Beyond serotonin: newer antidepressants in the future

Gopalkumar Rakesh, Chi-Un Pae & Prakash S. Masand

To cite this article: Gopalkumar Rakesh, Chi-Un Pae & Prakash S. Masand (2017): Beyond serotonin: newer antidepressants in the future, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2017.1341310

To link to this article: http://dx.doi.org/10.1080/14737175.2017.1341310

Accepted author version posted online: 09 Jun 2017.
Published online: 19 Jun 2017.

Submit your article to this journal

Article views: 45

View related articles

View Crossmark data
Beyond serotonin: newer antidepressants in the future

Gopalkumar Rakesh¹, Chi-Un Pae²,³ and Prakash S. Masand⁴,⁵

¹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; ²Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; ³Academic Medicine Education Institute, Duke-NUS Medical School, Singapore, Singapore; ⁴Global Medical Education, New York, NY, USA

ABSTRACT

Introduction: There are numerous antidepressants for the treatment of major depressive disorder (MDD) on the market. However, inadequate treatment response, therapeutic lag between drug administration and the onset of clinical improvement, and safety/tolerability issues with the use of contemporary antidepressants have accelerated the search for newer antidepressants with novel mechanisms of action.

Areas covered: The authors review novel antidepressants with rapid efficacy for diverse MDD symptoms and have fewer adverse effects (AEs). Mechanisms of action for novel therapeutic molecules are through glutamatergic, opiate, cholinergic receptors and neuroplasticity. We enumerate results from human trials with novel agents in all phases, highlighting proximity to approval and therapeutic potential based on quality of evidence.

Expert commentary: There is a huge unmet need to diversify conventional antidepressant targets. Glutamatergic and opiate agents may be most promising among newer therapeutic agents. It is also important to develop advanced but flexible synergistic treatment strategies with newer therapeutic agents that are usable in routine clinical practice. This would include combining newer molecules with existing antidepressants and using molecules that target specific symptom dimensions of MDD. These strategies would lead to a systematic approach to tackle treatment resistant depression (TRD) and treatment of residual symptoms in partially remitted MDD.

1. Introduction

There are unmet needs in the treatment of major depression. Reviewing 30 years of treatment research including randomized controlled trials (RCTs) for major depressive disorder (MDD), there is an average response rate of 54% for US-FDA-approved antidepressants compared with 37% for placebo, with a pooled relative difference of 12.5% and a number needed to treat of eight [1]. These numbers have been replicated by Tedeschini et al. showing average response rates of 54.3% and 37.9% for antidepressants and placebo, respectively, for MDD [2]. In the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial, which examined the effectiveness of treatments for MDD in a ‘real world’ setting, response or remission rates did not exceed 50% at any stage of the study [3]. Like most clinical trials, the response was defined as a 50% reduction in Hamilton Depression Rating Scale scores and remission was a target end point (score less than 7) [4]. Although the trial had a cumulative remission rate of 67%, remission rates toward treatment levels 3 and 4 hovered between 10% and 20% [3]. Although treatment-resistant depression (TRD) is conventionally defined as a lack of response to adequate trials of two agents from different treatment classes [5], there has been considerable debate in recent years about the validity of this definition [6–9]. The adequacy of a trial and appropriateness of looking at response versus remission in a trial have all been the subjects of debate. In the STAR-D trial, remission rates of 37% in patients who received level 1 treatment and 31% among those in level 2 [3] make a case for the fact that no remission or partial remission is the usual outcome at each stage of treatment.

From 2005 to 2010, the incremental economic burden of patients with MDD increased from $173.2 billion to $210.5 billion per year [10]. Reduced productivity at work and absenteeism contributed to 48% of this burden, and direct costs associated with treatment of the disease contributed to nearly 47% of the costs in 2010. However, medications contributed to only 13% of costs [10]. Medication costs are greater for patients with TRD, with a mean depression-related medication cost of $2639 per patient per year, compared with $939 for non-TRD patients [11]. The mean health-care expenditure (encompassing costs other than medication costs) for a patient with TRD was $10,000 per year, which is almost twice that of a patient without TRD [11]. A recent study that sought to examine the efficacy of medication combinations in patients with MDD (Combining Medications to Enhance Depression Outcomes – COMED) found no significant differences between starting combinations of different antidepressant medications or individual medications to treat MDD [12]. This suggests that our current pharmacologic armamentarium of antidepressants is inadequate for a substantial proportion of individuals with MDD. Therefore, novel antidepressants that are more effective at controlling symptoms...
and have fewer adverse effects with more rapid therapeutic effect are needed to allow optimal functional recovery in a greater proportion of patients.

Here, we review the current clinical data on antidepressants that have a variety of mechanisms including glutamatergic pathway (ketamine, esketamine, lanicemine, traxoprodil, rapastinel, CERC-301, AZD-6423, EVT-101, AV-101, D-cycloserine (DCS), AVP-786, BCI-632, basinglumirant); opiate pathway (buprenorphine, ALKS 5461, CERC-501); cholinergic pathway (scopolamine); triple reuptake inhibitors (amitifadine). Table 1 details key points on these agents. We also enumerate novel treatment agents with unconventional mechanisms of action modulating neuroplasticity (NSI-189), psychedelic agents, probiotics, and monoclonal antibodies. Finally, we discuss developments in modalities such as brain stimulation and summarize the importance of synergistic action from different modalities for treating MDD.

