Introduction: unmet needs in the treatment of major depressive disorder

Major depressive disorder (MDD) is one of the most common and disabling psychiatric conditions worldwide and is associated with significant disability and functional impairment. Although many medications are available for this complex disorder, antidepressant treatment is mainly limited by: delay in the onset of therapeutic effects, poor adherence and adverse long-term effects (in particular weight gain and sexual dysfunction). In addition, according to the STAR*D trial of Nierenberg et al., although most of the investigated patients responded to commonly available psychoactive treatments and achieved remission, they still suffered from at least one residual depressive symptom, which is a known predictor of relapse/recurrence in the long-term. Moreover, non-response to traditional antidepressants is another relevant issue, as more than 20% of MDD patients do not respond or don’t recover completely from their illness. These individuals may be considered as affected by treatment-resistant depression.

Given that first-line antidepressant medications mainly target the reuptake or breakdown of monoamines, this further highlighted the need to extend the knowledge on MDD pathogenesis and to promote the translation of such findings into novel, effective therapeutic agents. Over the last two decades, research have discovered several novel molecular targets which may be actively involved in the pathophysiology of MDD. This knowledge has provided intriguing insights into the development of novel antidepressant molecules, some of which have already passed rigorous clinical testing.

The aim of the present review was to summarize the relevant research on novel molecular/cellular targets and recently marketed antidepressant medications which may change the landscape of the treatment of major depression in the near future.
advantage in terms of safety and tolerability; in the early 1990s serotonin and norepinephrine reuptake inhibitors (SNRIs) were introduced, including venlafaxine, desvenlafaxine and duloxetine, together with modern SSRIs such as sertraline, paroxetine, and citalopram. The latter are generally regarded as first-line treatment for a depressive episode, but, as stated above, they result in the remission of only a subset of patients.

Whereas, the following treatment options are currently recommended for patients that do not respond to antidepressant treatment: 1) revision of the psychiatric diagnosis; 2) medication augmentation; 3) switch to another antidepressant medication. The substitution of first-line antidepressant with another first-line medication is currently the most commonly used therapeutic strategy. However, two consecutive trials with different psychoactive medications usually require approximately 6 weeks, and the delay in achieving adequate antidepressant effects is associated with relevant drop-out rates from treatment (at least 50% of patients), which commonly occurs within the first months of treatment. Thus, in order to correctly treat depression and achieve remission it would be fundamental to rapidly identify the correct treatment option.

Current guidelines advise against combination treatment has been commonly mainly due to the enhanced risk of medication interactions and poor tolerability. Whereas, the use of antidepressant combinations with additive mechanisms of action may represent a useful strategy before augmenting with medications of different classes. Interestingly, combining different pharmacological actions affecting multiple monoamine targets is associated with greater efficacy: this reinforces the notion that is may be possible to further improve the outcomes of depression by integrating novel pharmacological agents with different mechanisms of action.

Novel molecular targets of antidepressant drugs: neurotrophins and intracellular pathways

The neurotrophic hypothesis of depression. Neurotrophic factors play a fundamental role in neuronal development, growth, survival as well as neuroplasticity. Whereas, chronic stress is associated with a significant reduction in hippocampal neurotrophins levels and volume, as is commonly observed in depression. These and other findings support the neurotrophic hypothesis of depression, postulating that the long-term effects of stress/depression are mediated by a deficiency of neurotrophins. According to this hypothesis, altered neurotrophic signaling is viewed as one of the most relevant factors in the pathophysiology of major depression. Consistently, the latency of antidepressant action is explained with that of neuroplasticity, which is usually occurs after 3-4 weeks of treatment with traditional antidepressant drugs.

Hippocampal neurogenesis is regulated by several neurotrophic factors such as brain-derived-neurotrophic factors (BDNF), insulin-like growth factor I (IGF-I), and vascular endothelium growth factor (VEGF-B). Chronic mild stress has been reported to be associated in animal models with a general reduction of neurogenesis together with reduced hippocampal BDNF levels. Importantly, antidepressant drugs may reverse stress-induced changes and enhance neurogenesis by normalizing BDNF levels. Indeed, by inhibiting 5-HT2A/2C receptor, these molecules are able to reverse stress-induced downregulation of BDNF mRNA in the hippocampus leading to adaptations of synaptic strength that may mediate either some short- and long-term behavioral effects of these compounds.

