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REVIEW ARTICLE

The Role of CXCR3 in Neurological Diseases

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Abstract: ***Background*:** Neurological diseases have become an obvious challenge due to insufficient therapeutic intervention. Therefore, novel drugs for various neurological disorders are in desperate need. Recently, compelling evidence has demonstrated that chemokine receptor CXCR3, which is a G protein-coupled receptor in the CXC chemokine receptor family, may play a pivotal role in the development of neurological diseases. The aim of this review is to provide evidence for the potential of CXCR3 as a therapeutic target for neurological diseases.

***Methods*:** English journal articles that focused on the invovlement of CXCR3 in neurological diseases were searched *via* PubMed up to May 2017. Moreover, reference lists from identified articles were included for overviews.

***Results*:** The expression level of CXCR3 in T cells was significantly elevated in several neurological diseases, including multiple sclerosis (MS), glioma, Alzheimer's disease (AD), chronic pain, human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and bipolar disorder. CXCR3 antagonists showed therapeutic effects in these neurological diseases.

***Conclusion*:** These studies provided hard evidence that CXCR3 plays a vital role in the pathogenesis of MS, glioma, AD, chronic pain, HAM/TSP and bipolar disorder. CXCR3 is a crucial molecule in neuroinflammatory and neurodegenerative diseases. It regulates the activation of infiltrating cells and resident immune cells. However, the exact functions of CXCR3 in neurological diseases are inconclusive. Thus, it is important to understand the topic of chemokines and the scope of their activity in neurological diseases.

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1. INTRODUCTION

With the substantial prolongation of average life expectancy, the prevalence of neurological diseases increase markedly in the past decades, leading them to become a major public health problem [1, 2]. Unfortunately, few drugs are currently available to cure these diseases. Thus, new drugs for various neurological disorders are in desperate need. Chemokines are important modulators of neuroinflammation and neurodegenerative processes [3, 4]. These small proteins are important in the activation and migration of immune cells to lesion sites [5]. The chemokine receptor CXCR3, which belongs to the CXC chemokine receptor family, is a G protein-coupled receptor that plays a vital role in mediating chemotactic migration, cell proliferation, and survival [6-8]. CXCR3 is mainly expressed by various effector T lymphocytes including $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T cells, and natural killer (NK) cells [9, 10]. The principle chemokine ligands of CXCR3 are CXCL4, CXCL9, CXCL10 and CXCL11 [11-14]. CXCL4, a platelet-derived CXCR3 ligand, is weakly chemotactic for neutrophils, monocytes and fibroblasts [15]. Mainly induced by interferon gamma (IFN-γ), CXCL9, CXCL10 and CXCL11 are potent chemoattractants for monocytes, T cells, NK cells and dendritic cells. Although they share the same chemokine receptor CXCR3, these three ligands are regulated by unique promoters and exhibit distinct temporal and spatial expression patterns (Table **1**). Recent studies have shown that the chemokine receptor CXCR3 was expressed in central nerv-

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Table 1. Fundamental characteristics of CXCR3 and its ligands.

	CXCR3	CXCL4	CXCL9	CXCL10	CXCL11
Expression/ producer cells	$CD4^+$ Th1 cells; $CD8^+$ Tc cells NK cells	Platelets; Monocytes; T cells	Fibroblasts; Macrophages; Endothelial cells; Monocyte-derived dendritic cells	Monocytes; Neutrophils; Endothelial cells; Dendritic cells; NK cells; Fibroblasts; T cells	Fibroblasts; Astrocytes; Endothelial cells
Inducer	-	Thrombin	IFN-γ	TNF-α; IFN-α; IFN-β; IFN-γ	TNF-α; IFN-β; IFN-γ
Function	Leukocyte recruitment, inflammation, integrin activation, and chemotactic migration	Weakly chemotactic for neutrophils, monocytes and fibroblasts; Inhibit endothelial cell proliferation and migration; Promote blood coagulation and thrombosis	Promote the polarization of $CD4^+$ T cells into effector Th1/Th17 cells	Induce integrin activation; Generate directional migration of activated T cells, monocytes and NK cells	Drive $CD4^+$ T cell polarization into IL-10-producing Tr1 cells
References	[8, 26]	[27-29]	[30, 31]	[32, 33]	[7, 34]

