

## NEUROPLASTICITY IN DEPRESSION: A NARRATIVE REVIEW WITH EVIDENCE-BASED INSIGHTS

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### SUMMARY

Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide. The current pharmacological treatment options for MDD, which rely on the mono-amine hypothesis, has their limitations with respect to treatment non-response, partial response etc. This propels for a search for a novel neurobiological understanding of MDD that can lead to novel treatment options. A literature search strategy was thus employed using relevant keywords pertaining to the topic in PubMed, Embase and Google Scholar. Systematic reviews and meta-analyses, narrative reviews and clinical trials were reviewed to incorporate the most robust evidence-based literature available. A total of 37 publications were narrowed down based upon the topic. Alterations in brain neuroplasticity, as evidenced by changes in neurotrophic factors and from neuroimaging, has been found to be a strong patho-mechanism for MDD. This link has been exploited to stimulate psychopharmacological research to treat MDD.

**Key words:** neuroplasticity – depression – BDNF – antidepressant - ECT

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### INTRODUCTION

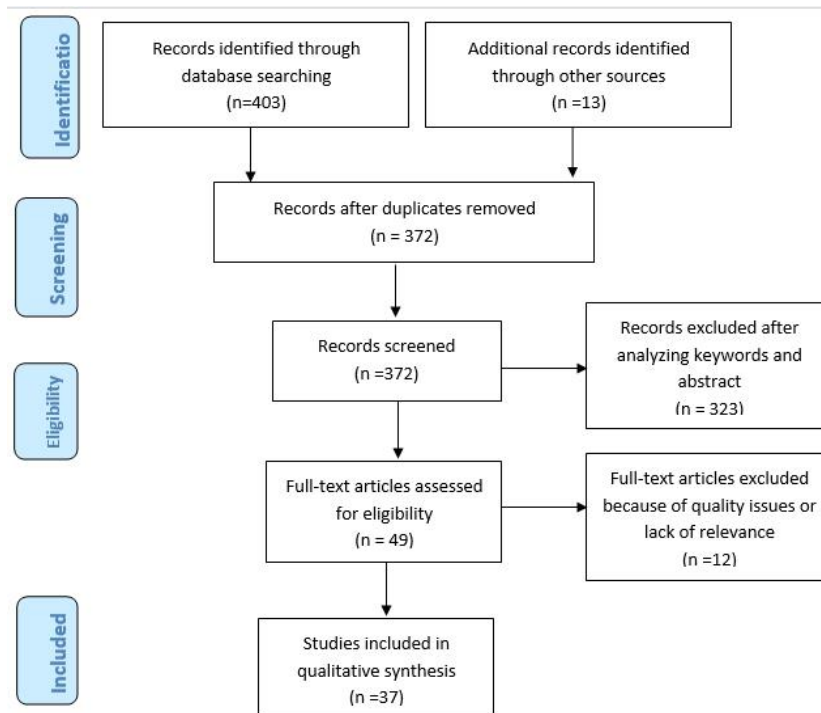
Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide that has an overall global lifetime prevalence rate of 20% and is among the leading contributors to the global burden of disease (Whiteford et al. 2013). It has widespread deleterious effects not only on the psychological apparatus of the sufferer, but it also affects the physical health and worsens any pre-existing illness/ disorder. Antidepressants and various form of psychotherapeutic interventions forms the major treatment options for depression. Majority of the work on finding a new antidepressant is based on the monoamine hypothesis of the disorder involving the serotonin (5HT), nor-epinephrine (NE) and the dopamine (DA) neurotransmitter system. The available antidepressant (AD) psychopharmacological armamentarium, alone or in combination, has shown higher rates of partial, non-response or delayed response with limited duration of efficacy (Gaynes et al. 2009). Since evidence for limitations in their antidepressant effect are accumulating, there remains a need to re-look MDD from a subtly different neurobiological perspective which might pave newer avenues in its management. Neuroplasticity forms the major chunk of this search. The neuroplasticity hypothesis of MDD offers to explain that distortion in neural plasticity is a primary patho-mechanism of the disorder (Price & Duman 2020). This has inputs from the monoamines (primarily 5HT), that along with their interplay with various neurotrophic factors, forms the pathological basis of the genesis of this psychiatric disorder. The

current paper gives a narrative review of the novel link between neuroplasticity and MDD in the light of existing neurobiological explanations of this disorder and attempts to provide a brief exploration of newer researched pharmacological options to treat this disorder.

