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Vortioxetine improves gastrointestinal motility and reduces intestinal inflammation in a cuprizone-induced multiple sclerosis model in mice

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MAIN POINTS

- Vortioxetine treatment significantly improved gastrointestinal motility in cuprizone-induced demyelinated mice, as evidenced by increased fecal pellet output and wet fecal weight, restoring values close to controls.
- Intestinal and colonic pro-inflammatory cytokine levels (TNF-α, IL-1β) elevated by cuprizone exposure were markedly reduced with vortioxetine administration, demonstrating its peripheral anti-inflammatory effects.
- These findings suggest that vortioxetine may have therapeutic potential for gastrointestinal dysfunction associated with demyelinating and neuroinflammatory conditions.

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ABSTRACT

Aim: To investigate the effects of vortioxetine on gastrointestinal motility and intestinal inflammation in a cuprizone-induced demyelination model in mice by evaluating pro-inflammatory cytokine responses.

Materials and Methods: Twenty-one C57Bl/6 mice (8 weeks old) were randomly allocated into three groups: Control, cuprizone, and cuprizone + vortioxetine (n = 7/group). Demyelination was induced by oral gavage of cuprizone (10 mg/kg) every other day for 5 weeks. Vortioxetine (10 mg/kg/day) was administered intraperitoneally for 5 weeks. Gastrointestinal motility was assessed by 24-hour fecal pellet count and wet fecal weight. At the end of the protocol, TNF-α and IL-1β levels in the stomach, intestine, and colon were measured by ELISA.

Results: Cuprizone administration significantly reduced fecal pellet output and wet fecal weight compared with controls ($p<0.0001$). Vortioxetine treatment restored both parameters toward control levels ($p<0.01$). Intestinal TNF α and IL 1β levels were markedly increased in the cuprizone group ($p<0.0001$) and were significantly decreased following vortioxetine treatment, reaching near-control values. Similar reductions were observed in colonic cytokine levels, whereas gastric cytokines were largely unaffected.

Conclusion: Vortioxetine improves gastrointestinal motility and attenuates intestinal and colonic pro-inflammatory cytokine expression in a cuprizone-induced demyelination model in mice. These findings suggest that vortioxetine has the potential to exert beneficial effects on the gastrointestinal function and highlight its potential as an adjunctive therapy for gastrointestinal comorbidities in multiple sclerosis.

Keywords: Cuprizone, Vortioxetine, Demyelination, Gastrointestinal motility, Inflammation

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INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS), characterized by immune cell infiltration, myelin loss, and axonal damage, resulting in both neurological and systemic complications [1]. Beyond its classical neurological manifestations, there is increasing evidence suggesting that MS causes disturbances in the gut–brain axis, including gastrointestinal (GI) dysmotility and alterations in inflammatory signaling [2]. Shared genetic risk factors, immune dysregulation, and chronic low-grade inflammation have been reported between MS and inflammatory bowel disease (IBD), with comorbidity between these conditions consistently documented [3,4].

The cuprizone model of demyelination is extensively utilized as an experimental model to study MS physiopathology. It induces oligodendrocyte loss, demyelination, microglial activation, and astrocytosis. Notably, cuprizone exposure elicits systemic and peripheral inflammatory responses, characterized by alterations in gut permeability, immune signaling, and gastrointestinal motility [5-7]. Consequently, this model facilitates the investigation of gut-related changes secondary to CNS demyelination, making it highly relevant for exploring gut–brain axis interactions in neuroinflammatory diseases.

In addition to immune-mediated demyelination, mood dis-

turbances and depression are common comorbidities in MS. There is growing recognition that pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) contribute not only in pathogenesis of MS but also to the development of depression and GI dysfunction through immune-mediated mechanisms [8-10]. Vortioxetine, a multimodal serotonergic antidepressant, has been shown to modulate serotonergic signaling both centrally and peripherally, polarize macrophages towards an anti-inflammatory phenotype, and positively influence gut microbiota composition [11-13]. Given that the majority of serotonin in the body is localized within the gastrointestinal tract, serotonergic antidepressants may directly affect gut motility and immune balance [14,15]. However, the effect of vortioxetine on gastrointestinal function in the context of neuroinflammatory demyelination such that is seen in MS has not yet been explored. Although the central antidepressant and anti-inflammatory actions of vortioxetine have been characterized, its effect on peripheral gastrointestinal inflammation and motility in demyelination models needs to be investigated.