Abbreviations: IFN-γ: interferon gamma; NK cells: natural killer cells; Tc cells: cytotoxic T cells; Th1 cells: type 1 T helper cells; Th17 cells: type 17 T helper cells; Tr1 cells: T regulatory-1 cells, TNF: tumor necrosis factor.

ous system (CNS) diseases and involved in their pathogenesis [16-20]. It was shown that the expression levels of CXCR3 and its ligands were elevated in the periphery blood and cerebrospinal fluid (CSF) of patients with neurological diseases [21-23], and were correlated with prognosis in certain cases [24]. Additionally, treatment with CXCR3 antagonists could alleviate bone cancer pain (BCP) induced mechanical allodynia [25]. These studies suggested an important role of CXCR3 in neurological diseases, indicating that targeting CXCR3 may reveal novel therapeutic interventions for the management of neurological diseases. Thus, here we summarize the current evidence supporting a role of CXCR3 in the pathogenesis of neurological diseases, including multiple sclerosis, glioma, Alzheimer's disease, chronic pain and human T-lymphotropic virus type 1-associated myelopathy.

2. MULTIPLE SCLEROSIS

Multiple sclerosis (MS), also known as disseminated sclerosis, is a chronic inflammatory disease of the CNS which is characterized by destruction of myelin and oligodendrocytes in the brain and spinal cord [35, 36]. Mounting evidence has suggested that CXCR3 plays a vital part in MS. Balashov *et al.* [21] first reported that CXCR3 positive T cells were increased in blood of relapsing/remitting and progressive MS compared with controls. They also found that CXCL10, one of the CXCR3 ligands, was expressed by astrocytes in MS brain lesions but not unaffected white matter of control or MS subjects. These results suggested that CXCL10/CXCR3 expression level may be used for immunologic staging of MS and provided a rationale for the use of agents blocking CXCR3 as a therapeutic approach in the treatment of MS. Using immunocytochemistry, Simpson *et al.* [37] confirmed the expression of CXCL9 and CXCL10, and their receptor CXCR3 in *post-mortem* CNS tissue from MS cases at different stages of lesion development. Their results showed that both macrophages and astrocytes were active in demyelinating lesions predominantly expressed CXCL9 and CXCL10, and CXCR3 was expressed by T cells and by astrocytes within the plaque. The differential expression of chemokines indicated that blocking chemokine receptors may serve as an anti-inflammatory therapy for MS. On the other hand, CXCL10 and CXCR3 were significantly increased in the CSF of patients with MS compared with controls [38-40]. Moreover, the increased level of CXCL10 was associated with clinical relapses in MS. Compared with secondary progressive MS, the concentration of CXCL10 was significantly greater in patients with relapsing/remitting, which was correlated significantly with CXCR3 expression on CSF $CD4^+$ T cells from patients with MS. In another study, Sindern *et al.* [41] demonstrated that the increased level of CXCR3 positive T-cells in the CSF was strongly associated with active MRI lesion appearance in patients with relapsing/remitting MS, which might be the result of migration of activated T-cells from the circulation into the CSF. Consistent with previous reports, this study confirmed the hypothesis that CXCR3 might be involved in the development of acute MS lesions, leading to therapeutic intervention *via* blocking CXCR3. By analyzing the expression of CXCR3 on peripheral lymphocytes in 18 MS patients, Mahad *et al.* [42] found that the increased expression of CXCR3 on peripheral blood $CD4^+$ lymphocytes was associated with all relapses and that the fluctuations of CXCR3 expression was significantly greater in patients with MS than controls. This study provided further evidence for the potential therapeutic value of CXCR3 antagonists. The therapeutic effect of IFN-β on patients with MS is well established [43-45]. After treatment with IFN-β for three months, Sorensen *et al.* [46]

found that the expression of CXCR3 on $CD4^+$ and $CD8^+$ T cells was significantly reduced, whereas the expression of other receptors (*e.g.* CCR1, CCR2, CCR3, CCR5) was unaltered. This results indicated that IFN-β may exert its therapeutic effect on MS patients by suppressing the expression of CXCR3.