2. Beyond the monoamine hypothesis of MDD – the glutamatergic hypothesis of MDD

Conventional views hold the ‘monoamine hypothesis of depression’ to be the predominant player in the pathophysiology of MDD. However, research over the last two decades has drawn increasing attention to the effects of the glutamatergic system on neurons and how these effects could be related to the pathophysiology and treatment of mood disorders [14]. Animal studies have shown that glutamate neurotransmission plays a central role in mediating structural remodeling in the brain (via dendritic remodeling and synaptic modulation) and altering brain structural volumes [15,16]. Glutamate plays a key role in mediating the structural effects of stress in both animal and human studies [17–20]. Stereological methods estimatethat glutamatergic excitatory neurons in the human neocortex account for 80% of all neurons and contribute to 85% of all synapses [21]. The remaining synapses are mainly comprised of inhibitory neurons that use GABA as their primary neurotransmitter. Our understanding of neurotransmitter systems has changed to encompass the fact that even though monoaminergic neurotransmission contributes to all forms of brain function (including biological drives from limbic circuitry, emotions, and cognition from other areas in the cortex), the output functions of these domains (cognition and emotion) are mediated in large part by brain architecture with excitatory and counterbalanced inhibitory neurotransmission [14]. Direct evidence for glutamate abnormalities in mood disorder comes from the analysis of cerebrospinal fluid (CSF) and brain

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Mechanism of action</th>
<th>Phase of study</th>
<th>Summary of experimental results/quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esketamine</td>
<td>Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and a dopamine reuptake inhibitor</td>
<td>Phase 3, FDA breakthrough designation for MDD</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Lanicemine</td>
<td>NMDA antagonist and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist</td>
<td>Terminated in 2013</td>
<td>Although the drug showed significant results in small studies, it did not fare as well in a double blind RCT/++</td>
</tr>
<tr>
<td>Amitifadine</td>
<td>Triple reuptake inhibitor</td>
<td>Phase 3</td>
<td>Recently reported RCT results reveals efficacy for a dose of 20 mg only on secondary end points but not on primary end points [13]</td>
</tr>
<tr>
<td>CERC-301</td>
<td>NMDA (NR2B receptor) antagonist</td>
<td>Phase 2</td>
<td>Phase 2 clinical trial put on hold by FDA Therapeutic potential for high dose (500 mg–1 g)/+++</td>
</tr>
<tr>
<td>EVT-101</td>
<td>NR2B antagonist</td>
<td>Phase 2</td>
<td>Front runner among new candidates given its unique mechanism of action as seen in animal studies/+++</td>
</tr>
<tr>
<td>D-Cycloserine</td>
<td>NMDA agonist</td>
<td>Phase 4</td>
<td>Awaiting phase 2 results for adjunctive treatment in MDD trial (NCT02153502) Reduced agitation in Alzheimer’s dementia. (AVP-786 for the treatment of agitation in dementia of the Alzheimer’s type) Ongoing phase 2 studies (NCT02484456 and NCT03078322)</td>
</tr>
<tr>
<td>Rapastinel</td>
<td>Weak partial agonist at glycine site of the NMDA receptor</td>
<td>Phase 3</td>
<td>Showed significant results in human trials, limitation is dissociative side effects Ameliorates suicidal ideation. Ongoing phase 2 study to assess antidepressant potential</td>
</tr>
<tr>
<td>BCI-632</td>
<td>mGlU2/3 antagonist</td>
<td>Phase 1</td>
<td>Has potential as an adjunctive treatment agent/++</td>
</tr>
<tr>
<td>Basinglumirant</td>
<td>mGlU5-negative allosteric modulator</td>
<td>Phase 2</td>
<td>Awaiting completion of phase 2a study results (NCT02218736)</td>
</tr>
<tr>
<td>AVP-786</td>
<td>NMDA/sigma-1 receptor antagonist</td>
<td>Phase 3 for MDD</td>
<td>Phase 3 for agitation in patients with dementia</td>
</tr>
<tr>
<td>AV-101</td>
<td>Glycine antagonist</td>
<td>Phase 2</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>AZD 6423</td>
<td>NMDA receptor antagonist</td>
<td>Phase 1</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Traxoprodil</td>
<td>RR2B selective NMDA receptor antagonist</td>
<td>Terminated by company</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Mu receptor modulator</td>
<td>Phase 2</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>ALKS 5461</td>
<td>Opiate receptor modulator</td>
<td>Phase 3</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>CERC-501</td>
<td>Kappa receptor modulator</td>
<td>Phase 2</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Cholinergic agonist</td>
<td>Phase 2</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>NSI-189</td>
<td>Benzylpiperazine-aminopyridine that stimulates neurogenesis</td>
<td>Phase 1</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Captodiamine</td>
<td>SHT2C antagonist, agonist at sigma-1 and D3 dopamine receptors</td>
<td>Phase 1</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
<tr>
<td>Clophenpropit</td>
<td>H3 antagonist</td>
<td>Phase 1</td>
<td>Currently in phase 3 trials, esketamine is closest to ketamine in mechanism of action without psychotomimetic side effects. Despite only one published RCT, it has breakthrough FDA designation for MDD with suicidal ideation/+++++</td>
</tr>
</tbody>
</table>

Grade quality of evidence – legend

High – ++++

Moderate – +++

Low – ++

Very Low – +

Agents in phase 1 and 2 trials do not have comments or quality of evidence stated.

RCT: randomized controlled trial; D-Cycloserine: DCS.
tissue from patients showing elevated glutamate content [22,23]. The role of glutamate, glutamine, and GABA in affective disorders has been addressed [14,24–34]. Neuroimaging studies using magnetic resonance spectroscopy have also showed abnormal glutamate metabolite levels within different brain regions of patients with MDD and bipolar disorder [35–37].

Both ionotropic (AMPA and NMDA) and metabotropic glutamate receptors play an important role in mediating the effects of stress in conjunction with glucocorticoid receptors in prefrontal cortex (PFC) and mineralocorticoid receptors in the hippocampus [14,15]. Mechanisms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus are also mediated by glutamate; the regulation of AMPA receptor density is a key mechanism behind these effects [38]. Traditional antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitor (SNRIs), tricyclic antidepressant (TCAs)) inhibit the presynaptic release of glutamate and ameliorate the glutamatergic effects induced by stress [20,39]. AMPA and NMDA receptors also seem to be primary mediators in this process.

2.1. Morphology and description of glutamate receptors

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system. Glutamate receptors can either be metabotropic or ionotropic. Metabotropic glutamate receptors (mGluRs) indirectly activate ion channels on the plasma membrane via a signaling cascade involving G proteins. While ionotropic receptors tend to relay information faster, metabotropic receptors are associated with a more prolonged stimulus. NMDA and AMPA receptors are predominantly postsynaptic, whereas metabotropic receptors are both presynaptic and postsynaptic.