Hippocampal neurogenesis may be also enhanced by VEGF as observed by the decline of immature neurons in VEGF-B knockout mice. Kiuchi et al. suggested that VEGF Flk-1 (a Receptor for VEGF) signaling plays a crucial role in ameliorating the adult hippocampal cell proliferation together with the survival of newly hippocampal neurons promoted by antidepressants. Interestingly, after silencing of hippocampal VEGF or using antagonists for its receptor Flk-1, VEGF antidepressant-like properties are interrupted and it has been reported that markers of newborn neurons as doublecortin were drastically reduced. Both electroconvulsive therapy (ECT) and some antidepressant medications are associated with the up-regulation of VEGF, and even the local VEGF administration increases hippocampal neurogenesis. Peripheral administration of IGF, a liver-secreted peptide under the control of growth hormone (GH), was reported to increase hippocampal cell proliferation, enhance exercise-induced increases in neurogenesis, and exert antidepressant-like properties are interrupted and it has been reported that markers of newborn neurons as doublecortin were drastically reduced. Both electroconvulsive therapy (ECT) and some antidepressant medications are associated with the up-regulation of VEGF, and even the local VEGF administration increases hippocampal neurogenesis.
be an effective target for the development of novel antidepressant agents. Furthermore, Malberg et al. 40 reported that medications inhibiting binding proteins for IGF-1 (thus, increasing the effects of free IGF-1), may produce both antidepressant-like or anxiolytic effects in mice. Overall, targeting VEGF 34 and IGF 41 42 has yielded interesting results and a new therapeutic strategy to develop innovative antidepressant agents. Other neurotrophic factors such as fibroblast growth factor-2 and nerve growth factor have also been proposed to enhance adult neurogenesis and may serve as novel potential therapeutic targets for the treatment of MDD. However, further studies are required to establish the clinical efficacy and tolerability of neurotrophic agents, and whether their effects are uniquely due to their impact on neuroplasticity 43.

The Cyclic Adenosine Monophosphate Pathway (CAMP) is an important intracellular cascade which is involved in the pathophysiology of major affective disorders; therefore, its components have been generally identified as possible targets for antidepressant agents 44. Notably, antidepressant-like effects have been provoked in animals by suppressing cAMP degradation with rolipram, or directly injecting cAMP 45 46. The PKA is activated by cAMP: consequently its activity is increased after chronic treatment with antidepressants 47. Once PKA is activated, it phosphorylates CREB, the involvement of which in the pathophysiology of major depression is well known. A close interaction between the cAMP cascade and VEGF expression has been suggested by Lee and colleagues 35; relevantly, antidepressant treatment has been associated with increased VEGF levels 35. Both BDNF and VEGF genes have been reported to be regulated by CREB 48-51; CREB, in particular, is a crucial regulator of BDNF synthesis and is virtually involved in most aspects of neuroplasticity 52 53.

Antidepressant medications may not only enhance the phosphorylation of CREB but also the Ca2+/calmodulin-dependent protein kinase II 54 55. Interestingly, chronic treatment with agomelatine has been reported to normalize hippocampal levels of phosphorylated p-CREB, mGlu2/3, and mGlu5 metabotropic glutamate receptors that are involved in the pathophysiology of major depression 56. It is important to note that some antidepressant drugs such as tianeptine are able to restore stress-induced changes of the transcription factor c-fos, which is considered one of the fundamental markers of the biochemical activity 57 58.

Notably, a novel target for antidepressants activity has been identified in the exchange protein directly activated by cAMP (EPAC) as supported from experimental data emerged from postmortem samples in the hippocampus of depressed individuals 59. EPAC is able to regulate the release of glutamate in central neurons, but the specific effects of this regulation is still unclear. There are two isoforms of EPAC proteins (EPAC1 and EPAC2), each having multiple domains, with one or two cAMP regulatory binding motifs, respectively 60 61. EPAC1 and/or EPAC2 proteins are expressed throughout the brain development, particularly in the hippocampus, striatum, and prefrontal cortex formation 45 62. Dwivedi and colleagues 59 reported that Rap-1, one of the major substrates of PKA, was significantly reduced in the prefrontal cortex and hippocampus of depressed subjects who died by suicide whereas protein level of only Epac-2 was significantly increased in the prefrontal cortex and hippocampus of these individuals. This differential regulation of Rap-1 and EPAC and their possible involvement in the pathophysiology of depression suggest that these molecules may be considered novel potential targets for antidepressant treatment.

