Letters to the Editor

Post-TBI Central Hypogonadism and PTSD

TO THE EDITOR: Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are frequently comorbid in veterans of the Iraq and Afghanistan wars (1). A possible explanation for the high comorbidity of these conditions is that TBI may induce behavior-affecting CNS neurochemical sequelae. This explanation is supported by data indicating that as many as 32%−42% of blast-exposed veterans display pituitary dysfunction (2, 3). Gonadotropin deficiency in particular has been reported in 5%−12% of veterans with blast-related TBI (2, 3).

Because there is significant overlap between the symptoms of male hypogonadism and PTSD, including anxiety, depression, sexual dysfunction, amotivation, poor stress tolerance, and irritability (4), central hypogonadism may contribute to PTSD symptomology in patients with a history of TBI, as illustrated by the following case:

> A 29-year-old male Marine veteran with PTSD and a history of two blast concussions, with brief loss of consciousness, presented with insomnia, emotional detachment, intolerance of crowds, hypervigilance, self-isolation, traumatic memories, hyperacusis, irritability, and explosiveness. These symptoms had persisted despite years of cognitive therapy and psychopharmacologic trials, including an ongoing sertraline and prazosin combination.
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> We tested thyroid, adrenal, and gonadal hormones; IGF-1; and prolactin and found hypotestosteronemia, with an early-morning total testosterone concentration of 240 ng/dL, followed 1 month later by a level of 210 ng/dL (250–800 ng/dL reference range at the Cincinnati Veterans Affairs Medical Center). The circulating luteinizing hormone measure was 0.8 mIU/mL (reference range 1.3–8.6 mIU/mL), consistent with central hypogonadism. This patient also had erectile dysfunction.
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> The patient, who weighed more than 200 lb, was started on testosterone gel, 1.62%, at a dosage of 60.75 mg/day. Within weeks of treatment initiation, he reported improved sleep, energy levels, sexual function, concentration, strength, and endurance. Importantly, his irritability and explosiveness were ameliorated and replaced with a sense of increased "calm" and tolerance for others. He even began going to the grocery store during peak hours, which he had previously avoided doing until after 1:00 a.m. These improvements have persisted for more than 1 year with continued testosterone supplementation, which maintains his circulating total testosterone concentrations near the middle of the reference range.

This case suggests that optimal treatment of PTSD may require the correction of accompanying hypogonadism. While a placebo effect cannot be ruled out, it is notable that the patient had failed years of other interventions. Correction of testosterone deficiency has been shown to improve response to antidepressant psychopharmacology (5), and it is possible the improvement in our patient's PTSD symptoms was a direct consequence of an improved sensitivity to antidepressant treatment. Regardless, this case demonstrates the importance of screening for endocrine abnormalities, particularly hypotestosteronemia, in individuals with both PTSD and a history of TBI.

