

## LETTERS TO THE EDITOR

# Seasonal and temperamental contributions in patients with bipolar disorder and metabolic syndrome

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Dear Editor,

I read with interest the article by Altinbas et al. (in this issue) suggesting that the prevalence of the metabolic syndrome in individuals with bipolar disorder is influenced by seasonality, with higher rates reported in the winter and spring months. They further opine that temperamental dimensions (e.g. depression) constitute a vulnerability factor to the seasonal influence. The article is appropriate in highlighting that their small sample size, open label design and absence of a control group, among other limitations, affect the inferences that can be drawn from their outcome. Their paper is hypothesis-generating rather than hypothesis-confirming.

The authors remind us that environmental factors (e.g. seasonality) affect susceptibility to allostatic load. It is amply documented that bipolar symptoms/episodes are affected by seasonality in susceptible subsets. It could be conceptualized that metabolic syndrome (e.g. obesity) is a phenotypic manifestation of an abnormal stress response with somatic manifestations. It would be interesting to know whether individuals with metabolic syndrome seasonality are more or less likely to also experience breakthrough symptomatology.

There is tremendous interest in conceptualizing bipolar disorder as progressive disorders.<sup>1</sup> I would conjecture that obesity and associated metabolic abnormalities are a cause and consequence of progression in bipolarity.<sup>2-4</sup> Indeed, this remains a testable hypothesis. My clinical impression is that individuals with bipolar disorder who exhibit susceptibility to symptomatic recurrence as a function of seasonality often present with "mixed presentations."<sup>5</sup> It is tempting to further speculate that obesity, which is depressogenic, may be affecting the symptomatic presentation of bipolar disorder, increasing the likelihood that these patients will present as "mixed." Again, my clinical impression is that bipolar patients that I have encountered over the last decade are more often mixed than they are euphoric, and I have wondered whether, in addition to the inappropriate use of antidepressants, obesity is changing the "face" of bipolar disorder.

I further applaud the authors for reminding us of possible temperamental contributions and giving us a "dose of reality" that there will be no unidimensional

explanation for psychiatric disorders that is coherent, comprehensive, and explanatory.

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### Disclosure

The author reports no conflicts of interest.

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## rTMS as an add-on treatment for resistant obsessive-compulsive symptoms in patients with schizophrenia: report of three cases

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Dear Editor,

Obsessive-compulsive symptoms (OCSs) occur in approximately 30% of patients with schizophrenia, probably reflecting reduced basal ganglia and prefrontal cortex connectivity, and are associated with poorer prognosis.<sup>1</sup> There is little systematic evidence of treatment effect on OCS schizophrenia, mostly derived from case reports and open label uncontrolled studies. Among new treatments, repetitive transcranial magnetic stimulation (rTMS) is a method of noninvasive electromagnetic neurostimulation that has demonstrated effect on verbal hallucinations and depressive symptoms.<sup>2,3</sup> Nevertheless, contradictory effects on obsessive-compulsive disorder

**Table 1** Results obtained in the three cases

Patient	Age, y	Illness duration, y	Gender	DSM-IV diagnosis	Medication used	Y-BOCS			BPRS		
						T1	T2	T3	T1	T2	T3
1	42	25	F	SZ	Clozapine 400 mg Citalopram 40 mg	33	24	29	15	10	11
2	27	9	M	SZA	Clozapine 600 mg Valproate 2000 mg	17	11	21	4	2	3
3	30	15	M	SZ	Clozapine 600 mg Valproate 1500 mg Amitriptyline 125 mg	24	23	24	32	11	26

BPRS = Brief Psychiatric Rating Scale; SZ = schizophrenia; SZA = schizoaffective disorder; y = years; m = male; f = female; T1 = baseline; T2 = after 20 repetitive transcranial magnetic stimulation sessions; T3 = 4 weeks after treatment cessation; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

(OCD) have been reported,<sup>2,4</sup> depending on the stimulation parameters used (frequency, place, total dose). Furthermore, there has been some evidence of effects on compulsions using the Mantovani's protocol (1 Hz over the supplementary motor area - SMA),<sup>5</sup> whilst dorsolateral prefrontal cortex failed to reveal consistent effect even at low or high frequency, and right or left hemisphere.

We report on three cases of comorbid schizophrenia or schizoaffective disorder and OCS under stable dose of neuroleptics receiving additional rTMS with the Mantovani protocol (1 Hz, SMA, 100% of motor threshold, 20 minutes, 20 sessions in 4 weeks), showing reduced OCSs after rTMS treatment. The protocol was approved by the Ethics Committee of the HCPA (Hospital de Clínicas de Porto Alegre - GPPG 10-0426), and patients and relatives provided informed consent.

All cases had treatment-resistant schizophrenia (n=2) or schizoaffective disorder (n=1) with at least 3 months under stable dose of clozapine. Diagnosis was based on the DSM-IV-TR criteria administered by the same trained psychiatrist (VMF) and reviewed by a senior psychiatrist (MIRL). Psychopathology was measured by the 18-item Brief Psychiatric Rating Scale (BPRS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The characteristics of the three cases are described in Table 1. All subjects displayed improvement on the BPRS and OCD symptoms after the add-on rTMS treatment, but with subsequent relapse after 4 weeks (Table 1).

