

Potential strategies to optimize the efficacy of antidepressants: Beyond the monoamine theory

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ABSTRACT

Depression is characterized by a feeling of sadness and a lack of pleasure, with impaired daily functioning and poor quality of life. The neurobiology and the pathogenesis of depression are not fully understood yet. Several hypotheses have been discussed including, monoamine theory, neurotransmission, oxidation, inflammation, glutamatergic transmission, neurotrophic factors, and others. Reviewing three decades of randomized controlled trials of antidepressants revealed that the antidepressants response rate is about 54% compared to a placebo response rate of 37%. Treatment-resistant depression (TRD) could be defined as an inadequate response to two different of antidepressants. In TRD, a combination strategy of using two FDA-approved antidepressants is used, which may predispose patients to adverse effects. Therefore, there is a compelling need to explore the potential “out of the box” adjuvants to antidepressants to provide higher and consistent response rates with high tolerability. These adjuvants could be medications available for other indications, food supplements, or even experimental drugs. This review will highlight potentially beneficial adjuvants to antidepressants such as nitric oxide modulators, NMDA antagonists, anti-inflammatory, antioxidants, mitochondrial modulators, insulin sensitizers, opioids, probiotics, and GABA agonists.

Keywords: antidepressants, efficacy, adjuvants, depression

INTRODUCTION

Depression is a global disorder [1] that prevails in 20% of individuals globally [2, 3]. Moreover, depression prevails once can be as high as 40%-50% in certain primary care or specialty settings [4]. According to literature, depression is associated with health and economic burdens on individuals and countries as it is directly related to work and social disability therefore leading to global economy losses [5, 6].

The neurobiology and the pathogenesis of depression are not fully understood yet. Several hypotheses have been discussed including neurotransmission and neurotrophic factors that try to explain the complex interaction between genetic and environmental factors [7, 8]. The different classes of available antidepressants are based on the monoaminergic deficiency hypothesis i.e., they increase the levels of the synaptic monoamines (serotonin, dopamine, and norepinephrine), these classes include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and others.

Challenges and Limitations of Antidepressants

One of the major problems with using antidepressants is nonadherence to proposed regimen. Patient nonadherence to

antidepressants is challenging. Factors associated with nonadherence include poor patient education and counseling by health care providers, the patient’s misperception of depression, the polypharmacy in case of geriatrics, stigma and other social barriers [9-13]. Yet, the major reason for nonadherence is the side effects the patients suffer from [14, 15].

Noncompliance with the dosing regimen, missed doses, and discontinuations within the first month of treatment have the highest tendency to occur as some of the side effects can improve within the first few weeks of treatment. In addition to non-adherence, the consistency of the antidepressant efficacy is another challenge [16]. In the best conditions, about 50% of patients experience inadequate responses to antidepressants [17, 18]. Reviewing three decades of randomized controlled trials of antidepressants revealed that the antidepressants response rate is about 54% compared to a placebo response rate of 37% [19]. Treatment-resistant depression (TRD) could be defined as an inadequate response to two trials of antidepressants [20]. In TRD, a combination strategy of using two FDA-approved antidepressants is used [21]. There is no substantial evidence regarding the safety or efficacy of this combination.

Almost 40% of patients taking antidepressants experience at least one side effect [22]. Gastrointestinal symptoms are the most predominant side effects, it was reported that SSRI and

SNRI antidepressants cause nausea and vomiting, constipation, anorexia, and dry mouth with varying intensities [23]. It was shown that the highest severity of nausea and vomiting, whereas it was shown severe anorexic effects [24]. The only exception from these effects being Mirtazapine showing only an increase in appetite without other simultaneous effects [23].

These side effects can be easily attributed to the increased levels of five-HT in the abdominal tract, where it plays a major role in the physiological control of gut function [25]. According to [26], where a study conducted in elderly patients to assess the tolerability of antidepressants, 7.3% suffered from more than one severe gastrointestinal side effect leading to the discontinuation of nonadherence to the medication used. It was also shown that an increase in the tendency of bleeding among their users due to the disturbance of hemostasis [27-29].

