debated that the clinical trials with antidepressant molecules is a challenging one. The negative outcome may possible due to higher positive response in the placebo-control group [36]. Khan and Schwartz have suggested to test antidepressant molecules in either (i) severely depressed patients or (ii) with flexible dosing regimen [36], so that the large effect of placebo treatment should be avoided. Alkeremes is awaiting result of its Forward-5 clinical trial. ALKS-5461 was given a fast-track status by the US Food and Drug Association (FDA) for treatment-resistant depression [37]. The molecules should demonstrate effectiveness in patients who are not well controlled with the use of the standard line of treatment such as SSRIs or SNRIs [37].

2.2. CERC-501 (LY-2456302)

CERC-501 is another potent and selective κ -opioidergic receptor antagonist that is being explored for the substance-use disorder and as an adjunct treatment of major depression [38]. The molecule is discovered by Eli Lilly & Co. and being developed for its clinical use by Cerecor, USA. In a preclinical study, the molecule showed rapid absorption profile ($T_{\max} = 1\text{--}2\text{ h}$) with good oral bioavailability (around 25%). CERC-501 at an ED₅₀ (effective dose in producing response in 50% of subjects) value of 0.33 mg/kg selectively occupies central κ -receptors without affecting other opioidergic receptors [39]. It has a 30-fold selectivity toward κ compared to μ - and δ -opioidergic receptors. When tested in the mouse model of behavioral despair, CERC-501 demonstrated its effectiveness in the forced swim test (FST) and also enhanced the antidepressant-like effect of both imipramine (a tricyclic antidepressant) as well as citalopram (an SSRI). It is also effective in alleviating nicotine withdrawal-induced behavioral symptoms [40]. In a clinical study, a single oral dose of 2–60 mg and multiple doses of 2, 10, and 35 mg were well tolerated by human subjects and displays a rapid oral absorption profile with a longer half-life of 30–40 h [41]. CERC-501 could reach its steady state after 6–8 days of once-daily dosing [41]. In this clinical study, the authors concluded that the molecule is well tolerated with no clinically significant adverse effects. In a clinical study involving 13 healthy volunteers, CERC-501 was found to have good blood–brain barrier (BBB) penetrability and the maximum saturation occurred after 2.5 h of a 10 mg dose [42]. The authors concluded that a 10 mg dose is sufficient for further clinical investigation of this molecule [42]. The phase II clinical trials are undergoing in evaluating its use for the treatment of depression and drug addiction.

3. Glutamate receptor modulators

Glutamate is an excitatory neurotransmitter that acts on both ionotropic (NMDA, AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor), and kainate) as well as metabotropic glutamatergic receptors (mGLUR1-8 divided into

three groups, group I–III). The following topics individually discuss the role of both ionotropic as well as metabotropic glutamatergic receptor modulators in major depression. The NMDA receptor blockers, such as ketamine in this category are known to produce a rapid antidepressant effect, but associated with its own problematic side effects. Therefore, molecules that possess similar efficacy compared to ketamine but with lesser toxic side effects are being explored in this category. Some of the molecules that are under clinical trials in this category include the following.

3.1. NMDA receptor modulators

In depression, the alteration in both GABAergic (γ -amino-butyric acid) and glutamatergic networks have been known [43]. An important role of the glutamatergic system in major depression is evidenced by the fact that ketamine, an NMDA receptor blocker, has shown to produce an antidepressant response in both animals as well as human studies [44]. One of the problems that is encountered with the use of conventional antidepressant agents is their lag period. These conventional antidepressant agents require at least 2–4 weeks of drug administration before they start showing their antidepressant effect. In contrast, ketamine and other newer NMDA receptor blockers have shown to produce a rapid antidepressant effect that could be seen even after a few hours of their administration. Ketamine has been found to be more useful in patients who have suicidal tendencies associated with depression [45]. The use of ketamine as an antidepressant in clinics is restricted due to its toxicity and abuse potential and therefore it is only reserved for the emergency cases where a quick antidepressant response is required [46]. There is an abuse incidence that has been listed in the literature with the prescription of ketamine in patients suffering from refractory major depression; the molecule could lead to loss of employment or an accidental death [47]. Due to its rapid and effective antidepressant potential, this drug class requires extensive exploration and the safer NMDA receptor blockers with antidepressant potential but lesser side effects should be identified [44,48]. In the following sections, we have discussed different NMDA glutamate receptor blockers that are under preclinical or clinical investigations in the treatment of major depression. We will first discuss the pharmacology of ketamine in this section before we elaborate other NMDA receptor blockers as antidepressant agents.

3.1.1. Ketamine (racemate or RS (\pm)-ketamine) or esketamine [(S+)-ketamine]

As discussed above, ketamine has shown to provide a rapid onset antidepressant effect in clinical settings. Ketamine is a non-competitive NMDA receptor antagonist that exists in two isoforms, S(+) and R(−) isoform [44]. There are different hypothesis that have been put forward describing the rapid antidepressant effect that is observed clinically with the use of ketamine. The NMDA receptors present at the inhibitory interneurons (GABAergic) push inhibition to the excitatory networks. One of the hypothesis regarding the mechanism of ketamine's antidepressant effect is through blocking the NMDA receptors at the inhibitory interneurons which in turn