Understanding these interactions could provide novel insights into bidirectional communication between the nervous and gastrointestinal systems and identify potential therapeutic targets for managing comorbid symptoms in neuroinflammatory diseases. In this study, we investigated the effects of vortioxetine on GI motility and pro-inflammatory cytokine expression (TNF-α and IL-1β) in a cuprizone-induced demyelination model. We hypothesized that vortioxetine, through its multimodal serotonergic and anti-inflammatory actions, would improve fecal excretion and attenuate intestinal inflammation in this model, thereby highlighting the contribution of the gut–brain axis to MS-related comorbidities.

MATERIALS AND METHODS

Animals and experimental groups

This was an experimental, randomized, controlled, parallel-group study designed to evaluate the effects of vortioxetine on gastrointestinal and inflammatory parameters in a cuprizone-induced demyelination model. A total of twenty-one C57Bl/6 mice (male and female, 8 weeks old, 19–21 g) were used in this study (Figure 1). Animals were randomly assigned to experimental groups using a simple randomization method based on a computer-generated random number sequence to ensure unbiased allocation (n = 7/group):

- Control: 1% methylcellulose solution (10 mg/kg, oral gavage) every other day for 5 weeks.
- Cuprizone (CUP): Cuprizone (10 mg/kg, oral gavage) dissolved in 1% methylcellulose solution, every other day for 5 weeks.
- Cuprizone (CUP) + Vortioxetine (VOR): Cuprizone (10 mg/kg, oral gavage, every other day for 5 weeks) plus vortioxetine (10 mg/kg/day, intraperitoneally) for 5 weeks, prepared in 5% 2-hydroxypropyl-β-cyclodextrin.

Only healthy C57Bl/6 mice with normal feeding and stool consistency were included in the study. Mice showing signs of gastrointestinal illness, dehydration, injury, or abnormal behavior prior to the experiment were excluded. During the experimental period, any animal exhibiting severe weight loss (>15% of initial body weight), persistent diarrhea, or signs of distress was removed from the study and excluded from subsequent analyses.

Animals were housed under controlled environmental conditions (21–24°C; 55–65% humidity; 12 h light/dark cycle) with ad libitum access to food and water. All procedures complied with the European Directive 2010/63/EU on the protection of animals used for scientific purposes and were approved by the Institutional Animal Care and Use Committee of Ege University (Approval No: 2024-017, Date: 2024-03-27). The study was conducted in accordance with the ARRIVE 2.0 (Animal Research: Reporting of In Vivo Experiments) guidelines.

All behavioral evaluations and biochemical analyses were performed by investigators who were blinded to the experimental group assignments to minimize observer bias.

Sample size was calculated using G*Power 3.1 software based on a One-way ANOVA model, with an effect size of 0.8, α = 0.05, and a statistical power (1–β) of 0.90. This analysis indicated that a minimum of seven animals per group would be sufficient to detect significant intergroup differences.

Induction of demyelination with cuprizone

Acute demyelination was induced by administering cuprizone (400 mg/kg/day) mixed in 1% methylcellulose and vortexed into a homogeneous suspension, given by oral gavage for 5 weeks, as previously described [16]. This experimental model produces prominent demyelination in the corpus callosum. Control and vortioxetine-only animals received the same vehicle without cuprizone.

Vortioxetine administration

Vortioxetine was dissolved in 5% 2-hydroxypropyl-β-cyclodextrin and administered intraperitoneally at 10 mg/kg daily for 4 weeks. This dose was selected based on previous studies on cognitive and depression-like behavior [17]. The vehicle (5% 2-hydroxypropyl-β-cyclodextrin) was administered to control and cuprizone group.

Measurement of fecal excretion

To evaluate gastrointestinal motility, mice were individually placed in a 40 × 40 × 40 cm open field for the final 3 days of the experiment to acclimate. On the last day, fecal pellets produced during a 24-h period were collected, counted, and weighed (wet and dry weights) as previously described [18].

