Antidepressants on Multiple Sclerosis: A Review of In Vitro and In Vivo Models

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Background: Increased prevalence of depression has been observed among patients with multiple sclerosis (MS) and correlated with the elevated levels of proinflammatory cytokines and the overall deregulation of monoaminergic neurotransmitters that these patients exhibit. Antidepressants have proved effective not only in treating depression comorbid to MS, but also in alleviating numerous MS symptoms and even minimizing stress-related relapses. Therefore, these agents could prospectively prove beneficial as a complementary MS therapy.

Objective: This review aims at illustrating the underlying mechanisms involved in the beneficial clinical effects of antidepressants observed in MS patients.

Methods: Through a literature search we screened and comparatively assessed papers on the effects of antidepressant use both in vitro and in vivo MS models, taking into account a number of inclusion and exclusion criteria.

Results: In vitro studies indicated that antidepressants promote neural and glial cell viability and differentiation, reduce proinflammatory cytokines and exert neuroprotective activity by eliminating axonal loss. In vivo studies confirmed that antidepressants delayed disease onset and alleviated symptoms in Experimental Autoimmune Encephalomyelitis (EAE), the most prevalent animal model of MS. Further, antidepressant agents suppressed inflammation and restrained demyelination by decreasing immune cell infiltration of the CNS.

Conclusion: Antidepressants were efficient in tackling numerous aspects of disease pathophysiology both in vitro and in vivo models. Given that several antidepressants have already proved effective in clinical trials on MS patients, the inclusion of such agents in the therapeutic arsenal of MS should be seriously considered, following an individualized approach to minimize the adverse events of antidepressants in MS patients.

Keywords: MS, antidepressants, EAE, neurotransmitters, in vivo, in vitro, immunomodulation
INTRODUCTION

Multiple Sclerosis and Depression

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS), involving inflammatory, neurodegenerative and autoimmune patterns in its pathogenesis (1, 2). Most frequently, the onset of MS is characterized by a clinical course of relapses and remissions (RRMS) present in almost 90% of MS patients (3). Current therapeutic means such as disease modifying therapies (DMTs) are mostly efficient during this stage, as CNS inflammation is still highly prominent and directly implied in the emergence of relapses (4, 5). Along with DMTs, antidepressants are often prescribed to MS patients as they are quite prone to manifest symptoms of depression and anxiety (6–8). In fact, studies report a 50% lifetime risk of major depression for MS patients (9).

Stress-Related MS Relapses

A significant factor that has been repeatedly held responsible for igniting MS relapses are stressful life events (SLEs) (10, 11). In MS patients, SLEs have proved to spark inflammatory activity by interfering with immune-mediated pathways that regulate autonomic functions, along with the Hypothalamic-Pituitary-Adrenal (HPA) axis (12). Hyper reactivity of the HPA axis is a common finding among MS patients (13). However, chronic stress compromises the ability of endogenous glucocorticoids to regulate inflammation in MS, as it desensitizes immune cells to their regulation by cortisol (12, 14). Resistance to the effects of glucocorticoids has been observed in animals undergoing chronic stress, suggesting that a similar pathway describes the impact of stress on MS patients (15).

Serotonin and MS

Serotonergic routes are highly responsible for modulating both our autonomic and neuroendocrine reactions to stressful stimuli, as serotonin constitutes a major HPA axis modulator (16, 17). In patients suffering from depression or anxiety, the serotoninergic network is significantly altered by accumulating stress, thereby severely impacting HPA axis function (18). This defect, however, has proved to be reversed upon antidepressant treatment (19, 20). On that premise, antidepressants could constitute a very promising add-on therapy for MS, as elevated bioavailability of serotonin in MS patients may be efficient in reversing the impact of chronic stress on disease progression.

With respect to serotonin or 5-hydroxytryptamine (5-HT), it displays immunomodulatory properties, interfering with T-cell activation, cytokine release from monocytes, and natural killer (NK) cell stimulation (21–25). Multiple pre-clinical studies have unanimously suggested that selective serotonin reuptake inhibitors (SSRIs) promote remission of the clinical signs of experimental autoimmune encephalomyelitis (EAE), the most prevalent animal model of MS, by curbing pro-inflammatory cytokine release (IFN-γ, TNF-a, IL-6, IL-7) and reducing T-cell proliferation (26–29).

In parallel, solid evidence provided by clinical trials has demonstrated that the use of the SSRI escitalopram in women with MS was effective in preventing stress-related relapses (30). To date, long-term impairment remains the inevitable outcome in most MS cases and current drugs fall short of addressing this fervent matter. It has been proved, however, that long-term disability is highly contingent on the build-up of tokens of impairment that remain after the cessation of each relapse (5). Minimizing relapse frequency is of grave importance for achieving a significant delay in the onset of severe impairment and therefore agents like SSRIs that have proved efficient in this field should be seriously considered as a complementary therapeutic option for all MS patients. Given however the individuality of each MS patient and the varying side events exerted by antidepressants, a personalized prescription of these drugs based on the needs of each patient would be highly recommendable (31).

Other Key Neurotransmitters in MS

Accumulating evidence suggests that several motor and non-motor symptoms of MS can be attributed to pathologically reduced levels of key neurotransmitters (32–38). Apart from serotonin (39), studies have detected abnormal fluctuations in the levels of noradrenaline (NE) and γ-aminobutyric acid (GABA) (29, 40) within the CNS of EAE mice. Since agents that increase GABAergic and monoaminergic transmission have been shown to moderate EAE severity (29, 41–43), antidepressants could be deemed as potential therapeutic compounds, capable of suppressing the clinical symptoms and neuropathological characteristics of MS (29, 40, 44).

It is worth noting that these key neurotransmitters display both neuronal and immunomodulatory properties, as 5-HT, NE and GABA not only regulate immune cell function (29, 36–38, 45), but also attenuate EAE severity through anti-inflammatory pathways (29, 41, 45). T-cells and macrophages express functional receptors and are capable of synthesizing 5-HT, glutamate, GABA and dopamine (DA) (21, 46, 47). Further, the alpha and beta 2 adrenergic receptors expressed on the surface of T-cells render them susceptible to regulation by adrenergic transmission (48). Similarly, T-cells and macrophages express functional GABA-A receptors, proving that the maintenance of key neurotransmitters at high concentrations is critical for immunomodulation (29, 49).

