Antidepressant Effect of 58 Sessions of rTMS in a Pregnant Woman With Recurrent Major Depressive Disorder: A Case Report

Sir: Repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective in depression in many studies. We report the case of a pregnant woman with recurrent major depressive disorder and panic disorder during her second pregnancy who received substantial benefit from 58 sessions of rTMS during pregnancy before giving birth to a healthy baby. Nineteen more sessions of rTMS were given during lactation.

Case report. Ms. A, a 30-year old in 2007, presented with recurrent major depressive disorder and panic disorder according to DSM-IV criteria. She had no other medical problem, no personality disorder, and no psychosocial stressor and had never used substances or alcohol. There was no significant feature in her family medical history.

She had had 5 episodes of major depression (in 1995, 1997, 1999, 2002, 2004). The first one in 1995 was the only episode with psychotic features, treated with antidepressant and antipsychotic drugs. Between the first and second episode, remission had not been attained; therefore, she had had to leave the university because of loss of functioning. In 1997, she had her second severe depressive episode despite the fact that she had been receiving maintenance pharmacologic treatment. By aggressive outpatient pharmacotherapy, she attained remission that lasted until 1999, by which time she had married, discontinued her antidepressant medications under the control of a psychiatrist before a planned pregnancy, became pregnant, gave birth to her first baby, and lactated. Four months after the delivery, when she had been lactating, the third episode occurred in 1999. Having discontinued the lactation, she received pharmacotherapy and psychotherapy for 4 years, during which time she was maintained in a state of partial recovery until the fourth depressive episode, in 2002. She received her first inpatient treatment and underwent 8 sessions of electroconvulsive therapy (ECT), which alleviated symptoms but did not, however, provide remission.

From the age of 18 to 27 years, she received pharmacotherapy continually except for 1.5 years (during the first pregnancy and lactation, 1998–1999), the only period in which remission had been attained. During that 9 years' course of illness, she had received monotherapy with amitriptyline 300 mg daily, sertraline 200 mg daily, and venlafaxine 600 mg daily; in addition to antidepressant medications, she had also been treated with zuclopenthixol, risperidone, olanzapine, lithium, thyroid hormone, carbamazepine, and valproic acid because of psychotic features at the first episode and the refractory nature of depression at later times.

In May 2004, the fifth episode was accompanied by panic attacks. Although she received psychotherapy and pharmacotherapy (fluoxetine 80 mg daily, clomipramine 150 mg daily, carbamazepine 400 mg daily, quetiapine 25 mg daily, and clonazepam 1.5 mg daily), she did not respond to 6 weeks' treatment and the clinical table continued to follow a very severe course.

Since no classical treatment, including ECT, had been able to provide remission, in June 2004, without cessation of drugs, we began rTMS (Magstim Super Rapid magnetic stimulator; The Magstim Company Ltd., Spring Gardens, Whitland/Carmarthenshire, Wales, U.K.) over the left dorsolateral prefrontal cortex. The intensity was 110% of the motor threshold, the frequency 25 Hz, 20 trains per session, 50 pulses per each train the duration of each train was 2 seconds followed by an interval of 28 seconds. Safety criteria reported by Wasserman[1] were exceeded because another study by our group[2] and our unpublished data on 178 patients (O.T., A.C., N.T., et al., 2004–2006) exceeding these criteria have produced satisfactory and safe results.

Scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) by rTMS sessions are shown in Table 1 and Figure 1. After the 15th session, the diagnosis of pregnancy was made. Forty-seven days had passed after the menstruation. She had been strictly prohibited from getting pregnant for many years because of aggressive and continuous pharmacotherapy, and she had reported that she had been using an effective form of birth control. Before rTMS, a pregnancy test had not been administered, because only 2 weeks had passed after the last menstruation. The patient did not report the delay of the expected menstruation because she ignored it since she sometimes experienced menstruation delay. She preferred to continue pregnancy, stop medications, and receive rTMS following informed consent. She was also under close obstetric follow-up. Neither maternal nor fetal complication occurred during pregnancy.

Four days after the 58th session, she gave birth to a healthy girl, at the term, in early 2005. The baby weighed 3200 g and was 49 cm tall. Complete physical and neurologic examination, screening tests for phenylketonuria and hypothyroidism, and hearing assessment of the newborn revealed no abnormalities. The newborn did not have congenital hip dysplasia, congenital cardiac disease, cleft lip, or cleft palate. There were no gastrointestinal, pulmonary, or muscular abnormalities. Twenty days later, we restarted rTMS to prevent depression relapse. She continued lactation.

Ms. A responded (response defined as a 50% decrease in HAM-D-17 score) to rTMS at the end of the 50th session (6 months after beginning rTMS, with rTMS given in varying intervals). She attained remission (remission defined as a HAM-D-17 score below 8) at the end of the 68th session, approximately 1 year after beginning rTMS. No seizure or other significant side effect occurred.

Although depression remitted with rTMS, since panic disorder was aggravated, the patient began treatment with fluoxetine (which was increased to 80 mg daily) once she stopped lactating 8 months after the delivery.

The patient received 35 sessions of rTMS in the first trimester, 15 sessions in the second trimester, 8 sessions in the third trimester (for a total of 58 sessions during the pregnancy), and 19 sessions during 7.5 months after the delivery. Depression was still in remission 22 months after the delivery. Panic disorder, followed up with no clinical scale, decreased during pregnancy and postpartum 6 months, but then recurred.

