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Can dextromethorphan-bupropion reduce mental pain in depressed individuals? A hypothesis-generating overview perspective

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Abstract

Globally, major depressive disorder, or MDD, is a leading cause of disability. It negatively impacts social interactions and significantly limits daily functioning, ultimately reducing life satisfaction. The prevalence rate is about twice as high in women as in males. It is believed that the genesis of major depressive disorder is complicated and includes biological, genetic, environmental, and psychological factors. Mental pain, although distinguishable, constitutes a crucial framework in major depressive disorder (MDD) as the pair may precipitate suicide risk. Mental pain, as conceptualized in Panksepp's emotional theory, is especially relevant when considering the key role of the opioid system, which can influence feelings tied to grief and separation. There has been a renewed interest in targeting the opioid system for antidepressant treatment in MDD and to soothe mental pain. Antidepressant drugs endowed with partial mu-opioid receptor (MOR) agonism and kappa-opioid receptor (KOR) antagonism might represent novel pharmacological tools to address unmet needs in MDD patients. The combination of dextromethorphan and bupropion is a well-tolerated, rapid-acting treatment option for adults affected by MDD. We hypothesized that dextromethorphan-bupropion could impact the reduction of mental pain in MDD patients by targeting the opioid system, as supported by Panksepp's theory. The combination of dextromethorphan with bupropion might deal with various aspects of mental pain, possibly improving treatment results.

Keywords Major depressive disorder, Mental pain, Opioid system, Antidepressant, Dextromethorphan-Bupropion

Introduction

Recurrent thoughts of death, somatic and cognitive symptoms, a persistently low mood, and a loss of interest or enjoyment in once-enjoyable activities are all hallmarks of major depressive disorder (MDD). The condition itself, a leading cause of disability globally, together with associated medical comorbidities, social problems, and impaired functional results, can all contribute to a lower quality of life for those with MDD. Since MDD is a complicated disorder, no single proven biology or environmental mechanism can adequately explain its complex pathophysiology. Instead, a confluence of biochemical, psychological, environmental, and hereditary variables appears to cause MDD, such as immune

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system dysfunction, a deficit of neurotrophins signaling, and alterations of glutamatergic system [1]. Pharmacological therapy with antidepressant drugs, psychotherapy, or a combination of the two is frequently used to treat major depression [2]. Additional biological therapies, such as electroconvulsive therapy, may also be available to patients with severe and/or treatment-resistant MDD. Physical symptoms of MDD include fatigue, appetite loss, and weight loss. Anhedonia is a hallmark of such a disorder, which often includes affective symptoms like guilt, sleep problems, cognitive difficulties, and a lack of motivation.

Mental pain has been the quintessential ingredient of suicide risk according to classical suicidology [3–5]. Mental pain, although often overlapping, is distinguishable from features of major depression. Orbach et al. et al. conceptualized mental pain as a perception of adverse changes in the self and its functions that are accompanied by negative feelings [6]. According to Shneidman, mental pain is the same as somatic pain: "It is how you feel as a person; how you feel in your mind or heart. It refers to how much you hurt as a human being. It is mental suffering, inner torment" [7]. It is called psychache (pronounced sik-ak). Psychache refers to hurt or misery. It is the pain of shame, guilt, grief, humiliation, hopelessness, loneliness, sadness, or anguish. It is how you feel inside. It is an ache in the mind [7]. In the case of rejection-producing features assimilable to mental pain, scholars found that the same cerebral circuits are activated when an individual experiences either somatic pain or mental pain [8]. So it postulated that mental pain, when it overcomes the threshold for sustaining the suffering, is deemed to be unbearable, and suicide is considered as a way out when other options fail to reduce it.

When determining whether someone needs psychiatric assistance, mental pain—which includes psychiatric diagnoses—is an essential framework [9]. The phenomenology of suicide was explained by mental suffering, or "psychache," according to seminal articles [3]. Suicide is an escape from unbearable suffering, which causes "perturbation of the mind," which refers to the degree of upset (disturbed, agitated, discomposed) that the person is and the situation in which suicide is likely to occur, according to Shneidman's model. As for mental pain in MDD, due to the limits of standard antidepressant treatments, there is more interest in looking at other drugs that could help to treat this harrowing experience. Pain and, in particular, mental pain are strongly associated with treatment-resistant depression [10]. Identification of the molecular mechanisms contributing to mental pain in MDD represents an essential step for the development of more efficacious drugs directed against novel pharmacological targets able to modify the clinical course and increase remission rates in clinical practice.

