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REVIEW

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Quetiapine Fumarate for the Treatment of Multiple Sclerosis: Focus on Myelin Repair

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SUMMARY

Multiple sclerosis (MS) is a central nervous system disorder that is associated with progressive oligodendrocyte and neuronal loss, axonal degeneration, and demyelination. Several medications that mitigate immune abnormalities reduce both the frequency of relapses and inflammation on magnetic resonance imaging, leading to improved outcomes for people with the relapsing–remitting form of MS. However, there are no treatments for the progressive forms of MS where neurons and axons continue to degenerate; here, neuroprotective therapies, or medications that rebuild myelin to confer axonal well-being, may be useful. Quetiapine fumarate is an atypical antipsychotic with reported remyelinating and neuroprotective properties in inflammatory and noninflammatory models of demyelination, including experimental autoimmune encephalomyelitis, and both cuprizone- and global cerebral ischemia-induced demyelination. Preclinical studies suggest that quetiapine may exert these effects by stimulating proliferation and maturation of oligodendrocytes, releasing neurotrophic factors, increasing antioxidant defences, scavenging for free radicals, and inhibiting activated microglia, astrocytes, and T lymphocytes. Additionally, quetiapine may be beneficial for psychiatric and nonpsychiatric symptoms of MS including depression, anxiety, insomnia, and possibly even pain. These data indicate that clinical trials are justified to determine the safety, tolerability, and efficacy of quetiapine fumarate in MS.

Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative condition of the central nervous system (CNS). Oligodendrocytes and the myelin that they form, as well as neurons and their axons, are destroyed. Several medications that mitigate immune abnormalities reduce both the frequency of relapses and inflammation on magnetic resonance imaging (MRI) leading to improved outcomes for people with relapsing–remitting MS (RRMS) [1]. However, there are no treatments for progressive forms of MS where neurons and axons continue to degenerate [2]. While efforts are still required to improve the immune modulators that are available for the treatment of RRMS, significant research activity is now being directed toward the next frontiers of MS therapy: myelin repair (remyelination) and neuroprotection [3–5]. Importantly, given that maintaining the integrity of the axon–myelin unit sustains the health of both components, therapies that promote remyelination may also provide neuroprotection and thus treat progressive MS by slowing the loss of neurons and axons. By restoring structure, remyelination may also restore function in all forms of MS.

Current research has focused on promoting remyelination in MS by creating new knowledge about the biological basis of remyelination and by evaluating new therapies to promote remyelination in experimental models of MS. Ultimately, this research needs to test potential remyelinating therapies in people with MS.

Mechanisms of Damage in MS

It is important to understand the mechanisms of damage to identify potential therapeutic targets. The etiology of MS is unresolved, and there are competing hypotheses on its immune origin. One hypothesis postulates that T lymphocytes are activated in the periphery and that activated T-cell subsets and other immune cells then enter the CNS from the "outside in" to produce pathology [1]. In this model, inflammatory cells penetrate the blood–brain barrier and then damage myelin and axons.

Activated T cells, macrophages, microglia, and astrocytes are some of the cell types that are implicated in acute inflammation seen in MS plaques [1,4–6]. Activated T cells can be directly toxic to neurons [7]. In addition, macrophages/microglia secrete a number of factors that can cause damage including tumor necrosis

factor-alpha (TNF-α), interleukin-1 beta (IL-1β), reactive oxygen species, glutamate, and peroxynitrite [5,8]. Due to the trophic support provided by myelin and oligodendrocytes to axons, damage to the former elements can compromise axonal integrity. Once demyelinated, axons conduct signals poorly and are particularly fragile and prone to injury because of axonal energy insufficiency [9].

An alternate hypothesis infers that the initial dysfunction is within the CNS, which leads to the leakage of CNS antigens into draining lymph nodes resulting in the activation of T cells and other immune cell subsets thus affecting immune function from the "inside out" [2]. For the "inside out" hypothesis, the initial dysfunction in the CNS need not be immunological or inflammatory. Potential pathological processes such as mitochondrial dysfunction in neurons or oligodendrocytes, axonal energy insufficiency, or inactivation of neural organelles such as peroxisomes may lead to neurodegeneration.

The Search for Remyelinating and Neuroprotective Medications for MS

Whatever the origin of MS pathology may be, the result is the activation and recruitment of immune cell subsets into the CNS, which then result in inflammation, demyelination, oligodendrocyte loss, and axonal/neuronal injury and death. Current medications for MS such as interferon-β, glatiramer acetate, fingolimod, and natalizumab are thought to provide clinical benefits primarily via immunomodulation; that is, they alter the nature of the immune system to reduce its potential to damage CNS elements [1]. However, while these treatments reduce relapses, none have been shown to slow progression of MS independent of their effect on relapses.

New therapies for MS should ideally possess three key characteristics. First, they should be able to enhance endogenous remyelination, thereby protecting denuded axons from degeneration. Second, they should offer neuroprotection, defined here as the capacity to reduce injury to neural elements. Finally, they should have an immunomodulatory role within the CNS to reduce microglial activation and decrease levels of proinflammatory leukocytes and their products. Such medications could be used as monotherapies for RRMS or progressive MS, or they can be used to augment the efficacy of currently approved medications for MS.

Quetiapine Fumarate as a Remyelinating, Neuroprotective and Immune-Modulating Agent: Evidence from Preclinical Studies

Quetiapine is an atypical antipsychotic with a broad spectrum of pharmacological activity [10–12]. It is administered in the form of a fumarate salt. Quetiapine fumarate has shown benefits in many conditions including mood disorders, anxiety disorders, psychotic disorders, insomnia, and possibly even pain disorders [13–17]. This medication is thus widely used in psychiatric and nonpsychiatric diseases. Interestingly, recent studies revealed that quetiapine possesses potent remyelinating and neuroprotective properties in animal models of demyelination, including cuprizone-induced demyelination [11,18–22], global cerebral ischemia [23], and experimental autoimmune encephalomyelitis (EAE; Table 1) [24].