The child's physical development and neurologic development were normal through 22 months; there was no diagnosis of disease, except a viral upper respiratory infection lasting a few days.

rTMS has been shown to be useful in the treatment of depression.[4–10] A pregnant woman receiving rTMS in the second trimester has been reported in another study.[11] Our patient received rTMS in all trimesters.

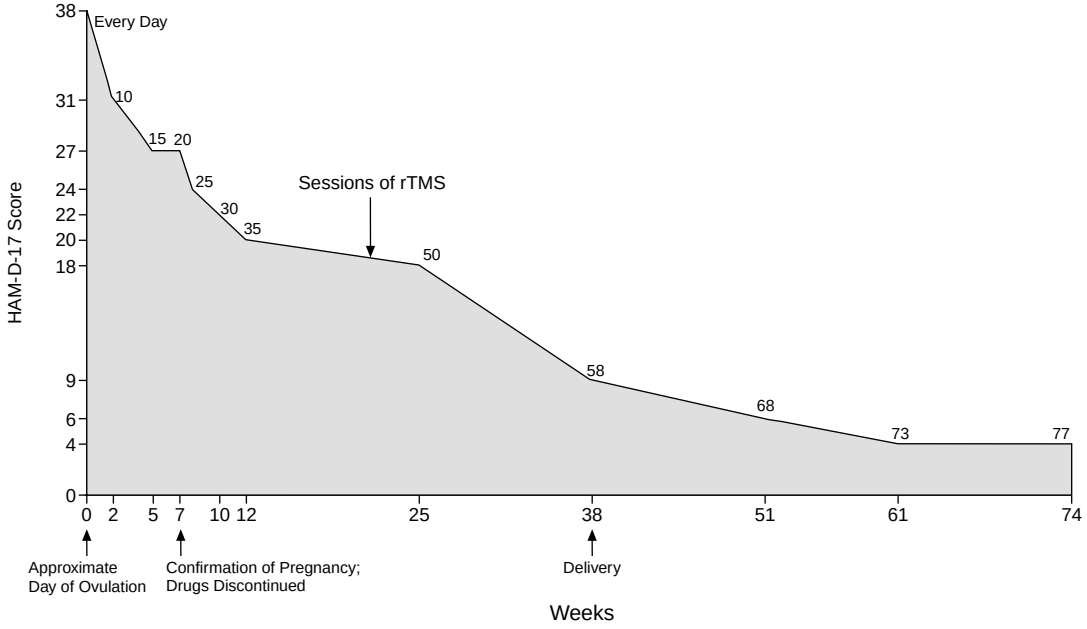
Varying of intervals between rTMS sessions was due to the patient's request and also regarding the literature

Table 1. HAM-D-17 Scores by rTMS Sessions[a]

	rTMS Sessions										
Variable	1–10	11–15	16–20	21–25	26–30	31–35	36–50	51–58	59–68	69–73	74–77
Interval between sessions	Every week day	Every third day	Alternate days	Every week day	Alternate days	Every third day	Weekly	Every third day	Weekly	Every 2 weeks	Every third week
HAM-D-17 score	31	27	27	24	22	20	18	9	6	4	4

[a]The patient's HAM-D-17 score was 38 before the start of treatment. On the day following the 15th session, the patient was confirmed to be pregnant. Four days after the 58th session, the patient gave birth to a completely healthy female baby. When the baby was 20 days old, rTMS was restarted. The patient responded (50% decrease in HAM-D-17 score) to rTMS at the end of the 50th session (6 months after beginning rTMS; rTMS was administered in varying intervals). She attained remission (HAM-D-17 score below 8) at the end of the 68th session, approximately 1 year after beginning treatment.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Figure 1. Decrease in HAM-D-17 Scores During rTMS Therapy



Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

reporting that daily stimulation is not essential.[12–14] It seems that although rTMS is effective, a greater number of sessions or sessions of longer durations than those reported in previous studies are needed to produce significant results. On the other hand, rTMS given at intervals may be useful to improve and maintain the mood.[11,12] Furthermore, even if rTMS is not useful in the acute treatment, improvement in mood may be observed a few months later.[12]

Although the fact that response and remission took nearly a year is more consistent with the natural history of depression than with a therapeutic response to rTMS, our patient's history of depression had tended to follow a chronic and recurrent course in that she had received pharmacotherapy and psychotherapy for a long time and underwent ECT without any significant recovery except during her first planned pregnancy and lactation. It may be suspected that pregnancy itself might have resulted in remission of depressive symptoms. However, contrary to clinical lore, pregnancy is not always a time of emotional well-being; pregnant and nonpregnant women have similar rates of depression.[15] Furthermore, our patient's first pregnancy had not resulted in remission; on the contrary, her first pregnancy was a planned pregnancy that occurred after remission, and depression subsequently recurred during lactation.

Finally, a few studies have employed rTMS in a small number of patients with panic disorder.[16,17] It seems that rTMS parameters given in depression may not prevent relapses in panic disorder.