disinhibits the excitatory networks. Second, blockage of NMDA receptors at rest by ketamine affects the downstream intracellular signaling processes. This inhibits different transcription factors, including elongation factor, which in turn lead to upregulation of BDNF, thus triggering synaptic plasticity [49]. Some patients that are non-respondent to the antidepressant effect of ketamine may be the carriers of a Val66Met (rs6265) single-nucleotide polymorphism, which is associated with the dysfunctioning of BDNF [50]. Besides its NMDA receptor blocking property, ketamine is an agonist at sigma-1 receptors [51] and also inhibits norepinephrine and serotonin transporters, thus increasing their synaptic concentrations [52]. These properties may also play an important role in the antidepressant effect of ketamine. Memantine, another NMDA receptor blocker, however, do not display rapid antidepressant effect because it does not have any action on NMDA receptors at rest and therefore devoid of any effect on the downstream signaling process (elongation factor) and upregulation of BDNF [49]. Rogoz and colleagues have demonstrated that the memantine, when combined with traditional antidepressant agents, fluoxetine, imipramine and venlafaxine, showed synergistic antidepressant-like effect in the forced swim test [53]. Although memantine has displayed antidepressant-like effect in animal models [54,55], however, it failed to demonstrate the same in a double-blind placebo-controlled study [56]. In contrary, in an open-labeled flexible dose study consisting of eight severely depressed patients (MADRS score = 31.9), there was a reduction in the MADRS score with memantine (20–40 mg/day) and the peak effect could be seen at 8 weeks and continued until 12 weeks [57]. The study was initiated with a 20 mg/day dosing profile and some patients were titrated to 30 or 40 mg/day dose of memantine. The treatment was well tolerated by patients. Kollmar and colleagues have reported a case study in which severely depressed patient with suicidal tendencies were admitted to the hospital and administered with intravenous ketamine twice in 2 weeks and then successfully maintained with memantine for treatment-resistant depression [58]. Memantine also possess mood stabilizing effect in patients suffering from bipolar disorder [59]. The antidepressant effect of memantine requires more careful investigation.

In a rat model of learned helplessness, a single infusion of R-ketamine into the infralimbic (IL) portion of medial prefrontal cortex (mPFC), CA3 and dentate gyrus (DG) region of the hippocampus have shown to produce antidepressant-like effect [60]. A single dose (15 mg/kg) of ketamine has shown to enhance the non-perforated synapse, number of neurons in a dentate gyrus region, and the total length of microvessels in the hippocampus region, when tested on Flinders Sensitive Line (FSL) of rats. The effect of ketamine starts around 100–110 min after its administration at a dose of 0.5 mg/kg when administered as a continuous infusion. Moreover, its antidepressant effect lasts until 7 days. The alpha phase half-life of ketamine is approximate 10–15 min, followed by a beta phase of 2.5 h, suggesting that it initiates a series of biochemical reactions in the body that could lead to such a sustained antidepressant effect.

A study carried out by Yang and colleagues compared the antidepressant effect of these two ketamine stereoisomers

and their ability to modulate BDNF expression and synapticity in the prefrontal cortex (PFC), CA3 and dentate gyrus regions of the hippocampus [61]. Yang and colleagues concluded that the R-ketamine is more potent and safer as compared to S-ketamine (Esketamine) in displaying antidepressant effect [61]. Zhang and colleagues have also shown that the antidepressant effect of R-ketamine is long-lasting compared to esketamine, when tested in dexamethasone treated juvenile mice [62]. Moreover, the use of esketamine (S-ketamine) is associated with behavioral problems, including hyperlocomotion, prepulse inhibition deficits as well as rewarding effect, suggesting its psychotomimetic activity [61]. The psychotomimetic activity of esketamine is further confirmed by Yang and colleagues in a study where they observed a loss of parvalbumin (PV)-immunoreactivity in the medial prefrontal cortex and hippocampus regions in mice administered with esketamine at a dose of 10 mg/kg once a week for a total of 8 weeks [63]. The psychotomimetic effect of esketamine was confirmed in monkeys where it causes the release of dopamine in the striatum region of the brain [64].

In a multicenter, double-blind, double-randomized, placebo-controlled study carried out in 30 patients suffering from major depressive disorder, doses of either 0.20 or 0.40 mg/kg of ketamine were administered over a 40 min duration and showed antidepressant effect within 2 h of its administration [65]. On day 2, an antidepressant effect was still observed in ketamine-treated patients compared to the placebo-control group. In this study, the MADRS was used as an assessment tool. It was found that the least squares mean changes were –16.8 (3.00) and –16.9 (2.91) 0.20 or 0.40 mg/kg doses, respectively. Patients administered with ketamine showed dissociation and other side effects dose-dependently [65]. Ketamine has also shown to effectively reduce the suicidal ideation that is associated with major depression [66–68]. Caddy and colleagues extensively studied different double blinded clinical trials and found that ketamine is the only NMDA receptor antagonist that has shown superior antidepressant effect compared to placebo-controlled group; although the authors also emphasized that the quality of these evidences was limited by risk of bias and small sample size [69]. There are more than 20 clinical trials that are undergoing gathering more evidences regarding the antidepressant effect of ketamine and other glutamatergic antidepressants.