### METHODOLOGY

The search strategy employed for the topic included a thorough literature search from three databases (PubMed, Embase and Google Scholar), with combination of key terms including 'neuroplasticity', 'depression', 'Major Depressive Disorder', 'synaptic plasticity', 'neurotrophic factors', 'BDNF' and 'neurogenesis'. The initial search returned 416 records from all the databases from where 372 articles were found after removing duplicates (Vide PRISMA flowchart, Figure 1).

Next, we determined the inclusion and exclusion criteria. The search results were confined to journal articles written in English and matching the eligibility criteria. We first reviewed the titles and abstracts for each of the 372 articles to determine its relevance and articles were excluded only if they did not report neuroplasticity in depression. Following the criteria set out above, 323 studies were eliminated, and 49 studies were retained. These studies were then evaluated by going through the whole article. At least three authors independently reviewed each abstract. Minor disagreements were addressed in a meeting that resulted in an agreement, and finally 37 articles were retained. The manuscript was drafted based upon these final articles.



**Figure 1:** Study selection, assessment, and inclusion (presented using the PRISMA flow diagram)

## WHAT IS NEUROPLASTICITY?

The concept of neuroplasticity is not new. The basic tenet of the plasticity model of central nervous system (here brain) proposes that human brain is not a rigid organ as was believed earlier, rather it's a malleable one that constantly generates, regenerates, wires and re-wires in response to various internal and external feedbacks. This is the theoretical basis of neural plasticity, a blanket term used to describe anatomical and physiological changes in the brain in response to various stimuli, by responding to them and effecting a change in structure, function and/ or connections (Cramer et al. 2011). It includes a host of inter-related mechanisms that encompasses neurogenesis (in some brain areas like the dentate gyrus), morphological modification of mature neurones involving axonal and dendritic arborization and pruning, an increase in spine density, synaptogenesis, and at a deeper functional level with Long Term Potentiation (LTP). Synaptic plasticity is a specific form of neuroplasticity wherein these changes occur to modify synaptic transmission according to subsequent stimuli. These mechanisms finally trickle down to dynamic and adaptive strengthening of the neuronal synapses and thus the entire brain (Duman et al. 2016).

## NEUROPLASTICITY AND DEPRESSION

The neuroplasticity hypothesis of major depressive disorder proposes dysfunction of neural plasticity as the basic patho-mechanism of this disorder (Duman et al. 2016). Evidence for this emerge from various neuroimaging techniques using various paradigms, animal models and also from post-mortem analysis of depres-

sed patients. These findings reveal alterations in neurogenesis, gene expression, intracellular signaling, neurotrophic factors, as well as alteration in neurotransmission, synaptic number and function, which has been observed/ studied in brain areas linked with depression (Price & Duman 2020).

The various brain areas which are implicated in MDD viz, the hippocampus, ventral tegmental area of midbrain and its connection with the nucleus accumbens of the limbic system (VTA-NAc), the prefrontal cortex (PFC), amygdala and the hypothalamis-pituitary axis (HPA), all are involved in a closely knit interplay with the monoamines for depression (Dean & Keshavan 2017). Recent accumulated evidence shows that neuroplasticity is the common mechanism linking all these brain areas with the neurotransmitters for the genesis of depression (Price & Duman 2020). Here also comes the role of neurotrophic factors viz, the Brain Derived Neurotrophic Factor (BDNF), Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor (IGF) etc (Levy et al. 2018). MDD is proposed to occur as a result of the myriad interactions of these neurotrophic factors (esp, BDNF) and the neurotransmitters (esp 5HT, Glutamate) in putative brain regions, being affected by various external and internal stimuli (eg, stress).

## NEUROTROPHIC FACTORS (NF) AND THEIR ALTERATIONS IN DEPRESSION

Of all the NFs, BDNF appears to play the major role in MDD. BDNF is a neurotrophin that has been implicated for neurogenesis, neuronal survival and synaptic plasticity. It exerts this neuroplastic effect mainly

through activation of the tropomyosin-related kinase receptor B (TrkB) (Levy et al. 2018). The role of BDNF in neuroplasticity comes from both in-vitro and in-vivo studies. BDNF stimulation of B27-deprived primary hippocampal cells has shown to promote dendritic outgrowth and spine formation (Park et al. 2016). In-vivo studies have employed rodent models to study BDNF and its role in neuroplasticity. BDNF microinjection in rat hippocampus has shown to induce LTP that triggers synaptic strengthening (Ying et al. 2002).