Wnt/β-Catenin pathway. Several intracellular processes such as neural differentiation 63, hippocampal formation 64 65, dendritic morphogenesis 66 67, axon guidance 68 69, synapse formation 70, spatial learning 71, and memory, including long-term potentiation (LTP), seem to be regulated by the Wnt/β-catenin pathway activity 44. Depressed patients and young subjects who died by suicide showed impairments of Wnt/β glycogen synthase kinase-3beta (GSK-3β) signaling as well as a significant decrease of β-catenin expression in the prefrontal cortex. Interestingly, antidepressant medications and mood stabilizers such as valproate, lithium, and antipsychotic drugs have been reported to control both GSK-3 β and β-catenin expression 72-78. These compounds may induce antidepressant-like effects or reduce anxiety by inhibiting GSK-3β, thus enhancing brain β-catenin levels 74 79-82. GSK-3β knock-in mice demonstrated impairment of cell proliferation throughout the subgranular zone (SGZ) of the dentate gyrus, a significant reduction of VEGF levels, and impaired neurogenesis in response to antidepressant drugs 83. The antidepressant-induced β-catenin increase has been observed in the SGZ of the dentate gyrus, both in membrane and nuclear fractions 76 84. However, there might be a complex interaction between the GSK-3 β-catenin pathway and other neurotransmitters which are implicated at complex levels in the pathophysiology of MDD.
As recently suggested by Pilar-Cuéllar and colleagues, the pharmacological modulation of the Wnt/β-catenin pathway will presumably represent one of the most innovative mechanisms for the treatment of neuropsychiatric disorders in the future (e.g. by block of GSK-3).

**mTOR pathway.** Rapamycin (TOR) genes are members of the phosphoinositol kinase-related kinase (PIKK) family of kinases. mTOR-signaling pathway is involved in intracellular processes such as synaptic plasticity, memory retention, and modulation of neuronal repair after injury. mTOR-signaling pathway can exist in two complexes – complex 1 (mTORC1) and complex 2 (mTORC2), depending on the presence of regulatory-associated protein of mTOR or rapamycin independent companion of mTOR, respectively. In neurons, mTORC1 is switched on by phosphorylation in response to various neurotransmitters such as BDNF. It has been suggested that the mTOR pathway is crucial for the regulation of synaptic plasticity. Reductions of synaptic proteins and impairment of mTOR signaling were observed in the prefrontal cortex of depressed individuals demonstrating its important role in the pathogenesis of MDD. Existing evidence reported that mTOR, which is phosphorylated by Akt and extracellular-regulated kinase (ERK), enables the translation of synaptic protein by activating p70S6 kinase (S6K) and inhibiting 4E-BPs, the inhibitory 4E binding proteins. It is important to mention that the mTOR-signaling pathway is activated after the acute administration of different NMDA receptor antagonists such as ketamine, Ro 25-6981, MK-801, or antagonists of the group II metabotropic glutamate receptors (mGlur2/3) such as MGS0039 and LY341495. All these compounds are characterized by rapid antidepressant effects. Some authors suggested that the ketamine-induced synaptogenesis appears to be consequent to the blocking of NMDA receptors at rest, resulting in the translation of rapid dendritic proteins and BDNF. Ketamine rapidly activates the mTOR pathway, enhances synapse formation, increases spine synapses density in the prefrontal cortex of rats, but also increases BDNF expression in the hippocampus leading to rapid antidepressant-like effects in humans and rats. The role of mTORC1 in the efficacy of ketamine was demonstrated by studies showing that pretreatment with a selective mTORC1 inhibitor such as rapamycin is able to drastically reduce the behavioral effects of ketamine. In addition, the mTOR inhibition by rapamycin blocks ketamine-induced synaptogenesis. However, mTORC2 is also supposed to play a role in ketamine antidepressant effect as it activates Akt and is involved in the organization of the actin cytoskeleton. Moreover, scopolamine (for more details see below), a muscarinic receptor antagonist able to induce rapid antidepressant effects, also augments mTORC1 and leads to enhanced synaptogenesis in the prefrontal cortex. Interestingly, electroconvulsive treatment has been suggested to activate the mTOR pathway inducing a VEGF enhancement.

In conclusion, the modulation of mTOR is a novel target for alternative therapeutic strategies for patients suffering from psychiatric disorders, in particular MDD.