Metabotropic (mGlu) receptors are currently divided into three different groups according to their DNA sequence homology, pharmacology profile, and intracellular signal transduction pathways. mGLU receptors 1 and 5 (belonging to group 1) are predominantly postsynaptic, mGLUR2 and 3 (group 2) are both presynaptic and postsynaptic, and 4, 6, 7, and 8 (group 3) are mainly postsynaptic [40]. NMDA, AMPA, and several metabotropic receptors including mGluR2/3 and mGluR5 appear to be important for the pathophysiology and treatment of MDD [34,41].

NMDA receptors have three subunit families: GluN1, GluN2A-D, GluN3A-B. The GluN1 subunit contains the glycine/D-serine binding site and the NR2 subunit contains the glutamate binding site [42,43]. The 2B, 2D, and 3A subunits are expressed early in development, suggesting their importance for synaptogenesis and synapse maturation. 2A and 2B are the predominant subunits in the adult hippocampus and cortex, and hence become therapeutic targets for the treatment of MDD [44]. NMDA receptors are usually heteromeric complexes consisting of two GluN2A and 2 GluN1 subunits with extracellular glycine and glutamate sites [42].

Recently, increasing work has been performed to understand the extra-synaptic localization of NMDA receptors and the effects of extra-synaptic glutamate release [45]. Studied in the context of glial loss because of stress, extra-synaptic glutamate release causes excessive stimulation of GluN2B receptors and mGLUR1 receptors, leading to a reduction in brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB), and the activation of apoptosis. This is opposite to the effects of intra-synaptic glutamate release on neuronal function and survival [45]. The activation of synaptic NMDA receptors promotes cell survival by activating BDNF and CREB. This becomes relevant to understand the mechanism of action of ketamine [34,44].

3. Ketamine and MDD

Ketamine is a noncompetitive open channel antagonist at NMDA receptors and has been used as an anesthetic since the 1960s. The route of administration affects its bioavailability, with intravenous administration making it 100% bioavailable and oral administration making only 20% available [46]. It is metabolized rapidly and has a plasma redistribution half-life of 4 min. Most studies published to date have used a racemic mixture of ketamine (composed of R and S enantiomers). Multiple studies have replicated the antidepressant effects of ketamine, and meta-analyses have been published on this subject [47–49]. The response in MDD peaks 2–4 h after administration, but ketamine typically has effects that last for several days following a single administration. There are less high quality data published on studies using repeated dosing. A single study showing no difference between the twice weekly and thrice weekly administration suggests that dosing can be spread out to maintain the antidepressant effects [50]. Ketamine is associated with unwanted effects that can last up to 2 h after administration; the most common are transient perceptual disturbances, dissociation, dysphoria, anxiety, dizziness, nausea, and a mild increase in blood pressure and heart rate [51].

To date, 12 RCTs have looked at the efficacy of ketamine in MDD [52]. These studies encompass ketamine monotherapy, ketamine for the augmentation of antidepressants, and ketamine for the augmentation of electroconvulsive therapy (ECT). A recent meta-analysis looked at effects of ketamine on a timeline continuum of 40 min, 80 min, 2 h, 4 h, 1 day, 2 days, 3 days, 7 days, and 14 days. For treatment response to ketamine, the odds ratio varied from 24.7 at 80 min and 2 h to 4.4 at 14 days. For the remission of symptoms, the odds ratio varied from 14.5 at 1 day to 1.5 at 14 days [52]. Other reviews have summarized ketamine studies in MDD [47–49] as well as in combination with ECT [53]. Trials to treat MDD with a combination of ECT and ketamine have shown mixed evidence, with some studies showing a significant improvement with fewer ECTs [54–56] and others showing no overall difference in the improvement trajectories [57,58]. In addition, the trial parameters were heterogeneous about the dose of ketamine used for intravenous infusion and ECT parameters (electrode placement and pulse width) [53].

Broadly speaking, the mechanism of action of ketamine is thought to be mediated through a surge in AMPA activation in the prefrontal cortex (PFC). This surge is mediated by increased glutamate release that is stimulated by NMDA receptor inhibition associated with a sub-population of inhibitory GABAergic interneurons or other means [59,60]. This surge activates AMPA receptors and the BDNF and mTOR pathways [61]. Ketamine also
inhibits extra-synaptic NMDA receptors, which causes synaptic remodeling [44].

An alternative hypothesis proposes that NMDA receptor antagonism blocks unstimulated activation of NMDA receptors and induces factor 2 kinase activity, rapid increases in BDNF, and the initiation of neurogenesis. It also decreases the activation of eukaryotic elongation factor 2 (eEF2) kinase, leading to a loss of eEF2 phosphorylation [62]. BDNF translation triggers tyrosine-related kinase B (TrkB) signaling, which leads to transphosphorylation and the downstream activation of extracellular signaling related kinases (ERKs) and protein kinase B (Akt) and the suppression of glycogen synthase kinase-3. The combination of these events activates mTOR, which in turn leads to increased synaptic proteins and spine densities resulting in synaptogenesis [63].

Some possible biomarkers for the antidepressant actions of ketamine have been postulated to be functional connectivity between the caudate nucleus and the medial prefrontal cortex (mPFC) [64], somatosensory evoked potentials [65,66], corticospinal excitability estimated using transcranial magnetic stimulation (TMS) [67] and plasma BDNF [68]. Niciu et al. details studies that postulate possible biomarkers for the antidepressant effects of ketamine [34].

Despite its remarkable profile, ketamine has side effects [51]. Psychodelic side effects comprise auditory and visual hallucinations, panic attacks, depersonalization, and de-realization [69,70]. These side effects appear at an infusion dose of 10–30 mg/h. Other central nervous side effects include sedation, dizziness, blurred vision, dysphasia, nystagmus, and impaired motor function which have also been shown to be present at similar doses [71]. Most studies with MDD use doses of 0.5 mg/kg which amounts to total doses between 30–35 mg. Ketamine impairs semantic memory [72]. Most central nervous system effects are reversible once infusion is terminated. Ketamine also causes cardiovascular stimulation (resulting in increased cardiac output and myocardial oxygen consumption) [73,74]. Most emergency room (ER) presentations due to recreational use of ketamine comprise a combination of central nervous system and cardiac side effects including chest pain, palpitations, nystagmus, hallucinations, and altered sensorium [51]. In chronic users of ketamine, urological side effects involving the bladder (wall thickening, ulcerative cystitis, and vesico-ureteral reflux) [75] and loss of gray/white matter in brains have also been seen.