3.1.2. AV-101 (4-CL-KYN)

AV-101 (L-4-chlorokynurenine or 4-Cl-KYN) is an orally active investigational antidepressant molecule that is being developed for the treatment-resistant depression. The molecule is a pro-drug that requires conversion into the active moiety. 4-Cl-KYN is transported similar to L-kynurenine (a key intermediate product resulting from the breakdown of tryptophan) in the brain leading to the release of the active moiety, 7-chlorokynurenine acid with the help of astrocytes (Figure 2). The molecule works by blocking the glycine B co-agonistic site of the NMDA receptor as shown in the (Figure 2). AV-101 is one of the most potent, specific glycine B blocker known to the mankind. It is known to produce the rapid and persistent antidepressant effect just like ketamine in animal models of

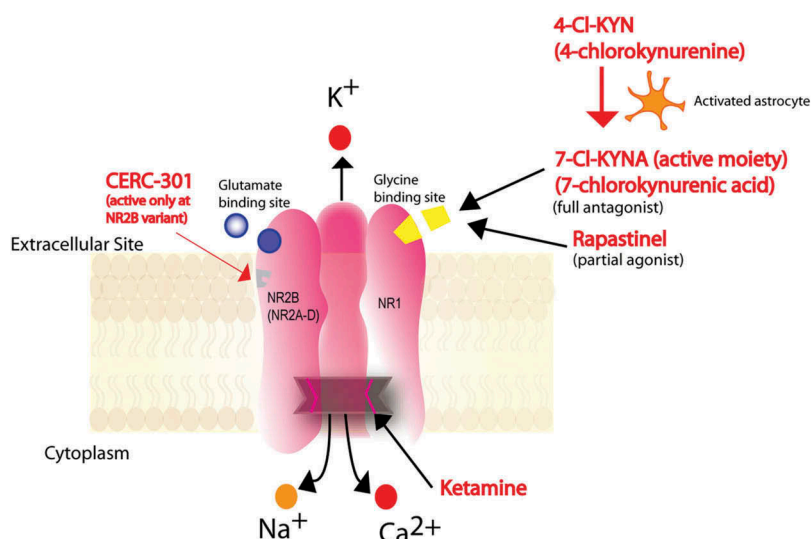


Figure 2. Site of action of rapastinel, CERC-301, ketamine and 7-Cl-KYNA on the NMDA receptors. Although ketamine has shown to block the NMDA receptors at rest, rapastinel as well as 7-Cl-KYNA acts on the glycine binding site on the NMDA receptors in different fashion, as discussed above.

behavioral despair [70]. However, unlike ketamine, the molecule does not have any psychotomimetic side effects [70] that makes it a distinguished molecule to test further in clinical trials. Furthermore, it has been shown in preclinical studies that the antidepressant-like effect of this molecule can be inhibited by glycine or NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide; an AMPA receptor antagonist) [70]. Besides its potent antidepressant effect, AV-101 is also being studied for the treatment of pain. It is safe and well-tolerated in two phase I clinical trials and devoid of any ketamine-related side effects. It is currently under phase II clinical trial for the treatment of major depressive disorder.

3.1.3. AVP-786

AVP-786 is being developed by Avanir Pharmaceuticals Inc. for the treatment of major depression and other central nervous system disorders, including schizophrenia and agitation associated with dementia in Alzheimer's disease [71]. It is a combination of deuterium modified dextromethorphan, and ultra-low dose quinidine. AVP-786 is an extension of Avanir's recently launched product, Nuedexta® (Avanir Pharmaceuticals; year of launch: 2011) which contains dextromethorphan and quinidine. Dextromethorphan is easily degraded in the liver with the help of CYP2D6 and therefore possess low bioavailability. It is combined with quinidine, a potent CYP2D6 inhibitor that enhances the bioavailability of dextromethorphan by preventing its degradation. The difference between AVP-786 and Nuedexta is that there is a deuteration of methyl groups in dextromethorphan part of AVP-786, so that it can escape the first pass metabolism and degradation by liver cytochrome enzymes. Due to the deuteration of the methyl group, AVP786 contains an ultra-low dose of quinidine (less than 5 mg) compared to that present in Nuedexta (10 mg).

Dextromethorphan is an NMDA receptor antagonist with sigma-1 receptor agonist properties and thus shows potent anti-depressant activity. As compared to ketamine, dextromethorphan is a weak NMDA receptor blocker [72]. The

antidepressant activity of dextromethorphan has been mainly linked with its sigma-1 receptor agonist activity or serotonin transporter inhibitor activity. Sigma-1 receptors have been the target in major depression. These receptors are non-opioid and non-phencyclidine types that exist in two isoforms, sigma-1 and sigma-2. Sigma-1 receptor modulators have shown antidepressant-like activity in preclinical animal models, while its antagonists prevented the effect of many conventional antidepressants [73]. Sigma-1 receptors modulate glutamatergic NMDA receptor function and the release of dopamine neurotransmitter [74]. In contrast to ketamine, dextromethorphan has strong potential to inhibit serotonin transporters that may also contribute largely to its antidepressant effect [72].

Nguyen and colleagues have published the antidepressant-like effect of dextromethorphan in the mouse forced swim test and confirmed its mechanism via sigma-1 receptor signaling pathway [75]. BD1063, a selective sigma-1 receptor antagonist prevented the anti-immobility activity of this molecule [75]. At 30 mg/kg intraperitoneal dose, dextromethorphan reduced the immobility period in the mouse forced swim test; however, it also resulted in an increase in the locomotor activity. In contrast, imipramine at a lower dose of 20 mg/kg reduced the immobility period and the effect was independent of alteration in the locomotor activity in these mice [75]. Quinidine at 30 mg/kg dose potentiated the antidepressant-like effect of dextromethorphan (10 and 30 mg/kg) in the forced swim test [75].

The product is currently in phase II clinical trial for the treatment of major depressive disorder and no results have yet been posted by the originator.

3.1.4. Rapastinel (GLYX-13)

Rapastinel, an Allergan molecule also known as GLYX-13, is a novel investigational molecule derived from the structural modification of B6B21, a monoclonal antibody, which possesses NMDA-glycine site functional partial agonistic properties [76]. Its site of action is indicated in the (Figure 2).

