Minocycline Augmentation of Pharmacotherapy in Obsessive-Compulsive Disorder: An Open-Label Trial

To the Editor: Most obsessive-compulsive disorder (OCD) patients treated with serotonin reuptake inhibitors (SRIs) show only partial reduction of symptoms.[1] Data suggest that OCD may be caused in part by glutamatergic dysfunction in orbitofrontal/basal ganglia brain circuits,[2,3] and prior trials of glutamate modulators (eg, riluzole, memantine) given as augmentation to SRIs suggest that from 30% to 54% of OCD patients respond.[4–8]

We conducted a 12-week, prospective, open-label study to assess whether SRI augmentation with minocycline, a tetracycline derivative with putative glutamate-modulating activity (ie, enhancing glial glutamate transport)[9] in addition to its antibiotic properties, would improve OCD symptoms.

Advantages of minocycline include low cost (riluzole is expensive) and US Food and Drug Administration (FDA) approval in adults and children > 12 years (memantine is FDA approved only in adults). Minocycline is the most widely prescribed antibiotic for chronic acne because its antibiotic resistance is lower than those of other tetracyclines and antimicrobials.[10] It has an excellent side

effect profile, even chronically: one study[11] showed that minocycline taken for 2 years was well tolerated, with no serious adverse effects.

Method. Adult outpatients (N = 9) aged 18 to 65 years who met *DSM-IV* criteria for OCD and had a Yale-Brown Obsessive Compulsive Scale (YBOCS)[12] score of ≥ 16 despite a therapeutic SRI dose were recruited from the community between July 2008 and July 2009 and gave informed consent after the study procedures were fully explained. Institutional review board approval was obtained for the study. Subjects' SRI dose was stable for at least 12 weeks (and concomitant psychotropic medications, for at least 4 weeks) prior to study entry. Subjects were excluded for current cognitive-behavioral therapy, comorbid psychiatric or medical conditions that made participation unsafe, or use of medications that reduced the bioavailability of minocycline. Patients were assessed by an independent rater who administered the YBOCS (primary outcome measure), Hamilton Depression Rating Scale (HDRS, 17-item),[13] and Hamilton Anxiety Rating Scale (HARS)[14] every 2 weeks. Response was defined as at least a 30% reduction on the YBOCS.[15]

Subjects received minocycline at 50 mg bid for 3 days to ensure no allergic reaction, then at the FDA-approved adult dosing of 100 mg bid for 12 weeks in addition to their SRI. This dosing is expected to produce brain minocycline concentrations in the range that antagonize glutamate effects on neurons.[16,17] All subjects completed the study, supporting the fact that minocycline was well tolerated. Outcome was analyzed using mixed-effects regression to model symptoms as a function of time.[18]

Results. Patient clinical characteristics are shown in Table 1. OCD severity was moderate: mean (SD) YBOCS score at baseline was 28.2 (3.9), and illness duration was 18.2 (10.4) years. Subjects were treatment-resistant: the mean number of prior SRI trials was 2.8 (1.6), 56% (5/9) had failed at least 1 adequate trial of antipsychotic augmentation, and 56% had failed an adequate trial of cognitive-behavioral therapy. They had a range of OCD symptoms; 1 subject had hoarding as the primary symptom domain.

As a group, patients showed no significant differences in YBOCS, HDRS, or HARS rate of improvement over time (mixed-effects regression: YBOCS, $z = -1.14$, $P = .25$; HDRS, $z = 0.60$, $P = .55$; HARS, $z = 0.12$, $P = .90$). However, 2 of 9 patients (22%) met and exceeded treatment response criteria (40% and 46% YBOCS reductions). Both of these patients reported early onset of their OCD symptoms. One had primary hoarding, and 1 no longer met criteria for OCD at study end. Both chose to continue minocycline treatment after study end.

These data suggest that minocycline augmentation of SRI pharmacotherapy may not improve OCD symptoms in all adult OCD patients, but may improve symptoms in those with early-onset OCD and those with primary hoarding. The robust response of 2 of 9 patients in this study coupled with the response of 2 other subjects (aged 16 and 17 years) with early-onset OCD in an identical parallel study of minocycline in adolescents (M.R., unpublished data, 2008) suggests that minocycline warrants further study. Early-onset OCD differs from later-onset OCD in phenomenology,

Table 1. Clinical Characteristics and Treatment History of 9 OCD Patients Treated With Minocycline in Addition to an SRI/SNRI

Patient No./ Age (y)/Sex/ Ethnicity	Age at OCD Onset (y)	OCD Symptom Domain[a]	Comorbid Diagnoses	Psychiatric Family History	No. of Prior SRI Trials	Previous Antipsychotic Augmentation?/ Previous CBT?	Current SRI/SNRI Daily Dose	Concomitant Psychiatric Medications	YBOCS Score Pretreatment/ Posttreatment	HDRS Score Pretreatment/ Posttreatment	HARS Score Pretreatment/ Posttreatment
#1/40/M/AA	30	Contamination, symmetry	MDD	None	4	No/yes	Fluoxetine 80 mg	None	24/30	7/0	8/0
#2/50/F/W	30	Contamination, hoarding, symmetry	None	GAD (mother)	6	Yes/yes	Duloxetine 60 mg	None	29/28	0/3	0/3
#3/24/M/W	22	Contamination, symmetry, forbidden thoughts	MDD, social phobia	OCD (father, paternal uncle and grandfather); substance abuse (sister)	2	No/no	Escitalopram 40 mg	Zolpidem, clonazepam	29/26	12/10	9/7
#4/42/F/W	17	Symmetry, forbidden thoughts	MDD	None	4	Yes/no	Fluvoxamine 150 mg	None	34/35	27/28	33/42
#5/54/M/W	20	Symmetry, forbidden thoughts	MDD	OCD (daughter)	2	Yes/no	Fluoxetine 80 mg	Lisdexamfetamine dimesylate	29/25	8/14	12/18
#6/53/M/W	23	Contamination, symmetry, forbidden thoughts, hoarding	MDD	OCD (father)	2	Yes/yes	Fluvoxamine 300 mg	None	29/29	0/3	0/2
#7/51/M/W	40	Hoarding, symmetry, forbidden thoughts	Social phobia, GAD	Substance abuse (maternal cousin)	1	No/yes	Sertraline 100 mg	None	23/22	8/10	7/7
#8/38/F/AA	11	Hoarding	MDD, dysthymia, specific phobia	Bipolar (mother, brother)	2	Yes/no	Fluoxetine 80 mg	Bupropion, desvenlafaxine	33/20[b]	16/5	14/5
#9/19/M/W	4	Symmetry, forbidden thoughts, hoarding	None	Bipolar (father, maternal uncle, paternal aunt and grandfather)	2	No/yes	Fluoxetine 80 mg	Clonazepam, lisdexamfetamine dimesylate	24/13[b]	3/1	1/2

[a]Symptom dimensions were based on a 4-factor model[19] and are listed in order of clinical severity for each subject. Contamination = contamination obsessions and cleaning compulsions; forbidden thoughts = forbidden thoughts including aggression, sexual, religious, and somatic obsessions and checking compulsions; hoarding = hoarding and saving obsessions and compulsions; symmetry = symmetry obsessions and repeating, ordering, and counting compulsions. [b]> 30% reduction in YBOCS score.

Abbreviations: AA = African American, F = female, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, M = male, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, SNRI = serotonin and norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor, W = white, YBOCS = Yale-Brown Obsessive Compulsive Scale.

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genetic risk, and SRI response.[20] Future studies should target early-onset OCD and focus on minocycline's mechanism of action.[21]

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