Cuprizone-Induced Demyelination

Cuprizone ingestion in mice induces rapid demyelination of multiple brain regions by chelating copper and killing oligodendrocytes, rather than through immunological mechanisms. Brain regions affected by cuprizone include the corpus callosum, hippocampus, cerebellum, caudate nucleus, and putamen [25]. Cuprizone administration leads to almost total demyelination of the corpus callosum and other regions after about 4–6 weeks, making this a model of "acute demyelination," which is not predominantly mediated by immune cells. When cuprizone is removed from the diet, endogenous remyelination occurs quickly during the following weeks. In contrast, prolonged cuprizone administration (>12 weeks) leads to significantly attenuated endogenous remyelination, making this a model of "chronic demyelination" [25].

A pivotal study by Xiao et al. [11] examined the administration of quetiapine (10 mg/kg/day PO) in C57BL/6 mice that were fed 0.2% cuprizone in the diet for 4 weeks. They found that while cuprizone-fed mice exhibited myelin breakdown in the whole brain

Table 1 Effects of quetiapine fumarate in preclinical models of demyelination/remyelination

Preclinical model
In vitro
↑Proliferation of NPCs in neurospheres [11]
↑Differentiation of NPCs into OLs [11]
↑Myelination in embryonic neocortical aggregate cell cultures [11]
Cuprizone-induced demyelination
↓Demyelination [11,18–22]
↓Loss of mature OLs [11,18–22]
↓Activated astrocytes [18]
↓Activated microglia [18]
↓MDA [21]
↑Catalase activity [21]
↑SOD1 activity [18]
↑Myelin restoration (Tx after cuprizone withdrawal) [22]
↑Repopulation of mature OLs (Tx after cuprizone withdrawal) [22]
Global cerebral ischemia-induced demyelination
↓Demyelination [23]
↓Activated astrocytes [23]
↓Loss of mature OLs [23]
↑Repopulation of mature OLs (postoperative Day 40) [23]
Experimental autoimmune encephalomyelitis
↓Demyelination [24]
↓Loss of mature OLs [24]
↓Activated astrocytes [24]
↓Activated microglia [24]
↓T-cell infiltrates [24]

↑, stimulated by quetiapine; ↓, attenuated by quetiapine; NPC, neural progenitor cell; OL, oligodendrocyte; Tx, treatment; SOD1, copper–zinc superoxide dismutase; MDA, malondialdehyde.

(especially in the cortex), the mice that received quetiapine for 5 weeks (started 1 week before cuprizone treatment) in conjunction with cuprizone treatment had significantly less myelin breakdown. The same study also showed that *in vitro* application of quetiapine—but not other typical and atypical antipsychotics—increased neural progenitor cell proliferation and stimulated the maturation of oligodendrocytes, as evidenced by increased levels of the myelin proteins, cyclic nucleotide phosphohydrolase (CNP), and myelin basic protein (MBP). Furthermore, quetiapine significantly increased MBP expression levels in rat embryonic neocortical aggregate cultures, suggesting that it facilitated myelination [11].

Other publications by the same group confirmed a beneficial effect of quetiapine on cuprizone-induced demyelination and behavioral deficits [18,19]. Additionally, they showed that quetiapine blocked the cuprizone-induced loss of mature oligodendrocytes and decrease in activity of copper–zinc superoxide dismutase (SOD1; one of three superoxide dismutases responsible for destroying free superoxide radicals), while preventing the accumulation of activated microglia and astrocytes in demyelinated lesions [18]. Another team used the same schedule to examine the effects of quetiapine on white matter in C57BL/6 mice, using MRI methods including T2-weighted imaging and diffusion tensor imaging (DTI) [20]. The authors confirmed that quetiapine treatment significantly attenuated cuprizone-induced changes in white matter. More recently, Xu et al. [21] examined the effects of quetiapine, clozapine, olanzapine, and haloperidol. Oligodendrocyte progenitor cells (OPCs) were prepared from rat embryos, and oligodendrocytes at different developing stages were labeled with specific antibodies. Levels of CNP and MBP in mature oligodendrocytes (OLs) were assessed by Western blot analysis, and malondialdehyde (MDA) levels and activity of catalase were evaluated as well for an assessment of oxidative stress and antioxidative status. The authors found that quetiapine and clozapine (but not olanzapine or haloperidol) ameliorated cuprizone-induced inhibition of differentiation of cultured OPCs into O4-positive cells, inhibition of maturation of O4-positive cells into CNP- and MBP-positive cells, and reduction in levels of CNP and MBP in mature oligodendrocytes. Here, quetiapine also possessed significant antioxidant properties—that is, it attenuated the cuprizone-induced increase in the lipid peroxidation product, MDA, and it reduced the cuprizone-induced decrease in catalase activity in cultured oligodendrocytes [21].

Uniquely, Zhang et al. [22] examined the effects of quetiapine postinjury in a model of "chronic demyelination." C57BL/6 mice were fed cuprizone for 12 weeks to induce chronic demyelination and oligodendrocyte degeneration. Subsequently, cuprizone was withdrawn and mice were administered quetiapine (10 mg/kg/day PO) for 0, 2, 3, and 4 weeks. Cuprizone treatment for 12 weeks resulted in severe demyelination, mature oligodendrocyte loss, and spatial working memory impairment in mice. Remyelination occurred naturally when cuprizone was withdrawn. Notably, however, quetiapine treatment during the recovery period significantly increased myelin restoration, enhanced repopulation of mature oligodendrocytes, and improved spatial working memory. Altogether, these results show that quetiapine blocks cuprizone-induced demyelination and increases remyelination after cuprizone is withdrawn.