4. New glutamatergic agents for MDD

4.1. Esketamine

Esketamine is an enantiomer of ketamine; it is a noncompetitive NMDA receptor antagonist and a dopamine reuptake inhibitor. Esketamine has eight-times more affinity for dopamine transporters [76,77], no affinity for sigma-1 receptors, and 3–4 times higher affinity for NMDA receptors [78–80]. A recent review highlighted the main differences between these two enantiomers of ketamine [81]. In a double blind RCT involving 30 patients with TRD, 0.20 mg/kg and 0.40 mg/kg esketamine exhibited significant reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores compared with placebo [82]. One study in mice found that arketamine was a more potent antidepressant than esketamine, with esketamine having possibly greater dopamine transporter inhibition and subsequently greater psychotomimetic side effects [83].

Esketamine is more tolerable to patients when used in clinical trials. As of 2017, it is in phase 3 clinical trials. The TRANSFORM trials (TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3) are comparing 4 weeks of twice daily intranasal esketamine combined with another oral antidepressant to other antidepressants such as duloxetine, sertraline, venlafaxine, and escitalopram combined with an intranasal placebo. These studies are currently recruiting participants and are sponsored by Janssen Pharmaceuticals (TRANSFORM-1, NCT02417064; TRANSFORM-2, NCT02418585; TRANSFORM-3, NCT02422186). The SUSTAIN-3 study is comparing intranasal esketamine to placebo (NCT02782104) in TRD patients. Recently, esketamine received a breakthrough designation by the FDA for MDD with suicidal ideation [84]. Overall, intranasal esketamine seems to closest to approval for treatment of MDD and holds great potential given its tolerability compared to ketamine.

4.2. Lanicemine

Developed by AstraZeneca, Lanicemine (AZD6765 or AR-R15896AR) has very similar pharmacological profile as ketamine, but without the same magnitude perceptual or cognitive side effects at doses that produce similar effects on PFC activity [85–88]. Small phase Ib and 2a studies showed signals suggesting rapid onset antidepressant effects. An RCT that randomized approximately 150 patients into three groups that received 100 mg lanicemine, 150 mg lanicemine, or placebo three times a week for 3 weeks showed that both doses had better efficacy than placebo at the predetermined primary end point. Interestingly, there were suggestions that the 100-mg dose performed better compared to that of 150-mg dose. The 100 mg dose of lanicemine was different from placebo at all visits; significant differences in the scores started from week 2 and persisted through week 5. It also ameliorated anxiety symptoms and showed dramatic changes in clinical global impression (CGI) scores. Unlike ketamine, which achieved immediate effects, lanicemine showed significant differences only from week 2 [88]. This could be in part related to the greater placebo response that was seen in the lanicemine study. A second phase 2b study randomized 302 subjects into three groups that received 50 mg lanicemine, 100 mg lanicemine, or placebo three times a week for 3 weeks, then once a week for 3 weeks, followed by once every other week for 6 weeks. The study failed to show superior efficacy for either dose of the drug compared with placebo at the predetermined primary end point, or any of the secondary end points. However, the interpretation of this study is complicated by a very high placebo response rate of 39% in this previously treated nonresponsive population. The story of lanicemine reminds us that molecules that display a novel effective mechanism of action may not necessarily translate to effectiveness/efficacy in clinical trials.

4.3. AZD 6423

AZD 6423 is another NMDA receptor antagonist that was developed by AstraZeneca; it is being investigated for reducing suicidal
ideation, which is one of the major burdens of MDD. AZD 6423 has finished a phase I trial, but the company has not yet posted the study results. The narrow therapeutic window of AZD 6423 may limit its development in the suicidality context, despite its potential ability to ameliorate suicidal ideation [89].

4.4. Traxoprodil/ifenprodil

Traxoprodil (CP-101,606) acts as an NMDA antagonist and is selective for the NR2B subunit. A study in rats showed that a single dose of CP-101606 enhanced hippocampal synaptic plasticity induced by high-frequency stimulation 24 h after dosing [90]. Preskorn et al. demonstrated promising clinical data on the antidepressant effects of traxoprodil in patients with TRD (a total of 30 patients with 15 in each arm). This placebo-controlled, double-blind study clearly showed that patients receiving CP-101606 had a greater decrease in both MADRS and Hamilton depression rating scale (HDRS) scores than placebo control subjects. Furthermore, 78% and 32% of CP-101606-treated patients maintained the response status for 1 week and 30 days after infusion, respectively [91]. As pointed out in a comment to the above study [92] and previous studies, traxoprodil is a successor to a compound called ifenprodil, which belongs to a family of compounds called phenylethanolamines [93]. Ifenprodil is an allosteric NMDA receptor modulator that prevents glutamate excitotoxicity in cell cultures. It inhibits NR2B NMDA receptors by increasing the sensitivity of the receptor to negative modulation by protons. Ifenprodil has serotonergic, alpha-adrenergic actions along with psychotomimetic side effects, which are absent with traxoprodil [93]. In a study by Preskorn et al. [91], six patients in the treatment arm had dissociative reactions; however, two patients from the placebo arm also had dissociative reactions.

4.5. CERC-301

CERC-301 is an NMDA receptor subunit (NR2B) selective antagonist. Although its mechanism of action is analogous to ketamine, it lacks its psychotomimetic side effects [94]. CERC-301 is orally bioavailable with an adequate safety profile at dose of 8 mg/day [95]. It has rapid onset antidepressant effects, as measured by changes in the HDRS, although these results were not corroborated with MADRS [94]. A completed trial used higher doses of 12 and 20 mg/day (NCT02459236) in 115 subjects; the results revealed a clinically meaningful treatment effect with the 20 mg dose on day 2 [13].

4.6. EVT-101

EVT-101 is a novel NR2B selective antagonist. Its binding profile at this receptor site differs from that of ifenprodil [96]. A phase 2 trial (NCT01128452) was started, but terminated due to a clinical hold issued by the FDA. Phase 1 trials found it to have good safety in humans (NCT00526968) [97].