It was justified that as serotonin reuptake inhibition will interfere with the blood serotonin uptake by platelets disrupting the coagulation cascade right at the beginning, where the initial step of platelet aggregation or the platelet plug formation, subsequently, the rest of the cascade will collapse leading to the continuation of bleeding [24]. This side effect is mostly associated with agents showing highest degree of reuptake inhibition, including the SSRIs citalopram and sertraline as well as the SNRI antidepressant venlafaxine [24, 30]. Cardiovascular symptoms in patients taking antidepressants are rare but are noteworthy to be mentioned regarding their serious nature. Different antidepressants show varying degrees of cardiovascular effects; all antidepressants, except for the SSRIs, have shown an increase in the basal heart rate levels with a decrease in HR variability (HRV), the highest increase attributed to TCA then SNRIs. Interestingly, patients taking SSRIs have shown lower HR than patients on placebo (66.87 bpm) according to [31]. Also, SSRI antidepressants namely citalopram has been linked to QTc interval prolongation leading to an increase in risk of arrhythmia [32].

Combining two antidepressants can predispose serious side effects, for example, combining SSRIs with tricyclic antidepressants or with monoamine oxidase inhibitors results in significant complications such as serotonin syndrome [33]. Augmenting antidepressants with another molecule (not necessarily an antidepressant) working via a different mechanism could provide remission of symptoms for example agents such as lithium, thyroid hormone, antiparkinsonian drugs, atypical antipsychotics and anticonvulsants (valproate, carbamazepine, gabapentin) are clinically used with marginal enhancement and with questionable safety [18]. Therefore, there is a compelling need to explore the potential "out of the box" adjuvants to antidepressants to provide higher and consistent response rates with high tolerability. In this review, several potential adjuvants will be discussed.

NITRIC OXIDE MODULATORS

Nitric oxide (NO) is produced from L-arginine by enzymatic conversion of the enzyme NO synthase (NOS) [34]. The endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS) are the three isoenzymes responsible for NO production. The later has a high affinity for Ca²⁺-calmodulin, is induced under stressful conditions such as inflammation to produce significant amounts of NO [35].

Upon its synthesis, NO can initiate several signal transduction pathways. The most characterized signal transduction pathway is the activation of soluble guanylate cyclase (GC) enzyme to produce cyclic guanosine monophosphate (cGMP) [35]. According to literature, an imbalance of NO metabolism in depression has been suggested. The bulk of evidence supports an increase in NO during depression. For example, NO and its metabolites were higher in suicide attempters with respect to the controls [36, 37], moreover, studies pointed out elevated NO levels in MDD patients, and interestingly NO levels were normalized after antidepressants therapy [38].

In support of NO potential role in depression, a growing body of evidence demonstrated that some antidepressants exert a NO-lowering effect. The study [39] revealed that L-arginine antagonized the effects of the classic tricyclic antidepressant, imipramine. Several medications were shown to exert antidepressant effects via NOS inhibition including tramadol, bupropion, venlafaxine lithium, and ketamine [40, 41]. Furthermore, many new investigational amino acid NOS modifiers have demonstrated interesting results such as L-NG-nitroarginine, L-NG-monomethyl arginine, and NG-propyl-L-arginine [42].

NMDA ANTAGONISM

Besides its role in neurodegenerative diseases, the N-methyl-D-aspartate glutamatergic receptor (NMDA) is an important player in the pathophysiology and treatment of depressive disorders [43]. NMDA is a ligand-gated calcium channel receptor that activates numerous downstream signal transduction pathways such as NO synthase leading to NO production [44]. NMDA receptors have three subunit families: GluN1, GluN2A-D, and GluN3A-B. GluN1 subunit contains the glycine/D-serine binding site and the NR2 subunit contains the glutamate binding site [45]. It has been hypothesized that the antagonism of NMDA receptors specifically the 2A and 2B subunits, the predominant subunits, in the adult hippocampus and cortex, results in antidepressant properties and hence represent pharmacological targets for the treatment of MDD.

Ketamine, the most studied anti glutamatergic drug, demonstrated antidepressant properties alone or as an adjuvant to antidepressants in more than 12 randomized controlled studies although the exact mechanism of action is not fully elucidated [46]. Although ketamine has excellent bioavailability, rapid onset of action, and long half-life that permits twice-weekly dosing, however it is associated with perceptual disturbances, dissociation, dysphoria, anxiety, and dizziness [47]. Other NMDA receptor antagonists with antidepressant effects have been studied such as lithium, ifenprodil, D-cycloserine, and amantadine [48, 49]. Memantine, and esketamine was delivered as a nasal spray adjuvant to antidepressants in a randomized controlled trial [50].