Global Cerebral Ischemia-Induced Demyelination

Experimentally induced global cerebral ischemia is an animal model of stroke as well as of late-life vascular depression. In this model, inflammation, oxidative stress, and elevated glutamate levels cause demyelination and oligodendrocyte and neuronal death [26]. Bi et al. [23] recently examined the effects of 2 weeks of quetiapine pretreatment (10 mg/kg/day IP) on the hippocampus of CD1 mice that underwent bilateral carotid artery occlusion and reperfusion. Their results revealed that quetiapine significantly reduced myelin breakdown and oligodendrocyte loss, compared with placebo-treated mice on postoperative Day 7, and enhanced maturation of oligodendrocytes on postoperative Day 40. In addition, the authors showed that ischemia induced depressive and anxiety-like behavioral changes, spatial memory impairment, and neurodegeneration in the hilus of hippocampus, whereas quetiapine significantly attenuated these changes [27,28].

Experimental Autoimmune Encephalomyelitis

Immune-mediated demyelinating models are commonly used for the preclinical screening of candidate MS therapies. In the hallmark MS model, EAE, animals are immunized against peptides of myelin proteins, such as myelin oligodendrocyte glycoprotein (MOG). The adaptive immune system produces myelin-reactive T cells that invade the CNS and attack myelin and axons, resulting in a characteristic ascending paralysis [29]. Quetiapine (10 mg/kg/day PO) was recently examined in MOG-immunized EAE C57BL/6 mice [24]. It was initiated on Day 16 postimmunization when mice had already succumbed to clinical signs (a clinical score of 0.5) and continued and for a total of 40 days. The authors found that EAE mice treated with quetiapine reached a clinical score of 1 (tail impairment) on a five-point scale, but stabilized at that level and did not display further deterioration. The untreated EAE mice continued to deteriorate and reached clinical scores of 3 (dysfunction of tail, hindlimb, and forelimb) of 5. Histological analyses revealed that the spinal cords from the immunized group without quetiapine treatment were weakly stained for MBP, especially in white matter tracts, which is evidence of demyelination [24]. By contrast, significantly more intense expression of MBP staining was observed in the quetiapine treatment group—approaching levels seen in unimmunized animals (controls). Likewise, oligodendrocyte numbers were depleted in untreated EAE animals, relative to controls, whereas they were significantly less depleted in EAE animals treated with quetiapine. Finally, quetiapine reduced activated macrophages/microglia, CD4 + and CD8 + T cells, and reactive astrocytes in the spinal cords of EAE mice [24]. Taken together, these results suggest that quetiapine possesses immune-modulating properties and may offer both inflammatory and noninflammatory neuroprotection in MS.

Potential Mechanisms of Quetiapine

The mechanism of quetiapine in reversing demyelination has been attributed to stimulation of the proliferation and maturation of oligodendrocytes as well as increasing the activity of SOD1 and the scavenging of free radicals, which thus alleviates oxidative

stress [11]. The antioxidant properties of quetiapine are intriguing because oxidative stress has been shown to play a deleterious role in EAE and MS [30,31]. *In vitro* studies showed that pretreatment with quetiapine upregulated the expression of SOD mRNA and prevented PC12 cells from apoptosis induced by N-methyl-4-phenylpyridinium ion and by withdrawal of serum from the culture medium [32,33]. In a similar vein, pretreatment with quetiapine overcame the cytotoxic effect of rotenone, an inhibitor of mitochondrial complex I activity and generator of free radicals, in PC12 cells [34]. Quetiapine also protected PC12 cells from β-amyloid peptide (25–35)-induced oxidative stress [35], blocked hydroxyl radical (OH*)-induced Aβ (25–35) aggregation, and scavenged the OH* produced in the Fenton system and in the Aβ (25–35) solution [36]. Likewise, quetiapine attenuated the inhibition of SOD1 activity by hydrogen peroxide in human erythrocytes [37] and reduced lipid peroxidation in human plasma [38]. In patients with schizophrenia, treatment with quetiapine (300 mg/day) was associated with increased SOD1 activity, relative to patients treated with other atypical antipsychotics and age-matched controls [39].

Another potential mechanism for the efficacy of quetiapine in preclinical models of demyelination may be its regulation of expression of BDNF and other neurotrophic factors. Studies show that BDNF plays a role in remyelination and neuroregeneration [40]. Following treatment with cuprizone, BDNF protein levels were reduced, indicating that it was depleted during the demyelinating process [41]. Other studies showed that BDNF reduced severity of EAE [42] and helped account for the therapeutic effect of glatiramer acetate in EAE [43,44]. Quetiapine has been shown to regulate the expression of several neurotrophic factors. For instance, quetiapine increased BDNF levels in the dentate gyrus of normal rats and blocked a decrease in BDNF expression in the rat hippocampus and neocortex induced by immobilization stress [45,46]. Quetiapine treatment also prevented the decrease in BDNF and basic fibroblast growth factor transcripts induced by MK-801, a noncompetitive antagonist of glutamatergic NMDA receptors [47]. Additionally, quetiapine was shown to prevent the decreased expression of synaptic proteins including postsynaptic density protein-95, synaptophysin, and BDNF in rat hippocampal neuronal cultures under toxic conditions induced by B27 deprivation [48]. Finally, both quetiapine and *N*-desalkylquetiapine were shown to induce release of glial cell-derived neurotrophic factor in C6 glioma cells [49,50]. These data suggest that a stimulatory effect of quetiapine on neurotrophic factors may result in benefits for people with MS.