### The inflammatory hypothesis of depression: antidepressant effects of anti-inflammatory compounds

Immune alterations are considered among the most relevant mechanisms involved in the pathophysiology of depression. Several lines of evidence have led to develop the inflammatory hypothesis of depression. First, a wealth of studies showed that serum levels of proinflammatory cytokines such as IL-1, IL6, and TNF-α are abnormally increased among depressed individuals. Furthermore, increases of pro-inflammatory cytokines seem to be linked with the occurrence of depressive-like symptoms such as sickness behavior, fatigue, lethargy, appetite loss. Whereas, Infliximab, or Etanercept administration, by neutralizing TNF-α and IL-1 are also associated with antidepressant effects. To further demonstrate this assumption, the repression of the purinergic 2X7 (P2X7) receptor, that activates the IL-1 release, is also supposed to play a role in ketamine antidepressant effect as it activates Akt and is involved in the organization of the actin cytoskeleton. Moreover, scopolamine (for more details see below), a muscarinic receptor antagonist able to induce rapid antidepressant effects, also augments mTORC1 and leads to enhanced synaptogenesis in the prefrontal cortex. Interestingly, electroconvulsive treatment has been suggested to activate the mTOR pathway inducing a VEGF enhancement.

In conclusion, the modulation of mTOR is a novel target for alternative therapeutic strategies for patients suffering from psychiatric disorders, in particular MDD.
have increased plasmatic cytokine levels compared to remitted patients \(^{122,123}\). Lastly, a higher incidence of depression among patients with chronic inflammatory diseases further supports the inflammatory hypothesis of depression \(^{124}\).

Interestingly, brain expression of IDO (an enzyme that converts tryptophan into kynurenine and quinolinic acid in microglia or kynurenic acid in astrocytes) is normally low but can be significantly induced by inflammatory cytokines. Lipopolysaccharide (LPS) administration induces depression-like effects in rodents, likely via NMDA receptor agonism by quinolinic acid (IDO-dependent) \(^{125}\). IDO activation is associated with a depletion of the precursor for serotonin by increasing the degradation of tryptophan \(^{125,126}\). Microglia is activated under stress, resulting in proinflammatory state (reviewed in) \(^{127}\). Conversely, chronic stress commonly reduces both the number and size of microglia, particularly in the hippocampus \(^{128}\). Furthermore, neurogenesis in the hippocampal dentate gyrus has been reported to be significantly impaired after long-term inflammatory nociception. Significant activators of the nociception-like neurokinin 1 (NK-1) receptor and BDNF in the limbic areas have been closely associated with MDD. Interestingly, imipramine inhibits pain- and stress-evoked down-regulation of hippocampal NK-1 receptor and BDNF gene expression in rats \(^{129}\). Thus, antidepressant medications seem to block those changes, which were induced in gene expression, contributing to long-term nociceptive sensory plasticity both in the spinal cord and limbic regions implicated in mood regulation.

It has been suggested that NK-1 receptor antagonists may exert relevant anxiolytic, antidepressant, and neuroprotective effects in the CNS representing promising drugs \(^{130}\). Preliminary evidence suggests that antidepressant drugs may successfully interact with immune inflammatory signaling pathways \(^{131}\). For instance, a significant reduction of LPS-induced pro-inflammatory cytokines such as TNF-\(\alpha\) and IL-6 and cytokine induced depressive-like behavior has been reported with antidepressant drugs use \(^{132-133}\).

According to animal studies, desipramine administration has been associated with increased IL-1\(\beta\) mRNA levels in rat hypothalamus \(^{134}\), while a significant up-regulation of phospholipase A2 (PLA2)-mediated arachidonic acid turnover has been observed after chronic antidepressant treatment in the rodent brain \(^{135,136}\). It is also important to note that resistance to commonly used antidepressants has been linked with higher levels of IL-6 and C Reactive Protein (CRP) \(^{137,138}\).

Adjunctive treatment with celecoxib, a selective COX-2 inhibitor, enhanced the therapeutic efficacy of reboxetine (a noradrenergic reuptake inhibitor) in subjects with MDD \(^{139,140}\). Thus, adjunctive treatment with antiinflammatory compounds may enhance the potential of traditional antidepressant drugs. Mendlewicz and colleagues \(^{141}\) found higher remission rates among MDD subjects who were previously nonresponsive to fluoxetine alone when acetylsalicylic acid (aspirin), a COX-1 inhibitor, was added to treatment. In MDD patients, adjunctive long-chain omega-3 fatty acids were associated with higher therapeutic efficacy of fluoxetine \(^{142}\) and citalopram \(^{143}\), respectively. Moreover, Peet and Horrobin \(^{144}\) reported a significant reduction of MDD symptom severity in depressed patients who were refractory to conventional antidepressant medications.

Overall, abnormally elevated immune-inflammatory signaling represents a pathogenic mechanism contributing to mood dysregulation in MDD; therefore, altered inflammatory pathways need to be carefully considered as new targets for novel antidepressant treatments.