ANTI-INFLAMMATORY

Neuroinflammation refers to the combined immune response and inflammation within the CNS. Growing lines of literature refer to the implication of neuroinflammation in depressive disorder, where microglia is implicated [51-53]. Microglia is activated to become amoeboid, which in

Table 1. Summary of different classes & mechanisms of adjuvants

Adjuvant	Mechanism	Examples	Reference
Mitochondrial modulators	↑Oxidative phosphorylation & ↓Mitochondrial DNA damage	Melatonin	[60, 115]
	↑Acetyl-CoA uptake	Acetyl-L-carnitine	
		Tramadol Bupropion Lithium	[40] [116] [117]
Nitric oxide modulators	Inhibition of nitric oxide synthase (NOS)	NOS inhibiting amino acids: L-NG-nitroarginine, L-NAME, L-NMMA (L-NG-monomethyl arginine), & NG-propyl-L-arginine Amidines: L-NIO, Ethyl-L-NIO, & Vinyl-L-NIO Indazole derivative: 7-NI & 7-NI-Br	[42]
Anti-inflammatory	↓Cytokines & Restore HPA axis balance	Corticosteroids	[118]
	↓Cytokines & prostaglandins	NSAIDs, Aspirin, Bilobalide, Ginsenoside, Rosmarinic acid, Salvanolic acid, & Hesperidin	Reviewed in [56]
	Inhibit COX-2, modulate 5-HT neurons	Celecoxib	[119]
	↓NF-κB signaling & subsequent TNF-α, IL-1β, & IL-6 production	Statins Proanthocyanidin Ginseng	[120-122] [123] [124]
	↓Neurotoxic factors released by microglia	Minocycline	[58, 125]
	↓TNF-α	Infliximab	[126]
	↑Neuropeptide Y (NPY) & heat-shock protein 72	<i>Hypericum perforatum L., Valeriana officinalis L., Passiflora incarnata L., Crocus sativus L., Curcuma longa L., Rhodiola rosea L., Coffea arabica L., & Cannabis sativa L</i>	[59, 127]
NMDA-receptor antagonists	↓Ca ²⁺ influx, ↓BDNF, ↓nitric oxide synthase (NOS), & ↓oxidative stress	Traxoprodil, Ifenprodil, Ketamine, Esketamine, Lanicemine, AZD 6423, D-cycloserine, Amantadine Memantadine, Ascorbic acid, & Zinc	[16, 49, 50, 128-133]
Antioxidants	Restore oxidative stress balance	Ascorbic acid, Zinc, Thiamine, & Curcumin	[77, 80, 134-136]
Insulin sensitizers	Regulate cerebral blood flow, affect monoamines release, & reuptake	Pioglitazone	[84]
Opioids	Possible modulation of 5-HT & HPA axis, Kappa antagonism produces antidepressant effect	Buprenorphine ALKS-5461	[88, 137, 138]
Probiotics	↓Inflammation, ↑GABA production, & attenuates HPA axis	<i>Bifidobacterium animalis, Streptococcus thermophiles, Lactobacillus bulgaricus, & Lactococcus lactis</i>	[139]
GABA agonists	Binding to β subunit of GABA receptor	Etifoxine	[102, 109]
		Valerenic acid	[112, 114]

responsible for the synthesis of cytokines including (TNF-α, IL-1β, and IL-6) [54], which in turn increase the levels of the presynaptic transporters of monoamines thus leading to their depletion from the synaptic space. Additionally, cytokines activate indoleamine 2,3 dioxygenase (IDO) enzyme that breaks down tryptophan, the precursor of serotonin to yield kynurenine that is converted into quinolinic acid and subsequently into glutamate [55, 56]. Anti-inflammatory agents can exert antidepressant effects by mediating neuroplasticity genes, neurotransmitter systems, suppressing COX-1 and COX-2 that produce inflammatory prostaglandins and glucocorticoid receptor pathways [57]. There is a wide range of anti-inflammatory potential adjuvants to antidepressants; however, appropriate choice should be based on the robust evidence of efficacy and tolerability profile. Minocycline, statins, non-steroidal anti-inflammatory drugs (NSAIDs), and eicosapentaenoic acid showed significant results as adjuvants [56, 58, 59] (Table 1).