Experimental autoimmune encephalomyelitis (EAE), a rodent model of human MS, is a $CD4^+$ Th1 cell- and Th17 cell-mediated demyelinating disease of the CNS [47]. The role of CXCR3 in EAE has been widely studied. Considering that CXCR3 and its ligands are elevated in MS patients, it was proposed that blocking CXCR3 or neutralization of its ligands would inhibit the development of EAE. However, Narumi *et al.* [48] reported that EAE rats treated with monoclonal antibody (mAb) against CXCL10 exacerbated the disease scores with less enlarged draining lymph nodes than treated with control mAb. The smaller draining lymph nodes in EAE rats treated with anti-CXCL10 mAb might be explained by the following mechanism: neutralization of CXCL10 causes an increased release of Th1 cells from lymph nodes, which results in increased migration to the CNS where CXCL11, another ligand for CXCR3, is induced as well. Moreover, CXCL10-deficient mice exhibited a reduced threshold for EAE induction and developed severe EAE after immunization with low doses of myelin oligodendroglial glycoprotein (MOG)p33-55 that produced minimal disease in wild-type littermates [49]. In another study, Muller *et al.* examined the function of CXCR3 signaling in EAE using CXCR3 deficient ($CXCR3^{-/-}$) mice [50, 51]. No significant difference was found in terms of time to onset and peak disease severity in $CXCR3^{-/-}$ and wild-type (WT) mice. However, $CXCR3^{-/-}$ mice had more severe chronic disease with increased demyelination and axonal damage. Additionally, the inflammatory lesions were more widespread throughout the CNS in $CXCR3^{-/-}$ mice than WT mice in which inflammatory lesions consisted of well-demarcated perivascular mononuclear cell infiltrates. Furthermore, $Foxp3^+$ regulatory T cells were significantly reduced in number and were scattered in the spinal cord of $CXCR3^{-/-}$ mice. These results suggested that CXCR3 signaling plays a major protective role in EAE by constraining $CD4^+$ T cells to the perivascular space in the CNS, promoting regulatory T cell accumulation and facilitating interaction of these cells with effector T cells, thus limiting autoimmune-mediated tissue damage. In a mouse model of neurotropic coronavirus-induced encephalomyelitis, Marques *et al.* [52] found that the accumulation of antibody secreting cells (ASC) in the CNS was mediated by CXCR3. In $CXCR3^{-/-}$ mice, both the total and virus-specific ASC were reduced greater than 80%. Furthermore, neither virus-specific ASC trafficking to bone marrow nor antiviral serum antibody was reduced relative to levels in control mice. Additionally, infected $CXCR3^{-/-}$ mice showed elevated levels of persisting viral RNA, sustained infectious virus, increased clinical disease and mortality. These results indicated that CXCR3 played a vital role in the recruitment of activated ASC into the inflamed CNS and highlighted its protective role during persistent infection. A further study demonstrated that CXCL10 is critical for the recruitment of ASC to the CNS vasculature and ASC entry into the CNS parenchyma in a mouse model of viral encephalomyelitis [53]. In this study, they found reduced CNS IgG and κ-light chain mRNA and virus-specific Ab as well as impaired ASC recruitment in $CXCL10^{-/-}$ rather than $CXCL9^{-/-}$ mice. Moreover, the ASC recruited to the CNS in $CXCL10^{-/-}$ mice restricted to the vasculature, whereas it was localized in the parenchyma in wild-type and $CXCL9^{-/-}$ mice. Recently, the CXCR3-CXCL10 axis was also demonstrated to have a role in recruiting pathogenic T lymphocytes in the brains of patients with Rasmussen encephalitis [54]. Using surgical specimens of children with Rasmussen encephalitis, they found that CXCR3 was expressed in cytotoxic T lymphocytes infiltrating the damaged areas of primary biopsies, whereas CXCL10 was expressed in neurons and astrocytes in the same areas. Additionally, *in vitro* study demonstrated that astrocytes upregulated the mRNA expression level of CXCL10 and the release of CXCL10 to the supernatants in response to infections, which was completely abolished by CXCR3 antagonist. These results suggested that astrocytes and neurons may recruit pathogenic T lymphocytes into areas of the brain of Rasmussen encephalitis through the CXCL10-CXCR3 axis.