The ability of quetiapine to reduce clinical symptoms and immune infiltrates in EAE and to inhibit activated astrocytes and microglia in EAE and cuprizone-demyelinated mice suggests that quetiapine may possess immune-modulating properties [18–24]. The effect of quetiapine on astrocytes could be because they contain serotonergic receptors and quetiapine and *N*-desalkylquetiapine act as a partial agonists or antagonists at multiple serotonergic receptors [6,10,12]. Intriguingly, the attenuation of the antigen-presenting capacity of astrocytes is believed to be the mechanism responsible for the beneficial effect of the selective serotonin reuptake inhibitor, fluoxetine, in EAE and deserves further study in MS [51,52].

Quetiapine possesses other immunomodulatory and antiinflammatory properties. In particular, a direct inhibitory effect of quetiapine was observed on the release of TNF-α and nitric oxide from activated murine microglia [53]. Moreover, quetiapine treatment decreased antitype II collagen-specific antibody, IL-6, IL-17, and prostaglandin E(2), and significantly improved clinical signs of murine collagen-induced arthritis [54]. Further, quetiapine significantly decreased levels of IL-2 and TNF-α (but increased IL-17 levels) in stimulated blood cells from 10 healthy females [55]. In schizophrenia, quetiapine treatment was associated with increased plasma levels of soluble IL-2 receptor (sIL-2R), relative to healthy controls [56]. As sIL-2R is the endogenous modulator of IL-2, which neutralizes excessive IL-2 [57], it is likely that increases in sIL-2R lead to inhibition of IL-2. These studies demonstrate that quetiapine may offer neuroprotection via immune modulation, in addition to nonimmune-mediated neuroprotection and remyelination.

It is unclear to what extent fumaric acid plays a role in the aforementioned remyelinating, neuroprotective, and immunomodulatory properties of quetiapine. Intriguingly, there is evidence that the fumaric acid ester, dimethyl fumarate (BG-12), reduced proinflammatory cytokines and infiltration of inflammatory cells into the CNS, exerted an antioxidant effect via the NR2 pathway, and attenuated severity of EAE [30,58]. In MS, recent clinical trials showed that BG-12 reduced the number of relapses, disease progression as well as the number of enhancing lesions in RRMS [59,60]. On the other hand, monomethyl fumarate and dimethyl fumaric acid exerted little or no protective effects on oligodendrocytes in the cuprizone model [61]. It would be of interest to determine whether other quetiapine salts also promote remyelination in mice.

Potential Clinical Benefits of Quetiapine Fumarate in MS

In addition to its potential role as a promoter of remyelination in MS, quetiapine may benefit some of the common comorbid disorders and symptoms in MS.

Psychiatric Symptoms

Depression frequently occurs in association with MS. The reported lifetime prevalence of major depression is estimated to range between 22% and 54% [62,63]. In addition to reducing health-related quality of life, untreated depression may contribute to poor adherence to medications and may explain the elevated suicide rates in MS [64]. Elevated rates of anxiety and bipolar disease have also been reported in MS, but the association is weaker [65,66]. Due to its strong affinity for multiple adrenergic and serotonergic receptors, quetiapine is efficacious in the treatment for mood disorders and may benefit MS patients with these conditions. Importantly, several large, placebo-controlled trials have shown that the efficacy of quetiapine (150–300 mg/day) exceeds that of some established antidepressants for unipolar and bipolar depression and for anxiety disorders [13]. By contrast, because of its very weak affinity for D_2 receptors, quetiapine is less efficacious for acute schizophrenia, and it produces fewer neurological side

effects than most other antipsychotics, even at doses as high as 800–1200 mg/day [67]. A low incidence of neurological side effects (i.e., Parkinsonism, akathisia, dyskinesia, and dystonia) is important because many patients with MS are already burdened with mobility restrictions such as weakness, impaired balance, ataxia, tremor, and spasticity.

Insomnia

Sleep disturbance is reported by 24–50% of patients with MS; it may contribute to the fatigue that is commonly associated with the disease and may exacerbate other symptoms of MS (e.g., neuropathic pain) and common comorbid psychiatric conditions (e.g., depression and anxiety) [68,69]. Problems with sleep may be associated with symptoms of MS (e.g., neuropathic pain, spasticity), side effects of drugs used to treat MS, and psychiatric symptoms secondary to the disease (e.g., depression and anxiety). Quetiapine immediate and extended release (IR and XR) possesses strong sedative properties, and they have a relatively short half-life (6–7 h, respectively), suggesting that they can be administered at bedtime or 1–2 h before bedtime without producing significant next-day drowsiness [70]. Indeed, research has shown that quetiapine is beneficial for the treatment of primary insomnia and insomnia secondary to pathological conditions such as major depression and Parkinson disease [16,71,72]. A sleep-improving effect is important for decreasing suicide risk [72] and may help explain the rapid onset of antidepressant action associated with quetiapine [73].

To characterize the time course of quetiapine's sedative properties, Datto et al. [70] conducted a crossover study in 60 healthy volunteers who were administered once-daily doses of quetiapine IR or XR, titrated to 300 mg/day over 5 days. Quetiapine IR produced a significantly greater sedative effect 1–4 h after dosing, relative to quetiapine XR. However, sedation induced by both formulations returned to normal 8–14 h after dosing, and significant tolerance to the initial morning sedation was observed by Day 5 of treatment. These data suggest that quetiapine IR or XR given once daily at bedtime may be helpful for the treatment of insomnia in MS.

Pain

Clinically significant pain is highly prevalent in MS. A recent meta-analysis (17 studies, n = 5319) showed a pooled overall pain prevalence of 63%. Specific pain syndromes included headache (43%), neuropathic extremity pain (26%), back pain (20%), painful spasms (15%), Lhermitte sign (16%), and trigeminal neuralgia (3.8%) [74]. Quetiapine and its active metabolite, *N*-desalkylquetiapine, share mechanisms of antidepressants and antipsychotics (e.g., duloxetine, amitriptyline, tiapride and haloperidol) that possess antinociceptive properties; therefore, quetiapine may be helpful for pain [10,75–77]. However—although preliminary data indicate that quetiapine may be helpful for the treatment of migraine and some symptoms of fibromyalgia—these findings need to be confirmed by larger, randomized, controlled trials [14,15,17]. Further research is also required to determine whether quetiapine has potential as a treatment for pain in MS.