MITOCHONDRIAL MODULATORS

Mitochondria have multi-tasks, beyond the generation of energy, mitochondria are responsible for Ca²⁺ level modulation and reactive oxygen species (ROS) regulation and

neuroplasticity [60]. It has been demonstrated that psychological stress impairs neuroplasticity and diminishes hippocampal neurogenesis thus leading to depression [61, 62]. The mitochondria of depressed patients showed a lower ATP production rate explaining chronic fatigue symptoms, a disrupted ratios of the electron transport chain enzyme [63], a higher NO synthesis rate and a higher mitochondrial membrane potential PMMP values in MDD patients as compared to controls [64].

Oxidative stress and mitochondrial impairment are always in a vicious cycle. Mitochondrial dysfunction leads to electron and free radical leakage, subsequently, the oxidative damage hits mitochondria and other cell components [65]. Animal models subjected to psychological stress have higher levels of oxidative stress markers in the blood, hippocampus, prefrontal cortex, and cortex [66, 67]. Clinically, impaired mitochondrial bioenergetics can be evaluated in peripheral cells such as muscle cells [68], platelets [69, 70], and peripheral blood mononuclear cells (PBMCs) [71]. Melatonin and acetyl-L-carnitine are two mitochondrial modulators with proven evidence as antidepressant adjuvants. Besides its use in sleep, melatonin protects the degradation of the mtDNA via enhancing oxidative phosphorylation. Acetyl-L-carnitine on the other hand modulates mitochondria by increasing acetyl-CoA uptake during the fatty acid oxidation process (Table 1).

ANTIOXIDANTS

Oxidative stress is defined as the inability of the cells to detoxify the increasing production of ROS. The formation of excessive amounts of ROS leads to subsequent oxidation of the nucleophiles (lipids, proteins, and DNA) thus leading to cell death [72]. A fast-growing body of evidence points out the implication of oxidative stress, in the pathophysiology of depression [73].

High levels of oxidative stress markers were seen lipid peroxidation, as measured by thiobarbituric acidic reactive substance (TBARS), and 8-hydroxy-2-deoxyguanosine (8-OHdG) and F2-isoprostanes, a marker of oxidative DNA and lipid damage respectively [74]. Altered levels of the antioxidant glutathione (GSH) were reported in postmortem brain samples of depressed individuals [75] and polymorphisms in the antioxidant enzymes super oxide dismutase (SOD) and catalase (CAT) genes were documented [73].

Numerous pieces of literature with striking evidence suggests the antidepressant role of several well-known antioxidants, herein we include ascorbic acid and curcumin, which are of importance due to their availability and high safety profiles. Ascorbic acid works as an antioxidant by directly binding and neutralizing free radicals however its antidepressant actions are yet to be uncovered. In one preclinical study, ascorbic acid exerted an antidepressant effect in mice, moreover, it potentiated the effects of fluoxetine and imipramine [76]. Another pilot study provided promising results of ascorbic acid in alleviating depressive symptoms in pediatric patients maintained on SSRIs [77]. Moreover, curcumin, a natural compound derived from the herb *curcuma longa* reported to be an effective antidepressant supplement [78] owing its effect to multi mechanistic approach including antioxidant properties by activating the Nrf2 signal transduction pathway that activates a battery of antioxidant defensive enzymes such as superoxide dismutase SOD [79], anti-inflammatory and mitochondrial function corrective mechanisms. Curcumin has demonstrated antidepressant activity in both preclinical trials [80, 81]. Please refer to **Table 1** for more examples.