Rapastinel activates NMDA receptors at low levels of NMDA receptor activity while it is an antagonist at the higher NMDA receptor activity [77]. Rapastinel penetrates the BBB very efficiently after an intravenous administration [78]. It has been given a fast track designation by the FDA in 2014. Unlike ketamine, which produced cognitive impairment, rapastinel has an excellent cognitive enhancing property, which makes it a unique compound compared to other antidepressant agents [79]. Through activation of NMDA receptors, it enhances the synaptic plasticity and thus improves the cognition process [76]. This phenomenon could be seen as an increase in the mature dendritic spines in the rat dentate gyrus as well as layer 5 of the prefrontal cortex regions, 24 h after its treatment [76]. Rapastinel could prevent ketamine-induced persistent deficit in novel object recognition task in mice [80]. The molecule like ketamine showed rapid and long-lasting antidepressant properties [76]. However, the antidepressant-like effect of R-ketamine is much longer than rapastinel [63]. It may be possible due to the inability of rapastinel to increase the BDNF-TrkB signaling process in the prefrontal cortex, dentate gyrus as well as the CA3 region of the hippocampus [63]. However, unlike ketamine, this molecule is devoid of any psychotomimetic actions. Rapastinel has shown to affect phosphatidylinositol 3-kinase/AKT/mTOR signaling pathway that may be partly responsible for its antidepressant effect [80]. The molecule is also being studied for the post-traumatic stress disorder where it is beneficial in enhancing synaptic plasticity and metaplasticity and thus improving cognition [81].

In a randomized proof of concept study, rapastinel or GLYX-13 was found to reduce the Hamilton Depression Rating Scale-17 (Ham-D17) scoring after its single intravenous administration at doses of 1, 5, 10, or 30 mg/kg, and the results were superior to the placebo-control group at days 1–7 [82]. The use of this molecule was devoid of any psychotomimetic side effects [82]. The molecule is currently in its phase III clinical trial for the treatment of major depression.

3.1.5. CERC-301 (or MK-0657)

CERC-301 (4-methylbenzyl (3S, 4R)-3-fluoro-4-[(pyrimidin-2-ylamino) methyl] piperidine-1-carboxylate) is an NMDA receptor subunit 2B (GluN2B) antagonist that is active in animal models of behavioral despair [83]. The molecule is being developed by Cerecor for the adjunctive treatment of patients with severe depression. It has demonstrated a high affinity for GluN2B receptors with an IC₅₀ (half-maximum inhibitory concentration) value of 3.6 nmol/L [83]. In preclinical studies, it has shown an extreme potency in displaying antidepressant-like effect in the forced swim test (ED₅₀ value of 0.3–0.7 mg/kg) [83]. In a phase I study, CERC-301 was well tolerable with rapid absorption (T_{\max} ~1 h) and a longer half-life (12–17 h) [83]. In a randomized double blind study in patients with severe depression and suicidal ideation, CERC-301 at 8 mg was not found to be effective in preventing the suicidal ideation [84,85]. This may be due to the low dose of CERC-301 administered to the patients. However, a dose of 8 mg was found to be safe and well tolerated by depressed patients. Cerecor is revising their phase II study with higher doses (12 or 20 mg) of CERC-301 in order to test its effect for the adjunctive treatment of major

depressive disorder [86]. A dose up to 20 mg did not produce any serious side effects and therefore could be safely administered in humans [87]. The molecule has gained fast track designation by the FDA.

3.2. Metabotropic glutamate receptor modulators

Metabotropic glutamate receptor modulators groups (group I, II, and III) have been listed to play an important role in the pathophysiology of major depression and anxiety disorders [88]. We have discussed the antidepressant effect of basimglurant in this article, as it is the most extensively studied antidepressants belonging to this category.

3.2.1. Basimglurant (RO4917523, RG7090)

Basimglurant (chloro-4-[1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]pyridine) is currently in a phase II clinical trials for the treatment of anxiety and major depression disorders. The molecule, being developed by Roche, has 10–100 times more potency compared to diazepam (a standard anti-anxiety drug) in animal models of anxiety disorders [89]. The molecule is also under clinical investigation for the treatment of Fragile X syndrome [89]. Basimglurant is a negative allosteric modulator of mGluR5 subtypes of receptors [90]. The mGluR5 receptors belong to the class C of the G-protein coupled receptors (GPCR) and present both in synaptic, extra-synaptic as well as peri-extrasynaptic locations and increase the activity of NMDA glutamatergic currents. Activation of this subtype of metabotropic glutamatergic receptors (mGluR5) could lead to a subsequent increase in the levels of calcium ions favoring the binding of calmodulin to mGluR5 and further displacement of CaMKII- α which then binds to the Glun2B subunit of NMDA receptors and activating it. It has been proposed that excess of glutamatergic receptors is detrimental to major depression and involved in its pathophysiological mechanisms. Therefore, blocking of mGluR5 receptors via using its negative allosteric modulator molecule, basimglurant, which could indirectly reduce the activation of NMDA receptors, and thus producing the antidepressant effect [91]. In this manner, one can reduce the side effects that are associated with the use of potent NMDA receptor blocker molecules such as ketamine, keeping similar or modest efficacy. Basimglurant may also favor targeting mGluR5 receptors on the GABAergic neurons, for example inhibitory CA1 interneurons present in the hippocampus area synapse with the glutamatergic synapse in the same region, which projects to nucleus accumbens and prefrontal cortex. Basimglurant by reducing the GABAergic inhibition in the CA1 pyramidal cells could result in enhancing glutamatergic synaptic signaling in the hippocampus area of the brain. Basimglurant may promote AMPA receptor-induced increase in BDNF release and activation of TrkB receptors [91].