To conclude, the clinical studies provided compelling evidence that CXCR3 is involved in the development of MS and its antagonists may become novel agents for the management of MS. However, further study with larger sample size and longer follow-up are warranted to investigate the feasibility of CXCR3 antagonists and its exact mechanism in alleviating MS. The animal studies also proposed a protective role of CXCR3 in EAE and may provide novel insights into intervention strategies. However, the underlying mechanisms of how CXCR3 exerts its protective role in EAE need further investigations.

3. GLIOMA

Gliomas account for the majority of neoplasms occurring in the CNS, and are one of the most aggressive types of human cancer [55, 56]. It was reported CXCR3 regulates cell invasion, migration and facilitates tumor metastasis to lymph nodes [57, 58]. Furthermore, the expression level of CXCR3 correlates with prognosis of breast cancer [59], colorectal cancer [60, 61] and renal cell cancer [62-64]. Maru *et al.* [65] first reported that CXCR3 and CXCL10 were increased in glioma cells compared with adult human astrocytes. Moreover, they found that the expression level of CXCR3 correlated with malignancy grade of glioma. Glioblastoma multiforme (GBM) is the most aggressive form of human glioma with mean survival approximately 12 months despite intensive and comprehensive treatment [66]. Liu *et al.* [67] examined the role of CXCR3 in GBM progression using the GL261 murine model of malignant glioma. They found that Murine glioma GL261 cells express CXCL10 *in vitro* and GL261 tumors express CXCL9 and CXCL10 *in vivo*. $CXCR3^{-/-}$ mice with glioma had significantly shorter median survival time and reduced numbers of tumor-infiltrated natural killer (NK) and natural killer T (NKT) cells in contrast with WT glioma mice. However, treatment with CXCR3 antagonist NBI-74330 suppressed GL261 tumor growth and increased median survival times of both tumor-bearing WT and $CXCR3^{-/-}$ mice compared with vehicle-treated groups, suggesting that CXCR3 may have an inhibitory effect directly on the tumor cells. Moreover, NBI-74330 had no im-

pact on tumor-infiltrated NK and NKT cells, which known to express CXCR3, suggesting that CXCR3 is not the primary means by which NK and NKT cells traffic into glioma. Thus, the absence of tumor-infiltrating NK and NKT cells rather than CXCR3 may account for the shorter survival time of tumor-bearing CXCR3$^{-/-}$ mice. Moreover, both CXCR3 and its ligands are expressed by murine and human glioma cell lines (A172, T98G, U87, U118 and U138). These results suggested that CXCR3 system may be a unique target for human GBM therapy. Recently, Pu *et al.* [24] investigated the potential prognostic value of CXCR3 in primary GBM and its relationship with the clinicopathological features. Using Kaplan–Meier survival curve analysis with a log-rank comparison of the 65 primary GBM patients, they found that the patients with higher expression levels of CXCR3 had shorter progression free survival and overall survival compared with those with lower expression levels of CXCR3. Using univariate Cox regression analysis, they found that high CXCR3 expression was a risk factor for primary GBM [$P < 0.01$, hazard ratio (HR) 2.336, 95 % confidence interval (CI) 1.341–4.071]. Furthermore, their multivariate Cox regression analysis showed that CXCR3 expression level was an independent prognostic factor for the overall survival of primary GBM patients. Taken together, these results suggested that CXCR3 might be a useful independent prognostic biomarker for primary GBM patients.

4. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is one of the most prevalent progressive neurodegenerative brain disorders worldwide characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions [68, 69]. Chemokines and their receptors were found to be associated with AD pathological changes [70-73]. Using *post-mortem* human tissues of AD patients, Xia *et al.* [72] provided the first immunohistochemical evidence that CXCR3 was constitutively expressed on a subpopulation of neurons and neuronal processes in the neocortex, hippocampal formation, striatum, cerebellum and spinal cord. Moreover, they found greatly upregulated CXCL10 positive astrocytes in AD patients compare with controls. Additionally, CXCL10 positive astrocytes were frequently associated with amyloid deposits, suggesting an active chronic inflammatory response related to amyloid deposits occurs in AD patients. Recently, Krauthausen *et al.* [22] examined the impact of CXCR3 in the amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mouse model of AD. They found that amyloid beta (Aβ) deposition and Aβ levels were significantly decreased in CXCR3$^{-/-}$ APP/PS1 mice compared with control APP/PS1 mice. Their *in vitro* and *in vivo* analysis of microglial phagocytosis showed that CXCR3 deficiency facilitated the microglial uptake of Aβ. Moreover, preincubation of CXCR3 antagonist increased primary microglial Aβ phagocytosis and reduced TNF-α secretion. Compared with control APP/PS1 mice, brain tissue from CXCR3$^{-/-}$ APP/PS1 mice had reduced concentrations of proinflmmatory cytokines and the microglia exhibited obvious morphological activation and reduced plaque association. Furthermore, Morris watermaze testing showed improved spatial memory of CXCR3$^{-/-}$ APP/PS1 mice compared with controls, suggesting that lack of CXCR3 attenuated the behavioral deficits of APP/PS1 mice. Taken together, these results indicated that CXCR3 signaling mediated development of AD-like pathology in APP/PS1 mice and suggested that CXCR3 had the potential to be a therapeutic target for AD. Furthermore, a very recent study reported that peripheral blood mononuclear cells of Alzheimer's disease patients control CCL4 and CXCL10 levels in a human blood brain barrier model. These studies indicated a pivotal role of CXCR3 in the pathogenesis of AD. However, further studies are warranted to explore the underlying mechanisms.

5. CHRONIC PAIN

Pain plays a vital role in protecting us against damaging stimuli [74-76]. However, chronic pain presents a major challenge due to its complex natural history, unclear etiology, and poor response to therapy [77-79]. There is compelling evidence supporting the involvement of neuroinflammation in chronic pain [80-84]. Our lab has been investigating the mechanisms of chronic pain for decades [85-91]. Previously, we have shown the involvement of CXCL10/CXCR3 signaling in BCP rat models [23, 92]. After intra-tibial inoculation of Walker 256 mammary gland carcinoma cells, the BCP model was established, indicated by downregulation of paw withdrawal threshold (PWT) and bone destruction. Our real-time polymerase chain reaction (PCR) and immunohistochemical analyses showed that both CXCL10 and its receptor CXCR3 were up-regulated in the spinal cord of BCP rats. Blocking the CXCL10/CXCR3 signaling *via* anti-CXCL10 antibody or CXCR3 antagonist AMG487 prevented the development of BCP and microglial activation. Moreover, inhibiting microglial activation attenuated CXCL10 upregulation in BCP rats. These results suggested that CXCL10/CXCR3 signaling participated in BCP *via* activation of microglia in rat models. Our further study revealed the cellular mechanism of how CXCR3 mediated BCP [25]. We confirmed that CXCR3 was significantly increased in the spinal cord of BCP rats and co-localized with either neurons, microglia, and astrocytes in the spinal cord, or non-peptidergic-, peptidergic-, and A-type neurons in the dorsal root ganglion (DRG). Moreover, spinal phosphorylation of Akt and extracellular signal-regulated kinase (ERK1/2) were markedly upregulated in BCP rats in a time-dependent manner. Meanwhile, CXCR3 was co-localized with either pAkt or pERK1/2. Blockage of either Akt or ERK1/2 attenuated the mechanical allodynia in BCP rats. Furthermore, CXCR3 antagonist AMG487 suppressed the upregulation of pAkt and pERK1/2. Taken together, these results indicated that the activation of spinal chemokine receptor CXCR3 mediated BCP through Akt-ERK pathway. A very recent study performed by Jiang *et al.* confirmed the pivotal role of CXCR3 in neuropathic pain [93]. They found that the expression of CXCR3 was significantly upregulated mainly in the spinal neuron following spinal nerve ligation (SNL). Moreover, CXCL10, a ligand of CXCR3, was also considerably increased in the spinal neurons and astrocytes in SNL mice. Additionally, inhibiting the expression of CXCR3 by CXCR3-/- mice and shRNA targeting the sequence of mice Cxcr3 as well as CXCR3 antagonist NBI-74330 attenuated SNL-induced mechanical allodynia and thermal hyperalgesia. More importantly, they revealed the epigenetic mechanism of how CXCR3 contributed to neuro-

pathic pain. These results suggested that targeting CXCR3 may alleviated the established choric pain and novel CXCR3 antagonist with fewer side effects should be developed.