Animal Models of MS

As already mentioned, MS is a chronic, autoimmune and demyelinating disease of CNS. While MS is only found in humans, many in vivo models have been developed to better simulate the pathophysiology of this disease. None of the in vivo MS models is perfect; none of these can reproduce the whole range of complex and diverse morphological and functional aspects of this CNS condition. Each one of them has its advantages and disadvantages, all of them have certain limitations. Albeit certain animal models of MS have proved to be valuable tools, mainly in the development of novel MS drugs (50).

According to a review on MS animal models, the experimental autoimmune encephalomyelitis (EAE) model is one of the most representative in vivo MS models as it imitates both the clinical and the pathological characteristics of this
condition, followed by the Virus-induced demyelination models (50).

The MS induction on in vivo models could be well categorized into three main classes. These include toxin-induced demyelination models, the virus-induced demyelination model mainly by Theller’s murine encephalomyelitis virus and the above-mentioned widely used experimental autoimmune encephalomyelitis (EAЕ) model (50, 51).

Toxin-induced demyelination models are based either on linear inoculation of gliotoxins in the white matter, including ethidium bromide (EtBr) and lyssolecithin, or on systemically administered toxins, with cuprizone being the most representative. These models offer duplicability, while the demyelinated area is distinct for further remyelinating studies. Furthermore, ethidium bromide, a toxic intercalating agent, affects both the nucleus DNA and the mitochondrial DNA, but offers well established predictable results, as the magnitude of demyelination is concentration-dependent. Lyso-phosphatidylcholine (lyssolecithin) has been used for almost 50 years. Its mechanism of action in the demyelinating process is based on its physicochemical properties, as it can act as a detergent-like agent with selectivity over the myelin-producing cells marking and engaging T and B cells, like activated macrophages. This method can also be implemented in non-human primates, while also the demyelination can be performed in a spatiotemporal manner. On the contrary, this method does not lead to any immune response resembling the one recognized during multiple sclerosis (50).

Certain other toxins possess analogous demyelinating toxic results but are not in general use. Examples include ionomycin, a calcium ionophore, 6-aminonicotinamide, an antimetabolite of niacin and diphtheria toxin. Antibody-mediated demyelination is also an acknowledged animal model of induced demyelination by galactocerebrosides antibodies. Finally, this class of methods included cuprizone, a copper-chelating agent, which has been shown to be toxic for myelin, affecting both white and grey matter leading to oligodendrocyte apoptosis, mitochondrial enzyme malfunction and activation of microglia. Like lyssolecithin, cuprizone can also be performed in a spatiotemporal manner while interest is focused on the combined use of cuprizone with other methods of demyelination induction like EAE.

There is growing indication that certain viruses are involved in the pathogenesis of MS, functioning like environmental triggers. The Epstein-Barr virus (EBV) is a typical example that has long been associated with autoimmune conditions including multiple sclerosis despite the exact cause still remains unknown (51). Viruses that have been used in vivo as MS inducers include Theller’s murine encephalomyelitis virus (TMEV), the canine distemper virus and the mouse hepatitis virus. The former is the most established and serves as a neurotropic viral infection model. TMEV can be separated into two main categories based on the virulence of the viral strains or subgroups and the qualification to induce demyelination. The effects of each viral subgroup extend from severe encephalitis to deadly encephalomyelitis, also being subject to the mouse strains. The most defiant are the BALB/c, C57BL/6J, C57BL/10, and C57/L mouse strains (50). This model can lead to both acute and chronic phase of CNS toxicity, outlined by CNS inflammation and neural apoptosis and affecting the subcortical gray matter, the hippocampus and the basal ganglia.

The most established in vivo model of MS is the EAЕ model which can mimic a broader spectrum of histopathological and immunological expressions of the disease. EAЕ can be induced via two different paths, the active immunization with myelin peptides (52) or the passively or adoptively transferred encephalitogenic T cells (53).

Active EAЕ requires mice, rats, guinea pigs or nonhuman primates, the use of a myelin-related antigen and concomitant injections of pertussis toxin, leading to activated myelin-specific T cells and encephalitogenic lymphocyte-mediated demyelination. Conversely passive EAЕ is based on the administration of activated, myelin-specific T cells. Passive EAЕ evolves faster, does not require any adjuvant and showcases better homogeneity, however its main limitation is that the myelin antigen-specific T cells might not have the desired encephalitogenic capacity, when used in vivo (54).

EAЕ is also affected by the animal strains or species used. The leading option for animals that can accurately imitate the pathophysiology of MS are mice and rats of different strains including Lewis, Dark Agouti (DA) and Brown Norway (BN). Additionally, non-human primates including common marmosets (Callithrix jacchus) and rhesus monkeys (Macaca mulatta), can also be used for in vivo experiments on MS (50).

Therefore, the aim of this review is to provide readers with a useful insight into pre-clinical findings regarding the immunomodulatory effects of antidepressants in in vivo and in vitro models of MS.

METHODS

Literature Search

We systematically searched the literature for studies investigating the effects of antidepressants on in vitro and in vivo models of multiple sclerosis. An electronic database literature search was conducted in PubMed, Cochrane and Scopus from inception through 17 April 2021 to provide us with results from in vivo and in vitro studies.

The following keywords were used: for in vivo studies (experimental autoimmune encephalomyelitis OR EAE) AND (MS OR sclerosis) AND antidepressant; for in vitro (In Vitro or cell culture) AND (MS or sclerosis) AND antidepressant. Retrieved articles were imported to EndNote. All articles were independently screened for duplicity and eligibility by author ES and ID.

Inclusion and Exclusion Criteria for In Vitro Papers

The inclusion criteria for in vitro research were the following: i) original research paper, ii) published in English, iii) use of antidepressant drugs/agents, iv) use of antidepressant agents as a monotherapy or combination treatments.

Articles were excluded if: i) the study did not evaluated MS, ii) the pharmacological agent had antidepressant properties but
no clinical use as an antidepressant iv) only the abstract was available, v) the research involved patients. In total, our search yielded 271 articles of which 6 were eligible as abstracts. Finally, after the full text of each article was retrieved and all our inclusion criteria were met, 4 articles were included (Figure 1).