Fava et al. [11] underscored the importance of transdiagnostic characteristics of mental anguish, highlighting its correlation with many psychiatric diseases. They cited the DSM-5 definition of mental anguish as "clinically significant distress" arising from symptoms of psychiatric disorders. The authors presented a thorough examination of the attributes of mental anguish in individuals suffering from psychiatric diseases and traumatic experiences. Mental pain signifies patient-reported outcomes, pertain to patients' accounts concerning their functioning or emotions associated with a health condition or its treatment. The authors defined mental pain in depression as a uniquely unpleasant and disturbing sensation characterized by severe tension and anguish.

The emotional systems, the understanding of feelings and the role of the opioids

Jaak Panksepp postulated that main emotional systems, like the grief system, are set in the mammalian brain and controlled by specific neurochemical pathways [12, 13]. Panksepp's theory suggests that the panic/grief and seeking systems are essential for understanding emotional feelings, especially concerning loss and attachment. This theory is especially relevant when considering the key role of the opioid system, which can influence feelings tied to grief and separation. Different studies suggest that using mu-opioid agonists can reduce panic/grief reactions, potentially helping with the deep sadness often linked to depression. Additionally, problems with these emotional systems may come from early trauma, highlighting the long-lasting effects of social stress on emotional health [14]. Panksepp's findings connect neurobiology with emotional well-being, showing possibilities for specific treatments for grief and depression. The relationship between opioids and emotional regulation is tied to how we process feelings. Studies show that opioid blockers can interfere with grief feelings, which results in more negative emotions and a feeling of disconnection [15]. This agrees with different studies showing that antagonists of mu-opioid receptor (MOR), such as naltrexone, can worsen mood and decrease positive feelings. According to Panksepp's Emotional Theory, opioids are closely associated with the separation distress (PANIC) system, which increases feelings of sorrow and sadness during times of loss or loneliness [12]. When this system is activated, it leads to strong emotional reactions, including a greater sense of emotional pain that can be lessened with low doses of opioids or MOR partial agonists such as buprenorphine [16, 17]. This indicates that opioids may help with grief symptoms by reducing excessive PANIC response, which could help stop ongoing emotional pain [18]. Therefore, understanding how opioids work helps us better understand emotional control and could lead to new treatments for grief-related issues.

The role of the opioid system in grief may also offer new pharmacological targets for the treatment, highlighting the clinical relevance of tackling emotional pain through methods connected to reward and social ties [19].

According to Panksepp [20], the same neurotransmitter systems that regulate physical pain also regulate the psychological anguish of social loss. Separation distress (as measured by isolation cries) was alleviated in dogs, guinea pigs, chicks, rats, and primates by plant opioids (such as morphine) as well as from endogenous brain opioids (especially β-endorphin), which are known to ameliorate physical pain [21]. To this end, administering opioid analgesics to individuals suffering "social pain" would be expected to reduce their distress associated with being shunned and reduce the intensity of activation in the brain regions responsible for the elaboration of such emotions.

The administration of opioid receptor antagonists should enhance both effects. It is well-known that we can provide solace to domestic animals by petting them. Monitoring the weeping of young animals while they are held or not held is a simple method for objectively studying such effects. The consequences are, of course, profound. When animals are gently touched, they cease to cry promptly. This contact comfort is partially mediated by the activation of brain opioid systems, as demonstrated by different preclinical and clinical studies [22]. Neurochemicals other than opioids contribute to the sensation of contact comfort. Primates have also been verified to release opioids in the brain through touch [23]. The opioid receptor antagonist naloxone has been shown to increase grooming in primates, possibly as a response to the adverse effects of reduced opioid levels in the brain. Primates groom each other for social comfort, and opiate medications may reduce the desire to be touched by promoting opioid self-satisfaction in the brain. Opioids that activate MOR are particularly effective in reducing the arousal of GRIEF/separation distress in animals. Opioid receptor blockers reduce the effectiveness of this contact, but socially isolated birds settle down and cry less.

Opioids that activate MOR are particularly effective in reducing the arousal of GRIEF/separation distress in animals [18].