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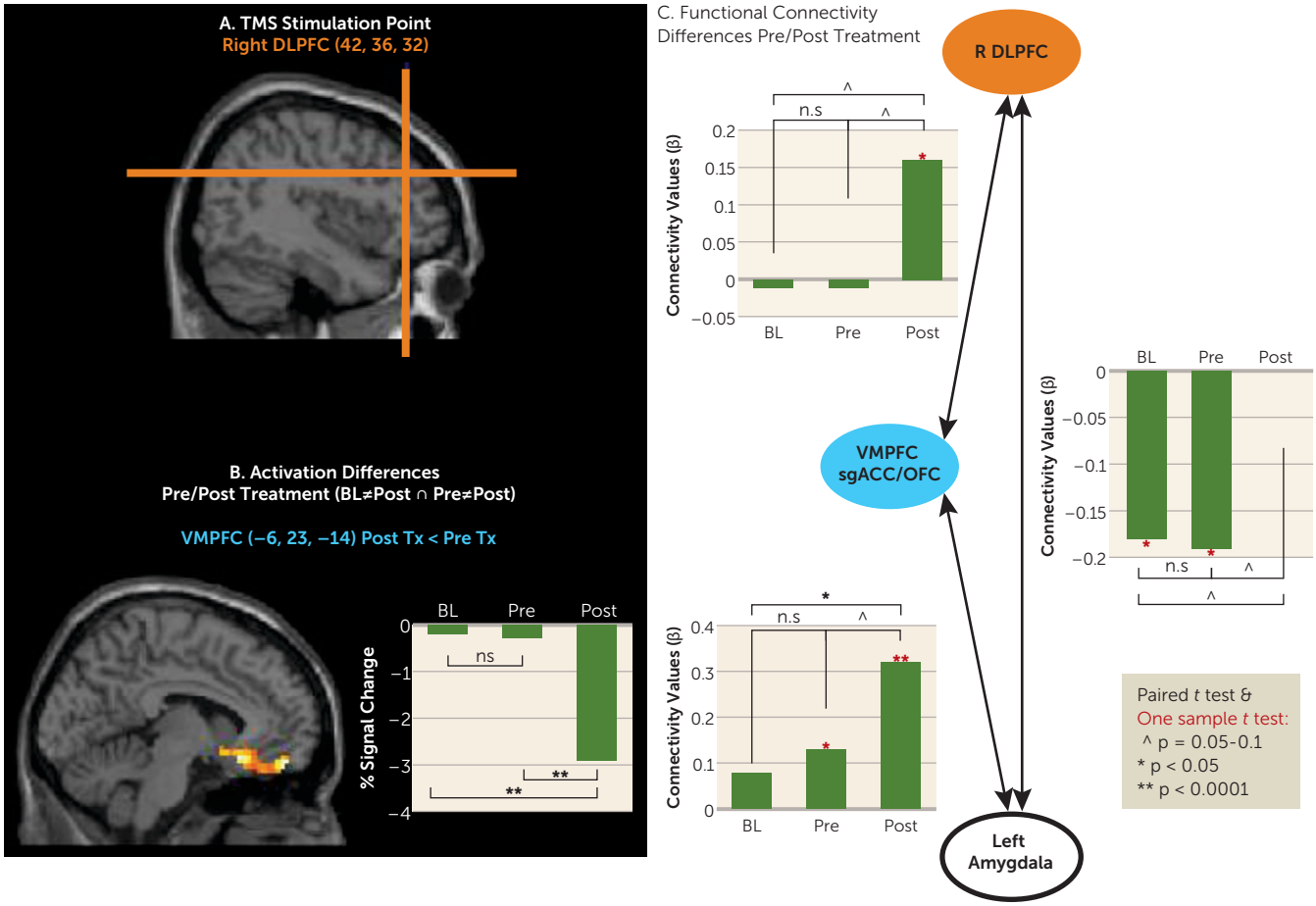
A Case Study of Clinical and Neuroimaging Outcomes Following Repetitive Transcranial Magnetic Stimulation for Hoarding Disorder

TO THE EDITOR: We tested the effect of repetitive transcranial magnetic stimulation (rTMS) on hoarding symptoms and neuroimaging in a 58-year-old woman. The rTMS treatment included 30 sessions (5 days/week, 1 Hz, 90% resting motor threshold, 900 pulses/session) and targeted the right dorsolateral prefrontal cortex (rDLPFC, located with structural neuronavigation). Value-based decision-making deficits may underlie hoarding symptoms. In healthy volunteers, neuromodulation of the rDLPFC lowers item valuation (1) and alters a value-based decision-making network (along with the ventromedial prefrontal cortex [VMPFC] and amygdala) (e.g., 2). Thus, we hypothesized that rDLPFC neuromodulation

FIGURE 1. Neural Correlates of the Discarding Decision-Making Task Before and After rTMS Treatment[a]



[a] Panel A depicts the rTMS stimulation point at the right dorsolateral prefrontal cortex (rDLPFC). Panel B depicts areas showing activation differences during the discarding task between baseline, pretreatment, and posttreatment scans (conjunction analysis; uncorrected $p<0.001$, $k=10$). Panel C shows changes in connectivity following treatment between the rDLPFC and the ventromedial prefrontal cortex (VMPFC), including subgenual anterior cingulate cortex (sgACC) and orbitofrontal cortex (OFC), and left amygdala. Connectivity for the rDLPFC-left amygdala at posttreatment was zero and is therefore not visible in the figure. Paired t tests compare connectivity between each time point (baseline compared with pretreatment, pretreatment compared with posttreatment, and baseline compared with posttreatment). One-sample t tests indicate whether the connectivity at a given time point significantly differs from a null hypothesis of no connectivity.

would improve hoarding symptoms and alter activation and functional connectivity of the DLPFC, VMPFC, and amygdala.

A stable 3-week baseline was established (Saving Inventory Revised [SI-R] score range was 60–66). All rTMS sessions were completed on schedule with only mild and transitory side effects (e.g., headache). Symptoms improved after treatment (SI-R=46), and gains were maintained over 2 months (SI-R=45). On the Clinical Global Impressions Scale, the patient was rated as "minimally improved" at posttreatment. At follow-up (with no additional treatment initiated), she was rated as "much improved" and no longer met diagnostic criteria for hoarding disorder. The patient reported being "very satisfied" overall with the treatment.

