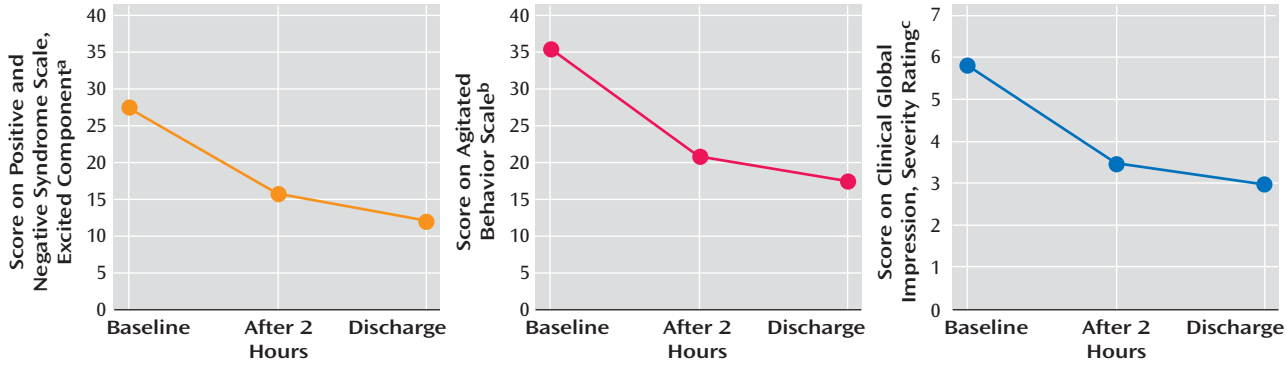
FIGURE 1. Scores of Agitated Patients After the First Intramuscular Injection With Olanzapine



[a] t=10.59, p<0.0001
[b] t=12.00, p<0.0001
[c] t=11.43, p<0.0001

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Improvement in Refractory Obsessive Compulsive Disorder With Dronabinol

TO THE EDITOR: It has been reported that 40%–60% of patients with obsessive-compulsive disorder (OCD) do not respond to first-line treatment. Treatment options for these patients include switching to another agent or augmentation (1). We report on two patients with treatment-resistant OCD and comorbid axis I disorders who responded to an augmentation with the cannabinoid dronabinol.

"Mrs. L" was a 38-year-old woman who was admitted with recurrent major depression and OCD (Yale-Brown Obsessive Compulsive Scale score: 20) after outpatient treatment with paroxetine (60 mg) for 8 months and cognitive behavioral therapy (CBT) were not efficacious. Switching to clomipramine (300 mg) resulted in partial response after 12 weeks of treatment. Based on the patient's report that smoking marijuana usually relieved her symptoms, an augmentation with dronabinol (2.5%; 10 mg t.i.d.) was started. The prior medication was continued. While undergoing treatment with dronabinol (2.5%), the patient's OCD symptoms decreased significantly within 10 days (Yale-Brown Obsessive Compulsive Scale score: 10).

"Mr. K" was a 36-year-old man with schizophrenia and OCD who was admitted for deterioration of psychotic and obsessive symptoms (Yale-Brown Obsessive Compulsive Scale score: 23). During his course of illness, Mr. K had been treated with antipsychotics (including haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole), both in monotherapy and in combination with selective serotonin reuptake inhibitors. His OCD symptoms in particular remained predominately treatment resistant. Treatment with clozapine (400 mg), which he had already received for more than 1 year (in combination with paroxetine [60 mg] for 13 weeks) resulted only in partial response of his psychotic and OCD symptoms. Switching paroxetine to clomipramine (for another 10 weeks), followed by an additional course of 18 electroconvulsive therapy treatments (right unilateral high dose), did not improve the patient's psychotic or OCD symptoms significantly. After the addition of dronabinol to ongoing treatment with clomipramine (150 mg) and clozapine (400 mg), a significant reduction of OCD symptoms was observed within 2 weeks (Yale-Brown Obsessive Compulsive Scale score: 15). In order to prevent psychotic deterioration, dronabinol (2.5%) was carefully increased to 10 mg b.i.d.

Apart from anticholinergic symptoms that preceded the addition of dronabinol (patient 1: dry mouth, constipation; patient 2: constipation, hypotension), both patients reported no side effects. In particular, there was no deterioration of psychotic or mood disorder symptoms.