In preclinical studies, basimglurant has been found to be orally active with longer half-life so that once daily dosing should be enough for the treatment of major depression [90]. The brain/plasma ratio was found to be in the range of 2–3, indicating that it has good BBB permeability [90]. In the rat-forced swim test, basimglurant was found to be effective at doses of 10 and 30 mg/kg, when administered orally.

Desipramine, a standard comparator molecule, reduced the immobility period at a dose of 100 mg/kg p.o. Further, basimglurant showed anxiolytic properties in rat Vogel conflict test at much lower doses compared to diazepam [90]. In microdialysis studies, it has been confirmed that the molecule does not affect the monoaminergic neurotransmission reuptake mechanism as it failed to show the increase in the monoamine levels in the frontal cortex as well as the nucleus accumbens regions of the rat brain [90]. Basimglurant has been found to be safer to use in preclinical studies [90]. In healthy volunteers, a 1 mg dose of [$^{12}\text{C}/^{14}\text{C}$]-basimglurant (2.22 MBq) was administered along with a concomitant i.v. tracer dose of 100 μg of [$^{13}\text{C}_6$]-basimglurant [92]. The molecule was found to have oral bioavailability of approximate 67% with a T_{max} of 0.71 h. The most part of the drug was excreted in urine (73.4%) with some portion excreted through feces (26.5%). The terminal half-life was found to be 77.2 ± 38.5 h, indicating its longer stay in the body [92]. Interestingly, basimglurant yields some glucuronide metabolites that could even be detected after 178 h of its administration [92]. In a phase II study, determining the efficacy and safety of basimglurant in patients suffering from major depressive disorder, the molecule at doses of 0.5 and 1.5 mg did not result in the mean change from baseline score on the MADRS scale compared to the placebo-control group [93]. However, in secondary endpoints, basimglurant at a dose of 1.5 mg was found to be superior than placebo in Quick Inventory of Depressive Symptomatology-Self-Report, Clinical Global Impression-Improvement mean score, and Patient Global Impression-Improvement mean scores [93]. These doses of basimglurant were found to be safer in these patients, except some patients felt dizzy after its administration [93]. More clinical trials are undergoing depicting the antidepressant property of basimglurant.

4. Neurotrophins

Neurotrophins are one of the important pathophysiological factors that have been studied in major depression. Different neurotrophins, such as BDNF, nerve growth factor (NGF), neurotrophin-3, and neurotrophin-4 have been linked to the pathophysiology of mood disorders. These molecules along with their receptor systems (tropomyosin-receptor-kinase B (TrkB)) are involved in signaling pathways at prefrontal cortex, CA3 and dentate gyrus regions of the hippocampus and play an important role in neurogenesis and synaptic plasticity [94]. Out of all the neurotrophins listed above, BDNF has been the most and well studied in major depression. A disturbance in the circuitry of BDNF could lead to depression [95], as demonstrated by Yao and colleagues in Nrf2 knockout mice [96]. The Nrf2 knock-out mice have higher levels of pro-inflammatory cytokines with reduction in BDNF [96]. Sulforaphane, an Nrf2 activator in these mice reversed the depression-like phenotype in social defeat test, suggesting its role in major depression [96].

The levels of neurotrophic factors, especially BDNF is reduced in depressed patients when analyzed in the post-mortem brain samples [95,97]. Antidepressant molecules have also shown to increase the levels of different neurotrophic factors in brain regions [98]. Antidepressants via

enhancing BDNF signaling could increase axon as well as dendritic sprouting. Rocha and colleagues in their recent meta-analysis study have concluded that BDNF levels could be an important bio-marker in quantifying the effect of electroconvulsive therapy in majorly depressed patients [99]. There are contrary findings in the literature, suggesting that there is no correlation between the levels of neurotrophic factors and the improvement of depression [100]. Allen and colleagues have shown that both ketamine as well as electroconvulsive therapy provides relief from depression immediately, however, the levels of BDNF are increased gradually, suggesting no direct relationship between two of them [101]. Therefore, the role of neurotrophins in the pathophysiology of mood disorders is still a topic of debate and requires further research. Various antidepressants based on the neurotrophic factor theory are under clinical development. Out of these, NS-189 has shown effectiveness and safety in phase IB clinical trial discussed in this article.

4.1. NS-189

It is a benzylpiperazine-aminopyridine derivative that is being developed by Neuralstem Inc. for the treatment of depression. The molecule has also shown its activity in *in vitro* mouse model of Angelman syndrome, a rare genetic disorder affecting 1 in 15,000 live births, leading to neurological complications. The molecule is effective in animal models of major depression and shown to enhance the neurogenesis phenomenon in the hippocampus as well as subventricular zone. A recent preclinical study has also shown the ability of NS-189 to enhance both short- and long-term potentiation (STP and LTP) in mouse hippocampal slices [102]. The molecule has been found to possess a half-life of around 17.4–20.5 h [102]. In a phase IB, double blind, placebo-controlled study, NSI-189 was found to be efficacious as an antidepressant agent in at least two of the depression scales, symptoms of depression questionnaire and cognitive and physical functioning questionnaire (CPFQ) [103]. Improvement in CPFQ scale indicated that these patients have better cognitive abilities compared to the placebo-control group and this may be directly correlated with its ability to enhance neurogenesis in the hippocampus region of the brain. Patients in this study were administered with 40 mg dose of NS189, 2–4 times a day for a total of 28 days [103]. All these patients (18 majorly depressed patients, including Caucasians, African American, Hispanics and Asians) had MADRS score approximately 25 or more at the time of initial screening [103]. However, small sample size of the study is the major drawback and need to be explored in the bigger clinical trial with more number of patients [103].