**Other potential therapeutic targets for the development of novel antidepressants in the serotonergic system?**

Serotonin or 5-hydroxytryptamine (5-HT) may be generally found in the serotonergic neurons of the raphe nuclei and their axonal projections \(^{145}\). Serotonergic transmission regulates a wide range of behaviors like mood, memory, sleep, appetite, aggression, and thermoregulation. Notably, serotonin is also involved in the modulation of hippocampal neurogenesis which is known to be abnormally impaired in both chronic stress and MDD. Administration of selective 5-HT1A and 5-HT2C receptor agonists was able to increase the number of newly formed neurons in the hippocampal dentate gyrus and/or olfactory bulb. Furthermore, stimulation of 5-HT1A and -2B receptors resulted in enhanced neurogenesis combined with antidepressant-like activity in the animal model. In order to identify novel therapeutic targets, an alternative antidepressant approach would consist in the administration of selective 5-HT1A or 5-HT2C receptor agonists that have shown specific anxiolytic/antidepressant properties based on animal models \(^{146-148}\).

In addition, it has been proposed that the stimulation of postsynaptic 5-HT1A receptors in the corticolimbic brain regions is related with antidepressant effects.
whereas the activation of presynaptic 5-HT1A receptors is linked with a higher propensity to major affective disorders, reduced response to antidepressants, and suicidal behavior. Chronic antidepressant treatment is linked with a desensitization of presynaptic 5-HT1A receptors drastically reducing the negative feedback related with these receptors. Moreover, the combination of 5HT2C antagonism with MT1 and MT2 melatonergic agonism (e.g., the mechanism of action of agomelatine) was shown to be effective in the treatment of MDD. Overall, 5-HT1A or 5-HT2C receptor agonists may provide an interesting alternative target for the treatment of MDD and need to be further implemented in the next future.

Dopaminergic and norepinephrinergic systems are highly involved in hippocampal neurogenesis. Dopamine reduction has been reported to abnormally reduce hippocampal cell proliferation as demonstrated after quinpirole administration, which was associated with subgranular zone proliferation provoked by D2 receptor stimulation, as well as following D3 receptor knockout or inhibition. According to Guiard et al., the effect of dopamine on hippocampal neurogenesis is indirectly mediated by 5-HT, norepinephrine, and other neurotransmitters suggesting the complex interaction between monoaminergic systems at this level. Norepinephrine might influence hippocampal neurogenesis, considering the extensive noradrenergic innervation of the adult hippocampus. Importantly, the norepinephrine depletion was found to weaken the proliferation, but not survival/differentiation of adult hippocampal granule cell progenitors. Given this context, the authors suggested that the hippocampal precursors of neurogenesis might be modified through the α2-adrenoceptor activity although their functioning still remained unclear. Alpha-2-adrenoceptors are identified as presumed targets in the development of rapid acting antidepressants. Various studies demonstrated increased α2-adrenoceptor expression as well as binding and functional actions within limbic brain areas in both patients with major depression and animal models of depression. Chronic antidepressant treatment has been found to down-regulate and desensitize α2-adrenoceptors, therefore proposed to mediate the therapeutic delay of antidepressant medications. Antidepressant drugs with α2-adrenoceptor antagonist properties, such as mirtazapine, are associated with more rapid behavioral effects, alone or in combination with other traditional antidepressants. Interestingly, the co-administration of α2-adrenoceptor antagonist yohimbine with fluoxetine or the tricyclic antidepressant imipramine hastens the antidepressant response in patients with MDD. Therefore, antagonism of the α2-adrenoceptor may be identified as a prospective target in the development of antidepressant monotherapy or combined antidepressant treatment. Similarly to antidepressants, cannabinoids may also reduce anxiety and depressive symptoms in the short term. Chronic antidepressant treatment with SSRIs and tricyclics was reported to alter the expression of cannabinoid (CB1) receptors and endocannabinoid levels (EC) in brain regions involved in the pathophysiology of mood and anxiety symptoms.