Inclusion and Exclusion Criteria for In Vivo Papers
Inclusion criteria for in vivo research were the following: i) original research paper, ii) published in English, iii) use of antidepressant drugs/agents, iv) use of antidepressant agents as a monotherapy or combination treatments, v) use of validated in vivo tests vi) induction of EAE in mice and rats.

Articles were excluded if i) the study did not evaluated MS, ii) no behavioral tests were used, iii) the pharmacological agent had antidepressant properties but no clinical use as an antidepressant iv) only the abstract was available, v) the article was a review or a case report. In total, our search yielded 59 articles of which 27 were eligible as abstracts. Finally, after the full text of each article was retrieved and all our inclusion criteria were met, 16 articles were included (Figure 1).

RESULTS
In Vitro Results
In our research we ended up with 4 studies on antidepressants use, on in vitro models of MS. All studies were performed in in vivo and in vitro models of MS. Cultures involved cells that were either human or rat and mice derived. Among the drugs examined in this review are the tricyclic antidepressants clomipramine, desipramine, imipramine, amitriptyline, the selective serotonin reuptake inhibitors fluvoxamine (55), and the serotonin-norepinephrine reuptake inhibitor (SNRI) drug venlafaxine (38). The antidepressant effects of these drugs on MS models were evaluated using various methods. Real-time PCR, Western blot analysis and ELISA assay were the most widely used techniques, apart from live-cell imaging, immunohistochemistry, immunostaining and immunofluorescence (IF).

Ghareghani et al. found that fluvoxamine enhanced cell proliferation, viability and differentiation of astrocytes, oligodendrocytes and embryonic neural stem cells (eNSCs) (55). Venlafaxine reduced the secretion of pro-inflammatory cytokines such as TNF-a, IFN-γ and IL-6, therefore suppressing inflammation in the CNS, while regulating NK cell and T-cell gene expression (38). Tricyclic antidepressant drugs were found to exhibit neuroprotective activity through elimination of neuronal loss. Reduced proliferation of T-cells and activated B-cells was observed, in tandem with suppression of TNF-a secretion (56).

Ghareghani et al. used murine embryonic neural stem cells from Lewis rat embryos to study the effects of fluvoxamine performing MTT assay to assess cell viability, Real-time PCR, Western blot analysis and Immunofluorescence (IF) analyses.

Fluvoxamine was found to act through the Notch signaling pathway, enhancing cell proliferation transcription factors at even low concentrations. Astrocyte, oligodendrocyte and neuron differentiation was observed to be upregulated which may be attributed to upregulation of the mRNA expression of Notch1, Hes1 and Ki-67 (55).

In their study Faissner et al. used cell cultures from both human (brain tissues and peripheral blood mononuclear cells) and murine (splenocytes) origin. Neurotoxicity was induced by rotenone, while HORAC assay, Flow cytometry, live cell

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FIGURE 1 | Flow chart of in vitro and in vivo results.
imaging. Immunocytochemistry and microscopy were performed. The researchers concluded that Clomipramine, Desipramine, Trimipramine, Imipramine and Doxepin all belonging to the tricyclic antidepressant class, exert beneficial effects in the treatment of MS. Prevention of neuronal loss and antioxidative effects were also observed, while T-cell and activated B-cell proliferation, TNF-a production and plasma membrane compromise were all reduced. These findings highlight an overall neuroprotective activity, that is of pivotal importance for a demyelinating autoimmune disease like MS (56).

In Vivo Results

The in vivo results indicated that SSRIs, such as sertraline, fluoxetine and fluvoxamine either delayed disease onset or ameliorated the clinical symptoms in EAE mice. SSRIs mitigated clinical scores and eliminated EAE symptoms, mainly through their actions on immunomodulatory cells. Sertraline-treated mice manifested milder clinical symptoms compared to the untreated EAE group, while sertraline displayed a dose-dependent inhibitory effect on the secretion of the pro-inflammatory cytokines IL-2, TNF-a and INF-γ. Similarly, the reduction of cytokines in mice serum (IL-6, IL-10, TNF-a and INF-γ) was also observed after fluoxetine treatment. Apart from cytokines, fluoxetine also reduced inflammation by directly impacting APC and naïve T-cells. In EAE rats, both fluoxetine (pretreatment/preventive) and fluvoxamine (symptomatic treatment) eliminated clinical symptoms and reduced IFN-γ secretion. Interestingly, fluvoxamine also inhibited the formation of demyelinating plaques, suppressed immune cell infiltration into the CNS and upregulated anti-inflammatory agents. Moreover, in a rat EAE model, duloxetine prevented cold allodynia and showed antinociceptive effects on cold hyperalgesia, thus alleviating some clinical signs.

Dose-dependent relief of mechanical allodynia in the bilateral hind paws of EAE mice was also observed after treatment with amitriptyline, a tricyclic antidepressant. In addition, pharmacological intervention with chronic application of amitriptyline in the mild MOG-EAE mice model resulted in a decreased startle reaction and increased hippocampal norepinephrine levels. Another group of researchers (57) utilized the combination treatment or nortriptyline (TCA) and desloratadine (antihistamine) to assess their therapeutic potential on EAE mice. This combination treatment moderated EAE severity by reducing CD4+T cell infiltration in the CNS and suppressing IFN-γ, IL-17 secretion, while boosting anti-inflammatory IL-4 levels. These findings are aligned with other observations supporting that imipramine reduces plasma levels of IL-4 and clomipramine decreases mRNA expression levels of IFN-γ, TNF-a, IL-17 and chemokine CCL-2. Overproduction of chemokine CCL-5 (also known as RANTES) was mitigated by desipramine, thus restoring glutamate exocytosis and presynaptic cortical defects (57).

In another study, researchers used splenocytes, encephalitogenic T cell clones, primary peritoneal macrophages and brain and spinal cord sections from female mice after the EAE protocol was performed in vivo. They conducted ELISA to determine the cytokine levels in the culture supernatants, while carrying out cell viability assay and real-time PCR after RNA isolation. Venlafaxine an SNRI drug was found to regulate the clinical and histopathological impact of EAE. Pro-inflammatory cytokines such as TNF-a, IFN-γ, IL-6, Ccl5 and IL-12 were downregulated while CNS inflammation was also reduced showcasing a potential efficacy in MS (38). According to Dawson et al, fingolimod inhibits the enzyme acid sphingomyelinase sharing a related mechanism of action with desipramine, a tricyclic antidepressant. The researchers used neural-derived cells and fibroblasts and observed that desipramine suppressed ASMase without inducing significant inhibition of other lysosomal hydrolases (58).