Toward a Trial of Quetiapine Fumarate in MS

The aforementioned literature indicates that quetiapine may have remyelinating and neuroprotective benefits in inflammatory as well as noninflammatory demyelinating conditions. In addition, quetiapine may benefit some common symptoms of MS, such as depression, anxiety, insomnia, and possibly even pain. We believe that the available preliminary data support undertaking a phase IIa clinical trial to determine the safety and tolerability of quetiapine fumarate in MS, followed by a phase IIb trial examining the effects of quetiapine on remyelination and other outcomes measures. This is important because there is only a very small list of agents that can enhance remyelination in experimental models, and it includes immunoglobulins of unknown specificities, prolactin, and an Fc fragment that inhibits a protein named LINGO [3,4]. In this light, recent demonstration that quetiapine enhances remyelination in various models of demyelination in mice provides a critical resource to address whether quetiapine can be used as a therapeutic agent for RRMS and progressive MS.

Safety and Tolerability of Quetiapine

Before undertaking a clinical trial of quetiapine, it is important to understand its safety and how it will be tolerated. The severity of adverse events (AEs) associated with quetiapine, particularly at low-to-moderate doses, is relatively mild compared with the severity of MS and with the side effects of current MS disease-modifying therapies. During an 8-week trial of quetiapine IR (300 mg/day) for bipolar depression (n = 340), the frequency of adverse effects differed between the quetiapine group and the placebo group [78]. In particular, the incidence of sedation was higher in patients treated with quetiapine (32% vs. 10%), as was the incidence of dry mouth (43% vs. 18%). In contrast, the incidence of headache was higher in patients treated with placebo (17% vs. 9%), whereas the incidence of fatigue was similar between the two groups (8% vs. 9%, respectively). Moreover, 6.5% of patients treated with quetiapine withdrew because of AEs (mostly due to sedation), compared with 0% of patients treated with placebo. Neurological AEs occurred in 6.6% of patients treated with placebo and in 12.3% of patients treated with quetiapine, but none of these symptoms led to treatment discontinuation in either group. In healthy volunteers, the most commonly reported AEs for quetiapine IR (300 mg) were dry mouth and dizziness (11.7% each), followed by headache and nausea (8.3% each), while the most commonly reported AEs for quetiapine XR were dry mouth and nausea (6.6% each) [70]. The incidence of any AEs was nonsignificantly greater in the quetiapine IR group than in the quetiapine XR group (21.7% vs. 9.8%, respectively). Conceivably, some of the AEs (e.g., sedation, dizziness) may be more problematic in patients with neurological diseases such as MS, compared with psychiatric patients or healthy subjects. On the other hand, it is reassuring that quetiapine was relatively well tolerated compared with placebo in patients with Parkinson and Alzheimer diseases [79,80].

Early registration trials of quetiapine IR for acute schizophrenia reported a minimal level of antidopaminergic side effects. There

were no significant increases in the frequency of neurological symptoms or prolactin release—regardless of dose (50–750 mg/day) compared with placebo [81,82]. More recently, Moteshafi and Stip [83] conducted a meta-analysis of 25 randomized trials (6–72 weeks of duration) that measured metabolic tolerability associated with quetiapine in patients with schizophrenia (n = 1683) versus mood disorders (n = 3411; major depressive and bipolar disorder). Treatment with quetiapine increased blood cholesterol levels by 8.05 mg/dL in patients with schizophrenia and decreased cholesterol levels by 2.8 mg/dL in patients with mood disorders ($P < 0.0001$). In addition, quetiapine increased triglycerides by 17.57–7.93 mg/dL in patients with schizophrenia and mood disorders, respectively ($P = 0.1$). Finally, quetiapine led to mean weight increases of 1.72–1.15 kg in patients with schizophrenia and mood disorders, respectively ($P = 0.1$). The results did not change when only short-term studies were considered. In the pivotal, long-term Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in schizophrenia (72 weeks; n = 1493), 16% of patients randomized to quetiapine evidenced >7% weight gain; the mean weight gain was 0.5 kg, at a rate of 0.2 kg per month of treatment [84]. Although the metabolic effects of atypical antipsychotics are a source of legitimate concern, especially in older patients, these effects seem of relatively low clinical significance in individuals without a high risk for metabolic disease. It is unclear whether patients with MS would exhibit a lower or higher sensitivity to quetiapine-induced metabolic changes, relative to the aforementioned groups.

Dosing

Data from D_2 receptor occupancy and brain stimulation reward studies indicate that 10 mg/kg of quetiapine in animals is roughly equal to oral treatment with 300 mg in humans—the threshold dose for an antipsychotic effect [85,86]. Previous data show that 300 mg of quetiapine IR at bedtime should not cause significant daytime sedation, especially following the development of tolerance [70]. This dose and formulation should therefore be tolerated by people with RRMS, where high levels of sedation could interfere with patients' ability to work. On the other hand, quetiapine XR is associated with a lower severity of side effects (due to more stable pharmacokinetics), greater pharmacokinetic coverage, and the ability to titrate more aggressively, indicating that it may offer the advantage of providing a more immediate and longer-lasting remyelinating/neuroprotective effect. Undoubtedly, however, some of these assumptions will need to be tested in a safety and tolerability trial of quetiapine in MS because patients with MS constitute a relatively novel population for treatment with this medication and because they may be more susceptible to AEs due to the brain injury that accompanies the disease.