The authors report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Wasserman, EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic

Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16
2. Tarhan N, Tan O, Baripoglu SK, et al. Transcranial magnetic stimulation in refractory depression. Presented in the 6th annual conference of the EEG and Clinical Neuroscience Society (ECNS) and Joint Meeting with the International Society for Neuroimaging in Psychiatry (ISNIP); Sept 29–Oct 2, 2004; Calif. Abstract published in the EEG and Clinical Neuroscience Society (ECNS) Journal 2004;35:4
3. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
4. Avery DH, Holtzheimer PE 3rd, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59:187–194
5. Rossini D, Lucca A, Zanardi R, et al. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. Psychiatry Res 2005;137:1–10
6. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003;60: 1002–1008
7. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry 2000;48:962–970
8. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233–237
9. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752–1756
10. Avery DH, Claypoole K, Robinson L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. J Nerv Ment Dis 1999;187:114–117
11. Nahas Z, Bohning DE, Molloy MA, et al. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. J Clin Psychiatry 1999;60:50–52
12. Koerselman F, Laman DM, van Duijn H, et al. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. J Clin Psychiatry 2004;65: 1323–1328
13. Lİ X, Nahas Z, Anderson B, et al. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? Depress Anxiety 2004;20:98–100
14. O'Reardon JP, Blumner KH, Peshek AD, et al. Long-term maintenance therapy for major depressive disorder with rTMS. J Clin Psychiatry 2005;66:1524–1528
15. Gotlib IH, Whiffen WE, Mount JH, et al. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol 1989;57: 269–274
16. Garcia-Toro M, Salva Coll J, Crespi Font M, et al. Panic disorder and transcranial magnetic stimulation. Actas Esp Psiquiatr 2002;30:221–224
17. Sakkas P, Psarros C, Papadimitrou GN, et al. Repetitive transcranial magnetic stimulation (rTMS) in a patient suffering from comorbid depression and panic disorder following a myocardial infarction. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:960–962

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Tardive Dystonia and Ziprasidone: A Case Report

Sir: Ziprasidone is an atypical antipsychotic with higher affinity for human serotonin-2A ($5\text{-}HT_{2A}$) receptors than dopamine-2 (D_2) receptors. It is reported to have minimal extrapyramidal side effects similar to that of placebo.[1] However, there are reports of acute dystonia with ziprasidone.[2,3] A MEDLINE/PubMed search using keywords *dystonia* and *ziprasidone* revealed no published reports of tardive dystonia with ziprasidone.

Case report. Mr. A, a 25-year-old unmarried man who had graduated from university and hailed from an urban middle class socioeconomic background, reported to our institute in 2005. On evaluation, he had family history of obsessive-compulsive disorder in his mother and dysthymia in his father. There was no significant past psychiatric/medical history or personal history. His premorbid personality had been well adjusted. Mr. A presented with an insidious-onset continuous illness of 2.5 years' duration that was characterized by delusions of persecution, delusions of reference, third-person auditory hallucinations, and second-person command hallucinations. He was diagnosed with schizophrenia, paranoid subtype (per DSM-IV). Treatment with ziprasidone, 40 mg initially and slowly increased to 120 mg/day, led to reduction of positive symptoms. However, he reported sedation and mild tremors of the hand (there was no bradykinesia or rigidity) without impairment in his daily routine activities during follow-up.

Three months later, he presented with 4 to 6 weeks' history of inability to stand upright, being bent to the left, and a mild-to-moderate degree of pain in the thoracic area, which was continuous in nature and caused significant emotional distress. Examination showed dystonic scoliosis of the thoracic spine with convexity to the right. No other muscle group was involved. The above clinical presentation satisfies the diagnostic criteria for tardive dystonia set forth by Burke et al. in 1982.[4] This truncal dystonia was impairing his daily activities as well as his social and occupational functioning. No concomitant medication was given during this period. There was no family history of similar abnormal movement disorder, nor was there a history of any substance use or trauma.

The ziprasidone dose was initially reduced to 80 mg/day. The dystonia did not improve, hence ziprasidone was further reduced to 40 mg/day and diazepam 10 to 20 mg/day was added during his sixth month of follow-up. During his seventh month of follow-up, the patient reported obsessive ruminations, obsessive doubts, compulsive checking, fleeting delusions, and elementary auditory hallucinations. Since there was worsening of schizophrenia symptoms, emergence of obsessive-compulsive symptoms, and no improvement in dystonia, he was admitted for evaluation and treatment. On examination, he had truncal dystonia, mild perioral-buccal-lingual dyskinesia, and postural tremors of hand (left > right). Neurologic opinion was taken. Liver and kidney function tests, including workup for Wilson's disease, were performed along with a magnetic resonance imaging scan of the brain. However, findings of all of the above investigations were within normal limits. Thus, the treating team decided to taper and stop ziprasidone 40 mg/day over a period of 6 days, and at the same time, clozapine was initiated, which was slowly increased to 300 mg/day for psychotic symptoms, along with escitalopram 20 mg/day for his obsessive-compulsive symptoms. During 2 months of treatment with these medications, tardive dystonia was reduced substantially, along with reduction of obsessive-compulsive symptoms.

Although ziprasidone is a new atypical antipsychotic with reported low potential for extrapyramidal side effects,[1] it may cause tardive dystonia. The patient in our case was young and male, both of which carry some risk factors. However, it is difficult to speculate about the contribution of family history of obsessive-compulsive disorder and dysthymia and the presentation of the schizo-obsessive-compulsive type in the etiopathogenesis of tardive dystonia. A remote possibility is that obsessive-compulsive disorder occurs because of basal ganglia dysfunction, and prescribing high doses of antipsychotics in schizophrenia with obsessive-compulsive symptoms may cause tardive dystonia. We recommend that clinicians be cautious in prescribing ziprasidone, especially in young male patients presenting with schizophrenia with obsessive-compulsive symptoms.

The authors report no financial affiliation or other relationship relevant to the subject of this letter.

REFERENCES

1. Weiden PJ, Igbal N, Mendelowitz AJ, et al. Best clinical practice with ziprasidone: update after one year of experience. J Psychiatr Pract 2002;8:81–97
2. Mason MN, Johnson CE, Piasecki M. Ziprasidone-induced acute dystonia. Am J Psychiatry 2005;162:625–626
3. Yumru M, Savas HA, Selek S, et al. Acute dystonia after initial doses of ziprasidone: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:745–747
4. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology 1982; 32:1335–1346

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Separation Anxiety Disorder and School Refusal in Childhood: Potential Risk Factors for Developing Distinct Psychiatric Disorders?