According to Taler et al, antidepressants, especially SSRIs, display an immunomodulatory activity by reducing immune cell viability and attenuating of pro-inflammatory cytokine secretion. In particular, their research demonstrated that treatment of EAE mice with sertraline alleviated the neurological symptoms of MOG-induced chronic EAE (42). In addition, fluoxetine suppresses the adaptive immune response in EAE through the reduction of cytokine release (IL-6, IL-10, TNF-a, IFN-γ) and induction of CD4 T-cell apoptosis (59, 60). Recently, a study indicated that the SNRI venlafaxine suppressed the secretion of the pro-inflammatory agents TNF-a, IFN-γ, IL-2 and chemokines in encephalitogenic T cell clones, splenocytes and macrophages, while increasing BDNF expression (38).

Furthermore, treatment of EAE mice with the SNRI venlafaxine ameliorated EAE symptoms in a dose-dependent manner. Venlafaxine exerted its beneficial effects through suppression or enhancement of mRNA expression of proinflammatory and anti-inflammatory factors, respectively. These proinflammatory factors include IFN-γ, TNF-a, IL-12, chemokine CCL-2, CCL-5. On the contrary, venlafaxine increased mRNA expression of the neurotrophic factor BDNF. Moreover, phenelzine a MAO inhibitor, has been used as a treatment in established EAE- female C57/BL6 mice. It was observed that phenelzine delayed the onset of clinical signs, reduced impairments, ameliorated locomotor function and demonstrated antinociceptive effects. The aforementioned benefits derive from phenelzine’s ability to normalize the levels of GABA and biogenic amines that have been shown to possess anti-inflammatory properties. In particular, phenelzine increased the levels of 5-HT, NE, DA within the spinal cord, brain and brainstem. Lastly, phenelzine normalized pre-synaptic excitatory synaptic densities in S1 and neuronal morphologies.

(Table 1, Table 2).

DISCUSSION

Among MS patients, depression constitutes a highly frequent comorbidity, as studies indicate a 25% prevalence of depression in MS (6, 70). This trend severely affects the quality of life perceived by MS patients, as following disability, depression is the second most impactful factor determining the health-related quality of life (71). Moreover, depression can compromise patient adherence to DMTs, further affecting MS
### TABLE 1 | Comparative assessment of in vitro studies on the effects of antidepressants in cell and slice cultures.

| Ref         | Drug           | Drug Con. | Cell culture/Slice                          | Methods                       | Intracellular signaling/ Transcriptional factors | Results                                                                 | Comments                                                                 |
|-------------|----------------|-----------|---------------------------------------------|-------------------------------|-------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Qhareghani et al. (55)** | Fluvoxamine  | 0.1- 1-5; 50-100 nM | Murine eNSCs (from Lewis rat embryos' SVZ zone) | MTT assay, Real-time PCR, Western blot, Neurosphere assay | Notch signaling, ↑mRNA expression of Notch, Hes1 and Ki-67, ↑protein levels of NICD | - ↑ cell viability (0.1-1-5 nM)  
- ↑ self-renewal capacity of NSCs (neurosphere formation) (1.5, 50 nM)  
- Toxic con (500 nM) ↑NSCs differentiation (1 and 5 nM)  
- ↑astrocytes and neuron differentiation (5 nM)  
- ↑oligodendrocyte differentiation (1 nM)  
- ↑IL-4, ↓IFN-γ | Flu acts through Notch signaling pathway to enhance cell proliferation |
| **Faissner et al. (56)** | Clomipramine | 10 μM | Human neurons (from brain tissues of therapeutically aborted 15-20 week-old fetuses) | FeSO₄⁺ - mediated neurotoxicity, -Chelation with iron, Anti-MAP-2 Ab staining, -mitochondrial electron transfer chain | - ↓proliferation of T-cells  
- ↑ serum lactate levels  
- Complete prevention of neuronal loss | -↓MBP in demyelination areas  
- ↑GFAP positive staining  
- ↓ serum lactate levels  
- Complete prevention of neuronal loss | -Fluvoxamine ameliorates the severity of EAE by inhibiting IFN-γ release and promoting IL-4 production from Th1 and Th2 cells, respectively  
- Fluvoxamine reduces demyelination areas by 0.81%  
- Serum lactate is an EAE and MS progression biomarker |
| | | 5 μM | Splenocytes (from female C57BL/6 mice) | FeSO₄⁺ - mediated neurotoxicity, HORAC assay, B-cell isolation | | | |
| | | 2 μM | PBMCs (from venous blood from healthy volunteers) | FeSO₄⁺ - mediated neurotoxicity, Anti-MAP-2 Ab staining, Live-cell imaging | | | |

(Continued)
| Ref | Drug | Drug Con. | Cell culture/Slice | Methods | Intradacellular signaling/Transcriptional factors | Results | Comments |
|-----|------|----------|-------------------|---------|-----------------------------------------------|---------|----------|
|     | Desipramine | Human neurons (from brain tissues of therapeutically aborted 15-20 week-old fetuses) | Ronetone-induced neurotoxicity | -Chelation with iron | ↓proliferation of T-cells | -Propidium iodide leaking inhibition | ↓neurotoxicity |
|     | Splenocytes (from female C57BL/6 mice) | | | | | ↓proliferation of T-cells | |
|     | Trimipramine | Human neurons (from brain tissues of therapeutically aborted 15-20 week-old fetuses) | | | | ↓proliferation of T-cells | |
|     | Splenocytes (from female C57BL/6 mice) | | Immunohistochemistry | | ↓proliferation of T-cells | | |
|     | Splenocytes (from female C57BL/6 mice) | | RT-PCR | | ↓transcripts encoding IFN-γ, TNF-α, IL-12, Ccl2 | | |
|     | \(25 \text{ mg/kg}\) | Blood samples (from female C57BL/6 mice with EAE) | | | ↓parenchymal inflammation with only a few cells in the meninges | -High brain to plasma ratio of Clomipramine |
|     | Doxepin | | | | ↓microglial activation and infiltration | -High brain to plasma ratio of Clomipramine |
|     | \(10^{-4}\) to \(10^{-8}\) mol/l | Encephalitogenic T cell clone 5-8 (MOG 35-55 specific, female SJL/J mice) | Determination of cytokines in culture supernatants by ELISA | ↓secretion of TNF-a and IFN-γ | | -The effect was more pronounced for IFN-γ and IL-12 p40 with an overall reduction of secretion by 50% |
|     | Naïve splenocytes (PLP 139-51 specific, from female SJL/J mice) | -→ PLP-specific T cells | | ↓secretion of TNF-a, IFN-γ, IL-6, Ccl5, IL-12 p40, ↓secretion of TNF-a and IL-6 | | -Venlafaxine reduced expression levels of Ccl5, IL-6 and TNF-a dose-dependently |
|     | Primary peritoneal macrophages (activated with LPS, from female SJL/J mice) | | Immunohistochemistry - GFAP immunostaining | | ↓CNS inflammation | | |
|     | 6-20-60 mg/kg | Brain and spinal cord sections (from female SJL/J mice with EAE) | | | ↓IL-12 p40, TNF-a, ↓transcripts of chemokines Ccl2 and Ccl5, ↓mRNA | | | (Continued)
prognosis (72, 73). Although to date, about 86% of depressive MS patients receive antidepressant therapy, depressive symptoms often remain, pointing towards an underdosage or poor matching of these drugs to each patient (74).