Tissue collection and biochemical analyses

At the end of the 5-week protocol, mice were anesthetized via a high-dose intraperitoneal injection of ketamine (80–100

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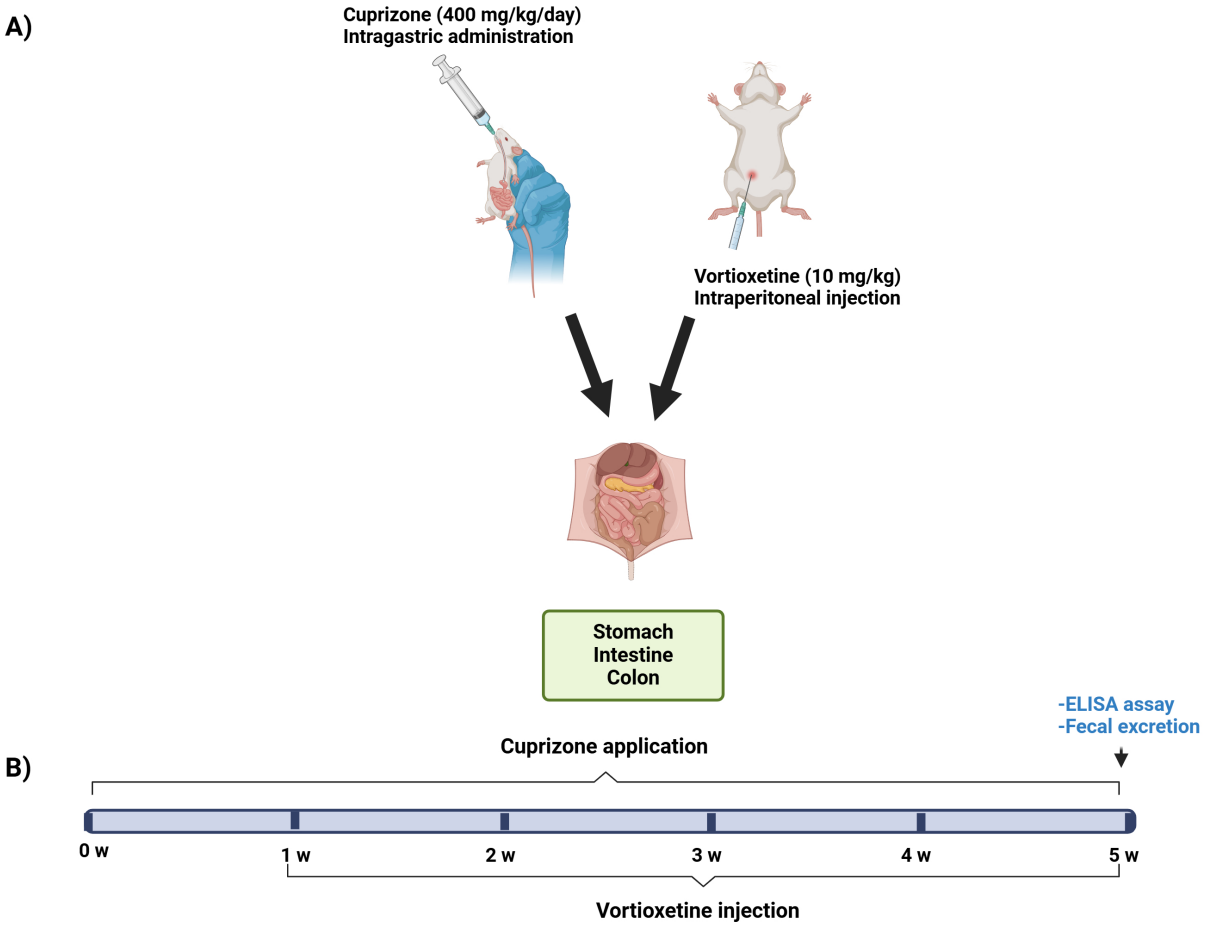

Figure 1. Experimental procedure. (A) Cuprizone (400 mg/kg/day) or vehicle was administered intraperitoneally. All murine tissues were extracted from the stomach, intestines, and colon. (B) Vortioxetine was administered intraperitoneally for 4 weeks, while cuprizone was administered intragastrically for 5 weeks. Upon completion of the experimental period, pro-inflammatory cytokines were assessed in all gastrointestinal tissues, and fecal excretion was quantified.