5. Triple reuptake inhibitor

This class of molecules prevents the reuptake of norepinephrine, serotonin as well as dopamine, the three neurotransmitters that play an important role in the physiological processes of the body and constitutes the mood of the person. The classical and well-accepted theory of major depression says that there is a decrease in the levels of the above-mentioned

neurotransmitters in the brain and the molecules that correct the levels of these neurotransmitters will be effective antidepressant drugs [104]. Although this theory fails to answer many of our questions in understanding the pathophysiology of major depression and the effect of different class of antidepressant agents, however, this theory is well-accepted by the researchers. A number of animal models based on this theory have been developed that are routinely used to screen new antidepressant molecules. Reserpine, which depletes different monoamines, is known to produce depression-like phase in animals [105]. Various antidepressants have shown to reverse this reserpine-induced depression phenotype. Some of the triple reuptake inhibitors that are under clinical investigation include:

5.1. Amitifadine (DOV 21,947)

Amitifadine (EB 1010; DOV 21,947) ([(+)-1-(3,4-dichlorophenyl)-3-azabicyclo-[3.1.0]hexane hydrochloride]) is a triple reuptake inhibitor that is being developed by Euthymics Bioscience Inc. for the treatment of major depression and alcohol and nicotine addiction/smoking cessation [106]. The molecule is orally active in the forced swim and tail-suspension tests with a minimum effective dose of 5 mg/kg [107]. The molecule is devoid of any alteration in the locomotor activity at doses of up to 20 mg/kg. Amitifadine has shown to prevent the reuptake of all the three neurotransmitters with an IC₅₀ value of 12, 23, and 96 mM for serotonin, norepinephrine and dopamine, respectively, when tested in human embryonic kidney cells [107]. A microdialysis study in rat suggested that the molecule increases the extracellular levels of three neurotransmitters, serotonin, norepinephrine, and dopamine in different brain regions [108]. The molecule relative potency to inhibit serotonin, norepinephrine, and dopamine is 1:2:8, suggesting that it is a serotonin preferring agent. Although the molecule increases the level of dopamine, it does not alter the locomotor activity, suggesting that it does not have an abuse potential. In a 6-week multicenter, randomized, double-blinded, placebo-controlled clinical trial involving 63 majorly depressed patients, amitifadine was administered at a dose of 25 mg twice daily for 2 weeks and then the dose was titrated to 50 mg twice daily for 4 weeks [109]. Some patients were randomized in to the placebo group. At the end of 6 weeks, amitifadine was found to be superior to placebo group in reducing the MADRS total score. Tran and colleagues have mentioned that the difference between amitifadine and placebo for mean change from baseline in MADRS score was 3.8 [109]. However, Marks and colleagues have concerns about the data from Tran and colleagues, and mentioned that there is only 2.2 difference between the amitifadine and placebo for mean change from baseline in MADRS score, and the placebo constitutes 82% effect of amitifadine [110]. As mentioned by Tran and colleagues, the patients also have an improvement in Clinical Global Impression-Improvement (CGI-I) and anhedonia factor scoring [109]. However, there was no significant improvement in Clinical Global Impression-Severity (CGI-S) and Ham-D17 scoring, although there was a trend toward improvement [109]. Patients have found a significant improvement in some of the depression characteristics, including

sadness (both apparent and reported), difficulty in concentrating, lassitude and inability to feel, compared to placebo treatment group. The molecule did not have any serious side effects compared to placebo treatment group, suggesting that the molecule is safe to use at these recommended doses [109]. Interestingly, amitifadine did not increase any sexual side effects as well as weight gain that is commonly observed with the chronic use of SSRIs [111]. A phase IIB/IIIA clinical trial regarding its antidepressant effect has been completed that further evaluated the effect of amitifadine in depressed population and the results are yet awaited.

5.2. Tedatioxetine (LU AA24530)

LU AA24530 is discovered by Lundbeck and investigated both by Lundbeck as well as Takeda for the treatment of major depression as well as anxiety disorders. It is included under the category of triple reuptake inhibitors that enhances the levels of norepinephrine, serotonin, and dopamine via blocking their transport system. Tedatioxetine also increases the level of acetylcholine when estimated in rat brain. Moreover, the molecule has also an antagonistic activity on serotonergic 5-HT₃ and 5-HT_{2C} receptors and thus considered as multimodal antidepressant agent similar to vortioxetine. In a phase II clinical study, LU AA24530 was well tolerated in patients suffering from major depression and the molecule significantly resulted in the improvement over the primary endpoints on the key secondary parameters, compared to a placebo-control group. Vortioxetine was also being studied along with LU AA24530 and the successful clinical development of vortioxetine led Lundbeck and Takeda decided not to proceed with LU AA24530 [112]. Therefore, the molecule is not presently in the clinical development.