Serum BDNF has been found to be low in patients with MDD (Molendijk et al. 2014). Brain BDNF has been proposed to be a better marker for depression and its expression has been found to be lower in Anterior Cingulate Cortex (ACC) of depressed patients in post-mortem analysis compared to healthy subjects (Youssef et al. 2018). A reduction of brain BDNF and TrkB has also been found in hippocampus of post-mortem brain studies of those who died by suicide (Pandey et al. 2008).

The most compelling link proposed for the association between BDNF and MDD comes from the stress model of MDD. While acute stress invokes a transient fight and flight response involving the autonomic nervous system, it's the chronicity of stress that underlays various forms of psychiatric disorders including MDD (Dean & Keshavan 2017). Chronic stress is linked with depression by decreasing BDNF expression that leads to neuronal atrophy and synaptic dysfunction (and hence plasticity) in hippocampus and PFC (Duman et al. 2016). This results in deficient neuroadaptation, decreased coping and cognitive deficits very frequently seen in MDD.

Serotonin (5HT), the principal neurotransmitter associated with the pathophysiology of MDD has been proposed to have distinctive neuroplastic capability. 5HT and its receptors has close molecular connections with BDNF and other neurotrophic factors. It also modulates glutamatergic neurotransmission and N-methyl D-aspartate (NMDA) receptor mediated plasticity (Kraus et al. 2017, Deutschenbaur et al. 2016). 5HT is also linked with cell adhesion molecules which are important for neuroplasticity (Varea et al. 2007). There is also indirect evidence for the role of 5HT in neuroplasticity in MDD which comes from treatment with antidepressants especially the selective serotonin reuptake inhibitors (SSRIs). Antidepressants have been demonstrated to increase BDNF levels as found in post-mortem brain (dentate gyrus, hilus and supragranular region of hippocampus) of treated depressed patients than those who were treatment naive (Chen et al. 2001). Chronic treatment with the SSRI Fluoxetine has shown neurogenesis in dentate gyrus of hippocampus (Micheli et al. 2018).

The role of Glutamate and NMDA receptors cannot be overlooked here. Glutamate, being an excitatory neurotransmitter needs to function optimally (the balance between excitotoxicity and optimal excitatory functioning) for an adequate dendritic branching and synaptic functioning. It plays a crucial role in neuronal migration, neurogenesis and pruning, where both the

metabotropic and ionotropic receptors appears to be involved. An excessive glutamatergic neurotransmission has been found to cause excitotoxicity wherein dendritic retraction, neuronal atrophy and loss occurs (Jia et al. 2015, Deutschenbaur et al. 2016). Glutamatergic neuronal synapses, for their optimal functioning are regulated by circuit activity and function, including activity-dependent release of BDNF and downstream signaling pathways. Stress, as described before, leads to decreased BDNF expression and release which leads to depression (Deutschenbaur et al. 2016). The role of Glutamate in depression is strengthened by the fact that ketamine, a NMDA receptor antagonist, has an antidepressant activity. Ketamine exerts its antidepressant effect through NMDA receptor antagonism on inhibitory gamma-aminobutyric acid (GABA)-ergic neurons, that results in disinhibition of glutamate transmission. This causes a burst of glutamate release, which has been proposed to increase BDNF release and function, thus ultimately causing an increase in synaptic protein synthesis and thus synaptogenesis. These new synapses and their connectivity maintain proper circuit function and thus normal mood and emotional state, a proposed mechanism for ketamine's antidepressant effect (Deutschenbaur et al. 2016). The NMDA receptor is also responsible for LTP which is a major form of use-dependent synaptic plasticity. NMDA receptor activation leads to easier stimulation of pyramidal neurons. Therefore, the synaptic efficacy increases persistently, resulting in LTP (Lau et al. 2009). These are important for neuroplastic effect on the hippocampus, mediated by BDNF, which is one of the target brain regions impaired in depression.

## EVIDENCES FOR NEUROPLASTICITY IN DEPRESSION FROM NEUROIMAGING

One of the most important evidence for reduced/disturbed neuroplasticity in certain brain regions in depression comes from neuroimaging. These have shown volume and connectivity distortions in hippocampus, PFC, Ventral striatum and amygdala, which singly and along with their functional connectivity with other brain areas, have repeatedly shown to have a neuropathogenic role in MDD (Levy et al. 2018). Grey matter volume in these brain areas provides an indirect indicator of neuronal density and changes in grey matter volume (GMV) are considered the surrogate marker of neuroplasticity (Zatorre & Fields 2012).