Sir: Separation anxiety disorder refers typically to younger children who are extremely unwilling to separate from major attachment figures (e.g., parents, grandparents, older siblings) or from home.[1] Separation anxiety disorder can dramatically affect a child's life and his parent's life by limiting the ability to engage in ordinary activities, for example, regular school attendance due to excessive worry about potential harm toward oneself or one's primary caregivers. School refusal is reported in about 75% of children with separation anxiety disorder, and vice versa, separation anxiety disorder is reported in about 80% of children with school refusal.[2] Furthermore, studies show that school refusal is significantly associated with anxiety and affective disorders.[3] However, only few data suggest that separation anxiety disorder is a risk factor for developing psychiatric disorders when children grow up.[4] To evaluate this hypothesis, we reexamined 10 school refusers who had been treated for separation anxiety disorder for ongoing school refusal, separation anxiety disorder, and further psychiatric disorders.

Method. Five male and 5 female former school refusers with separation anxiety disorder, who had been treated for 12 weeks with cognitive-behavioral therapy at the Department of Child and Adolescent Psychiatry of Innsbruck Medical University, Austria, were followed up until summer 2006. Follow-up assessment was conducted between 2 to 8 years (mean = 4.4 years) after their discharge. At follow-up, children were aged 9 to 14 years (mean age = 12.7 years) and lived in a community setting. History of separation anxiety disorder and school attendance were assessed in an interview with the patient and a parent. Separation anxiety disorder and other psychiatric disorders were evaluated with the children's version of the Diagnostic Interview for Mental Disorders in Children and Adolescents,[5] a standardized lifetime diagnostic interview of psychiatric syndromes for children and adolescents according to DSM-IV diagnostic criteria, which is an expanded German version of the Anxiety Disorders Interview Schedule.[6]

Results. Persisting symptoms of school refusal were only seen in 1 boy. However, all children presented at least 2 psychiatric disorders, 1 of them presented 3, 2 of them presented 4, and 2 of them presented 5, with some psychiatric disorders in partial remission, including separation anxiety disorder. Psychiatric disorders that were found are attention-deficit/hyperactivity disorder (N = 6), oppositional defiant disorder (N = 4), conduct disorder (N = 1), major depressive disorder (N = 1), social phobia (N = 1), specific phobia (N = 3), panic disorder with agoraphobia (N = 3), obsessive-compulsive disorder (N = 3), and specific developmental disorders of scholastic skills (N = 2). Two children were rated with functional enuresis in complete remission.

At follow-up examination, all 10 subjects met DSM-IV criteria for at least 2 psychiatric disorders. Only 1 of 10 patients had persistent separation anxiety disorder. Three patients were fully remitted, whereas 6 patients were in partial remission of separation anxiety disorder. These results support the hypothesis that school refusers with separation anxiety disorder are at high risk for developing subsequent mental disorders. Further research should also clarify whether separation anxiety disorder is a specific risk factor for other anxiety disorders, or whether separation anxiety disorder in children is a general factor of vulnerability for a broad range of psychiatric disorders.[2,7] In conclusion, clinicians have to be aware that school refusers with separation anxiety disorder are predisposed for developing distinct psychiatric disorders and probably require further treatment even after remission of separation anxiety disorder.

The authors report no financial affiliation or other relationships relevant to the subject of this letter.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Masi G, Mucci M, Millepiedi S. Separation anxiety disorder in children and adolescents: epidemiology, diagnosis, and management. CNS Drugs 2001;15:93–104
3. Egger HL, Costello EJ, Angold A. School refusal and psychiatric disorders: a community study. J Am Acad Child Adolesc Psychiatry 2003;42:797–807
4. Aschenbrand SG, Kendall PC, Webb A, et al. Is childhood separation anxiety disorder a predictor of adult panic disorder and agoraphobia? a seven-year longitudinal study. J Am Acad Child Adolesc Psychiatry 2003;42:1478–1485

5. Schneider S, Unnewehr S, Margraf J. Kinder–DIPS. Diagnostisches Interview bei Psychischen Störungen im Kindes und Jugendalter. Berlin, Germany: Springer Verlag; 1998
6. Di Nardo PA, O'Brien GT, Barlow DH, et al. Reliability of DSM-III anxiety disorder categories using a new structured interview. Arch Gen Psychiatry 1983;40:1070–1074
7. Foley DL, Pickles A, Maes HM, et al. Course and short-term outcomes of separation anxiety disorder in a community sample of twins. J Am Acad Child Adolesc Psychiatry 2004;43:1107–1114

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Using Functional Behavioral Assessment to Study the Effects of Citalopram on the Obsessive-Compulsive Verbalizations of a Woman With Obsessive-Compulsive Disorder and Mental Retardation

Sir: Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by repetitive thoughts and/or ritualistic behaviors.[1] Approximately 2% to 3% of the general population is diagnosed with OCD, with children more likely to be diagnosed than adults.[2] People with OCD often experience diminished functioning in school, work, or community contexts, particularly in relation to social relationships.

One common observation made by investigators studying OCD is that behaviors associated with this disorder are often exacerbated by stressful social situations.[3] This observation suggests that OCD-related behaviors can be sensitive to social reinforcers. However, such social situations often confound a variety of socially mediated reinforcers and contingencies, and no assessment methodology has been successful in identifying operant functions associated with OCD-related behaviors.

