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# Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation

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ABSTRACT

Blockade of the inflammatory cytokine tumor necrosis factor (TNF) in depressed patients with increased inflammation has been associated with decreased depressive symptoms. Nevertheless, the impact of TNF blockade on sleep in depressed patients has not been examined. Accordingly, sleep parameters were measured using polysomnography in 36 patients with treatment resistant major depression at baseline and 2 weeks after 3 infusions (week 8) of either the TNF antagonist infliximab ($n = 19$) or placebo ($n = 17$). Markers of inflammation including c-reactive protein (CRP) and TNF and its soluble receptors were assessed along with depression measured by the 17-item Hamilton Depression Rating Scale. No differences in sleep parameters were found as a function of infliximab treatment over time. Nevertheless, wake after sleep onset (WASO), the spontaneous arousal index and sleep period time significantly decreased, and sleep efficiency significantly increased, from baseline to week 8 in infliximab-treated patients with high (CRP > 5 mg/L) ($n = 9$) versus low inflammation (CRP $\leqslant$ 5 mg/L) ($n = 10$), controlling for changes in scores of depression. Stage 2 sleep also significantly decreased in infliximab-treated patients with high versus low inflammation. Decreases in soluble TNF receptor 1 significantly correlated with decreases in WASO and increases in sleep efficiency in infliximab-treated subjects with high inflammation. Placebo-treated subjects exhibited no sleep changes as a function of inflammation, and no correlations between inflammatory markers and sleep parameters in placebo-treated patients were found. These data suggest that inhibition of inflammation may be a viable strategy to improve sleep alterations in patients with depression and other disorders associated with increased inflammation.



## 1. Introduction

Alterations in sleep are among the most common symptoms of major depression, with greater than 75 percent of depressed patients reporting significant sleep disruption (Lam, 2006; Nutt et al., 2008; Tsuno et al., 2005). Sleep disturbances in depression are associated with decreased quality of life, increased risk for suicide, and an impaired response to conventional antidepressant therapy, which occurs in up to 30% of depressed patients (Nutt et al., 2008; Rush et al., 2006). Compared to healthy controls, patients with major depression have consistently demonstrated changes in sleep architecture as measured by polysomnography including decreases in sleep efficiency, slow wave sleep, Stage 2 sleep and the latency to rapid eye movement (REM) sleep as well as increases in REM density (Thase, 2006, Benca and Peterson, 2008) (Arfken et al., 2014).

One pathophysiologic mechanism that may be involved in some of the sleep changes found in depression is inflammation (Benedict et al., 2009; Imeri and Opp, 2009; Irwin et al., 2008; Krueger, 2008; Krueger et al., 2001; Motivala et al., 2005; Opp, 2005). Markers of inflammation, including inflammatory cytokines and their receptors, acute phase proteins such as c-reactive protein (CRP), chemokines, and adhesion molecules have been found to be elevated in a significant proportion of depressed patients in multiple studies (Dowlati et al., 2010; Miller et al., 2009). Moreover, a rich literature in laboratory animals and humans has shown that inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1 induce marked alterations in sleep architecture (Imeri and Opp, 2009; Krueger, 2008; Opp, 2005). For example, in humans, administration of cytokine inducers such as endotoxin disrupts non-REM sleep in a dose dependent manner,

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leading to decreased slow wave (Stage 3/4) sleep at high doses (Mullington et al., 2000.) Similarly, administration of the inflammatory cytokine interferon alpha has been shown to increase wake after sleep onset (WASO), increase spontaneous arousals and increase sleep period time, while decreasing sleep efficiency and slow wave sleep (Raison et al., 2010). Poor sleep quality before and during IFN-alpha treatment has been found to predict the development of IFN-alpha-induced depression, which occurs in up to 30–50% of patients depending on the dose (Capuron et al., 2002; Franzen et al., 2010; Musselman et al., 2001; Prather et al., 2009). Interestingly, the pattern of sleep disruption during IFN-alpha treatment including decreased sleep continuity, sleep fragmentation and increased spontaneous arousals has also been observed in disease states associated with high inflammation such as rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus (Abad et al., 2008; Ranjbaran et al., 2007). Of note, although there are similarities between sleep changes in depression and inflammation, in contrast to findings in patients with depression, administration of IFN-alpha was associated with increased Stage 2 sleep and increased REM latency (Raison et al., 2010).

In addition to the capacity of inflammatory cytokines to disrupt sleep architecture, a number of studies have demonstrated that sleep deprivation can increase inflammatory markers both at the protein and molecular level, leading to increases of IL-6 and activation of the inflammatory signaling molecule nuclear factor kappa B (Irwin et al., 2006, 2008). These data raise the question of whether inflammation in depression is the cause or consequence of sleep alterations.