It is now becoming evident that the normalization of hippocampal neurogenesis caused by antidepressants may be associated with the glucocorticoid hormones. Fitzsimons et al. reported that anti-glucocorticoids might revert depressive symptoms by promoting neurogenesis in the ventral hippocampus. Mice that are heterozygous for glucocorticoid receptor (GR) showed a depression-related phenotype, that is, elevated learned helplessness on the behavioral level and neuroendocrine alterations with HPA axis overdrive. Moreover, they had abnormally impaired BDNF levels and altered neurogenesis further repressed by restraint stress. Traditional antidepressants are known to modulate GR activity as they might affect neurolasticity through their potential to modulate both BDNF and 5-HT, potentially influencing HPA axis, which is subsequently able to affect hippocampal neurogenesis and neuronal functioning. Moreover, the antidepressant effects of chronic fluoxetine treatment were described to be linked to the maturation of newborn neurons together with the HPA axis inhibition. The down-regulation of hippocampal neurogenesis may affect HPA axis functions observed in chronic stress or depressed patients. In addition, the normalization of stress related HPA axis abnormalities following pharmacological inhibition of the orexinergic system was con-
connected with antidepressant effects. Thus, another potential class of medications with antidepressant action could be anti-glucocorticoid treatments which are reported to diminish stress-induced depressive symptoms by increasing neurogenesis. Estrogens (the estrogen receptors (ER) α and β) might regulate synaptogenesis and dendrite length, also activating intracellular signaling pathways that control the formation of synapse, and cause antidepressant effects in behavioral models of depression. Clinical studies reported the neuroprotective effects of estrogens against cognitive decline during normal aging but also Alzheimer’s symptoms, whereas laboratory evidence provided insight into the mechanisms through which estrogens may induce changes in brain neuroplasticity. Specifically, electrophysiological studies suggested that estrogens are able to promote changes in synaptic plasticity within the central nervous system. New selective estrogen ligands showed an advantageous potential reversing the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression. As a whole, the 17β-estradiol-mediated neuroprotection has been characterized by initial studies but there is an urgent need to elucidate the impact of estrogens on different signaling pathways involved in the regulation of cell survival and death.

Vilazodone, vortioxetine, brexpiprazole (OPC-34712), and amitifadine

Vilazodone acts by inhibiting serotonin reuptake and by partial agonism of 5-HT1A receptors. It has been approved as antidepressant by the US Food and Drug Administration in 2011. Importantly, 5-HT1A partial agonism has been associated with the improvement of depressive, anxiety, and aggressive symptoms. According to clinical studies, vilazodone at 40 mg daily dose is associated with a significant antidepressant response as demonstrated by the improvements at the MADRS and HAMD-17 total scores after one week of treatment and a significantly higher response rate than placebo at week 8 based on MADRS total score. Vilazodone has demonstrated a good tolerability profile similar to that observed with SSRIs with diarrhoea, nausea, and somnolence as the most relevant treatment-emergent adverse events.

Similarly, vortioxetine acts as a partial agonist at the 5-HT1A receptor, and a SERT, HT3, and 5-HT7 inhibitor. It has been recently approved in Italy for the treatment of major depression. The antagonistic effects on 5-HT7 receptors of this drug are associated with improvements of sleep, circadian rhythms, and mood. Based on preclinical studies, vortioxetine has been associated with a more pronounced and rapid recovery of 5-HT neuronal firing when compared with other SSRIs. When compared with placebo, vortioxetine was associated with significant improvements from baseline to week 6 in the mean change of MADRS total score in a sample of 429 patients with severe MDD. Alvarez and colleagues reported significant and earlier improvements vs. placebo according to HAMD-24 total scores for both 5 and 10 mg daily doses of this medication from week 1 (when compared with venlafaxine from week 2). A better tolerability profile when compared with that of 225 mg venlafaxine was also observed. Brexpiprazole (OPC-34712) is a novel promising medication for the treatment of MDD, with similar structural characteristics and pharmacological properties to aripiprazole. Brexpiprazole has a broader activity across multiple monoamine systems, reduced partial agonism on D2 receptors, and enhanced affinity for 5-HT1A, 5-HT2A and 5-HT7 receptors. It has been proposed as an adjunctive treatment in MDD. Relative to placebo, brexpiprazole as adjunctive treatment has been associated with significant improvements on MADRS total score in patients with insufficient response to other antidepressants.

Furthermore, amitifadine (DOV 21,947)/DOV-216,303 amitifadine (previously DOV 21,947) and DOV 216,303 (a racemic mixture of which amitifadine is one of the enantiomers) are other two interesting molecules currently under development to treat MDD. Both are serotonin-NE-dopamine reuptake inhibitors and promising therapeutic options, although prior trials on other triple-reuptake inhibitors such as SEP225289 (Sepracor Inc., 2009) and GSK372475 had yielded conflicting results. However, amitifadine is a serotonin preferring triple-reuptake inhibitor with lower affinity for the dopamine transporters, differently from SEP225289 and GSK372475. Such differences in the relative affinities for the three transporters may explain the improvements in pharmacology, tolerability, and efficacy observed in the earliest studies for these novel compounds. Amitifadine has been associated with markedly and persistently increases in extracellular concentrations of serotonin, noradrenaline, and dopamine in the prefrontal cortex. Time-dependent significant reductions in HAMD scores were observed both with DOV 216,303 and citalopram. Based on a post-hoc analyses,
amitifadine was reported to be particularly effective for anhedonia and did not exert significant sexual side-effects or other serious adverse events over 6 weeks 204.