Given the usefulness of functional behavioral assessment in treating the behavioral problems of other populations,[4] there may be some utility to incorporating such an approach into the assessment of OCD-related behaviors.[5] The focus of such assessments is to identify the types of operant functions associated with the problem behavior. A first step in conducting a functional behavioral assessment of OCD-related behaviors is the development of a protocol for distinguishing between different types of operant functions (e.g., positive vs. negative reinforcement).[6,7]

In the current investigation, we used an analogue functional analysis procedure to assess the obsessive-compulsive verbalizations of a woman with OCD and mental retardation. Our goal was to use 2 common forms of social reinforcement[8,9] that might maintain the obsessive-compulsive verbalizations and then study the effects of a selective serotonin reuptake inhibitor, citalopram, on the obsessive-compulsive verbalizations.

Case report. Ms. A, a 49-year-old woman, was dually diagnosed in 2006 with OCD and mild mental retardation. The OCD diagnosis was made on the basis of DSM-IV criteria. Her specific behaviors relating to her OCD diagnosis were derived from clinical interviews. Ms. A struggled with a great deal of anxiety that appeared to have increased since the death of her husband. She reported fears consistent with OCD obsessions (e.g., "I don't go to the second floor because I'm afraid I might jump out," "I don't go to funerals because I'm afraid I might jump in the hole," and "I don't like to drive by water because my staff might drown me"). She voiced contamination fears, reporting she felt the need to wash her hands after shaking hands with others and that she preferred to avoid this contact altogether. She had other generalized anxieties, such as becoming quite anxious if watching scary movies.

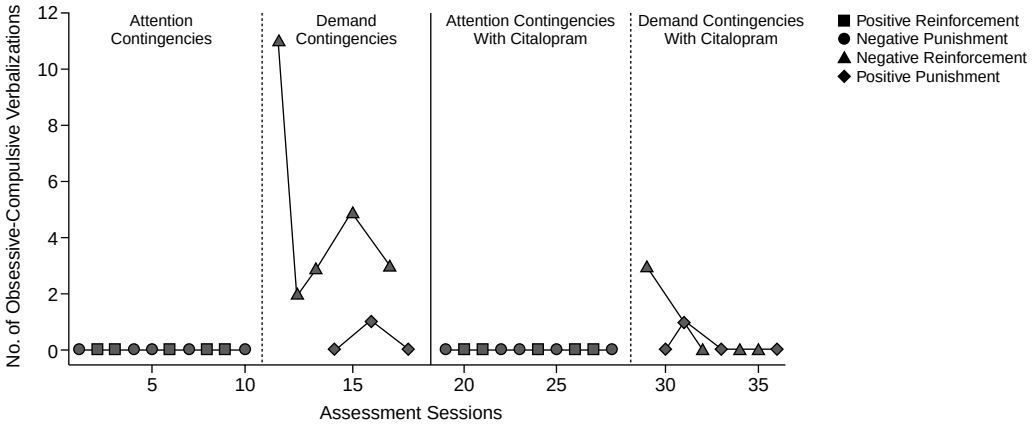
Her psychiatrist referred her to the Vanderbilt University Behavior Analysis Clinic to determine if obsessive-compulsive verbalizations had an environmental (social) component. All sessions were conducted in the living room of her home. Prior to baseline, her daily medication regimen was stabilized at clonazepam (1 mg), haloperidol (150 mg q. month), quetiapine fumarate (50 mg), and valproic acid (500 mg). No changes were made in these medications for the duration of the study.

Obsessive-compulsive verbalizations were scored as frequency counts using a paper-and-pencil system. Two independent observers scored 100% of sessions. Interobserver agreement was estimated by dividing the smaller value by the larger and multiplying by 100%. Interobserver agreement was 100%. A combined A-B multielement design was used to study obsessive-compulsive verbalizations during an analogue functional analysis.[10] Four experimental conditions were analyzed within the multielement design. The first 2 conditions tested the positive reinforcer functions associated with attention. The positive reinforcement condition provided brief social interactions from a therapist when obsessive-compulsive verbalizations occurred. A second condition, negative punishment, reversed this reinforcement contingency by removing attention when obsessive-compulsive verbalizations occurred.[11] The second pair of conditions tested the negative reinforcer functions associated with demands. The negative reinforcement condition terminated requests by a therapist when obsessive-compulsive verbalizations occurred. The next condition, positive punishment, initiated requests by a therapist each time an obsessive-compulsive verbalization occurred.

Once a baseline pattern was established, we assessed the effects of citalopram on the obsessive-compulsive verbalizations under the same set of conditions. During the drug assessment, citalopram was titrated to 20 mg q.d. She received citalopram for 8 weeks before the functional behavioral assessment with citalopram was conducted.