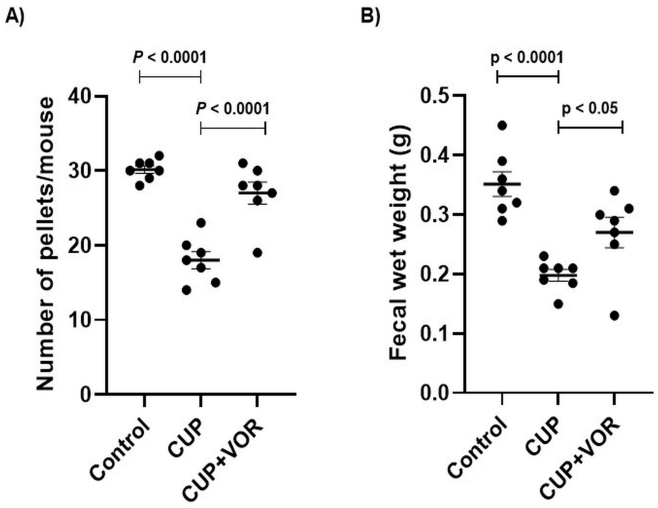

Figure 2. Fecal excretion analysis. (A) Number of pellets (24h) ($F(2, 18) = 31.51$; $P<0.0001$). (B) Fecal wet weight (g) ($F(2, 18) = 14.97$; $P<0.0001$). Values are mean ± SE of n = 7 animals. Statistical analysis was performed using One-way ANOVA followed by Sidak's post hoc test.

mg/kg) and xylazine (12 mg/kg), followed by cardiac perfusion with saline. Stomach, intestine, and colon tissues were collected, weighed, and homogenized in cold phosphate-buffered saline (PBS, pH 7.0–7.2). Homogenates were centrifuged at 5000 × g for 5 min, and supernatants were stored for cytokine analyses.

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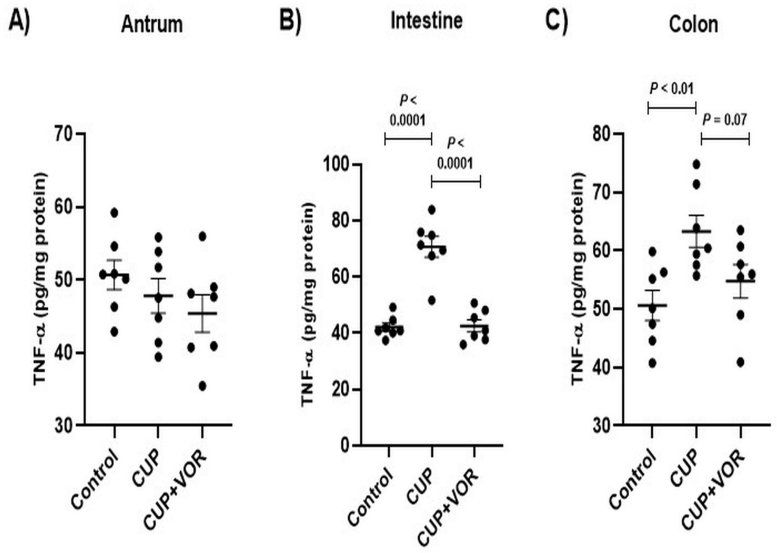

Figure 3. TNF-α levels in gastrointestinal tract tissues. (A) Antral TNF-α levels (F (2, 18) = 1.28; P>0.05). (B) Intestinal TNF-α levels (F (2, 18) = 38.96; P<0.0001). (C) TNF-α level in the colon (F (2, 18) = 5.62; P<0.05) Values are mean ± SE of n = 7 animals. Statistical analysis was performed using One-way ANOVA followed by Sidak's post hoc test.