Novel options for reducing the psychic pain of depression are provided by each of the aforementioned neurotransmitter systems (e.g., opioids and oxytocin), which are not presently being currently used in clinical settings but can represent novel pharmacological tools for the treatment of mental pain in MDD [22]. Indeed, ultra-low-dose buprenorphine and other opioids that are reasonably safe might be considered highly effective antidepressants for individuals who have not found relief from conventional monoaminergic antidepressants [24].

New perspectives for the treatment of MDD

A significant percentage of patients with MDD fail to respond to existing treatments despite numerous antidepressant trials and augmentation strategies. Approximately 20% of patients with MDD experience treatment-resistant depression (TRD), typically characterized by a lack of response to two or more trials of antidepressant medications [1]. Additionally, the maximum efficacy of first-line antidepressants, including serotonin-selective reuptake inhibitors (SSRIs), is postponed, with delays of several weeks to months before observable benefits. The monoamine systems, encompassing serotonin, noradrenaline, and dopamine, have historically dominated depression research and treatment. However, a growing consensus is that advancing drug discovery requires exploration beyond these monoamine systems to identify new pharmacological targets and, most importantly, to enhance patient outcomes. Recent revelations on the neurobiology of treatment-resistant depression (TRD) have illuminated the involvement of various novel factors in the pathophysiology of major depression, encompassing the glutamatergic system, modifications in the immune system, dysregulation of neurotrophins, and epigenetic changes triggered by chronic stress [1].

The glutamatergic system has become a significant focus of research [25]. A shift from the monoamine hypothesis of depression to a neuroplasticity hypothesis focused on glutamate may represent a substantial advancement in the fundamental premise directing research for new medications and cures. Despite the existence of multiple classes of monoamine-based drugs, a considerable number of patients fail to achieve durable remission of depressive symptoms. The current deficiency of pharmacotherapies for treatment-resistant depression underscores the opportunity to develop new drugs that focus on innovative mechanisms of action, such as glutamate transmission and related pathways [26].

The identification of the swift antidepressant effects of intravenous ketamine has resulted in a transformative change in the drug discovery process for depression [27]. The investigation of the molecular mechanisms that underpin the clinical efficacy of ketamine and esketamine has paved new avenues in translational pharmacology for treatment-resistant depression (TRD), particularly highlighting novel pharmacological targets such as the opioid system. This stems from the evidence that partial agonism at the mu-opioid receptor (MOR) is a contributing molecular mechanism to the effectiveness of these rapid-acting antidepressants [28].

Jelen et al. [22] reported several studies showing that the endogenous opioid system is directly implicated in the regulation of mood and is dysregulated in depression. As a result, there has been a renewed interest in targeting

the opioid system to enhance the response to antidepressant treatment in MDD. These authors argued that in addition to its primary function in pain processing, the opioid system in humans is responsible for regulating a diverse array of physiological functions, including respiratory, gastrointestinal, endocrine, and immune functions [29]. It is essential to recognize that this system regulates responses to acute and chronic stress and modulates human temperament, reward, and well-being. The expression of endogenous opioid peptides and associated receptors in limbic and cortical brain regions involved in regulating behavioral functions, such as emotion, mood, motivation, and reward processing, is high. The alterations of these pathways (e.g. the mesolimbic pathway) and regions play a key role in the pathophysiology of MDD. An increasing amount of evidence suggests that the modulation of these processes is directly related to the opioid system. MOR neurotransmission appears to play a crucial role in the regulation of social hedonic capacity, according to evidence from animal models of depression [22]. Therefore, in the context of MDD research and drug development, it would be a worthwhile target to look into. Ketamine, a dissociative anesthetic, and uncompetitive NMDA receptor antagonist that also functions as a partial agonist of the MOR, has become a novel antidepressant, according to Jelen et al. [30].