Conclusion

Quetiapine fumarate is an atypical antipsychotic with reported remyelinating and neuroprotective properties in inflammatory and noninflammatory models of demyelination, including EAE, and cuprizone- and global cerebral ischemia-induced demyelination. Preclinical studies suggest that quetiapine may exert these effects by stimulating proliferation and maturation of oligodendrocytes and release of neurotrophic factors, increasing antioxidant defences, scavenging for free radicals, and inhibiting activated microglia, astrocytes, and/or T lymphocytes.

Although there are currently no published studies examining whether quetiapine promotes remyelination in MS, future studies may try to answer this question using imaging techniques such as MRI texture analysis, quantitative magnetic transfer imaging (MTR), and DTI, and by collecting biomarkers (e.g., serum neurotrophic factors, antioxidants) [87,88]. Future studies should also examine if quetiapine may be beneficial in other conditions that require myelin repair.

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Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Nylander A, Hafler DA. Multiple sclerosis. *J Clin Invest* 2012;**122**:1180–1188.
2. Stys PK, Zamponi GW, van Minnen J, Geurts JJ. Will the real multiple sclerosis please stand up? *Nat Rev Neurosci* 2012;**13**:507–514.
3. Zhornitsky S, Yong VW, Weiss S, Metz LM. Prolactin in multiple sclerosis. *Mult Scler* 2013;**19**:15–23.
4. Franklin RJ, ffrench-Constant C, Edgar JM, et al. Neuroprotection and repair in multiple sclerosis. *Nat Rev Neurol* 2012;**8**:624–634.
5. Tselis A, Khan OA, Lisak RP. Approaches to neuroprotective strategies in multiple sclerosis. *Expert Opin Pharmacother* 2010;**11**:2869–2878.
6. De Keyser J, Laureys G, Demol F, Wilczak N, Mostert J, Clinckers R. Astrocytes as potential targets to suppress inflammatory demyelinating lesions in multiple sclerosis. *Neurochem Int* 2010;**57**:446–450.
7. Siffrin V, Radbruch H, Glumm R, et al. In vivo imaging of partially reversible th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. *Immunity* 2010;**33**:424–436.
8. Domercq M, Vázquez-Villoldo N, Matute C. Neurotransmitter signaling in the pathophysiology of microglia. *Front Cell Neurosci* 2013;**7**:49.
9. Loers G, Aboul-Enein F, Bartsch U, Lassmann H, Schachner M. Comparison of myelin, axon, lipid, and immunopathology in the central nervous system of differentially myelin-compromised mutant mice: A morphological and biochemical study. *Mol Cell Neurosci* 2004;**27**:175–189.
10. Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB, Roth BL. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* 2008;**33**:2303–2312.
11. Xiao L, Xu H, Zhang Y, et al. Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. *Mol Psychiatry* 2008;**13**:697–708.
12. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: Selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* 2004;**3**:353–359.
13. Zhornitsky S, Potvin S, Moteshafi H, Dubreucq S, Rompré PP, Stip E. Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: A systematic review of the placebo-controlled monotherapy and add-on trials. *Int Clin Psychopharmacol* 2011;**26**:183–192.
14. Hidalgo J, Rico-Villademoros F, Calandre EP. An open-label study of quetiapine in the treatment of fibromyalgia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;**31**:71–77.
15. Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: A pilot, randomized, double-blind, placebo-controlled 12-week trial. *J Clin Psychopharmacol* 2012;**32**:684–687.
16. Tassniyom K, Paholpak S, Tassniyom S, Kiewyoo J. Quetiapine for primary insomnia: A double blind,