4.7. D-cycloserine

Augmentation using 1 g/day of DCS for TRD showed that DCS is a partial agonist at the N-methyl-D-aspartate receptor (NMDAR)-associated glycine modulatory site. At high doses, it acts as a functional NMDAR antagonist. Twenty-six treatment-resistant MDD patients participated in a double blind, placebo-controlled, 6-week parallel group trial that added a gradually titrated high dose (1000 mg/day) of DCS to their antidepressant medication. DCS treatment was well-tolerated, no psychotomimetic effects, improved the depression symptoms, as measured by the Hamilton Depression Rating Scale (p = 0.005) and Beck Depression Inventory (p = 0.046). Of the 13 subjects treated with DCS, 54% had a 50% HAMD score reduction versus 15% of the 13 patients randomized to placebo (p = 0.039). A significant (p = 0.043) interaction was registered between treatment response and pretreatment glycine serum levels [98]. A previous study from the same group using a lower dose of DCS (250 mg/day) as an add-on therapy to existing the antidepressant regimen did not show any difference in outcome measures (HDRS and Hamilton anxiety rating scale) when compared with placebo [99].

4.8. Rapastinel

Rapastinel (GLYX13) is a new antidepressant that appears to act as a functional selective weak partial agonist of an allosteric site in the NMDA receptor. It is a centrally active, intravenously administered, amidated tetrapeptide. It belongs to a family of compounds called glyxins and is derived by the structural modification of B6B21 (a monoclonal antibody that binds to and modulates the NMDA receptor). It preferentially enhances the conductance of NR2B-containing NMDA receptors at rat Schaffer collaterals in the CA1 area of the hippocampus [100]. Enhancing the extent of hippocampal LTP and toning down the intensity of LTD, it also aids the performance of hippocampal-dependent spatial navigation tasks in rats [101]. A phase 2A single dose study of rapastinel in a group of 116 patients with MDD and a poor response to antidepressants showed differential responses for different doses. The 5 mg/kg and 10 mg/kg doses yielded significant differences in HDRS-17 from placebo at day 1 post-infusion, which continued to day 7; however, the 30 mg/kg dose was no different from placebo. Less than 5% of the study population reported any adverse effects, and these were all mild to moderate. Some of the side effects reported were headache, somnolence, dizziness, dysgeusia, and fatigue [102]. Another unpublished study reported weekly dosing with 5 mg/kg and 10 mg/kg rapastinel or placebo. The study had two phases; in the first phase, patients who had failed at least one antidepressant received either the drug (5 mg/kg and 10 mg/kg) or placebo weekly for 6 weeks. They received the drug if they were depressed and were shifted to placebo when they had a 50% response. They were then shifted back to the drug when they became depressed as per the HDRS. After this phase, called stabilization, they were randomized to two doses or placebo in phase 2. This was a phase of randomized withdrawal, with weekly placebo (n = 55), 5 mg/kg rapastinel (n = 51), and 10 mg/kg rapastinel (n = 54). In the first phase,
with just weekly dosing of the drug, the HDRS score decreased but increased after placebo [103]. Rapastinel is currently in large phase 3 trials for MDD.

4.9. BCI 632- mGLU2/3 antagonist

BCI-838 (a prodrug of BCI-632, also known as MGS0039) is a mGLU2/3 antagonist. Even though initial trials showed promise in MDD, later trials were not as successful (NCT01546051-2012). A probable mechanism of action could be the lack of a regulatory response in the presence of excess glutamate levels, mediated by receptor antagonism.

4.10. RG-7090 (basimglurant)

Basimglurant is a potent, selective, and safe mGlu5-negative allosteric modulator with good oral bioavailability and a long half-life that is supportive of once-daily administration in humans [104]. Animal studies showed significant antidepressant and anxiolytic properties [105,106]. A phase 2b RCT with 1.5 mg of the drug versus placebo (n = 596) showed minimal differences in outcome measures (MADRS scores) when compared with placebo [107]. However, it is possible that higher doses may have different effects and so more trials are warranted.

4.11. AVP-786

AVP-786 is a NMDA/sigma-1 receptor antagonist that is undergoing phase II clinical trials developed by Avanir Pharmaceuticals. The two major components of AVP-786 are deuterium-modified dextromethorphan (DXTM) and ultra-low-dose quinidine [108]. Dextromethorphan (DXM) acts as an NMDA receptor antagonist, sigma-1 receptor agonist, and inhibitor of the 5-HT/norepinephrine transporter. However, its mechanism of action as an antidepressant has not been explored. Some proposed mechanisms include mTOR activation, 5-HT transporter inhibition, modification of neuronal plasticity, and increased neuronal regeneration and survival. Indeed, DXTM exhibits ketamine-like rapid-acting, treatment-resistant, and conventional antidepressant effects in anecdotal reports [109].

4.12. AV-101

AV-101 (4-chlorokynurenine) is an antidepressant molecule; it is an oral prodrug that gets converted to 7-chlorokynurenic acid in vivo [110]. 7-Chlorokynurenic acid is a halogenated derivative of L-kynurenine and a potent antagonist at the glycine site of the NMDA receptor [111]. L-kynurenine is synthesized from tryptophan which is an amino-acid precursor for both serotonin and niacin. 7-Chlorokynurenic has been shown to have antidepressant properties as well as a connection with pathophysiology of schizophrenia (Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis). Kynurenine aminotransferases (KAT1 and 2) are involved in the conversion of AV101 into the active molecule, which has neuroprotective and antidepressant properties and has completed phase 1 safety trials. A phase 2 trial is underway currently, administering 1440 mg of the drug daily for 2 weeks as monotherapy (NCT02484456); another trial looks at adjunctive treatment with 1440 mg and is yet to start recruiting (NCT03078322) [112].

5. Opioid receptor agents for MDD

Multiple studies have shown a role for endogenous opioids in mood regulation and abnormal m- and k-opioid tone in MDD [113-115]. Opioid receptors are densely distributed in rostral anterior cingulate, amygdala, thalamus, insula which are all areas germane to emotional regulation [113,114]. They also play a central role in reward processing as characterized from animal studies [115-118]. Kappa receptor antagonism selective to mu receptors yields antidepressant actions. Previous animal studies have characterized this in models of depression [41,116,117]. Prior reports in animals showcased the roles played by elevated CREB in the response to stress in the nucleus accumbens, with dynorphin aiding the process to combat stress [119]. In these animal model anxiety studies, kappa receptor antagonists (KOR) produced anxiolytic and antidepressant effects, which became the basis for subsequent translational studies in humans [118,120].