INSULIN SENSITIZERS

Association between insulin resistance and depression is well established [82]. Depression prevails more among diabetic patients, prediabetics, and women with polycystic ovarian syndrome [83]. Association between insulin resistance and depression can be explained in various mechanisms. Firstly, depression is associated with disruption to the hypothalamic-pituitary adrenal axis, causing an increase in cortisol that triggers hyperglycemia and insulin resistance IR. Secondly, depression is associated with chronic inflammation leading to insulin resistance [84]. Insulin has been shown to alter central nervous system (CNS) concentrations of neurotransmitters such as dopamine [85] and norepinephrine [86]. It has been demonstrated that treating depression results in decreasing insulin resistance [82]. Specifically, SSRIs appear to improve insulin sensitivity [87], on the other hand, insulin sensitizers improve depressive symptoms. For example, pioglitazone, an insulin sensitizer demonstrated antidepressant properties in a short-term follow up study [82].

OPIOIDS

Rationale behind opioid use in depression is not new [88], in fact, the use of natural opioid derivatives has been used to alleviate melancholia for centuries [89]. A growing number of animal studies have highlighted the potential importance of opioid receptors in development and alleviation of depression [90].

As suggested by preclinical and clinical evidence, the link between depressive episodes and β -endorphin, (an endogenous opioid receptor agonist) is established. For example, the infusion of β -endorphins into depressed patients resulted in mood elevation as reviewed in [88].

The μ -opioid receptor binding in the posterior thalamus may be a potential biomarker for treatment response and depression severity, furthermore, evidence suggests overexpression of mu (μ)-opioid receptors in the brain of depressed suicide victims [91, 92]. The κ opioid receptor antagonism seems to be implicated with depressive symptoms, antidepressant effects on animal models were seen using κ opioid receptor antagonists as seen on the forced swim tests and other paradigms [93-96].

PROBIOTICS

Mood can affect the function of the gut and vice versa in humans and animal studies, where evidence suggests a change in the gut microbiota composition in relationship with the duration and severity of psychological stress [97]. According to animal models, GABA enhancement, anti-inflammatory and the hypothalamic-pituitary adrenal axis rebalance role are the suggested mechanisms explaining the relationship between altered gut microbiota and depression. Elevated serum lipopolysaccharide (LPS) concentrations are associated with depression, emerging evidence demonstrated a role of the probiotic bacteria *L. farciminis* in lowering LPS via an HPA-mediated mechanism [98, 99].

GABA AGONISTS

GABA receptor is an ion channel gated chloride conducting receptor composed most frequently of alpha, beta, and gamma subunits assembled as a pentameric structure, forming a central pore [100, 101], the activation of GABA receptors leads to chloride influx thus leading to hyperpolarization. Benzodiazepines, the famous GABA agonist class, is often combined with antidepressants to overcome their latency [102], however, benzodiazepines are associated with significant adverse, which include sedation, cognitive alterations, risk of abuse, and dependency [103-105].

Ideally, the proper use of benzodiazepines should not exceed four weeks [106], however, they are becoming highly demanded by patients as they are abused, which represents a public health problem [107]. Therefore, employing non-addictive GABA agonists could represent safe and effective adjuvant for the classical antidepressants, these include etifoxine a synthetic molecule, and valerianic acid, which is the principal active constituent of *Valeriana officinalis*.

Etifoxine is a synthetic non-benzodiazepine drug of the benzoxazine family with anxiolytic effects that act via an

agonist mechanism in the GABA receptor precisely the β_2 or β_3 subunits, a distinct binding site than benzodiazepines [102], furthermore, etifoxine modulates the action of neuro-steroids in the same receptor [108].

Although growing lines of evidence showed significant anxiolytic effects of etifoxine with fewer side effects compared to benzodiazepines [109, 110], no studies tried to explore the potential synergy between etifoxine and antidepressants. Valerianic acid is the main active constituent of valerian, one of the most widely used herbs for anxiety as an over-the-counter supplement [111]. Valerianic acid anxiolytic action is based on interacting with β -3 subunits of the GABA receptor [112-114]. According to our knowledge, no previous studies explored the role of valerianic acid as a potential augmenter to antidepressants.

CONCLUDING REMARKS

In conclusion, numerous potential augmenters to antidepressants are available with various strategies and mechanisms. The selection criteria and hence the implementation of these augmenters in the clinical practice are crucial. The heterogeneity of data, study designs, and measurement tools in this field remain the greatest challenge.

Future directions should focus on accelerating the onset of action of antidepressants in order to overcome adherence challenges, this could be implemented by the employment of well established, potentially effective, non-addictive and proven safe “add-on” agents in well designed long-term studies.

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