From 2 to 5 sessions were completed per day, 2 to 4 times per week. Each session was 5 minutes in length with a 5-minute interval between sessions. During all sessions, 2 therapists were present. The first set of contingencies assessed the effects of social attention as positive reinforcement for the obsessive-compulsive verbalizations.[11] During positive reinforcement sessions, therapists were seated near the patient. No social interaction occurred. If the patient made an obsessive-compulsive verbalization, a therapist directed a social comment toward her (e.g., "Why are you scared of going to the doctor?"). During negative punishment sessions, therapists were seated near the patient and conversed with her every 5 to 10 seconds about non-OCD topics (e.g., "It is a sunny day today"). If an obsessive-compulsive verbalization was emitted, social interaction was terminated until no obsessive-compulsive verbalizations were

Figure 1. Frequency of Obsessive-Compulsive Verbalizations Across Functional Behavioral Assessment Sessions With and Without Citalopram[a]



[a]The first 2 conditions tested the positive reinforcer functions associated with attention (i.e., attention contingencies). The positive reinforcement condition provided brief social interactions from a therapist when obsessive-compulsive verbalizations occurred. A second condition, negative punishment, reversed this reinforcement contingency by removing attention when obsessive-compulsive verbalizations occurred. The second pair of conditions tested the negative reinforcer functions associated with demands (i.e., demand contingencies). The negative reinforcement condition terminated requests by a therapist when obsessive-compulsive verbalizations occurred. The next condition, positive punishment, initiated requests by a therapist each time an obsessive-compulsive verbalization occurred.

emitted for 30 seconds. The second set of contingencies assessed the effects of escape from demands as negative reinforcement for obsessive-compulsive verbalizations. During negative reinforcement sessions, statements relating to her OCD topics were made every 30 seconds (e.g., "You need to go exercise at the YWCA this afternoon") (the YMCA had a pool in the facility). If an obsessive-compulsive verbalization was made, therapists ceased making statements until no obsessive-compulsive verbalization had been emitted during the previous 30 seconds. During positive punishment sessions, therapists were seated near the patient, but no social interaction occurred. If an obsessive-compulsive verbalization occurred, a statement relating to her OCD topics was made by a therapist (e.g., "You have a doctor's visit tomorrow") (the doctor's office was on the second floor of a multistory building).

The number of obsessive-compulsive verbalizations emitted during the analogue functional analysis conditions is shown in Figure 1. No obsessive-compulsive verbalizations were emitted during the attention conditions. This finding suggests that she did not make obsessive-compulsive verbalizations to obtain social attention as positive reinforcement. During the negative reinforcement condition, obsessive-compulsive verbalizations were emitted a mean of 4.8 times (range, 2–11). During the positive punishment condition, only 1 obsessive-compulsive verbalization occurred. These data suggest that her obsessive-compulsive verbalizations were sensitive to negative reinforcement contingencies (i.e., escaping or avoiding stimuli). After establishing a baseline, citalopram was administered. No obsessive-compulsive verbalizations were observed in the attention conditions, similar to baseline. In the negative reinforcement condition, 3 obsessive-compulsive verbalizations were observed in the first session, but none afterward.

Our findings suggest that the obsessive-compulsive verbalizations of a woman dually diagnosed with OCD and mental retardation were sensitive to escape from demands, but not social attention. These findings are the first functional analysis of obsessive-compulsive verbalizations and suggest these verbalizations can serve a social reinforcement function. The administration of citalopram, against a baseline of other medications, reduced negatively reinforced obsessive-compulsive verbalizations, suggesting that citalopram may reduce the noxious properties of stimuli that the obsessive-compulsive verbalizations typically avoided or escaped.

The use of functional analyses was successful in identifying social reinforcers associated with the obsessive-compulsive verbalizations. The use of the same stimulus in relation to the same response, but under distinct contingency arrangements, may prove a useful approach that could improve the success of functional analysis outcomes.[12,13] This technique is the first functional analysis of obsessive-compulsive verbalizations in a patient with OCD. Future research will be needed to know (a) if such an approach is necessary in analyzing OCD-related behaviors, (b) whether it is more efficacious than other functional behavioral assessment approaches, and (c) whether the differential contingency approach can be extended to other behaviors and populations of interest.

Our findings regarding citalopram need to be viewed as preliminary because of the single-case nature of this study and the other medications the patient was receiving. If replicated, these findings suggest that a functional approach to the assessment of OCD-related behaviors may yield some insight into the reasons these behaviors occur. In addition, this methodology may allow for a behavioral analysis of the effects of commonly prescribed psychotropic medications on behaviors of psychiatric interest.

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REFERENCES

1. Miguel EC, Leckman JF, Rauch S, et al. Obsessive-compulsive disorder phenotypes: implications for genetic studies. Mol Psychiatry 2005;10:258–275
2. Zohar AH. The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin North Am 1999;8:445–460
3. Barrett P, Healy L, March JS. Behavioral avoidance test for childhood obsessive-compulsive disorder: a home-based observation. Am J Psychother 2003;57:80–100
4. Hanley GP, Iwata BA, McCord BE. Functional analysis of problem behavior: a review. J Appl Behav Anal 2003;36:147–185
5. Friman PC, Hayes SC, Wilson KG. Why behavior analysts should study emotion: the example of anxiety. J Appl Behav Anal 1998;31: 137–156
6. Hammond LJ. The effect of contingency upon the appetitive conditioning of free-operant behavior. J Exp Anal Behav 1980;34:297–304
7. Lattal KA. Contingency and behavior analysis. Behav Analyst 1995; 18:209–224
8. Derby KM, Wacker DP, Sasso G, et al. Brief functional assessments techniques to evaluate aberrant behavior in an outpatient setting: a summary of 79 cases. J Appl Behav Anal 1992;25:713–721
9. Iwata BA, Dorsey MF, Slifer KJ, et al. Toward a functional analysis of self-injury. J Appl Behav Anal 1994;27:197–209
10. Kennedy CH. Single-Case Designs for Educational Research. Boston, Mass: Allyn and Bacon; 2005
11. Iwata BA, Pace GM, Dorsey MF, et al. The functions of self-injurious behavior: an experimental-epidemiological analysis. J Appl Behav Anal 1994;27:215–240
12. Catania AC. Learning. 4th ed. Boston, Mass: Cambridge Center for Behavior Analysis; 1998
13. Kennedy CH, Meyer KA. The use of psychotropic medication for people with severe disabilities and challenging behavior: current issues and future directions. J Assoc Persons Sev Handicaps 1998;23:83–97