Numerous short-term RCTs have shown the rapid (within 24 h) and substantial efficacy of intravenous racemic (R, S)-ketamine administered at subanaesthetic doses (0.5–1.0 mg/kg) and intranasal esketamine, (28–84 mg) in adults with TRD [31–33]. Kristal et al. have proposed that the antidepressant effects of ketamine are mediated through the blockade of NMDA receptors on γ-aminobutyric acid (GABA)-ergic interneurons [31]. These interneurons are frequently responsible for suppressing glutamate release from pyramidal neurons. This disinhibition of pyramidal neurons induces an acute glutamate surge [34, 35]. This surge, in turn, activates post-synaptic AMPA receptors, activating neuroplastic signaling pathways and synaptogenesis [36]. Recent studies have elucidated various mechanisms that contribute to the clinical efficacy of fast-acting antidepressant medications, encompassing effects on neural circuits and molecular pathways characterized by a complex pharmacodynamic profile. This profile has been recently detailed and updated in the NbN (https://nbn2r.com/), which includes agonism at MOR, D2 receptors, and σ1 receptors, antagonism at 5-HT2, muscarinic, and nicotinic receptors, as well as inhibition of Noradrenaline, Dopamine, and Serotonin Transporters [28]. It has been posited that ketamine and esketamine mitigate anhedonia by inhibiting NMDAR-dependent burst firing in the lateral habenula, known as the "anti-reward center" [37].

Ketamine's antidepressant effects can also be influenced by its actions on a variety of other neurotransmitter systems, including opioid systems, in addition to its glutamatergic effects [30].

Ketamine has been demonstrated to induce opioid receptor-dependent analgesia [38–40], enhance opioid analgesic effects [41], decrease opioid tolerance and opioid-induced hyperalgesia [42], and induce MOR-dependent respiratory depression at higher doses [43]. However, the opioid system's involvement in the lower concentrations of ketamine that are used to induce antidepressant effects is not as well understood. Ketamine's transient therapeutic effects may be contingent upon the opioid system's activation.

A second investigation on mice indicated that the activation of opioid receptors is "essential but insufficient" for ketamine to mitigate depressive-like behavioral symptoms and decrease activity in the lateral habenula. This essential anti-reward center has a role in the pathophysiology of depression [44]. While ketamine did not exhibit direct MOR agonist properties in this work, it was essential to demonstrate some MOR action to inhibit the NMDA receptor [44]. The notion of "crosstalk" between the MOR and glutamatergic receptor systems is supported by evidence that opioid receptor activity can modulate NMDA receptor activation [45] and that MOR and NMDA receptors are localized in some brain areas [46]. Both receptors may contribute to the antidepressant effects of ketamine [47]. It has been posited that the activation of the MOR system may enhance the antidepressant effects of ketamine by exerting a permissive influence on NMDA antagonism and subsequently facilitating the restoration of neurotrophin signaling.

In this scenario, antidepressant drugs endowed with partial MOR agonism and kappa-opioid receptor (KOR antagonism might represent novel pharmacological tools to treat mental pain and suicidal ideation. Interestingly, different clinical studies have demonstrated the clinical efficacy of buprenorphine in MDD [22], and a multisite randomized, double-blind, placebo-controlled trial has investigated the efficacy of ultra-low-dose sublingual buprenorphine as an adjunctive treatment as a time-limited treatment for severe suicidal ideation [48]. This trial involved individuals exhibiting serious suicidal thoughts without a history of substance misuse, who were randomly randomized to receive either buprenorphine or a placebo in a 2:1 ratio in conjunction with their current individual therapy [48]. The principal end measure was the alteration in suicidal ideation, evaluated by the Beck Suicide Ideation Scale following each of the four weeks of treatment. Patients receiving ultra-low-dose buprenorphine (starting dosage, 0.1 mg once or twice a day; mean final dosage = 0.44 mg/day) demonstrated a more pronounced decrease in Beck Suicide Ideation Scale scores

than those given a placebo at both 2 weeks and 4 weeks. The concurrent use of antidepressants and a diagnosis of borderline personality disorder did not affect the response to buprenorphine. No withdrawal symptoms were seen with the termination of treatment post-trial. The brief, time-limited use of modest doses of sublingual buprenorphine was associated with a decrease in suicidal thoughts in highly suicidal patients lacking a history of substance misuse.

Dextromethorphan-Bupropion in major depressive disorder

Dextromethorphan, usually used to treat coughs, is now being looked at for its possible role as a kappa-opioid receptor (KOR) antagonist, which could provide a new path to treat depression. KOR antagonists are known to exert a relevant preclinical efficacy in stress-induced animal models of depression [49]. Therefore, we hypothesize that KOR antagonism can contribute to the antidepressant action of dextromethorphan. Similarly, along this line, the KOR antagonist and partial MOR agonist buprenorphine significantly reversed the depressive phenotypes induced in animal models of chronic mild stress [50], and it also exerts a clinically relevant efficacy in MDD [22].