Findings encompassed in this review have documented the efficacy of antidepressants in promoting oligodendrocyte maturation and proliferation (55). In MS patients, demyelination is often accompanied by compensatory remyelinating activity, an effect that is principally mediated by oligodendrocyte maturation (75). Therefore, agents like antidepressants or phosphodiesterase inhibitors (76) that stimulate the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes also boost remyelination, thus exerting a neuroprotective effect. This effect can also be indirectly attained through suppression of cytokines that curb Oligodendrogenesis. The regulation of T cell proliferation and stimulation by antidepressants reported in some studies of this review (38, 56) is of great significance, as these aspects are directly involved in MS pathogenesis. Myelin-reactive T cells are present in MS patients and held accountable for igniting demyelination, therefore the suppression of their activation, proliferation and migration constitute a very salutary property displayed by antidepressants. Lately, the role of B cells in MS has also been described as crucial, involving actions like the orchestration of effector T cell activity through antigen presentation and priming, as well as the secretion of proinflammatory cytokines (77, 78), rendering them principally responsible for the formation of a proinflammatory milieu in the CNS (79).

Studies included in this review also reported the suppression of proinflammatory cytokines induced by antidepressants. Along with several established proinflammatory cytokines such as IL-2, IL-6, IL-12, IL-17, TNFa and IFNy, antidepressants were also found to reduce serum levels of anti-inflammatory cytokines IL-4 and IL-10, though there has been some evidence supporting some of their immunostimulatory properties (80, 81).

Although MS is considered a Th1 autoimmune disease in which prevails a CD4+ immune response, CD8+ T cells seem to play a pivotal role in the pathogenesis of major depressive disorder (MDD). Clinical studies revealed that CD8+ T cells are increased in MS patients with depression compared to those without, being traceable in their serum during active phases (82). According to other studies, however, CD4+ T cells also seem to be augmented during MDDs in MS (83).

In a clinical scope, antidepressants have proved to be efficient not only in tackling depression comorbid to MS (84, 85), but also even in minimizing stress-related relapses, as shown by the clinical trials of escitalopram on female MS patients (30). Therefore, the use of antidepressants is not only a consolation therapy to improve the quality of life in MS, but also has the potential to significantly modify the course of the disease. Other antidepressants such as vortioxetine combine their antidepressant properties with an enhancing effect on patients’ cognition (86–88). This constitutes a very significant aspect, as about half of MS patients are estimated to manifest cognitive impairment (89). This agent however has neither yet undergone clinical trials on MS patients nor is its efficacy on cognitive enhancement unanimously accepted (90).

Regarding antidepressant use in MS, several adverse events of these drugs could potentially overlap some of the existing deficits that are to be found in MS patients, therefore exacerbating them. To draw an example, SSRIs are known to cause sexual dysfunction, a state that might be already prominent in MS patients, even reaching 85% in female MS patients (91). Therefore, given the heterogeneity of the clinical course of MS in each individual patient, a personalized and patient-oriented approach is necessary to ensure both safety and efficacy in the use of antidepressants in MS (31, 92).

Antidepressants, however, also have the capacity to alleviate numerous MS symptoms. Bupropion can benefit MS patients suffering from chronic fatigue, as this drug has been clinically shown to improve the fatigue severity scale when tested on a patient with MS (93, 94). Fatigue accounts for one of the most prevalent symptoms among MS patients, severely impacting their experienced quality of life. However, the multifactorial and diverse nature of this symptom impedes its management, calling for personalized treatments (95). Therefore, although randomized-controlled trials (RCTs) with numerous participants are required to secure this observation, the identification of a soothing effect of antidepressants on fatigue would constitute a highly significant discovery.

### TABLE 1 | Continued

| Ref       | Drug     | Drug Conc. | Cell culture/Slice | Methods                          | Intracellular signaling/Transcriptional factors | Results                                                                 | Comments |
|-----------|----------|------------|-------------------|---------------------------------|-----------------------------------------------|-------------------------------------------------------------------------|----------|
| Dawson et al. (58) | Desipramine | 20 µM, 40 µM | Neural-derived cells (LA-N-5 and HOG) | Lyosomal hydrolase assay RT-PCR Western blot (with anti-ASMase polyclonal Ab) | Displacement of ASMase from the late endosomal/lysosomal membrane -Inhibition of ASMase -No inhibition of β-D-glucosidase | expression of BDNF (for high doses of Venlafaxine) | cord tissue of EAE mice at day 48 after disease induction Desipramine reduced ASMase without significant inhibition of other lysosomal hydrolases |

Results of in vitro papers classified by type and concentration of antidepressant agent, cell or slice culture, methods, intracellular signaling, results and comments.
### TABLE 2 | Comparative assessment of in vivo studies on the effects of antidepressants on disease scores and progression.