5.3. Ansofaxine (LY03005, LPM570065)

Ansofaxine is another triple reuptake inhibitor that is under clinical development by Luye Pharma Group for the treatment of major depressive disorder. Although it is a prodrug of desvenlafaxine (dual reuptake inhibitor of serotonin and norepinephrine), however, ansofaxine also prevented the reuptake of dopamine besides serotonin and norepinephrine. In a preclinical finding, ansofaxine was found to be converted into desvenlafaxine when tested in rats. In a rat-forced swim test, ansofaxine (0.06 mmol kg⁻¹ p.o.) was found to be active at 0.5, 1, and 2 h of its oral administration and reduce immobility time more efficacious than desvenlafaxine. Desvenlafaxine was found to be only effective after 1 h of administration, suggesting that ansofaxine has a better antidepressant profile. In phase I clinical study, ansofaxine was found to be safe and well tolerable in healthy volunteers [113]. The company has got approval for phase II and phase III clinical trials in China for the treatment of major depression.

6. Conclusion

Current treatments for major depression are inadequate and associated with different kinds of side effects, including weight gain as well as sexual problems. Therefore, there is a

Table 1. Highlights of different novel investigational molecules for the treatment of major depression.

Name of the molecule	Clinical trial phase	Highlights	References
ALKS 5461	Phase III	<ul style="list-style-type: none"> In a phase II study, 2/2 mg but not 8/8 mg doses of ALKS 5461 provided a significant improvement in depression score Some of the most common adverse effect associated with ALKS 5461 includes gastrointestinal (52.5%) and neurological (46.8%) In a phase III study, the 2/2 mg dose of ALKS 5461 resulted in improvement in the MADRS scale, however, the results could not reach statistical significance (Forward-4 study). In addition, the Forward-3 study did not provide any significant improvement when compared to the placebo group. The company is waiting for its results of Forward-5 study 	[34,35,37]
CERC-501(LY-2456302)	Phase II	<ul style="list-style-type: none"> CERC-501 is effective in animal models of behavioral despair, such as forced swim test (FST) The molecule possesses rapid absorption profile with good oral bioavailability in preclinical animal models The molecule penetrates blood–brain barrier (BBB) easily and a single oral dose of 2–60 mg and multiple doses of 2, 10, and 35 mg are safer to be administered in humans 	[38–42]
Esketamine	Phase II	<ul style="list-style-type: none"> Ketamine has shown to provide a rapid and long-lasting antidepressant effect Esketamine possesses greater binding potential and biological potency compared to R(–) isoform Ketamine is administered as an intravenous infusion and doses of 0.20 or 0.40 mg/kg of administered over 40 min could result in the antidepressant effect within 2 h Ketamine has also shown to effectively reduce the suicidal ideation associated with major depression However, its use is limited only to the emergency cases of major depression as it is associated with various adverse effects 	[60–69]
AV-101 (4-Cl-KYN)	Phase II	<ul style="list-style-type: none"> AV-101 is one of the most potent, specific glycine B blocker The molecule is a pro-drug that requires conversion into the active moiety Similar to ketamine, AV-101 has produced the rapid and persistent antidepressant effect However, unlike ketamine, the molecule does not have any psychotomimetic side effects It is safe and well tolerated in two Phase I clinical trials 	[70]
Dextromethorphan and deuterated dextromethorphan (AVP-786)	Phase II	<ul style="list-style-type: none"> AVP-786 is an extension of Avanir's recently launched product, Nuedexta A deuteration of methyl groups in dextromethorphan could escape the first pass metabolism and degradation by liver cytochrome enzymes A 30 mg/kg intraperitoneal dose of dextromethorphan is active in the mouse forced swim test. However, there was also enhancement in the locomotor activity associated with dextromethorphan 	[71,72,75]
Rapastinel (GLYX-13)	Phase III	<ul style="list-style-type: none"> Rapastinel penetrates the BBB very efficiently after an intravenous administration The molecule is a unique in the sense that it also enhance the cognitive abilities along with its antidepressant effect The molecule like ketamine provides rapid and long-lasting antidepressant properties, however; its effect is much shorter than ketamine GLYX-13 was found to reduce the Hamilton Depression Rating Scale-17 (Ham-D17) scoring after a single intravenous administration at doses of 1, 5, 10, or 30 mg/kg, without producing any psychotomimetic side effects 	[76–82]
CERC-301(or MK-0657)	Phase II	<ul style="list-style-type: none"> CERC-301 is active in animal models of behavioral despair, such as forced swim test (ED50 value of 0.3–0.7 mg/kg) CERC-301 at a 8 mg dose was found to be safe and well-tolerated by depressed patients; however, it is not effective in preventing the suicidal ideation Cerecor is revising their phase II study with higher doses (12 or 20 mg) of CERC-301 in order to test its effectiveness as an adjunctive treatment of major depressive disorder 	[83–87]
Basimglurant	Phase II	<ul style="list-style-type: none"> Basimglurant is 10–100 times more potent compared to diazepam (a standard anti-anxiety drug) in animal models of anxiety disorders In preclinical studies, basimglurant has been found to be orally active with longer half-life In the rat-forced swim test, basimglurant has been found to be orally effective at doses of 10 and 30 mg/kg The molecule has an oral bioavailability of approximate 67% with a T_{max} (time to reach maximum concentration) of 0.71 h in humans In a phase II study, basimglurant at doses of 0.5 and 1.5 mg did not result in significant improvement in the primary endpoint, for example, the mean change from baseline score on the MADRS scale In secondary endpoints, basimglurant at a dose of 1.5 mg was found to be superior than placebo 	[89–93]

(Continued)

Table 1. (Continued).