Rapid acting antidepressant effects: the potential of glutamatergic compounds

Modern antidepressant medications may work by reversing neuroplasticity impairments associated with chronic stress and MDD and restoring the abnormal changes observed in specific neural circuits 48 52 54 205. Although conventional antidepressants predominantly modulate norepinephrine, dopamine, and/or 5-HT systems 206, the interest towards glutamatergic system is growing in terms of importance 43. It is well established that the majority of molecular and biological impairments of neuroplasticity are associated with the cytotoxic action of glutamate. For instance, the antidepressant-mediated inhibition of stress-induced morphological changes in both the hippocampus and amygdala is dependent on glutamatergic transmission 207. In addition, according to animal models stress-induced morphological changes in the hippocampus are reversed by pharmacological manipulation of glutamatergic system 207 208.

Importantly, a critical role of N-methyl-D-aspartate (NMDA) and a-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors activation in inducing morphological changes associated with neuroplasticity such as reduction of dendritic length and branching, spine density, and hippocampal volume has been suggested by multiple evidence 209 210. NMDA receptors are composed by two major subunits, NR1 and NR2 as functional NMDA receptors are tetramers and are comprised of two NR1 subunits and two NR2 subunits. NR2b subtype may be commonly found in extrasynaptic locations and has been explored as a new target for blocking glutamate excitotoxicity damage 211. NR2b antagonists may show antidepressant effects exerting antidepressant-like activity similarly to ketamine (for more details see below) but without exerting significant adverse effects 192 193. The structural remodeling of neurons leading to reversible modifications such as reduced neurogenesis, neuronal shrinkage and decreased growth may be, at least partially, mediated by glutamate if present at certain concentrations as well as by glucocorticoids levels 212. The inhibition of glutamate release by NMDA receptors may prevent this structural remodeling 213 214.

Both antidepressants and electroconvulsive shock therapy can reverse glutamate impairment, particularly in the anterior cingulated cortex of subjects with MDD 215. The antidepressant tianeptine has been reported to prevent the retraction of hippocampal CA3 pyramidal neurons apical dendrites together with increasing granule cell proliferation 49. Differently from fluoxetine, tianeptine prevents an excessive release of glutamate in the basolateral nucleus of the amygdala. NMDA receptor antagonists such as ketamine have been associated with rapid antidepressant action in TRD patients 100 216. Ketamine may be considered as safe and well-tolerated in the short-term period for nonpsychotic depressed patients when administered at a subanesthetic dose of 0.5 mg/kg over 40 minutes as well 217. Duncan et al. 218 reported that ketamine represent a novel and promising option to treat both MDD and TRD patients according to its earlier efficacy. It was shown to drastically reduce depressive symptoms within the first 5 days in contrast with the delayed action of currently available antidepressant medications, requiring 4 to 6 weeks. Ketamine seems also effective in reducing suicidality among TRD patients according to its rapid onset of action on core depressive symptoms, as well as hopelessness 219. It was suggested that (S)-ketamine is approximately 4 times more active than its (R)-enantiomer given its better pharmacokinetic properties and higher tolerability 219 220. (S)-ketamine has also been reported to induce less psychomimetic adverse effects such as dissociation and hallucinations relative to (R)-enantiomer. Several studies showed that rapid-acting antidepressants are able to enhance glutamate transmission, mTORC1 signaling as well as synaptogenesis 103 192 193 but other relevant mechanisms need to be mentioned. The rapid induction of neuroplasticity is supposed to be one of the main mechanism underlying the antidepressant effect of ketamine 221. Duman et al. 98 focused on the additional activity of ketamine to rapidly reverse both behavioral and neuronal changes associated with chronic stress presumably due to the stimulation of BDNF signaling. Unfortunately, ketamine has important psychotomimetic effects that may seriously limit its utility and require additional studies.

Memantine is another N-methyl-D-aspartate receptor (NMDAR) antagonist, a dimethyl derivative of amantadine. It showed good tolerability 222 and demonstrated preliminary hints of antidepressant efficacy based on animal models of depression 223. Moryl and colleagues 224. More specifically, memantine may be associated with antidepressant-like activity by reducing immobility time in the forced swim test. There are
also evidence suggesting that combining memantine with traditional antidepressants may be effective in the treatment of MDD. The enhanced antidepressant action may be observed only when fluoxetine was administered with memantine indicating that the combined effect of traditional antidepressants and NMDA antagonists is necessary to induce any antidepressant effects 225.