Based on data from case reports and small clinical trials suggesting that cannabinoids can reduce symptoms of tic disorder (2) and on findings from genetic studies linking tic disorder with OCD (3), we hypothesized that cannabinoids

might also reduce OCD symptoms. Moreover, there is evidence suggesting that besides serotonergic and dopaminergic systems, glutamatergic hyperactivity is involved in the pathophysiology of OCD (4, 5). This view is supported by data suggesting the efficacy of glutamate modulating drugs, such as topiramate, memantine, riluzole, or N-acetylcysteine, in the treatment of OCD (6). It has been reported that cannabinoids inhibit glutamate release in the CNS (7, 8). Additionally, cannabinoid type 1 (CB_1) receptors are distributed abundantly in the striatum (8), a brain region frequently associated with OCD. Hence, it can be speculated that the anti-obsessive effect observed in our patients may have been a consequence of the glutamate modulation of the cannabinoid dronabinol. Since it is well known that cannabinoids may trigger psychotic symptoms in patients with schizophrenia (8), caution is warranted when prescribing for patients with a history of the disorder.

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Maintenance Treatment With Transcranial Magnetic Stimulation in a Patient With Late-Onset Schizophrenia

TO THE EDITOR: A recent meta-analysis (1) concluded that repetitive transcranial magnetic stimulation (rTMS) efficiently reduces resistant auditory hallucinations in patients with schizophrenia (effect size=0.76). Nevertheless, treatment is presently only provided over short periods of time, and little is known about longer-term impact. Maintenance treatment protocols have been developed, and we previously described a case report involving a maintenance protocol with a weekly, once-a-day stimulation (2); however, we failed to demonstrate long-term benefits. To our knowledge, the case presented below is the first report of a twice-daily transcranial magnetic stimulation as efficacious for auditory hallucinations, both in acute and maintenance treatment.

"Ms. A," a 55-year-old right-handed, postmenopausal woman who had DSM-IV late-onset schizophrenia with an illness duration of 2 years, was referred for transcranial magnetic stimulation treatment. She was noted to have benzodiazepine addiction involving the use of lorazepam (9 mg/day). She had been suffering from resistant auditory hallucinations for 2 years (very frequent and loud, with >5 critical and command voices). She was unresponsive to four antipsychotic medication trials lasting >4 months each, including haloperidol (5 mg/day), amisulpride (1200 mg/day), olanzapine (15 mg/day), and risperidone (8 mg/day). A detailed assessment did not reveal any other pathology or transcranial magnetic stimulation contraindications. Auditory hallucinations were assessed using the Auditory Hallucination Rating Scale (3), and positive symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS). Lorazepam withdrawal was completed without exacerbation of the psychotic symptoms (Auditory Hallucination Rating Scale score: 34). Four months after her initial presentation, the patient gave informed consent and was included in a transcranial magnetic stimulation protocol. Twice-a-day, 1000 low-frequency repetitive stimulations (1 Hz) were administered to the temporoparietal cortex at 100% of motor threshold over a 5-day period. The patient's current dose of risperidone was maintained during treatment with transcranial magnetic stimulation. After the first course, auditory hallucinations were moderately improved, with a 35% reduction in her Auditory Hallucination Rating Scale score, which did not change over the next several months, as observed in a follow-up assessment. However, the patient's general SAPS score improved, with a 30% reduction in severity.

Six months after the first course of transcranial magnetic stimulation therapy, the patient presented with a relapse of hallucinations. A new transcranial magnetic stimulation course, with the same parameters, was conducted. This second course was followed by a once-per-month, twice-daily maintenance protocol (one session in the morning, the other in the afternoon on the same day). The patient's auditory hallucinations were greatly improved, by 80%, and her SAPS score decreased from 38 to 16. This maintenance course was associated with a remission of auditory hallucination symptoms, with a stabilization of SAPS scores at 10 over the next 6 months. Presently, more than 1 year later, Ms. A is not receiving any antipsychotic medication, and her Auditory Hallucination Rating Scale and SAPS scores remain at 0.

Our case raises the question as to whether twice-daily transcranial magnetic stimulation may be useful in some patients as a possible maintenance intervention. Certainly, further research will help us to understand whether the benefits observed in this single case might also be evident in larger studies.