randomized controlled trial. *J Med Assoc Thai* 2010;**93**:729–734.
17. Krymchantowski AV, Jevoux C, Moreira PF. An open pilot study assessing the benefits of quetiapine for the prevention of migraine refractory to the combination of atenolol, nortriptyline, and flunarizine. *Pain Med* 2010;**11**:48–52.
18. Zhang Y, Xu H, Jiang W, et al. Quetiapine alleviates the cuprizone-induced white matter pathology in the brain of C57BL/6 mouse. *Schizophr Res* 2008;**106**:182–191.
19. Xu H, Yang HJ, McConomy B, Browning R, Li XM. Behavioral and neurobiological changes in C57BL/6 mouse exposed to cuprizone: Effects of antipsychotics. *Front Behav Neurosci* 2010;**4**:8.
20. Chandran P, Upadhyay J, Markosyan S, et al. Magnetic resonance imaging and histological evidence for the blockade of cuprizone-induced demyelination in C57BL/6 mice. *Neuroscience* 2012;**202**:446–453.
21. Xu H, Yang HJ, Li XM. Differential effects of antipsychotics on the development of rat oligodendrocyte precursor cells exposed to cuprizone. *Eur Arch Psychiatry Clin Neurosci* 2013 [Epub ahead of print].
22. Zhang Y, Zhang H, Wang L, et al. Quetiapine enhances oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination. *Schizophr Res* 2012;**138**:8–17.
23. Bi X, Zhang Y, Yan B, et al. Quetiapine prevents oligodendrocyte and myelin loss and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice. *J Neurochem* 2012;**123**: 14–20.
24. Mei F, Guo S, He Y, et al. Quetiapine, an atypical antipsychotic, is protective against autoimmune-mediated demyelination by inhibiting effector T cell proliferation. *PLoS ONE* 2012;**7**:e42746.
25. Kipp M, Clarner T, Dang J, Copray S, Beyer C. The cuprizone animal model: New insights into an old story. *Acta Neuropathol* 2009;**118**:723–736.
26. McTigue DM, Tripathi RB. The life, death, and replacement of oligodendrocytes in the adult CNS. *J Neurochem* 2008;**107**:1–19.
27. Yan B, Bi X, He J, et al. Quetiapine attenuates spatial memory impairment and hippocampal neurodegeneration induced by bilateral common carotid artery occlusion in mice. *Life Sci* 2007;**81**:353–361.
28. Yan B, He J, Xu H, et al. Quetiapine attenuates the depressive and anxiolytic-like behavioural changes induced by global cerebral ischemia in mice. *Behav Brain Res* 2007;**182**:36–41.
29. Ransohoff RM. Animal models of multiple sclerosis: The good, the bad and the bottom line. *Nat Neurosci* 2012;**15**:1074–1077.
30. Lee DH, Gold R, Linker RA. Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: Therapeutic modulation via fumaric acid esters. *Int J Mol Sci* 2012;**13**:11783–11803.
31. Dasgupta A, Zheng J, Perrone-Bizzozero NI, Bizzozero OA. Increased carbonylation, protein aggregation and apoptosis in the spinal cord of mice with experimental autoimmune encephalomyelitis. *ASN Neuro* 2013;**5**:e00111.
32. Qing H, Xu H, Wei Z, Gibson K, Li XM. The ability of atypical antipsychotic drugs vs. haloperidol to protect PC12 cells against MPP+-induced apoptosis. *Eur J Neurosci* 2003;**17**:1563–1570.
33. Bai O, Wei Z, Lu W, Bowen R, Keegan D, Li XM. Protective effects of atypical antipsychotic drugs on PC12 cells after serum withdrawal. *J Neurosci Res* 2002;**69**:278–283.
34. Tan QR, Wang XZ, Wang CY, et al. Differential effects of classical and atypical antipsychotic drugs on rotenone-induced neurotoxicity in PC12 cells. *Eur Neuropsychopharmacol* 2007;**17**:768–773.
35. Wang H, Xu H, Dyck LE, Li XM. Olanzapine and quetiapine protect PC12 cells from beta-amyloid peptide (25-35)-induced oxidative stress and the ensuing apoptosis. *J Neurosci Res* 2005;**81**:572–580.
36. Xu H, Wang H, Zhuang L, et al. Demonstration of an anti-oxidative stress mechanism of quetiapine: Implications for the treatment of Alzheimer's disease. *FEBS J* 2008;**275**:3718–3728.
37. Miljević Č, Nikolić-Kokić A, Nikolić M, et al. Effect of atypical antipsychotics on antioxidant enzyme activities in human erythrocytes (in vitro study). *Hum Psychopharmacol* 2013;**28**:1–6.
38. Dietrich-Muszalska A, Kontek B, Rabe-Jabłońska J. Quetiapine, olanzapine and haloperidol affect human plasma lipid peroxidation in vitro. *Neuropsychobiology* 2011;**63**:197–201.
39. Padurariu M, Ciobica A, Dobrin I, Stefanescu C. Evaluation of antioxidant enzymes activities and lipid peroxidation in schizophrenic patients treated with typical and atypical antipsychotics. *Neurosci Lett* 2010;**479**:317–320.
40. Lühder F, Gold R, Flügel A, Linker RA. Brain-derived neurotrophic factor in neuroimmunology: Lessons learned from multiple sclerosis patients and experimental autoimmune encephalomyelitis models. *Arch Immunol Ther Exp (Warsz)* 2013;**61**:95–105.
41. VonDran MW, Singh H, Honeywell JZ, Dreyfus CF. Levels of BDNF impact oligodendrocyte lineage cells following a cuprizone lesion. *J Neurosci* 2011;**31**:14182–14190.
42. Linker RA, Lee DH, Demir S, et al. Functional role of brain-derived neurotrophic factor in neuroprotective autoimmunity: Therapeutic implications in a model of multiple sclerosis. *Brain* 2010;**133**:2248–2263.
43. Lee DH, Geyer E, Flach AC, et al. Central nervous system rather than immune cell-derived BDNF mediates axonal protective effects early in autoimmune demyelination. *Acta Neuropathol* 2012;**123**:247–258.
44. Skihar V, Silva C, Chojnacki A, et al. Promoting oligodendrogenesis and myelin repair using the multiple sclerosis medication glatiramer acetate. *Proc Natl Acad Sci U S A* 2009;**106**:17992–17997.
45. Xu H, Qing H, Lu W, et al. Quetiapine attenuates the immobilization stress-induced decrease of brain-derived neurotrophic factor expression in rat hippocampus. *Neurosci Lett* 2002;**321**:65–68.
46. Park SW, Lee SK, Kim JM, et al. Effects of quetiapine on the brain-derived neurotrophic factor expression in the hippocampus and neocortex of rats. *Neurosci Lett* 2006;**402**:25–29.
47. Fumagalli F, Molteni R, Bedogni F, et al. Quetiapine regulates FGF-2 and BDNF expression in the hippocampus of animals treated with MK-801. *NeuroReport* 2004;**15**:2109–2112.
48. Park SW, Lee CH, Cho HY, et al. Effects of antipsychotic drugs on the expression of synaptic proteins and dendritic outgrowth in hippocampal neuronal cultures. *Synapse* 2013;**67**:224–234.
49. Shao Z, Dyck LE, Wang H, Li XM. Antipsychotic drugs cause glial cell line-derived neurotrophic factor secretion from C6 glioma cells. *J Psychiatry Neurosci* 2006;**31**:32–37.
50. Di Benedetto B, Kühn R, Nothdurfter C, et al. N-desalkylquetiapine activates ERK1/2 to induce GDNF release in C6 glioma cells: A putative cellular mechanism for quetiapine as antidepressant. *Neuropharmacology* 2012;**62**:209–216.
51. Yuan XQ, Qiu G, Liu XJ, et al. Fluoxetine promotes remission in acute experimental autoimmune encephalomyelitis in rats. *NeuroImmunoModulation* 2012;**19**:201–208.
52. Mostert JP, Koch MW, Heerings M, Heersema DJ, De Keyser J. Therapeutic potential of fluoxetine in neurological disorders. *CNS Neurosci Ther* 2008;**14**:153–164.
53. Bian Q, Kato T, Monji A, et al. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-gamma. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;**32**:42–48.
54. Kim H, Bang J, Chang HW, et al. Anti-inflammatory effect of quetiapine on collagen-induced arthritis of mouse. *Eur J Pharmacol* 2012;**678**:55–60.
55. Himmerich H, Schönherr J, Fulda S, et al. Impact of antipsychotics on cytokine production in-vitro. *J Psychiatr Res* 2011;**45**:1358–1365.
56. Igue R, Potvin S, Bah R, et al. Soluble interleukin-2 receptor levels correlated with positive symptoms during quetiapine treatment in schizophrenia-spectrum disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;**35**:1695–1698.
57. Rubin LA, Nelson DL. The soluble interleukin-2 receptor: Biology, function, and clinical application. *Ann Intern Med* 1990;**113**:619–627.
58. Thöne J, Ellrichmann G. Oral available agents in the treatment of relapsing remitting multiple sclerosis: An overview of merits and culprits. *Drug Healthc Patient Saf* 2013;**5**:37–47.
59. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;**367**:1098–1107.
60. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;**367**:1087–1097.
61. Moharregh-Khiabani D, Blank A, Skripuletz T, et al. Effects of fumaric acids on cuprizone induced central nervous system de- and remyelination in the mouse. *PLoS ONE* 2010;**5**:e11769.
62. Patten SB, Metz LM, Reimer MM. Biopsychosocial correlates of major depression in a multiple sclerosis population. *Mult Scler* 2000;**6**:115–120.
63. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorders and multiple sclerosis. *Arch Neurol* 1987;**44**:376–378.
64. Stenager EN, Stenager E, Koch-Henriksen N, et al. Suicide and multiple sclerosis: An epidemiological investigation. *J Neurol Neurosurg Psychiatry* 1992;**55**:542–545.
65. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: Population-based evidence of an association. *Neurology* 2005;**65**:1123–1235.
66. Marrie RA, Fisk JD, Yu BN, et al. Mental comorbidity and multiple sclerosis: Validating administrative data to support population-based surveillance. *BMC Neurol* 2013;**13**:16.
67. Honer WG, MacEwan GW, Gendron A, et al. A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2012;**73**:13–20.
68. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler* 2008;**14**:1127–1130.
69. Kaminska M, Kimoff RJ, Schwartzman K, Trojan DA. Sleep disorders and fatigue in multiple sclerosis: Evidence for association and interaction. *J Neurol Sci* 2011;**302**:7–13.
70. Datto C, Berggren L, Patel JB, Eriksson H. Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: A randomized, double-blind, crossover study in healthy adult subjects. *Clin Ther* 2009;**31**:492–502.
71. Juri C, Chaná P, Tapia J, Kunstmann C, Parrao T. Quetiapine for insomnia in Parkinson disease: Results from an open-label trial. *J Clin Neuropharmacol* 2005;**28**:185–187.
72. Pompili M, Rihmer Z, Gonda X, Serafini G, Sher L, Girardi P. Early onset of action and sleep-improving effect are crucial in decreasing suicide risk: The role of quetiapine XR in the treatment of unipolar and bipolar depression. *Riv Psichiatr* 2012;**47**:489–497.
73. Cutler AJ, Montgomery SA, Feifel D, Lazarus A, Aström M, Brecher M. Extended release quetiapine fumarate