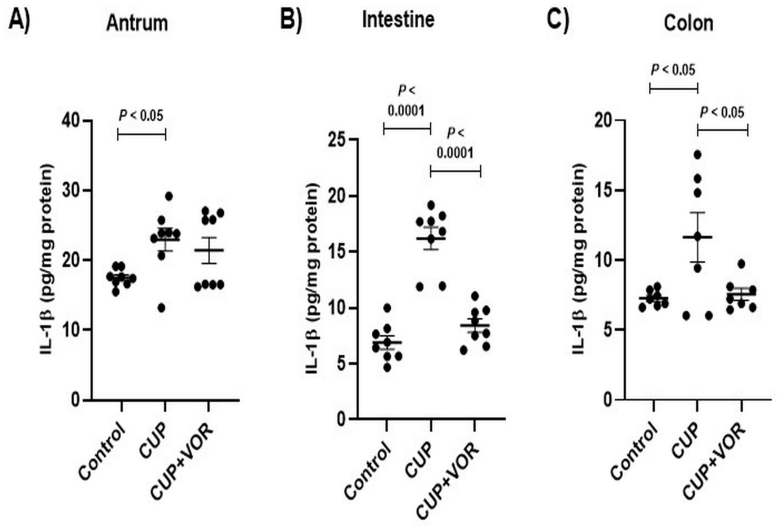

Figure 4. IL-1β levels in gastrointestinal tract tissues. (A) Antral IL-1β levels (F (2, 21) = 1.14; P>0.05). (B) Intestinal IL-1β levels (F (2, 21) = 44.35; P<0.0001). (C) IL-1β level in the colon (F (2, 18) = 5.35; P<0.05) Values are mean ± SE of n = 7 animals. Statistical analysis was performed using One-way ANOVA followed by Sidak's post hoc test.

ELISA for TNF-α and IL-1β

Concentrations of TNF-α and IL-1β in the stomach, intestine, and colon were determined using commercial ELISA kits (Elabscience, TNF-α: E-EL-M3063; IL-1β: E-EL-M0037) following the manufacturer's instructions. Results were expressed as pg/mg protein.

Statistical analysis

Statistical analysis were performed using GraphPad Prism 9 (Boston, USA). Data were first tested for normality using the Shapiro–Wilk test and for homogeneity of variances using Levene's test. For data that show normal distribution and equal variances, One-way ANOVA followed by Sidak's post hoc test was used to test intergroup differences. All tests were two-tailed, and differences were considered statistically significant at $p<0.05$. Results are presented as mean ± standard error (SE).

RESULTS

Fecal excretion

Quantification of fecal pellets over a 24 hour period showed a marked reduction in animals exposed to cuprizone com-

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pared with controls (MS: 18.0±1.1 vs. Control: 30.1±0.5; P<0.0001; Figure 2A). Vortioxetine treatment significantly increased the number of fecal pellets in the CUP+VOR group (27.0±1.4; P<0.0001), approaching values observed in controls.

Similarly, wet fecal weight was significantly reduced in the cuprizone group (0.19 ± 0.009 g) compared to the control group (0.35±0.02 g; P<0.0001; Figure 2B). Daily intraperitoneal administration of vortioxetine for 5 weeks resulted in a significant increase in wet fecal weight (0.27±0.02 g; P<0.01 vs. cuprizone).

TNF α levels

TNF α concentrations in the gastric antrum did not differ significantly among the groups (Control: 50.6 ± 2.0; CUP: 47.8 ± 2.3; CUP+VOR: 45.4 ± 2.5 pg/mg protein; Figure 3A).

In the intestine, TNF α levels were significantly elevated in the cuprizone group (70.6±3.7 5 pg/mg protein) compared to the control group (42.1±1.4 5 pg/mg protein; P<0.0001). Vortioxetine treatment restored intestinal TNF α concentrations to near control levels (42.5±2.1 5 pg/mg protein; P< 0.0001 vs. cuprizone; Figure 3B).

In the colon, TNF α levels were also increased in the cuprizone group (63.3±2.7 5 pg/mg protein) compared with controls (50.6±2.5 5 pg/mg protein). Although vortioxetine administration reduced colonic TNF α concentrations, this reduction did not reach statistical significance (P=0.07; Figure 3C).

IL 1β levels

ELISA analysis revealed a significant elevation of IL 1β levels in the gastric antrum of cuprizone-induced dmyelinization model (22.9±1.63 5 pg/mg protein) compared with controls (17.5±0.43 5 pg/mg protein; P<0.05), whereas vortioxetine treatment did not produce a significant effect at this site (Figure 4A).