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Clinical Pearls to Manage Cyberchondriacs

Sir: "Doctor, I saw on the Internet that drug X works well for people with diagnosis Y. I think I have Y; can you try X for me?" This has become almost a daily statement in most physicians' offices today. The number of people searching for medical information online in the United States increased from 54 million in 1998 to 97 million in 2001 and 110 million in 2002.[1] A study of U.S. physicians in 2003 indicted that 85% of 1050 physicians polled had experienced patients' bringing Internet information to a visit.[2] This can place a lot of extra responsibility and pressure on a physician to change a treatment regimen. It may also create a "digital divide" in the patient-physician relationship[3] or make a stronger alliance for therapy. A few physicians may even take a defensive role and see Internet-obtained patient information as a challenge to their therapy.

This phenomenon poses a unique problem in psychiatry due to the nature of mental illnesses. With paranoia, suspiciousness, grandiosity, and formal thought disorders already in place, how does one convince a patient that we still have his or her best interest at heart? Patients who are searching the Internet for answers are very likely already sensitive to their symptoms and somatic sensations, as in the case of hypochondriacs. The information revolution is changing the old notion of a hypochondriac into a "cyberchondriac."

With the Internet revolution, input from patients is becoming imminent in daily practice. How does one handle the information our patients provide to us? What does one do when a patient insists on changing treatment based on something he or she found on the Internet? Can one use these opportunities to further strengthen the therapeutic alliance? Here is a 4-step approach that may be helpful to sort through the perils of information overload.

1. Assess the competency of the patient. This is relevant in all practices, but has a unique importance in psychiatry. Does the patient have psychosis, is she or he disorganized, is she or he grandiose? Does the patient have borderline intellectual function? Is there a dementia or cognitive impairment present? Does the patient have a guardian?
2. Assess quality of the material presented. Does the material reflect on evidenced-based medicine? Is this a case report, or is it a double-blind, placebo-controlled study? How many patients failed with the treatment? Was any bias or conflict of interest involved in obtaining the study results? Is this a commercial advertisement by a pharmaceutical company?
3. Discuss risk/benefits/alternatives to treatment. If the information looks credible, can the treatment be implemented? Are there formulary issues? Are there more side effects than with the patient's current treatment? Can the patient afford it? Is there anything bothersome with the patient's current treatment? Is there another possibility to the proposed treatment and the current treatment? Could the proposed change be used as augmentation?
4. Make a clinical decision with the patient. Ultimately, it is your decision. You have to write the prescription and be comfortable with the choice. The rapport that you have with the patient will best determine what happens next. But, if you have taken the steps above with the patient, chances are it will be a mutual decision upon which both can agree.

Tips for managing the Internet-informed patient are listed in Table 1.

Table 1. Tips for Managing the Internet-Informed Patient

Be neutral; do not judge the material without collaborative research
If you have Internet access in your office, go to the Web site during the visit
If family are involved, see if they can come to the next visit
Schedule follow-up to gather other information if 1 session is not enough
Keep up on current literature/ad campaigns
Keep a listing of Web sites that you find easy to use and of evidence-based medicine material

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REFERENCES

1. Taylor H. Cyberchondriacs Update. Harris Interactive. 2002. Available at: http://www.harrisinteractive.com/harris_poll/index.asp?PID=299. Accessibility verified October 30, 2006
2. Murray E, Lo B, Pollack L, et al. The impact of health information on the Internet on health care and the physician-patient relationship: national US survey among 1,050 US physicians. J Med Internet Res 2003;5:e17
3. Lorence D, Park H. Web-based consumer health information: public access, digital division, and remainders. MedGenMed 2006;8:4

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Prevention of Deep Vein Thrombosis in a Patient With Delirium Tremens

Sir: Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is a significant cause of morbidity and mortality in hospitalized patients. Although the incidence in psychiatric inpatients has not been well studied, hospitalized patients in a psychiatric ward commonly have several risk factors for deep vein thromboembolism such as increased body weight, dehydration, prolonged hospitalization, use of antipsychotics, and immobilization due to sedative administration or mechanical restraints.[1] We report the case of a patient with schizophrenia and alcoholic pancreatitis who was physically restrained in the psychiatric ward for severe alcohol withdrawal delirium prior to development of deep vein thromboembolism.

Case report. Mr. A, a 35-year-old man with a history of DSM-IV–defined schizophrenia and alcohol dependence since 24 years of age, was admitted to the emergency department in late 2006 with abdominal pain. Prior to admission, lack of control of schizophrenic symptoms with antipsychotics had led to use of alcohol as a coping behavior. Specifically, for the prior few months he had been taking olanzapine 10 mg daily, but his alcohol consumption had been increasing. He had consumed 500 mL of alcohol in 2 days prior to admission. The patient's height and weight were 168 cm and 50.2 kg, respectively (body mass index = 17.8 kg/m^2). Laboratory tests revealed elevated serum amylase.

After abdominal computed tomography (CT), he was diagnosed with acute pancreatitis of Balthazar grade E, the most severe form in the severity grading system according to CT criteria.[2] Oral intake of medications was stopped, including antipsychotics. Gabexate mesilate 1500 mg/day and ulinastatin 300,000 units/day for 10 days were started. On the third day, the patient developed delirium tremens and became delusional and aggressive. Injections of haloperidol 25 mg and flunazepam 4 mg could not calm him, and he was physically restrained in a prone position: 5-point restraint with cuffs for all 4 extremities and a device at the waist were used. Because he continued to struggle after being restrained, and because excessive physical activity can aggravate pancreatitis, injectable haloperidol 40 mg/day and orally disintegrating olanzapine tablets 30 mg/day were given.