The hippocampus, being a major component of the limbic system, is highly vulnerable to both acute and chronic stress. This vulnerability predisposes hippocampal dysfunction, which translates into cognitive and emotional disturbances, both of which are important psychopathological disturbances in MDD (Kim et al. 2015). The molecular mechanisms underlying this is ascribable to reduction of BDNF expression (discussed earlier) which results in neuronal and synaptic loss and thus reduced neuroplasticity. This neuronal loss is evident as loss of GMV in Magnetic Resonance Imaging

(MRI) studies of hippocampus and other brain areas. Hippocampal GMV loss is revealed in patients suffering from both first episode and recurrent depression in MRI (Cole et al. 2011, Frodl et al. 2007). This finding gets further strengthened with a meta-analysis that showed volumetric reduction in hippocampus in those patients with MDD who either had an illness duration of more than 2 years or with recurrence of the disorder (at least more than one episode) (McKinnon et al. 2009). However, there lies a debate whether hippocampal GMV reduction predates depression or is an aftermath of the disorder (Sheline 2011). This decrement in hippocampal volume is because of reduced neurogenesis and differentiation in certain areas, specifically the dentate gyrus, often mediated by chronic stress and its deleterious effect on the HPA axis (Eisch & Petrik 2012). This has also been ascribed to reduced cell numbers, predominantly astroglial and granule cells, and reduced cell and neuropilin volumes mainly in the anterior hippocampus in animal models and also in post-mortem analysis of depressed patients (Willard et al. 2013, Stockmeier et al. 2004). Reduction in hippocampal volume has also been associated with childhood maltreatment as like any form of chronic stress as mentioned before (Teicher et al. 2012). These studies showing reduced cell numbers, neuropilin and grey matter volumes indicate an impairment of developmental or adult neuroplasticity in MDD. Recently, explored shreds of evidence point to stress-induced microglial activation as a key contributor to synaptic remodelling (Singhal & Baune 2017), however, the way antidepressants or brain stimulation affect microglial responses in humans is still to be understood. Altogether, these findings provide further evidence of the crucial role of the hippocampus in depression and the mediating role of an altered neuroplasticity.

The PFC is also affected in MDD as evidenced by a reduction in volumes of its different areas in patients with a diagnosis (Drevets 2000). This is supplemented with post-mortem brain findings of depressed patients which showed reduced neural cell size, neural and glial cell densities as well as synapse number in the dorsolateral and subgenual PFC (Cotter et al. 2002). The ventral striatum is also linked with the neuroplastic pathophysiology of MDD. The anhedonia component of MDD is mainly associated with this neuroanatomical area, wherein a reduced activation of the VTA-NAc (mesolimbic) tract is observed (Belujon & Grace 2017). Stress, whether acute or chronic has also been found to bring about changes in this dopaminergic reward system. Chronic stress has been studied (by using various paradigms in rodent models) to bring about a change in this reward pathway unlike stress which are acute and transient in nature. Prolonged exposure to unavoidable stressors decreases DA and DA metabolite in the NAc of stressed animals. Rats exposed to unavoidable stress for 3 weeks in an experimental stress paradigm show reduced DA release in the NAc shell (Mangiavacchi et al. 2001). There are contradictory findings as well that shows no change in DA release in

NAc after exposure to Chronic unpredictable mild stress (CUMS), a paradigm akin to chronic stress in mice (Di Chiara & Tanda 1997). This VTA-NAc reward pathway is also susceptible to chronic stress induced neuroplastic changes that affects the dendritic spine structure and density in the medium spiny neurones of NAc, a proposed model for depression, though contradicted (Baik 2020).

The amygdala is also intricately involved in the cognitive and emotional (esp. anxiety and fear) aspects of the depressive symptom rubric, which is amenable to antidepressant treatment (Godlewska et al. 2012). Being an important part of the limbic system, amygdala has been studied by neuroimaging techniques and on rodent stress paradigms to study its role in depression. While an increase in amygdalar volume in MRI brain studies of depressed patients has been found (Vassilopoulou et al. 2013), few others showed the opposite (Bellani et al. 2011). Depressed patients tend to highlight the negative aspects of their life more (selective abstraction), which could explain amygdalar hyperactivity in neuroimaging of depressed patients presented with negative/ threatening stimuli (Hamilton & Gotlib 2008). Amygdala is also sensitive to neuroplastic changes in MDD. Exposure to chronic stress in an experimental set-up in mice has shown an increased dendritic arborization, elongation, and spine density, that indirectly provides evidence for increased amygdalar synaptic connectivity and thus synaptic plasticity (Vyas et al. 2006). All these neuroimaging evidence thus provides ample evidence for the association between neuroplasticity and its changes in various putative brain regions which are implicated for MDD and thus further strengthens the neuroplastic hypothesis of the disorder.