Finally, the non-selective muscarinic (M) receptor antagonist scopolamine has been also associated with a rapid antidepressant-like effect 75 226. Scopolamine inhibits all five receptors located at pre- and postsynaptic sites and it is associated with modulation of both cholinergic and glutamatergic transmissions. It was suggested that postsynaptic M1 receptors can regulate long-term synaptic depression (LTD) through the induced AMPA/NMDA receptors internalization 227. The inhibition of these receptors induced by scopolamine is associated with enhancing synaptic plasticity and synaptogenesis suggesting that this medication may determine the inhibition of muscarinic activation of GABA firing as well as the dis-inhibition of glutamate release 192.

The possible role of miRNAs

Finally, a further alternative antidepressant strategy needs to be reported. MicroRNAs (miRNAs), which regulate gene expression by targeting the three prime untranslated region (3′-UTR) of genes, have been demonstrated to play a significant role in neurogenesis 228, thus they may need to be considered as new targets in the treatment of major neuropsychiatric conditions 216 229 230. Exploring miRNAs effects may help to develop new molecular strategies aimed at modulating the expression of certain genes with an interesting potential in the antidepressant field 231. To date, more studies are still required to thoroughly explore the specific role of miRNAs in depression-related disorders as well as investigate detailed information about the possible use of miRNAs as new therapeutic targets for antidepressant activity.

Conclusion

The present review examined the main novelties in the field of antidepressant pharmacology, by including a brief overview of novel agents and potential innovative molecular targets with their implications and future perspectives. Over the last 20 years, the theoretical landscape has radically changed: the classic serotonergic view of depression has been integrated with substantial knowledge on other monoamines and specific intracellular signaling pathways. In addition to 5-HT, dopaminergic and norepinephrinergetic systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival, while neuroplasticity is now recognized as a crucial factor in the pathogenesis of depression. Furthermore, several intracellular pathways (e.g., cyclic adenosine monophosphate pathway, Wnt/B-Catenin Pathway, and mTOR pathway) may function as final common mechanisms for these systems. Thus, the direct modulation of intracellular pathways represents an exciting perspective for novel treatment strategies in MDD.

Current models of depression have recognized a prominent role also to other pathophysiological mechanisms, such as neuro-inflammation and chronic stress, which constitute the basis for further advancement in the field of psychopharmacology. Immune/inflammatory abnormalities have been also hypothesized to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of MDD. Indeed, part of the clinical efficacy of current antidepressant medications may already work by reducing immune inflammatory signaling pathways; thus, altered inflammatory pathways need to be carefully considered as novel alternative targets for developing novel antidepressant treatments. Estrogen ligands are an additional endocrine target, currently in the early phase of development. Selective agonists have been proposed to reverse the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression. Similarly, molecules that target the cannabinoid system may also reduce anxiety and depressive symptoms and are potential targets for novel antidepressants.

Glutamate transmission is already targeted by novel antidepressants. Drugs targeting specific glutamate receptors have been already marketed after demonstration of their efficacy 4. The noncompetitive NMDA receptor antagonist ketamine has been identified as one the most intriguing therapeutic option for patients with MDD and TRD. Ketamine is associated with a rapid and prolonged glutamate burst stimulating the BDNF-mTORC1 cascade, and leads to increased synaptic connections in specific brain areas such as the prefrontal cortex 232. The acute synaptogenic action of ketamine is rapid and is not associated with excitotoxicity. However, future studies are required to test long-term clinical efficacy in both MDD and TRD.
The efficacy of scopolamine, a muscarinic agent, largely depends on glutamate transmission, and also showed rapid effects.

Despite these exciting perspectives in the field of antidepressant drug discovery, clinicians continue to be challenged by the need to manage MDD while addressing several unmet needs in terms of tolerability, efficacy and long-term acceptability. Thus, further studies are urgently needed to translate preliminary evidence into tangible advances for our patients.

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Take home messages for psychiatric care

• Over the last 20 years, the classic serotonergic view of depression has been significantly integrated with substantial knowledge related to the contribution of other monoamines and specific intracellular signaling pathways

• In addition to 5-HT, dopaminergic and norepinephrine systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival. Modern antidepressant drugs such as ketamine may act by reversing neuroplasticity impairments and enhance synaptogenesis

• Immune/inflammatory abnormalities have been suggested to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of major depression

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