One strategy to address the relationship between sleep and inflammation in patients with depression is to block cytokines and thereby potentially reverse sleep alterations. For example, antagonism of TNF with the fusion protein etanercept reversed alterations in REM sleep in patients with alcohol dependence and insomnia (Irwin et al., 2009). Interestingly, TNF is reliably elevated in depressed patients (Dowlati et al., 2010), and TNF blockade has been shown to have antidepressant activity in inflammatory and autoimmune diseases including psoriasis and Crohn's disease (Persoons et al., 2005; Tyring et al., 2006). In addition, a recent study found that TNF blockade improved depressive symptoms in patients with treatment resistant depression (TRD), but only in patients with high baseline inflammation as reflected by a CRP > 5 mg/L (Raison et al., 2013).

In the current study, we endeavored to determine whether TNF blockade may also improve sleep parameters in TRD patients with high inflammation (CRP > 5 mg/L). Special emphasis was placed on sleep alterations previously associated with cytokine (IFN-alpha) administration including decreased sleep continuity and depth as previously described (Raison et al., 2010). Moreover, we examined whether changes in sleep as a function of infliximab were associated with changes in markers of TNF activity including plasma concentrations of TNF and its soluble receptors, soluble TNF receptor 1 and 2 (sTNFR1 and sTNFR2).

## 2. Methods

### 2.1. Sample

Subjects included in this study were participants in a previously published single-site, parallel-group, randomized, double-blind trial of infliximab versus placebo for antidepressant non-responders with a diagnosis of major depression according to the *DSM-IV* criteria as assessed by the Structured Clinical Interview for *DSM-IV* (SCID) (First MB, 1997; Raison et al., 2013). Subjects were recruited from television, radio, newspaper and internet advertisements and were men and women between the ages of 25 and 60 years. All subjects were on a stable antidepressant regimen or off all antidepressant therapy for at least 4 weeks prior to baseline. No changes in antidepressant treatment were allowed during the study. All participants were required to have experienced moderate treatment resistance in the current depressive episode, as determined by a score of 2 or higher on the Massachusetts General Hospital Staging method for treatment resistance (Petersen et al., 2005), and to exhibit moderate severity of depression as determined by a score of 14 or higher using the Quick Inventory of Depressive Symptomatology, Self-Report (Trivedi et al., 2004) at screening and a score of $\geqslant$20 on the 17-item Hamilton Depression Rating Scale (HAM-D)-17 at randomization (Hamilton, 1960). Exclusion criteria included the presence of any autoimmune disorder (confirmed by laboratory testing); a history of tuberculosis (confirmed by chest X-ray, tuberculin skin testing, and blood testing) or being at high risk for tuberculosis exposure; the presence of hepatitis B or C or human immunodeficiency virus infection (confirmed by laboratory testing); evidence of active fungal infection; a history of recurrent viral or bacterial infections; a history of cancer, excluding basal cell or squamous cell carcinoma of the skin (fully excised with no recurrence); the presence of an unstable cardiovascular, endocrinologic, hematologic, hepatic, renal, or neurologic disease (determined by physical examination and laboratory testing); a history of schizophrenia (determined by SCID); active psychotic symptoms of any type; substance abuse and/or dependence within the past 6 months (determined by SCID); active suicidal ideation determined by a score of 3 or higher on item #3 of the 17-item Hamilton Depression Rating Scale (HAM-D)-17 (Hamilton, 1960); and/or a score of less than 28 on the Mini-Mental State Examination, indicating more than mild cognitive impairment (Folstein et al., 1975).

Subjects were also excluded if they had more than moderate sleep apnea or periodic limb movement disorder (PLMD) at baseline as evidenced by an apnea-hypopnea (AH) index greater than 30 or a PLM index greater than 50. All participants provided written informed consent, and all procedures were approved *a priori* by the Institutional Review Board of Emory University, Atlanta, Georgia. The study was registered at clinicaltrials.gov (NCT00463580) in April 2007, and the CONSORT diagram has been previously published (Raison et al., 2013).

### 2.2. Study procedures

Participants were enrolled between December 2008 and March 2011. To achieve similar representation of baseline inflammatory status in each group, group assignment, determined at screening, was stratified based on a CRP > 2 mg/L or $\leqslant$2 mg/L. A CRP concentration of 2 mg/L was chosen because it is the central value in the "medium" relative risk category of inflammation (1–3 mg/L) recommended by the American Heart Association and the Centers for Disease Control and Prevention (Pearson et al., 2003). Group assignment was also stratified by sex. Following screening for inclusion and exclusion criteria, all participants reported to the infusion center in the Emory Division of Digestive Diseases on 3 separate occasions (baseline, 2 weeks, and 6 weeks) to receive an infusion of either infliximab (5 mg/kg) or placebo over 120 min through an indwelling catheter. The baseline visit was scheduled no later than 1 month after screening. The dosing protocol and scheduling of infliximab infusions were matched to the standard induction regimen for treatment of inflammatory bowel disease (Rutgeerts et al., 2004). Independent pharmacists dispensed infliximab or placebo in a 250-mL saline bag according to a computer-generated randomization list, blocked in units of 4, provided by a study statistician. The placebo was matched to infliximab on the basis of color and consistency when dissolved in saline. Infliximab



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