Dextromethorphan's properties as an NMDA antagonist and sigma-1 receptor agonist, in addition to its norepinephrine and serotonin reuptake-blocking features, substantially influence the science fundamental to the overall antidepressant approach. This agent integrates the NMDA antagonist dextromethorphan with the norepinephrine-dopamine reuptake inhibitor bupropion.

Dextromethorphan undergoes rapid metabolism via cytochrome P450 2D6 (CYP2D6), reducing its bioavailability and complicating the attainment of therapeutic plasma concentrations after oral administration. Bupropion and its metabolites act as CYP2D6 inhibitors. The co-administration of bupropion with dextromethorphan results in substantial increases in dextromethorphan exposure across all assessed doses in three Phase I studies. Bupropion, due to its unique centrally-acting mechanisms, serves as an effective metabolic inhibitor of dextromethorphan, indicating potential for pharmacological synergy and clinical application in various neuropsychiatric disorders.

As discussed above, recent antidepressant drug development has concentrated on the antagonism of NMDAs, including ketamine and esketamine in combination with MOR agonism [51]. In this scenario, the hypothesis has also been reinforced not only with esketamine, considering its micromolar binding affinity for NMDA receptors comparable to that for MOR, but also with the interesting case of dextromethorphan [52]. The pharmacodynamic profile of dextromethorphan is characterized by NMDA antagonism combined with MOR/Sigma-1 agonism associated with 5HTT inhibition and an activation of mTOR signaling, resulting in AMPA receptor activation and the following synaptogenesis [53]. It is also well known that neuroinflammation significantly contributes to treatment resistance in MDD [1] and also that the anti-inflammatory action of NMDA antagonists/MOR-agonists critically contributes to their rapid antidepressants efficacy as demonstrated from preclinical evidence in different animal models of depression [27]. Interestingly, dextromethorphan exerts a neuroprotective and anti-inflammatory effect by inhibiting microglial activation through the HSP60-NFKB signaling pathway [54]. This mechanism can contribute to its overall antidepressant efficacy in MDD.

Literature suggest that the combination of bupropion and dextromethorphan is a rapid-acting and well-tolerated therapeutic option for patients affected by MDD [55]. Tabuteau et al. [56], in a randomized, double-blind, multicenter, parallel-group study on patients diagnosed with moderate or severe MDD, compared dextromethorphan-bupropion to the active comparator sustained-release bupropion. In comparison to the active comparator bupropion, dextromethorphan-bupropion demonstrated rapid, substantial, and statistically significant antidepressant efficacy on the MADRS total score, the primary efficacy variable, as well as on various other clinician- and patient-reported measures of depression severity in this randomized controlled trial. Dextromethorphan-bupropion markedly reduced depressive symptoms, as evidenced by the MADRS total score at week 1; by week 2 and at all following intervals, statistically significant differences compared to bupropion were observed. Between weeks two and six, the treatment difference on the MADRS (dextromethorphan-bupropion change minus bupropion change) averaged around 5 points at each interval (range: 4.5–5.6 points), demonstrating both significance and temporal stability. At week 2, dextromethorphan-bupropion showed a statistically significant decrease in MADRS total score from baseline compared to bupropion, and patients reported a quick improvement in global measures, with statistically significant changes noted at week 1 on the CGI-I and at week 2 on the CGI-S. At week 2, dextromethorphan-bupropion exhibited a statistically significant reduction in the MADRS total score from baseline compared to bupropion, with patients reporting rapid improvement in global global. Statistically significant alterations were observed at week 1 on the CGI-I and week 2 on the CGI-S.

Iosifescu et al. [57] conducted the GEMINI trial, a phase 3, double-blind, randomized controlled study ($n = 327$) that assessed the safety and efficacy of dextromethorphan-bupropion relative to placebo over 6