5.1. Buprenorphine

In a seminal study involving 88 patients administered with 0.1-0.8 mg/day (mean 0.44 mg/day) of buprenorphine or placebo for 4 weeks, buprenorphine was found to ameliorate suicidal ideation at 2 and 4 weeks. There were no withdrawal symptoms following discontinuation [121]. A Phase 2 study will compare buprenorphine with venlafaxine XR and placebo in older adults with MDD (NCT02181231).

5.2. ALKS 5461

ALKS 5461 is a 1:1 combination of two molecules: buprenorphine and samidorphan. Buprenorphine is a weak partial agonist of the μ-opioid receptor, an antagonist/very weak partial agonist of the κ-opioid receptor, and to a lesser extent an antagonist of the δ-opioid receptor [122]. Samidorphan (previously called ALKS 33) is a preferential antagonist of the mu opioid receptor (but also a weak partial agonist of the kappa and delta opioid receptors) [123]. The combination of these two drugs putatively results in the functional blockade of kappa receptors, with negligible activation of mu receptors. An initial double blind RCT showed that the combination was capable of exerting antidepressant effects within 7 days of administration [113]. It was granted fast track designation by the FDA for TRD in October 2013.

In a multisite two-stage RCT with buprenorphine/samidorphan doses of 2 mg/2 mg and 8 mg/8 mg, both doses showed remarkable improvement in clinical scores over the course of 4 weeks. The doses of 2 mg/2 mg had greater efficacy over the other two arms at both stages of the study. The patient pool had MDD that was treatment-resistant to SSRI and SNRI [124]. The earlier Focused on Results with A Rethinking of Depression (FORWARD) trials (FORWARD-3,4) showed that low doses of the drug are no better than placebo. FORWARD-5 was a phase 3,
randomized, double-blind, multicenter, placebo-controlled, sequential parallel comparison design study that evaluated the safety, tolerability, and efficacy of two doses of ALKS 5461 (2 mg/2 mg and 1 mg/1 mg) as an adjunctive treatment in patients with MDD who had an inadequate response to a stable dose of either an SSRI or an SNRI. The study randomized 407 subjects, and the 2 mg/2 mg dose yielded significant antidepressant outcomes compared with placebo ($p = 0.018$). The most common side effects were nausea, dizziness, and fatigue.

5.3. CERC-501
CERC-501 (originally known as LY-2456302) is a potent, selective, short acting antagonist of the kappa opioid receptor. It is being studied as an augmentation agent for TRD. In clinical trials, CERC-501 displayed rapid oral absorption and a terminal half-life of approximately 30–40 h in healthy subjects [125]. The plasma exposure of CERC-501 increased proportionally with increasing doses, and reached steady state after 6–8 days for once-daily dosing [125]. A proof-of-concept trial of CERC-501 for the augmentation of antidepressant therapy in TRD (RAPID KOR) was initiated in April 2015. The study used daily doses of 10–20 mg and was recently terminated (NCT01913535). An ongoing clinical trial called Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FASTMAS) will evaluate the antidepressant effects of the drug with biological correlates (NCT02218736).

6. Cholinergic system modulation – scopolamine
Cholinergic system modulation has also been touted to have antidepressant properties. This was evident from initial studies with physostigmine showing that it exacerbated depressive symptoms or induced depressive symptoms in manic patients [126–128]. A pilot study evaluating the role of the cholinergic system in the cognitive deficits associated with MDD showed that the antimuscarinic drug scopolamine had antidepressant benefits. A randomized placebo-controlled clinical trial showed the efficacy of the IV infusion of 4 µg/kg scopolamine compared with placebo ($p = 0.002$) [129]. Two subsequent RCTs that evaluated the effect of multiple infusions separated by 3–5 days reported similar results [129,130]. A recent review detailed the studies done to date, and reported the antianxiety effects seen with scopolamine administration, greater antianxiety effects in women compared with men, as well as its side effects [131]. The side effects seen were transient drowsiness, blurred vision, dry mouth, and light-headedness [132]. Scopolamine exerts antidepressant effects by acting on the MTORC1 complex via the mTOR pathway and thereby inducing synaptogenesis [133].

7. Anti-inflammatory agents as antidepressants
Studies showing a relationship between T-cell activation and MDD, as well as elevation of pro-inflammatory cytokines in MDD (notably IL-2, IL-6, IL-8, IL-12, TNF-alpha, and IFN-alpha) advocate for a central role for inflammation in the pathophysiology of MDD [134–136]. Other key mediators seem to be lipopolysaccharides, peptidases, and omega 3 fatty acids. There seems to be a complex relationship between stress, inflammation, and MDD as suggested by various inflammatory hypotheses of MDD, involving cytokines, oxidative and nitrosative pathways, and neurodegenerative pathways, respectively [135,137,138].

Inflammatory markers (including interleukins and cytokines including TNF-alpha) are consistently elevated in patients with MDD [139]. Agents such as polyunsaturated fatty acids (PUFAs), N-acetyl cysteine (NAC), infliximab, aspirin, and COX-2 inhibitors such as celecoxib have been used to treat MDD. A meta-analysis investigating anti-inflammatory agents in unipolar depression found that PUFAs were efficacious as adjunctive treatments for MDD if the eicosapentaenoic acid concentration was >60% ($p < 0.001$) [140]. This meta-analysis also found that celecoxib and aspirin had statistically significant effects for the treatment of MDD [140]. A trial assessing the administration of infliximab (5 mg/kg) at weeks 0, 2, and 6 found that patients with elevated C-reactive protein levels were benefitted greatly [141]. Another meta-analysis looking at the effect of these agents in bipolar depression found a moderate and statistically significant antidepressant effect ($p = 0.002$).