## **UTILIZING NEUROPLASTICITY IN TREATING DEPRESSION: EVIDENCE FROM EXISTING TREATMENTS FOR MDD**

Researchers have explored ways to tackle neuroplasticity to promote healing and recovery. Although these efforts are still in the primitive stages, there is favourable evidence that the dynamic qualities of the brain may play a central role in how one manages stress and mental illness, depression being one of the fore-runners (Cramer et al. 2011). Medications have been shown to affect neuroplasticity in animal trials and in few human studies. As noted previously, antidepressant medications can reverse the effects of various types of chronic stress on both behaviour and brain structure. The current treatment armamentarium for depression includes pharmacotherapy, somatic treatments like Electroconvulsive therapy (ECT) and Repetitive Transcranial Magnetic Stimulation (rTMS) in conjunction with exercise and psychotherapy. Nearly all these treatment modalities effects neuroplasticity that spirals down to their efficacy in MDD.

Antidepressants (AD) may promote neuroplasticity by an increase in BDNF mRNA levels (Cattaneo et al. 2010). This activates the tyrosine kinase receptors and triggers the intracellular cAMP-dependent protein kinase and mitogen-activated protein kinase etc. These then activate transcription factors like the cAMP-responsive element binding-protein (CREB) which ultimately leads to translation (protein synthesis). The end results are structural changes in specific regions in the brain, one of the mechanisms underlying the treatment of MDD (Rădulescu et al. 2021). Of special mention here is the role of synaptic serotonin in stress-induced dendritic remodelling. An increase in AD induced serotonin in serotonergic synapses has been found to increase and strengthen neural plasticity (Rădulescu et al. 2021). SSRIs have been shown to promote hippocampal neurogenesis by increasing BDNF (Cattaneo et al. 2010). These are one of the putative mechanisms in the treatment of MDD.

ECT has also been shown to strongly enhance brain neuroplasticity. ECT has been shown to increase hippocampal volume in volumetric MRI brain study in patients with depression (Nordanskog et al. 2010). It has been shown to induce brain BDNF and hippocampal neurogenesis in rodent brain model, suggesting its role in synaptic plasticity (Angelucci et al. 2002). Since increase in BDNF is closely associated with successful treatment of MDD, ECT has one possible anti-depressant mechanism here, which further proves the role of neuroplasticity in MDD.

rTMS, a novel neuromodulation therapy, can also find a mention here. In a sham-controlled study that investigated the longitudinal effects of rTMS on the volumes of the hippocampus and amygdala and cortical thickness in patients with Treatment Resistant Depression (TRD), it was observed that patients who received rTMS on left DLPFC vs sham had significant increase in cortical thickness in the paralimbic cortex which was independent of an actual treatment response. The authors concluded that this is due to neuroplasticity induced by rTMS in their patients with MDD (Dalhuisen et al. 2021).

Exercise has also been found to modulate neural plasticity, thus playing an important role in the treatment of MDD. It has also been demonstrated to increase brain BDNF, thus playing a role in the treatment of depression (TaheriChadorneshin et al. 2017).

Of special mention here is the role of NMDA receptor antagonist Ketamine, which recently got FDA approval for the treatment of depression (Deutschenbaur et al. 2016). Harnessing the glutamatergic neuronal activity in the neuroplastic pathophysiology of depression, Ketamine has shown its effect by increasing BDNF and thus synaptic and neuronal plasticity (mentioned above).

All these established pharmacological (AD, Ketamine, ECT and rTMS) and non-pharmacological (Exercise) approaches to treat MDD thus has been found to eventually effect brain neurotrophic factors and neuroplasticity in managing depression. This further provides indirect evidence as to the role of neuroplasticity in MDD.