6. HUMAN T-LYMPHOTROPIC VIRUS TYPE 1-ASSOCIATED MYELOPATHY

Human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a rare neurodegenerative disease characterized by chronic inflammation in the spinal cord [94, 95]. Recently, Ando *et al.* [96] investigated the possible role of CXCL10/CXCR3 signaling in chronic inflammation of HAM/TSP. They found that the expression level of CXCL10 was markedly high in the CSF of HAM/TSP patients and a great deal of CSF cells expressed the CXCL10-binding receptor CXCR3, which mainly consist of $CD3^+$ cells (>90%) and small populations of $CD14^+$ and $CD19^+$ cells. Their immunofluorescence results showed that astrocytes were the major producers of CXCL10 in the spinal cords of HAM/TSP patients. Co-culture of human astrocytoma cells with $CD4^+$ T cells from HAM/TSP patients revealed that astrocytes produce CXCL10 in response to IFN-γ secreted by $CD4^+$ T cells. Moreover, the chemotaxis assays results suggested that CXCL10 induced migration of peripheral blood mononuclear cells to the CNS and that anti-CXCL10 neutralizing antibody could disrupt this migration. These results demonstrated that HTLV-1 infected cells in the CNS produced IFN-γ that induces astrocytes to secrete CXCL10, which recruits more infected cells to the area *via* CXCR3, constituting a T helper type 1-centric positive feedback loop that results in chronic inflammation.

7. BIPOLAR DISORDER

Bipolar disorder (BD) is a severe disorder with high prevalence that affect mood and cognitive functions, and its pathophysiology remain largely unknown [97]. Emerging lines of evidence has shown an association of BD with the immune system [98-101]. Brietzke *et al.* [102] first examined serum chemokine levels in 30 BD patients and to compare these results with those obtained with 30 healthy subjects. They found that the serum levels of CXCL10 were increased and CCL24 levels were decreased in BD patients in contrast with controls, suggesting an association between BD and changes in chemokine level. It is worth mentioning that CCL24 is an eotaxin, which not only binds CCR3 and recruit eosinophils and Th2 cells, but also act as an antagonist of CXCR3 [103, 104]. Barbosa *et al.* [17] further investigated the plasma levels of chemokines in 70 BD patients in different neuropsychiatry states (35 in euthymia and 35 in mania) compared with 50 healthy controls. Their results showed that BD patients had increased plasma levels of CXCL11, CCL24, CXCL10, and decreased plasma levels of CXCL8 in contrast with healthy controls. Moreover, these chemokines levels were not significantly different between BD patients in euthymia and in mania. Furthermore, the logistic regression stressed the main effect of increased plasma levels of CXCL10 and decreased plasma levels of CXCL8 to BD. These studies indicate that CXCL10, CXCL11 and their receptor CXCR3 should be further investigated with regard to their potential role as longstanding markers of BD.

CONCLUSION

By reviewing the current evidence, we discussed the possible involvement of CXCR3 in neurological diseases. These studies provided hard evidence that CXCR3 plays a vital role in the pathogenesis of MS, glioma, AD, chronic pain, HAM/TSP and bipolar disorder. CXCR3 is a crucial molecule in neuroinflammatory and neurodegenerative diseases. It regulates the activation of infiltrating cells and resident immune cells. However, the exact functions of CXCR3 in neurological diseases are inconclusive. Thus, it is important to understand the topic of chemokines and the scope of their activity in neurological diseases. Further studies focused on chemokines and neurological diseases may lead to the discovery of novel therapeutic strategies for patients suffering from various neurological disorders connected with neuroinflammation. It is worth mentioning that the caution must be taken when considering CXCR3 as therapeutic target since it can mediate both beneficial and harmful effects during the course of CNS diseases.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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