8. Triple reuptake inhibitors – amitifadine
Amitifadine (EB1010, formerly DOV 21947) is a triple reuptake inhibitor of serotonin, norepinephrine, and dopamine that was developed by Euthymic Biosciences. A small clinical trial showed that it had significant antidepressant effects in a small sample of patients. Initial animal studies seemed to show an antidepressant response. The drug inhibits the dopamine transporter with 5–10 times weaker potency than it inhibits the serotonin or norepinephrine transporters [142]. A 6-week, multicenter, randomized, double-blind, parallel, placebo-controlled study evaluated the efficacy and tolerability of amitifadine (25 mg or 50 mg) in 63 patients with MDD. At the end of 6 weeks, the drug showed significant differences compared with placebo in HDRS and CGI-S scores ($p = 0.028$); however, this was questioned by a later publication that questioned the methodology of the trial [143]. Only 47% of the patients on amitifadine completed the trial, although no serious side effects were reported [144].

9. Miscellaneous agents
9.1. Histamine (H3) antagonists
Unlike the serotonergic and noradrenergic systems, histaminergic modulation in the central nervous system has not been studied thoroughly. Histaminergic (H) neurons are in the tuberomammillary nucleus in the hypothalamus, and these neurons project to many cerebral regions that are associated with the pathophysiology of depression. The modulation of H receptors may change cognitive function, sleep, motor activity, and eating behavior, all of which are related to symptoms of depression. Indeed, altering H levels was associated with antidepressant-like effects in previous animal studies using forced-swim tests [145]. However, the exact role of H has not been thoroughly investigated because of its complex mechanisms of action with other neurotransmitters and neuromodulators. The H3 receptor is one of the most promising recent drug targets for psychiatric
disorders including depression because it is an auto receptor on histaminergic neurons but a heteroreceptor on nonhistaminergic neurons [146]. Given its pharmacological profile, H3 antagonists may decrease histamine, inhibit the cAMP-dependent protein kinase cascade and calcium/calmodulin pathway, and potentiate the release of other neurotransmitters (i.e. acetylcholine, dopamine, GABA, 5-HT, and peptides) [147]. In a recent animal study, the H3 antagonist clonazolam exerted antidepressant effects and reserved memory deficits [145].

9.2. Captodiamine

Captodiamine is an 5HT2C antagonist and agonist at sigma-1 and D3 dopamine receptors that affects dopamine turnover. In a seminal animal study, captodiamine had effects on hypothalamic CREB phosphorylation and subsequently BDNF transcription. However, no human trials have been performed as of yet [148].

9.3. NSI-189

NSI-189 is a benzylpiperazine-amiophyridine and a novel chemical compound that stimulates human hippocampal neurogenesis in vitro cell cultures and mouse hippocampal neurogenesis in vivo. It exerts specific effects on accelerating neurogenesis in the hippocampus and sub-ventricular zone, but nowhere else in the central nervous system. The drug was developed by Neuralstem; safety data are available, and no major adverse effects have been reported. In a phase 1b study, 40 mg TID of the drug had significant antidepressant effects acutely as well as over a maintenance period of 84 days [149,150]. Trials with bigger sample sizes are underway (NCT02695472 and NCT02724735).

10. SAGE-217

This is a positive allosteric modulator of the GABA receptor that is being developed by SAGE therapeutics. It is an oral active formulation of SAGE-547 (otherwise known as brexanolone which is a proprietary injectable formulation of allopregnanolone) (NCT02288504). SAGE-547 showed preliminary significant results in an open label trial for treatment of postpartum depression. It is currently in phase 3 testing (NCT02942017 and NCT02942004).

11. Psychedelic agents under consideration as antidepressants

Naturally occurring hallucinogens like psilocybin, N, N-dimethyltryptamine (DMT), and D-lysergic acid diethylamide (LSD) have shown promising results in small studies as potential agents for treatment of MDD and anxiety disorders [151]. DMT is the principal psychotropic component of ayahuasca – a psychogenic brew obtained by boiling leaves of various plants used for therapeutic rituals in some South American countries. There has been renewed interest in using hallucinogens for treatment of MDD primarily because of differences in their mechanism of action (greater 5HT2A agonism) when compared to SSRIs [152]. One open label trial evaluated the effect of 2 doses of psilocybin with psychological support, showing promising reduction of patient-reported depressive symptoms [153]. One RCT evaluated the efficacy of low (1–3mg/70kg) and high doses (22–30 mg/kg) of psilocybin in patients with cancer, finding significant reduction in depressive symptoms (p < 0.001) with high dose administration of psilocybin [154]. An open label trial of ayahuasca also showed significant reduction of depressive symptoms with good tolerance and minimal side effects [155,156]. There is potential for using hallucinogenic compounds to treat depressive symptoms in patients with terminal illnesses like cancer [157,158]. As pointed out by a systematic review on effectiveness of psychedelics on treatment of mental illness, more RCTs are needed to delineate treatment potential of these compounds balancing therapeutic potential with recreational abuse potential [151,152].

12. Neurostimulation

Multiple studies have shown the efficacy of ECT compared with algorithm-based pharmacological treatment [159,160]. The recently published results of the Prolonging Remission in Depressed Elderly (PRIDE) study showed that the combination of ultra-brief right unilateral ECT and venlafaxine could improve efficacy [161,162]. TMS has made steady progress in becoming a robust treatment modality for MDD. Evidence from studies supports the efficacy of two protocols in moderate MDD when given daily for 4–6 weeks using a figure-8 coil: (1) high frequency TMS (HF-TMS) (>5 Hz) over the left dorsolateral prefrontal cortex (DLPFC), 3000 pulses per session; and (2) low-frequency TMS (LF-TMS) (<1 Hz) over the right DLPFC, more than 1200 pulses per session [163]. A head-to-head comparison of HF-TMS and LF-TMS involving the 1 Hz and 10 Hz protocols, respectively, did not show any differences between these two protocols [164]. However, the study was underpowered and the literature is limited in this respect. The effects of TMS are maintained over course of months [165]. A recent review detailed new developments in the field of neurostimulation, such as synchronized TMS (sTMS), deep TMS (dTMS), and low-frequency magnetic stimulation (LFMS) [106].

Deep TMS uses an H-coil for penetrating the stimulation to deeper structures. Its efficacy has been demonstrated in multiple studies [166,167]. However, no studies have compared the efficacy of H coils to figure of 8 coils in MDD [106]. In sTMS, individually tailored alpha frequencies are used to influence the stimulus delivery; the goal of the approach is to influence thalamo-cortical oscillations. A trial showed a statically significant reduction in HAMD-17 in per protocol subjects but not in the ITT subgroup [168].