In contrast, intestinal IL 1β levels were markedly increased in the cuprizone group (16.2±0.9 5 pg/mg protein) compared to controls (6.8±0.5 5 pg/mg protein; P<0.0001). Vortioxetine administration significantly decreased intestinal IL 1β by approximately 50% (8.4±0.5 5 pg/mg protein; P<0.0001 vs. cuprizone; Figure 4B).

Similarly, colonic IL 1β concentrations were elevated in cuprizone mice (11.6±1.7 5 pg/mg protein) compared to controls and were significantly reduced following vortioxetine treatment (7.5±0.4 p5 pg/mg protein; P<0.05; Figure 4C).

DISCUSSION

This study demonstrates that cuprizone-induced demyelination disrupts gastrointestinal motility and increases intestinal pro-inflammatory cytokines. Importantly, vortioxetine treatment restored fecal output and attenuated TNF-α and IL-1β levels, suggesting a modulatory effect on gastrointestinal function and inflammation.

Gastrointestinal motility disorders are common in inflammatory and neurodegenerative diseases, particularly IBD and MS, and significantly affect quality of life [19-21]. Alterations in microbiota, visceral sensitivity, and CNS signaling contribute to these symptoms [22]. Serotonin which is the major neurotransmitter in the enteric nervous system, plays a key role in regulating intestinal motility and immune homeostasis [23,24]. The results of our study showed that vortioxetine improved motility and fecal consistency and they are supported by previous clinical observations, including Seddighnia et al. [25] who reported similar improvements in patients receiving vortioxetine. The majority of serotonin is produced in enterochromaffin cells of the gut, and specific receptors such as 5-HT7 and 5-HT3 modulate anti-inflammatory effects and motility [26,27]. These data suggest that serotonergic antidepressants, particularly multimodal agents such as vortioxetine, may exert benefits beyond mood regulation.

The gut–brain axis has gained attention as a key link between the CNS and gastrointestinal function. Experimental models, including experimental autoimmune encephalomyelitis (EAE) and cuprizone, have shown that demyelination is accompanied by gut microbiota changes, gliosis, and loss of enteric neurons, resulting in slowed intestinal motility [5,28,29]. Previous studies demonstrated that vortioxetine can modulate the gut microbiome and enhance synaptic plasticity [30]. These mechanisms may contribute to the improvements in motility observed in the present study.

There is a well-documented bidirectional association between MS and IBD, supported by shared genetic susceptibilities and immune mechanisms [3]. Dysregulation of cytokines, particularly TNF-α and IL-1β, plays a central role in the pathogenesis of both diseases [31,32]. Our findings that vortioxetine reduced intestinal cytokine levels highlight a potential role for serotonergic modulation in attenuating systemic inflammation in demyelinating disorders.

Limitations

This study has several limitations. First, histopathological analyses of gastrointestinal tissues were not performed; therefore, structural changes such as mucosal integrity and inflammatory cell infiltration could not be evaluated. Also, microbiota composition was not assessed, which would have provided valuable insights into the gut–brain axis. Finally, the study was limited to biochemical and motility endpoints and did not include behavioral or functional assessments of gastrointestinal activity. Future studies with larger cohorts, detailed histological and microbiome analyses, and additional behavioral assessments will be required to confirm and extend these findings.

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CONCLUSION

In conclusion, this study demonstrates that vortioxetine ameliorates gastrointestinal dysmotility and attenuates intestinal pro-inflammatory cytokine expression in a cuprizone-induced demyelination model. These findings highlight the potential role of serotonergic modulation in restoring gut–brain axis integrity under neuroinflammatory conditions.

Based on these results, future research should focus on elucidating the underlying mechanisms through detailed histopathological, neurochemical, and microbiome analyses. In addition, studies using larger cohorts, different dosages, and long-term treatment protocols, as well as behavioral and functional assessments of gastrointestinal activity, are warranted. Translational studies in patients with multiple sclerosis, particularly those with gastrointestinal comorbidities, will be crucial to determine whether vortioxetine can offer therapeutic benefit beyond its antidepressant effects.

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Author Contributions: A.O: Conceptualization, Methodology, Software, Data Curation, Investigation, Formal Analysis, Writing – Original Draft, Supervision; P.K: Investigation; Methodology.

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