Name of the molecule	Clinical trial phase	Highlights	References
NS-189	Phase II	<ul style="list-style-type: none"> The molecule is effective in animal models of major depression and shown to enhance the neurogenesis phenomenon in the hippocampus as well as subventricular zone NS-189 enhances both short- and long-term potentiation (STP and LTP) in mouse hippocampal slices NSI-189 has been found to be effective as an antidepressant in at least two of the depression scales 	[102,103]
Amitifadine	Phase III	<ul style="list-style-type: none"> The molecule is orally active in the forced swim and tail-suspension tests Although the molecule increases the level of dopamine, it does not alter the locomotor activity, suggesting that it does not have an abuse potential Amitifadine has been found to be superior to placebo group in reducing the Montgomery-Åsberg Depression Rating Scale (MADRS) total score However, there was no significant improvement in Clinical Global Impression-Severity (CGI-S) and Ham-D17 scoring The molecule did not have any serious side effects compared to placebo treatment group The use of amitifadine did not increase any sexual side effects as well as weight gain 	[106–111]
Tedatioxetine	Phase II	<ul style="list-style-type: none"> In a phase II clinical study, LU AA24530 was well tolerated in patients suffering from major depression and the molecule significantly resulted in the improvement over the primary endpoints 	[112]
Ansofaxine	Phase II	<ul style="list-style-type: none"> In a rat-forced swim test, ansofaxine (0.06 mmol/kg, p.o.) was found to be active at 0.5, 1, and 2 h of its oral administration. The molecule reduces the immobility period with greater efficacy compared to desvenlafaxine In a phase I clinical study, ansofaxine was found to be safe and well tolerable in healthy volunteers 	[113]

continuous research on exploring novel drug targets and unique molecules for the treatment of this disorder. Some of these novel targets are discussed in this article, and the highlights have been summarized in Table 1. There are not enough animal models of major depression that mimics the human-state and therefore there is always an approximation while transferring the data from animal studies to human clinical trials. Many of these molecules could fail in clinical trials due to high response in the placebo-controlled group and an utmost care should be taken while recruiting the patients for such trials. Drug molecules with faster onset of action, high efficacy as well as lower side effects is the need of the hour. Ketamine as well as other NMDA receptor antagonists provide faster onset of antidepressant effects, however, these molecules are associated with side effects, and there is always an abuse potential associated with their use. Therefore, safer NMDA receptor antagonists such as rapastinel, CERC-301 may be the future drugs for the treatment of major depression. Similarly, opioid receptor modulators hold promise in the treatment of major depression and some of these molecules such as ALKS-5461 provides faster antidepressant effect and is in late clinical trials for the treatment of this disorder. Triple reuptake inhibitors, when discovered, were considered to be superior to the existing anti-depressant molecules, however, its superiority has not yet been demonstrated in any of the clinical trials. Finally, the molecules that enhance the level of BDNF also hold the future of antidepressant therapy, especially in patients who experience cognitive decline associated with depression. Some of these molecules mentioned above could show up in the clinics soon and hopefully treat patients with treatment-resistant depression. There are other

investigational molecules that are in clinical trials for the major depression, however, this articles could not list all those novel targets due to the space limitation.

7. Expert opinion

The area of exploring novel drugs for the treatment of major depression holds great significance, as the ultimate goal is to provide relief to patients suffering from treatment-resistant depression as well as to prevent recurrence/relapse in such patients.

Various conventional/existing drug molecules follow the monoaminergic theory of major depression. Some of these drug molecules pose serious side effects such as weight gain, sexual, and cardiovascular problems, drug interactions in patients who are chronically taking these molecules. Patients often experience relapse in their disease condition with the use of such drugs. Although there are some wonderful antidepressants (fluoxetine, venlafaxine) available in the market; however, approximately 30–40% of patients suffering from major depression do not get relief. Another important limitation of these conventional antidepressants is the slower onset of antidepressant action (around 2–4 weeks). Therefore, it is very important to explore various novel drug molecules and targets for the treatment of major depression.

Researchers are now targeting some other novel drug targets, including glutamate receptors (ionotropic and metabotropic), GABAergic, melatonergic, neurogenesis, neurosteroids, and triple reuptake inhibitor molecules for the treatment-resistant depression. There is a successful discovery of molecules that provide rapid antidepressant effect, for

example, ketamine (NMDA receptor blocker), AV-101 (NMDA receptor glycine-binding site antagonist), and rapastinel (mixed antagonist/agonist of an allosteric site of the glycine site of the NMDA receptor). Ketamine has its own problems such as psychotomimetic side effects, however; the molecules like AV-101 and rapastinel does not have any such psychotomimetic adverse effects and therefore may be preferred over ketamine in treatment resistant depression. Rapastinel has an additional advantage over ketamine-like drugs because of its cognition enhancing capabilities, which is severely compromised in patients suffering from major depression. Ketamine have also been successfully tested in severely depressed patients where it provided immense relief. These molecules definitely hold the future for the treatment of major depression where quicker onset of action is required, for example, in emergency cases and where severe suicidal ideation could be seen.

Relapse is an important parameter that could be taken into consideration while discovering new drugs for major depression. The research in this area is lacking in the fact that we are still not clear whether these newly discovered molecules could provide relapse in patients suffering from major depression. Therefore, there should be a prolonged follow-up among the patients who have been administered these molecules, in order to explore the long-term picture of such molecules.

Finally, there is a strong need to develop adequate animal models of major depression that could mimic the human disease condition. There is a limitation of developing genetic models of major depression, as the disease is an interplay of multiple genes and not due to any single gene. In addition, there is a need for careful designing of the clinical trials and analyzing the data when it comes to exploring antidepressant molecules. Some of the effective molecules such as ALKS 4561 could not find superiority over the placebo group in the clinical trials. It may be generally due to the high response rate of the placebo group in such clinical trials. Such molecules hold a great promise and future for the treatment of depressed patients and require more exploration.

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