| Study | Type of antidepressant | Dose | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design (Species) Age/gender/ Weight | Methods | Clinical results | Biological results |
|-------|------------------------|------|---------------------------|--------------|------------------------------------------------------|------------------------------------------|---------|-----------------|-------------------|
| Taler et al. (42) | SSRIs | 5mg/kg | Immunization (SC) with Mog/peptide encompassing amino acids 35-55 of rat | Onset 14/15 dpi and increasing severity 18-25 dpi | 7 days after EAE induction | 5 groups (10 mice each) | Cell viability assay Thymidine incorporation ELISA | Sertraline attenuates neurological symptoms and clinical progression of disease Paroxetine does not affect the clinical score of EAE | Sertraline may serve as an add-on option especially in co-morbid major depression |
| Bhat et al. (59) | SSRIs | 20mg/kg | Immunization (SC) with peptide proteolipid protein PLP 139-151 {100mg PLP 139-151 in emulsion 1:1 with CFA containing 4mg/ml M. Tuberculosis H37Ra} | Onset 10 dpi and peaked 15dpi | Once daily/orally I) at the time of immunization (delayed-onset model) II) at the time of peak disease (day 13) (amelioration model) | 10 per treatment group at the time of immunization I) vehicle group II) fluoxetine group At the time of peak disease (day 13) I) vehicle group II) fluoxetine group | ELISA kit Flow cytometry Cell proliferation assay | Decline in mean clinical scores in both groups Fluoxetine delayed onset of EAE and reduced peak illness severity (13-15 days) Ameliorated established EAE | Immune response (both in vivo/in vitro) ↓ cytokines (TNF-a, INF-γ, IL-6, IL-10) ↓ inflammation by directly acting on APC and naive T-cells ↓ activation-induced cell death (AICD) (FAS-ligand mediated mechanism) ↓CD4-T-cell apoptosis |
| Yuan et al. (60) | SSRIs | 10mg/kg | (IP) 200μg of guinea pig spinal cord | Onset of clinical symptoms (piloerection) approximately 4-5 dpi Peak | Once daily (Fx or saline) | 4 groups, 15 per group | ELISA kit | ↓ of EAE clinical symptoms (Fx 10/Fx 20) Elimination of inflammatory foci and demyelination in the spinal cord (Fx10) | Pro-inflammatory cytokines INF-γ in serum (Fx10 on day 16) No difference in serum concentration of TNF-a |
| | | 20mg/kg | Fluoxetine | for 14 days prior to immunization | | | | |

(Continued)
| Study | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design (Species) Age/gender/ Weight | Methods | Clinical results | Biological results |
|-------|---------------------------------------------------|------|--------------------------|--------------|----------------------------------------------------------|------------------------------------------|---------|-----------------|------------------|
| Thibault et al. (61) | SSRIs | 30 mg/kg | EAE induced | Onset of clinical signs 9dpi | Once daily (i.p) after the 14 day post EAE induction | 6 groups | 5 weeks old female Lewis rats | Actimetry scores | Duloxetine prevented cold allodynia and showed anti-nociceptive effect on cold hyperalgesia (21 to 28 dpi) | Duloxetine relieved cold hyperalgesia on tail region Duloxetine does not prevent mechanical hyperalgesia |
| | | | -solely by MBP | | | | | | |
| | | | - MBP plus Cyclosporine A (injected subcutaneously three times/week for 21 days) | | | | | | |
| | | | (1ml CFA/ 4 mg Mycobacterium butyricum/ 500 lg of MBP in 0.1 ml of saline) | | | | | | |
| Ghareghani et al. (55) | SSRIs | 50mg/kg | (SC) 200µl of a 1:1(V/V) mixture of 1g of Guinea Pig Spinal Cord (GPSC) in 1 ml PBS and | Onset of clinical signs day 12 | Treatment initiated (IP) from clinical onset (d 12) for 6 consecutive days (12-17d) | 3 groups. | 8-12 week old | Immunofluorescent analysis ↓ clinical scores | ↓ pro-inflammatory cytokine INF-γ in serum (Continued) |
| Study | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose | Induction of EAE Protocol | Signs of EAE Preventive or symptomatic treatment (drug administration) | Study Design (Species) Age/gender/ Weight | Methods | Clinical results | Biological results |
|-------|---------------------------------------------------|------|--------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------|--------|-----------------|-------------------|
| Fluvoxamine | complete Freud's adjuvant (CFA) and 1mg/ml enriched M. tuberculosis bacteria | 10mg/kg | (after immunization) | 7 per group | Adult Lewis rats 150-175g body weight (BW) | Western blotting HPLC | ↓ immune cell infiltration into CNS | ↑ anti-inflammatory IL-4 |
| Peruga et al. (62) | (TCA) | 20 days after immunization | 10-12 weeks old female C57BL/6 mice | MOG-EAE mice displayed: | Rotarod | ↑ EAE amelioration | |
| Amitriptyline | Immunization (SC) with 50µg MOG 35-55 | 10mg/kg | (Mild EAE protocol) | Once daily (IP) | 1) control/saline (n=5) | Light/dark box | ↑ startle reaction | |
| | Immunization (SC) with 50µg MOG 35-55 | (Suboptimal immunization protocol-mild EAE) | 60d.p.i Mild motor deficits (tail weakness) | 6 groups | 2) control/saline + amitriptyline (n=5) | Startle response | ↑ LH behavior (depressive-like) | |
| | Immunization (SC) with 50µg MOG 35-55 | 5mg/kg | Immunization (SC) with 100 µl of an emulsion containing 200µg of or 100 M. Tuberculosis H37Rv and 50µg of PLP 139-151 or PLP 178-191 in CFA | Onset of remission approximately 15-20 dpi | 3) MOG + saline (n=11) | Learned helplessness (LH) | ↑ depressive-like behavior | |
| Podojil et al. (57) | (TCA) | 20 days after immunization | 5 groups, 10 per group | MOG-EAE mice displayed: | ELISA | ↓ exploratory behavior | |
| | Nortriptyline and Nortriptyline + desloratadine (CRx-153) | 5mg/kg | Treatment for 21 days via oral gavage | I) vehicle-control | Reversed phase HPLC/MSc/MS | Combination treatment | |
| | | 10mg/kg | other EAE | II) desloratadine (3mg/kg) | Delayed type hypersensitivity (DHT) assay | [des(3mg/kg) + nor (10mg/kg)] | |
| | | | | III) nortriptyline (3mg/kg) | Flow cytometry | ↓ infiltration to the CNS of CO4+ T cells | |