## UTILIZING NEUROPLASTICITY IN TREATING DEPRESSION: NEWER TREATMENT INSIGHTS?

Research is ongoing to exploit neuronal and synaptic plasticity for treating MDD. The past few years has borne witness to this and on days to come, many novel mechanisms of therapy will be in place with an endeavour to overcome the apparent pharmacodynamic limitations of currently available AD therapy in treating the disorder. The BDNF and TrkB signalling pathway is the major endpoint of such research. BDNF itself cannot be used to alleviate depressive symptoms because of its poor blood-brain barrier (BBB) penetrability and its transient half-life (Levy et al. 2018). Recent research novelty has thus shifted its focus on TrkB receptor pathway instead (Tsai 2007). These includes the TrkB agonists like 7,8-Dihydroxyflavone (DHF) which has been studied extensively to have shown antidepressant properties (Levy et al. 2018). DHF administration has been demonstrated to show neurogenesis in mice hippocampus (Liu et al. 2010). Unlike BDNF, DHF has properties like good BBB penetrability, and it has been used with promising results in various animal models in disorders that exhibited BDNF deficiency like MDD, Cognitive decline etc (Liu et al. 2016). Other promising TrkB agonists studied are Deoxygedunin, which mimics BDNF and induces neurogenesis (Nie et al. 2015) LM22A-4, TDP-6, TAM-163 and BMS355349 (Levy et al. 2018).

TrkB antagonists like ANA-12 and Cyclotraxin-B has also been studied in this context. While the former is a selective partial agonist, the later acts as an antagonist in the BDNF/ TrkB signalling pathway (Levy et al. 2018). Cyclotraxin-B has been demonstrated to be capable of altering TrkB-dependent molecular and physiological processes such as synaptic plasticity, neuronal differentiation and BDNF-induced neurotoxicity. Its administration in mice brain has shown anxiolytic property but no significant antidepressant activity (Cazorla et al. 2010).

There are other newer molecules studied in this context which emerged after ketamine has shown to be effective for MDD. One such is Lanisemine, a non-selective NMDA antagonist, which has shown a rapid onset of antidepressant activity in TRD (Zarate et al. 2013). Other molecules acting on NMDA and other glutamatergic receptors are majorly investigational and details of them can be found in a near recent review (Gerhard et al. 2016).

The current review is not without any limitations. It has reviewed literature pertaining to those which mentioned evidence of neuroplasticity to be a core brain mechanism working in depression from neurochemistry and neuroanatomical (neuroimaging) perspectives. A systematic review on this topic would have provided better and focused insights into this. Secondly, the studies included have not specifically mentioned whether neuroplastic brain changes are a cause or effect of the clinical syndrome called depression. This is important,

since in case of the later, we need to speculate whether newer molecules targeting neurotrophic factors implicated in neuroplasticity (for depression) will actually cause a statistically significant remission of symptoms of depression or not. If the former holds true, then research should move in the direction of finding appropriate treatments for preventing the onset of depression. Another question that arises here is whether neuroplastic brain changes are state or trait markers in depression. If the later holds true, then it might have an importance from an endophenotypic point of view. Despite the above, it needs to be mentioned that neuroplasticity is a novel way to understand depression. In years to come, this might stimulate further research into looking for neuroplastic properties of the existing antidepressants alongside the novel emerging treatment methods as discussed above.

## CONCLUSION

Growth factors, neurotrophins and neuroplasticity thus finds a major role in the pathogenesis of MDD. It's a well-knit highly concerted mechanism that also involves the well-known monoamines in the neurobiological understanding of the disorder. There still lies controversy as to whether these neuronal and synaptic changes are a precursor to the disorder, or they are a consequence/ aftermath of depression or even whether they are an epiphenomenon to it. Newer investigational molecules have shown subtle promise in their antidepressant effects as like the age-old antidepressants and somatic treatment modalities, and these strengthens us to believe in the neuroplastic hypothesis of the disorder. Future research will be needed to harness this novel neurobiological area in order to better understand the pathology of MDD so as to formulate newer and novel pharmacological treatments for depression. Ketamine has already found its place in this psychopharmacological armamentarium albeit with many controversies, but it seems that this has opened the door to the inflow of other novel agents.

### Contribution of individual authors:

Shiv Kumar Mudgal was involved in study conceptualization, data collection and writing the first draft.

Santanu Nath was involved in study conceptualization, data collection and finalizing studies for inclusion in the review. He wrote the full draft.

Jitender Chaturvedi was also involved in study conceptualization and designing. he was involved in drafting the manuscript along with other authors and checking the final manuscript.

Suresh Kumar Sharma was involved in study conceptualization and checking the final manuscript before submission.

Jaydeep Joshi was involved in study designing, a part of data collection and modifying the final manuscript before submission.

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