Because of uncontrollable delirium tremens, he was transferred to the psychiatric ward on the sixth day, where he developed visual hallucination, delusions, and severe tremor, all of which subsided within a week. Because olanzapine was not effective in controlling schizophrenic symptoms prior to admission, it was discontinued, along with haloperidol, on the 10th day, at which time oral risperidone 6 mg daily was initiated. He was calm for several days, but on the 16th day he suddenly became agitated with persecutory delusions. It was presumed that the patient's schizophrenia was refractory to risperidone and that the schizophrenia had recurred due to the cessation of olanzapine and haloperidol. Electroconvulsive therapy (ECT) was performed under general anesthesia and muscle relaxation with succinylcholine. Compression stockings were started to prevent deep vein thromboembolism.

On the 25th day, after his 5th ECT session, follow-up abdominal CT scans revealed thrombosis in the left internal iliac vein. The remaining ECT sessions were cancelled. Chest CT scans and echocardiography revealed no signs of pulmonary embolism. Combined oral warfarin 3 mg/day and subcutaneous heparin calcium 20,000 units/day were given for a week. Oral warfarin was continued to maintain prothrombin time/international normalized ratio (PT/INR) of 1.5 to 2.5. CT scans 19 days after detection of thrombosis showed reduction in thrombus size, and the patient was discharged 2 days later. Serum levels of proteins C and S were within normal limits. There was no familial history of thrombosis. Oral warfarin 3 mg/day was continued for 6 months after discharge.

Our patient had several risk factors for deep vein thromboembolism. Apart from dehydration on admission, immobilization due to inpatient physical and chemical restraint may have contributed to his thrombosis. Alcoholic pancreatitis, which induces systemic hypercoagulable states,[3] may have been an additional risk factor for deep vein thromboembolism.

To our knowledge, an association between delirium tremens and deep vein thromboembolism has not been reported. However, patients with severe delirium tremens represent a high-risk group for deep vein thromboembolism. The first risk factor is dehydration, which is common to all stages of withdrawal. The second is immobilization due to restraint, and the third is use of antipsychotics. Although benzodiazepines are typically used for sedation, antipsychotics are often necessary for patients with severe delirium tremens with hallucinations.

Patients with delirium tremens are likely to have other complications due to excessive alcohol use, one of which is trauma. One study found that trauma within 3 months significantly increases risk of deep vein thromboembolism.[3] Patients with trauma and alcohol withdrawal symptoms are at increased risk for other complications, including pneumonia, which is also a risk factor for deep vein thromboembolism.[4] Finally, alcoholic pancreatitis may also be a predisposing factor for deep vein thromboembolism. Coagulation abnormalities related to severity of pancreatitis are known to occur, one of which is elevation of D-dimer,[3] which was observed in our patient. There is 1 case report of pulmonary embolism occurring after ECT.[5] Although our patient did not develop pulmonary embolism, exceptional care needs to be taken when ECT is to be performed in patients with deep vein thromboembolism risk factors.

Delirium tremens is commonly observed in inpatients with regular alcohol consumption and is usually preceded by the

typical signs and symptoms of early withdrawal, such as agitation, irritability, tremor, and disturbed sleep. However, treatment priority was given to the patient's pancreatitis in our case, which resulted in neglect of assessment of the prodromal symptoms of delirium tremens. Prodromal symptoms should not go unheeded because treating early alcohol withdrawal may prevent development of delirium tremens in some cases. Delirium tremens, however, can have its onset in the absence of early withdrawal symptoms, and we must not forget to focus on risk factors of deep vein thromboembolism when delirium tremens does occur.

The American College of Chest Physicians 2004 guidelines[6] recommend venous thromboembolism prophylaxis in acutely ill medical patients such as those with congestive heart failure or severe respiratory disease or who are confined to bed with risk factors such as active cancer, previous venous thromboembolism, sepsis, acute neurologic disease, or inflammatory bowel disease. In addition to mechanical prophylaxis, unfractionated heparin and low–molecular-weight heparin are recommended for venous thromboembolism prophylaxis in this setting. An association between delirium tremens and deep vein thromboembolism has not been reported previously, and it is not usually considered a risk factor for deep vein thromboembolism. Thus, deep vein thromboembolism prophylaxis is not generally started when severe alcohol withdrawal is present. However, patients with delirium tremens typically present with multiple risk factors for deep vein thromboembolism, and further studies must be undertaken to determine guidelines for deep vein thromboembolism prophylaxis in these patients.

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REFERENCES

1. Laursen SB, Jensen TN, Bolwig T, et al. Deep venous thrombosis and pulmonary embolism following physical restraint. Acta Psychiatr Scand 2005;111:324–327
2. Balthazar JE, Ranson HCJ, Naidich PD, et al. Acute pancreatitis: prognostic value of CT. Radiology 1985;156:767–772
3. Salomone T, Tosi P, Palareti G, et al. Coagulative disorders in human acute pancreatitis: role for the D-dimer. Pancreas 2003;26:111–116
4. Zakai NA, Wright J, Cushman M. Risk factors for venous thrombosis in medical inpatients: validation of a thrombosis risk score. J Thromb Haemost 2004;2:2156–2161
5. Mamah D, Lammle M, Isenberg KE. Pulmonary embolism after ECT. J ECT 2005;21:39–40
6. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl 3):338S–400S

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