LFMS uses a portable electromagnetic device to administer a low-field stimulation, and has shown some promising results [169]. A multisite trial is underway currently to explore the efficacy of LFMS (NCT01654796, Trial of Low Field Magnetic Stimulation Augmentation of Antidepressant Therapy in Treatment-Resistant Depression (RAPID)).

13. Depressive symptom profile that new agents could treat

A specific area that new agents could target would be as mainstream or adjunctive agents for TRD. Candidates like rapastinel
that channel neuroplastic effects in addition to glutamatergic action have potential to treat depressive symptoms and cognitive deficits that accompany unipolar or bipolar depressive episodes. Esketamine has received breakthrough designation from FDA to treat MDD with suicidal ideation. Candidates like CERC-501 which are being tested in the FASTMAS trial. This envisages a new model of drug testing wherein the goal is to explore a candidate molecule’s effects on potential circuits in the brain-mediating symptoms the drug is intended for. This trial with CERC-501 (NCT02218736) will test effect on reward-related circuitry using a monetary incentive delay task.

14. Expert commentary

We continue to elucidate the pathophysiological basis of MDD. The story of ketamine is like the story of clozapine, with reverse engineering used to try and decipher how the drug works once its effects are seen. A common downstream pathway for the action for ketamine is synaptogenesis; however, the timescale of its effects seems to coincide with the activity of the mTOR pathway. Only one study has tried to measure these biomarkers peripherally in living patients [170]; therefore, more studies are needed to characterize these potential biomarkers for treatment response in MDD. NMDA receptors have substantial inhibitory action in the raphe nucleus and as a consequence it is reasonable to speculate that agonism and antagonism of this receptor changes raphe neural activity leading to differential release of serotonin in the raphe nucleus.

With neurostimulation techniques comes the opportunity to try them in combination with glutamatergic agents other than ketamine. Despite the equivocal response obtained with ECT and ketamine, there is room for research into combinations of other forms of neurostimulation techniques and ketamine. Treatment candidates like NSI-189 and opiate molecules attempt to harness alternative pathophysiological mechanisms of MDD beyond serotonin. As evident from Table 1, agents that do look promising and close to approval seem to be esketamine, rapastinel, and ALKS 5461. More studies are needed to elucidate how psychedelic agents could treat MDD. Based on recent studies on gut microbiome–brain axis, probiotics could be promising treatment candidate for MDD [171]. Monoclonal antibodies designed to treat MDD are candidates for the future [172].

There is an unmet need for more trials to test the efficacy of these agents alone and in combination with currently FDA-approved serotonergic antidepressants. Focus on the inflammatory hypothesis of MDD and neuroplasticity driving the treatment response would be instrumental in designing new molecules. This advocates for the fact that there may be other mechanisms that mediate MDD beyond the monoamine and glutamatergic hypotheses [173]. With advent of new treatments, a pertinent goal for the future is personalized precision medicine for MDD using a combination of biomarkers that target genomics, serum markers, imaging, and EEG [156, 157].

15. Five-year view

A journey for potential antidepressants has transcended TCAs, SSRI’s and finally glutamatergic agents like ketamine. The landscape of the field in the next 5 years would be speculative. We would like to point attention to NSI-189 which has a unique mechanism of action and acts via neurogenesis. Histone deacetylase inhibitors also look promising to treat depressive disorders given their potential for sensory extinction and consolidation of long-term memory in animal models via epigenetic changes. For human trials, stereotactic application to specific brain regions would be required.

Key issues

- There is a huge unmet need in the treatment of MDD as shown by studies like STAR-D and CO-MED. Burgeoning costs related to treatment, reduced productivity and absenteeism are evidence for the same too.
- Glutamatergic receptors mediate synaptic plasticity through LTP and LTD. Glutamatergic antidepressants like ketamine, esketamine, trazopridol and rapastinel have shown promise in treatment of MDD.
- Through basic science studies and translation of this work to human trials, opioid agents like buprenorphine, ALKS 5461 and CERC-501 have shown efficacy in treatment of MDD.
- Histamine antagonism, cholinergic modulators like scopolamine, anti-inflammatory agents and novel molecules such as NSI-189 are upcoming candidates for treatment of MDD.
- Modalities like neurostimulation have potential for being combined with glutamatergic agents to leverage synergistic neuroplasticity in treatment of MDD.

Funding

This paper was not funded.

Declaration of interest

P.S. Masand is a consultant to Allergan, Lundbeck, Otsuka, Pfizer, Sunovion and Takeda. He receives research support from Allergan and Merck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Writing assistance was utilised in the preparation of this manuscript, it was funded by P.S. Masand and carried out by Laura Cobb.

References

Papers of special note have been highlighted as either of interest (-) or of considerable interest (-) to readers.

   • This reference is a meta-analysis of antidepressant trials for MDD.
   • Publications 1 and 2 point out the efficacy and effectiveness of currently used antidepressants in meta-analyses
The search for new antidepressants was fuelled by the STAR-D trial that objectively evaluated the effectiveness of current antidepressants


This details an overview of various definitions of treatment-resistant depression, providing a new perspective


74. Cornerstone paper for using esketamine to treat MDD


92. Hashimoto K. Comments on an innovative design to establish
109. Lauterbach EC. Treatment resistant depression with loss of antide-
111. Liu BB, Luo L, Liu XL, et al. 7-Chlorokynurenic acid (7-CTKA) pro-
pipeline/av-101.
114. Kennedy SE, Koepp RA, Young EA, et al. Dysregulation of endo-
118. Carlezon WA Jr., Krystal AD. Kappa-opioid antagonists for psychia-
123. Wentland MP, Lu Q, Lou R, et al. Synthesis and opioid receptor binding properties of a highly potent 4-hydroxy analogue of nal-
124. Fava M, Memisoglu A, Thase ME, et al. Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inad-
125. Lowe SL, Wong CJ, Witcher J, et al. Safety, tolerability, and phar-


139. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139:230–239.


- A potential compound that treats MDD with inducing neuroplasticity


- Elucidates the potential for psychedelics to be treatment agents for MDD and anxiety in a review of all published studies


- A recent systematic review on trials of novel antidepressant agents