(Continued)
| Study                     | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose                     | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design | (Species) Age/gender/Weight | Methods | Clinical results | Biological results |
|--------------------------|-----------------------------------------------------|--------------------------|---------------------------|--------------|----------------------------------------------------------|--------------|----------------------------|----------|----------------------|---------------------|
| Di Prisco et al. [63]    | (TCA)                                               | 10mg/kg                  | Immunization (SC) with incomplete Freud's adjuvant containing M. Tuberculosis 4mg/ml and 200μg of myelin oligodendrocyte glycoprotein MOG 35-55 | Onset of disease 13 +/-1 dpi | Administration of desipramine (dissolved in drinking water) 13 after immunization (acute) or starting from immunization day for 14 consecutive days (chronic) | 4 groups. | 6-8 weeks female C57BL/6 mice | Rotarod  | Acute treatment: ↓ neuronal defects and anxiety related behaviors | Acute treatment |
|                          |                                                     |                          |                           |              | IV) desloratadin (10mg/kg)                               |              | 18 per group 18-20g body weight (BW) | Light dark box | Chronic treatment: ↓ anxiety related behaviors | Chronic treatment (Results at 13 dpi) |
|                          |                                                     |                          |                           |              | V) nortriptyline (10mg/kg)                               |              | I) control mice | Open field test | Both treatments (acute/chronic) didn't improve motor activity or severity of clinical signs | ↓ overexpression of CCL5 in the cortex of EAE mice Long lasting restoration of Glutamate exocytosis and cAMP production (↑cAMP) |
|                          |                                                     |                          |                           |              | 5 groups, 10 per group                                  |              | II) EAE mice | Radioactivity measurement cAMP - Quantification assay ELISA kit |                      | |
|                          |                                                     |                          |                           |              | I) vehicle-control                                      |              | III) Control +DMI (acute) control +DMI (chronic) |                      |                      | |
|                          |                                                     |                          |                           |              | II) des(1mg/kg) + nor (5mg/kg)                          |              | IV) EAE mice +DMI (acute) EAE mice +DMI (chronic) |                      |                      | |
|                          |                                                     |                          |                           |              | III) des(1mg/kg) + nor (10mg/kg)                        |              |                      |                      |                      | |
|                          |                                                     |                          |                           |              | IV) des(2mg/kg) + nor (10mg/kg)                         |              |                      |                      |                      | |
|                          |                                                     |                          |                           |              | V) des(3mg/kg) + nor (10mg/kg)                          |              |                      |                      |                      | |
|                          |                                                     |                          |                           |              | 10-plex LiquiChip (level of cytokines)                  |              |                      |                      |                      | |

(Continued)
| Study                | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose     | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design (Species) | Methods | Clinical results | Biological results |
|---------------------|-----------------------------------------------------|----------|---------------------------|--------------|------------------------------------------------------------|------------------------|---------|-----------------|---------------------|
| Pollak et al. (64)  | (TCA) imipramine                                    | 10mg/kg  | Immunization on day 0 and 7 with 300μg MOG | Early onset (day 9) of hyperacute EAE (haEAE) characterized by brain hemorrhage and high mortality rate | Beginning on day 0 mice were either non-handled or injected daily with saline or imipramine | 3 groups               | female C57BL mice 4.5-7g body weight (BW) | Observations in motor deficits, food intake, BW, sucrose drinking and social exploration | Imipramine treated group ↑ survival rate Attenuated haEAE-associated decrease in BW |
| Faissner et al. (65) | (TCA) clomipramine                                  | 25mg/kg  | Immunization (SC) (C57BL/6 mice) with 50μg MOG | Acute EAE-treatment | 1-EAE-delayed clomipramine treatment (vehicle (PBS) n=6) | 6-8 weeks female C57BL/6 mice Approximately 20 g body weight BW 8-10 weeks | Flow cytometry Immunocytochemistry Microscopy Live-cell imaging Histological analyses | 1-EAE-delayed clomipramine treatment Disease onset was delayed 2-EAE-early clomipramine treatment Suppression of clinical signs Amelioration of weight loss Attenuation of meningeal inflammation Reduction of microglial activation (less axonal damage) |
| B. Biozzi ABH-EAE    | mouse model (progression model) Application of 150 μl emulsion in both sides of hind flanks. Emulsion prepared as follows. | Chronic EAE-treatment | 1- Treatment initiated at remission (days 31 till 42) 2- treatment from clinical onset (days 13 till 50) treatment initiated from clinical onset (day 18) | II) clomipramine (IP) n=7 | Treatment initiated at remission (days 31 till 42) | PCR LC-MS | 1-Treatment initiated at remission (days 31 till 42) No significant difference 2- treatment from clinical onset (days 13 till 50) Reduction of clinical severity of the first relapse (days 14-20) and second relapse at... |... (Continued)
| Study          | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose          | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design | (Species) Age/gender/Weight | Methods | Clinical results | Biological results |
|---------------|----------------------------------------------------|---------------|---------------------------|--------------|-------------------------------------------------------------|--------------|-----------------------------|---------|----------------|-----------------|
| Vollmar et al. [38] | (SNRI) 6,20,60mg/kg | Immunization (SC) with 200μg proteolipid protein (PLP) 139-151 | Onset of clinical signs approximately day 10 | Treatment (p.o) initiated at the day of EAE induction | Age 6-12 weeks | Immunohistochemistry | Treatment initiated at EAE induction (oral pretreatment), (day of adoptive transfer) (14 d): Venlafaxine suppressed EAE in a dose dependent fashion; reduces histopathological manifestation of EAE (20mg/kg) after 3wk treatment. Treatment initiated at the beginning of clinical onset: Significant dose dependent reduction of EAE (6,60mg/kg) reduces mRNA expression in spinal cord tissue of EAE | Venlafaxine | late chronic phase (days 42-50) treatment initiated from clinical onset (day 18) | Reduction of clinical severity |
| Venlafaxine | After in vitro restimulation with 10 μg/ml (PLP) 139-151 for 4d, 5*10^6 to 2*10^7 cells were injected IP into syngeneic recipients | /or after the onset of clinical symptoms. | l) control (PBS) female SJL/J mice | ELISA kit | Cell viability assay | Real time PCR | Osmotic pump pretreatment: Reduced peak of disease and ameliorated relapses | mRNA expression of pro-inflammatory cytokines INF-γ, TNF-a, IL-12, chemokines Ccl2 and Ccl5 | mRNA expression of BDNF |
TABLE 2 | Continued