The patient completed a computer simulation discarding task during functional magnetic resonance imaging at baseline, postbaseline, and posttreatment. The task entailed viewing pictures of household items presented on a screen. The patient indicated via finger press whether to keep or discard each item (for a detailed task description, see 3). Alternate versions were used to limit practice effects. The patient discarded more items over time (baseline=57%, postbaseline=67%, posttreatment=83%) and made discarding decisions faster (2,686 ms, 2,509 ms, and 1,955 ms, respectively). Compared with baseline, there was a decrease in VMPFC activation ($p<0.001$, $k=10$) but no activation changes in the DLPFC and amygdala. Functional connectivity between the rDLPFC stimulation point (a 5 mm diameter sphere) and the VMPFC (at activation, a 1 cm sphere) tended to increase (with a significant change in functional connectivity at posttreatment only), and the rDLPFC-left amygdala (mask defined by the FSL Harvard-Oxford atlas) functional connectivity tended to decrease. The VMPFC-left amygdala functional connectivity significantly increased at posttreatment (Figure 1).

This case demonstrates the potential for rTMS to treat hoarding disorder and suggests a neural mechanism of

treatment. Results are consistent with research indicating that the VMPFC, and its connectivity with the DLPFC and amygdala, is critical to optimizing goal-directed choices during value-based decision-making and can be modulated using rTMS (e.g., 2). Replication of our results is needed using controlled designs, and generalization of treatment effects to other clinical populations characterized by decision-making deficits (e.g., obesity, addiction) should be explored.

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Sudden-Onset Dystonia in a Patient Taking Asenapine: Interaction Between Ciprofloxacin and Asenapine Metabolism

TO THE EDITOR: Asenapine is a newer second-generation antipsychotic that is primarily metabolized by uridine 5′-diphospho-glucuronosyltransferase 1A4 (UGT1A4) and cytochrome P450 (CYP)1A2 (1). When asenapine is coadministered with inducers or inhibitors of CYP enzymes, antipsychotic plasma levels may be reduced or increased, respectively, resulting in a reduced effectiveness of the antipsychotic or an increased risk of adverse events (2). Here, we report a potential drug-drug interaction leading to an adverse effect during a psychiatric inpatient hospitalization.

A 44-year-old nonsmoking single white woman with a history of bipolar I disorder was admitted for worsening depressed mood. She had been treated with 5 mg h.s. of asenapine for 1.5 months prior to admission. Her history included a severe dystonic reaction to haloperidol. Home medications were continued and included 20 mg/day of baclofen, 60 mg/day of dexlansoprazole, 20 mg/day of fluoxetine, 1 mg/day of lorazepam, and 2,250 mg/day of divalproex. For treatment of a urinary tract infection, 500 mg b.i.d. of ciprofloxacin was initiated at admission. Thirty-three hours after starting ciprofloxacin, the patient was noted to be unable to close her jaw, consistent with an acute dystonic reaction. She was given 50 mg of diphenhydramine intramuscularly, and the dystonia resolved. Ciprofloxacin was discontinued and switched to 100 mg b.i.d. of nitrofurantoin, and asenapine was continued with no further complications at the time of discharge.

DISCUSSION

This report highlights a potential drug-drug interaction between asenapine and ciprofloxacin that has not been previously reported. Ciprofloxacin is a potent inhibitor of CYP1A2 but not of UGT1A4 (1); interactions between it and second-generation antipsychotics that are metabolized through the CYP1A2 pathway have been reported. According to a published case report, coadministration of ciprofloxacin and olanzapine increases olanzapine serum levels (3). Ciprofloxacin pharmacokinetics (a half-life of 4 hours and steady state after 3 days [1]) demonstrate that it was the identifiable precipitant of this patient's dystonia. Other possible contributing factors include the effect of inflammation and infection, including urinary tract infections, on down-regulation of CYP1A2 (4) as well as potential inhibition of asenapine glucuronidation by valproate (5). These factors may have exacerbated the patient's symptoms, although the dystonia was not noted until after initiation of ciprofloxacin. Utilization of a rating scale to assess the likelihood of drug-drug interaction indicated that this inference is "probable" (6).

This case may serve as a reminder that we must be mindful of drug-drug interactions when prescribing second-generation antipsychotics.

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