weeks. Among the 327 randomized individuals, 163 were administered dextromethorphan-bupropion, whereas 164 received a placebo. The primary endpoint was to compare the reduction in MADRS scores from baseline to week 6. The authors indicated that dextromethorphan-bupropion was superior in producing a statistically significant decrease in MADRS scores from baseline to week 6. The COMET trial was a Phase 3, long-term, open-label study assessing efficacy and safety in adult patients with DSM-5-defined major depressive disorder without psychotic symptoms [58]. The study included a total of 865 participants, consisting of 265 patients from previous controlled studies with dextromethorphan-bupropion and 611 additional patients. Newly enrolled patients were required to demonstrate a minimum of 25% improvement by week 6 to remain in the experiment. Out of all enrolled patients, 110 completed 12 months of therapy. Patients received the same dosage of dextromethorphan-bupropion as in prior studies, taken bi-daily for up to 12 months. The average reduction in MADRS score from baseline was 21.1 points at week 6, sustained at 23.9 points at 6 months and 23.0 points at 12 months. The clinical response and remission were sustained throughout the 12 months. Jones et al. [59] conducted the EVOLVE open-label, long-term study, enrolling one hundred and forty-five patients who received dextromethorphan-bupropion at doses of 45 – 105 mg twice daily for up to 15 months. The authors documented essential improvements in the Cognitive and Physical Functioning Questionnaire, the Hamilton Anxiety Rating Scale, the Sheehan Disability Scale, and the MADRS total scores. Each assessment score produced significant and consistent results by the end of the first week. The predominant adverse effects encompassed COVID-19 infection, nausea, headache, xerostomia, vertigo, and sleeplessness. Five patients experienced serious adverse effects.

McIntyre et al. [60] conducted a pooled post hoc analysis of data from two double-blind, randomized, controlled trials lasting six weeks, evaluating dextromethorphan-bupropion in adult patients with major depressive disorder (MDD). The authors indicated a positive association between the MADRS Anhedonia subscale and SDS scores during the 6-week treatment period. By Week 6, the enhancement from baseline on the anhedonia subscale was – 10.1 for dextromethorphan-bupropion, in contrast to -7.6 for the control group. The response rates for anhedonia symptoms were considerably higher for dextromethorphan-bupropion (18.6%) compared to the control group (6.6%) at Week 1. Moreover, the most frequently reported adverse responses (≥ 5% and double the incidence of placebo) associated with dextromethorphan-bupropion included dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.

Conclusions

In this perspective article, we hypothesized that dextromethorphan-bupropion could impact the reduction of mental pain in patients with major depression by acting on the opioid system, as supported by Panksepp's theory. Although the action on an opioid system of dextromethorphan is reduced compared with other opioid agonists, this MOR activity should be reconsidered in combination with the NMDA receptor antagonism and, in particular, with the ability of this drug to interact with NMDAR subtypes containing GluN2D subunit known to be hyperactive in depression and upregulate tonic Ca2 + currents [53]. Dextromethorphan, acting as a low-potency NMDAR antagonist for GluN2D subtypes, can exert its rapid antidepressant effects in the absence of dissociative side effects. Bupropion, on the other hand, is known for its interaction with dopamine and norepinephrine transporters, which may help with the emotional pain that comes with major depressive disorder. The combination of dextromethorphan with bupropion might target various aspects of mental pain, possibly improving treatment results. To this end, thorough long-term clinical studies with proper assessment of mental pain in major depression disorders are needed. Mental pain might constitute a psychiatric emergency when it overcomes the threshold to be sustained. In this regard, suicide risk is often considered a way out when other solutions fail to provide relief.

We believe that addressing mental pain in clinical practice points to major patient-related outcomes. Emphatic understanding of mental pain is crucial, and personalized treatment is of utmost importance. If our hypothesis is to be confirmed, possibly a reduction of mental pain could also be achieved through partial MOR agonism combined with KOR antagonism. In such regard, new perspectives would be unveiled for the treatment of major depressed patients experiencing such pain.

Author contributions

M.P. fist conceptualized the work and provided intellectual stimulus for the hypotheses. M.P. and I.B. reviewed the literature and analyzed available sources. M.P and D.E. translated concepts in the biological perspective. M.P and F.C. provided in-depth analysis of biological mechanisms and formulated the main implications for the translational neuroscience perspective. All authors contributed to drafting the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

N/A.

Conflicts of interest

The authors declare no conflicts of interest. Prof. M Pompili wishes to disclose that in the last five years, has received lectures and advisory board honoraria or has engaged in clinical trial activities with Angelini Pharma, Allergan, Janssen, Lundbeck, Merck Sharp and Dohme, Otsuka, Rovi, Pfizer Inc, Fidia, Viatris, Recordati, Boehringer Ingelheim, Newron, GSK, Neopharmed Gentili, and Teva, all of which are unrelated to this article.

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