| Study | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose | Induction of EAE Protocol | Signs of EAE Preventive or symptomatic treatment (drug administration) | Study Design (Species) Age/gender/ Weight | Methods | Clinical results | Biological results |
|-------|---------------------------------------------------|------|--------------------------|--------------------------------------------------------------------|-------------------------------------------------|---------|-----------------|---------------------|
| Benson et al. (66) | MAO-i | 15mg/kg Subcutaneous 50µg MOG | Onset of clinical signs approximately 10-14 d (clinical grade 1) | Treatment (IP) initiated from clinical onset (after immunization) and every second day for 14 days (n=14) or daily for 14 consecutive days (n=5) | 3 groups | 10-12 week-old Female C57/BL6 | Open field assays | ↓ clinical score | ↑ levels of 5-HT spinal cord (lumbar, thoracic, cervical) ↓ levels of 5-HT, NE, DA within spinal cord, brain, brainstem PLZ treatment every second day causes less inhibition of MAO B |
| Musgrave et al. (40) | MAO-i | 15mg/kg Subcutaneous 50µg MOG | Onset of clinical signs day 15 (clinical grade 3) | Acute treatment (IP) (PLZ 30mg/kg single dose at the “peak” of disease-clinical score ≥3) | 4 groups | Female C57/BL6 | Open field assays | Daily (chronic) treatment -Delayed onset of clinical signs | Acute treatment |
| | phenelzine | 30mg/kg | | | | | | |
| | phenelzine | | | | | | | |

(Continued)
| Study | Type of antidepressant (SSRI, SNRI, MAO inhibitors) | Dose | Induction of EAE Protocol | Signs of EAE | Preventive or symptomatic treatment (drug administration) | Study Design (Species) Age/gender/Weight | Methods | Clinical results | Biological results |
|-------|--------------------------------------------------|------|--------------------------|--------------|--------------------------------------------------|------------------------------------------|---------|------------------|-------------------|
| Potter et al, 2018 (67) | (MAO-i) phenelzine | 15mg/kg | Subcutaneous 50μg MOG 35-55 | Onset of clinical signs day 14-17 dpi | Treatment onset 7 days after immunization. Daily (IP) injection of either vehicle or phenelzine (15 mg/kg). | II) control-vehicle (CFA)+ PLZ III) EAE | HPLC | Reduced impairments | Daily (chronic) treatment restores 5-HT levels in the ventral horn. ↑levels of 5-HT, NE in brainstem, cerebellum. No difference in QABA PLZ normalized presynaptic excitatory synaptic densities in S1; reduced VGLUT1+ density (↑VGLUT1 reactivity); normalized cortical iba-1+ reactive microglial cells in S1 (↓excessive cortical Glu release, ↓cortical microgliosis); normalized neuronal morphologies |
| Khan et al, 2014 (68) | amitriptyline | 1,3 and 7mg/kg | Subcutaneous 200μg MOG 35-55 mixed with Quillaja sapon. Three different doses of QuilA (15, 30, 45μg) were assessed | Mechanical allodynia in the bilateral hind paws was fully developed by 28-30 dpi | At 30-55 dpi treatment onset with amitriptyline (IP) | Groups IV) EAE + Amitriptyline (7mg/kg) Sham-mice (n=7)/ EAE-mice (n=32) | FA imaging (FAI) | Dose-dependent relief of mechanical allodynia in the bilateral hind paws of EAE mice |
| Stephan et al, 2002 (69) | Imipramine | 10mg/kg | Guinea pig MBP (50μg per rat) | Onset of clinical signs | Chronic imipramine pre-treatment (daily via drinking water) started at the age of 6 weeks | 4 groups (EAE induction 14wk) | Open field test | IMI reversed the increase of deprivation-induced emotionality | ↑plasma levels of IL-4 |

(Continued)
With respect to neuropathic pain, the SNRI duloxetine has been proved to adequately treat this distressing symptom prevalent in more than 25% of MS patients (96), as signified in a double-blind RCT (97). This drug has already received FDA approval for the treatment of peripheral neuropathy in diabetic patients, therefore its inclusion in MS therapy would not be far-fetched. Venlafaxine has also demonstrated some promising qualities regarding neuropathic pain (98), while also tackling the issue of migraines. Although the prevalence of migraines in MS remains unclarified, the importance of their treatment has been repeatedly stressed, as this comorbidity has been correlated with a more symptomatic clinical course of MS (99). Finally, duloxetine has been clinically documented to relieve stress urinary incontinence (100–102), without having yet been tested on MS patients that exhibit this symptom. However, on MS patients suffering from overactive bladder syndrome, a precursor of urinary incontinence, duloxetine was found to be efficient (103).

Taken together, this evidence suggests that antidepressants have proved to be highly effective not only in treating depression in MS patients (85), but also in alleviating numerous distressing symptoms that these patients exhibit (31). Nonetheless, apart from relieving MS comorbidities, antidepressants have even proved to alter disease course and delay progression by curbing stress-related relapses that form a significant pharmacological target in RRMS (30). This clinical background further intensifies the importance of our findings, as basic research studies incorporated in this review unanimously attested to the benefits of antidepressants in MS, both in vitro and in the EAE animal model. Regarding in vivo MS models, one of the limitations of this review is that it examined only the EAE animal model, which however constitutes the most prevalant and representative animal model currently used in MS research.

However, clinical trials on the matter remain scarce and inconclusive due to the relatively confined number of participants and the uniqueness of each trial, rendering their comparison futile (31). Therefore, clinical testing of antidepressant agents in MS should be further intensified to provide us with reliable assumptions, as existing evidence remains promising.

CONCLUSION

All things considered, antidepressants have proved effective both in alleviating EAE, an animal model of MS and in vitro, displaying salutary immunomodulatory and anti-inflammatory properties. Clinical studies have also verified the efficacy and safety profile of antidepressants in MS. However, this field warrants further research that would elucidate the underlying mechanisms of action of these agents in MS and highlight their eligibility as a complementary MS therapy.

AUTHOR CONTRIBUTIONS

ES: manuscript writing, editing, acquisition of data. ID, SS, AA, AM, TA, KS: Analysis and interpretation of data. CS: manuscript editing. GP: manuscript writing, review of the final manuscript. All authors contributed to the article and approved the submitted version.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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