monotherapy in major depressive disorder: A placebo- and duloxetine-controlled study. *J Clin Psychiatry* 2009;**70**:526–539.
74. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. *Pain* 2013;**154**:632–642.
75. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;**12**:CD008242.
76. Nagashima W, Kimura H, Ito M, et al. Effectiveness of duloxetine for the treatment of chronic nonorganic orofacial pain. *Clin Neuropharmacol* 2012;**35**:273–277.
77. Seidel S, Aigner M, Ossege M. Antipsychotics for acute and chronic pain in adults. *J Pain Symptom Manage* 2010;**39**:768–778.
78. Thase ME, Macfadden W, Weisler RH. Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 2006;**26**:600–609.
79. Ondo WG, Tintner R, Voung KD. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 2005;**20**:958–963.
80. Paleacu D, Barak Y, Mirecky I, Mazeh D. Quetiapine treatment for behavioural and psychological symptoms of dementia in Alzheimer's disease patients: A 6-week, double-blind, placebo-controlled study. *Int J Geriatr Psychiatry* 2008;**23**:393–400.
81. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: Efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. U.S. SEROQUEL Study Group. *J Clin Psychopharmacol* 1996;**16**:158–169.
82. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 1997;**42**:233–246.
83. Moteshafi H, Stip E. Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: A meta-analysis. *Expert Opin Drug Saf* 2012;**11**:713–732.
84. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;**353**:1209–1223.
85. Kapur S, VanderSpek SC, Brownlee BA, Nobrega JN. Antipsychotic dosing in preclinical models is often unrepresentative of the clinical condition: A suggested solution based on in vivo occupancy. *J Pharmacol Exp Ther* 2003;**305**:625–631.
86. Zhornitsky S, Potvin S, Stip E, Rompré PP. Acute quetiapine dose-dependently exacerbates anhedonia induced by withdrawal from escalating doses of d-amphetamine. *Eur Neuropsychopharmacol* 2010;**20**:695–703.
87. Fox RJ, Cronin T, Lin J, et al. Measuring myelin repair and axonal loss with diffusion tensor imaging. *AJNR Am J Neuroradiol* 2011;**32**:85–91.
88. Zhang Y, Zhu H, Mitchell JR, Costello F, Metz LM. T2 MRI texture analysis is a sensitive measure of tissue injury and recovery resulting from acute inflammatory lesions in multiple sclerosis. *Neuroimage* 2009;**47**:107–111.