As far as we are aware, this is the first report of the effects of add-on rTMS on the treatment of OCSs in refractory schizophrenia. These three cases provide initial evidence for the use of the Mantovani protocol (SMA) in this group of patients, in addition to previous effects of rTMS on auditory hallucinations.<sup>2,3</sup>

This report must be viewed as initial evidence requiring further studies with larger number of cases and double-blind sham control group. The number of cases (n=3) precluded statistical testing and displayed relatively large age, gender and diagnosis heterogeneity. Nevertheless, despite the limitations that hinder further generalization, patient diagnosis and psychopathology were consistently assessed, and cases had no significant variations in

terms of drug dose and psychosocial environment over the observational period. This reinforces the need of additional studies with larger sample size, less variability of age, gender and diagnosis, longer follow-up, and use of additional tools (functional magnetic resonance imaging-positron emission tomography, fMRI-PET) to elucidate efficacy, duration, and underlying mechanisms of action of the rTMS treatment<sup>5</sup> in comorbid schizophrenia-schizoaffective disorder-OCS.

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## Disclosure

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## Cotard's syndrome and major depression with psychotic symptoms

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Dear Editor,

Cotard's syndrome is a rare clinical event, characterized by negation delusion (individuals feel major changes in their bodies and deny the existence of one or several parts of their organs or bodies) and nihilistic delusion (individuals believe that they or all people are dead).<sup>1</sup> First described in 1880 by Jules Cotard as negation delirium,<sup>2</sup> the term Cotard's syndrome was proposed in 1893 by Emil Regis.<sup>3</sup> We describe the case of a patient admitted to the psychiatric ward of Hospital Ulysses Pernambucano, in Recife, northeastern Brazil and diagnosed with Cotard's syndrome.

M., 59 years old, male, was brought to the psychiatric emergency service of the hospital with complaints of insomnia, soliloquy, attempts to escape from home, suicide attempts by throwing himself in front of moving cars, and nonsense talk. He had dropped out of drug treatment two months earlier. The patient reported hearing voices making comments about him and giving him commands, as well as the existence of animals eating his body. He informed that he no longer had a body, but rather only a spirit, as he was already dead. He did not fear anything, as no one could kill him again (*sic*). Upon clinical examination, he was barefoot, wearing only shorts (no shirt), showed an unkempt beard and poor hygiene. He also showed alert consciousness, partial disorientation to time, a suspicious attitude, worn-out appearance, personal self-reference, deeply depressed mood, psychomotor retardation, insisting that he was not worth anything, that nobody wanted him there for 60 days already, and that he was paying for what he had done wrong. He also reported not having blood pressure, or blood, and that his body was broken, and that something very bad was about to happen. The patient was diagnosed with Cotard's syndrome secondary to major depression with psychotic symptoms. He was treated with imipramine 150 mg/day and risperidone 4 mg/day for 60 days, and was discharged asymptomatic afterwards.

Even though this disorder was first described by Cotard as a new type of depression, Regis later proposed that this syndrome could be associated with several medical conditions, e.g., psychotic depression, schizophrenia, neurosyphilis, and multiple sclerosis.<sup>3,4</sup> Comorbidity between Cotard's syndrome and Capgrass syndrome (individuals believe that family members have been replaced with doubles) is also common.<sup>4</sup> Currently, Cotard's syndrome is no longer classified as an independent disorder in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) or in the International Classification of Diseases, Tenth Revision (ICD-10). Rather, in the DSM-IV-TR, nihilistic

delusion is classified as a mood-congruent delusion within a depressive episode with psychotic features.<sup>4</sup>

It is important to emphasize that our case was absolutely compatible with the different descriptions available in the literature for Cotard's syndrome, with features such as a depressed mood, nihilistic delusion, and delusions of guilt and immortality.<sup>5</sup>

Treatment of Cotard's syndrome should focus on the underlying condition. Even though electroconvulsive therapy has been the treatment most frequently indicated in the literature, some reports of the combined use of psychotic and antidepressant drugs can also be found when psychotic depression is the underlying illness. Despite the absence of reports describing the combined use of imipramine and risperidone, the therapy was effective in remitting psychotic depression symptoms in our patient.

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### Disclosure

The authors report no conflicts of interest.

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## The utility of intravenous clomipramine in a case of Cotard's syndrome

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Dear Editor,

We present a case of Cotard's syndrome in a 50-year-old female patient with no known prior history of medical or psychiatric illness. The patient went to the emergency department accompanied by a family member. She had been experiencing progressive depressive symptoms

for 2 months. The patient presented with sadness, anhedonia, fatigue, insomnia, apathy, feelings of self-depreciation, and emotional instability, which was not related to any life-events. In the previous week, she started to feel hopelessness and anger; she also believed that her body was putrid. The mental state examination revealed depressive mood associated with psychomotor retardation, ruminative thoughts of death, delusional ideas of ruin, nihilistic delusions concerning her own body, and absence of insight. Physical and neurological examination, basic blood investigations, cerebral computed tomography, illicit drug screening, and electroencephalography showed no relevant alterations. There was no personal history of substance misuse.

She was admitted to the psychiatric department. Initial treatment consisted of paroxetine 20 mg/day and olanzapine 15 mg/day. After 4 days, there was no therapeutic response and her depressive symptoms were aggravated, showing mutism and poor collaboration. Because the standard oral antidepressant failed and the patient refused to feed and take oral medication, glucose-saline solution and intravenous clomipramine were started. Clomipramine is one of the few antidepressants that are available for parenteral administration. Increments of 25 mg of clomipramine were added daily reaching the maximum dose of 100 mg/day after 4 days. At this time, the patient showed improvement in her clinical status and began to feed normally. We started oral clomipramine, which was raised to 150 mg/day with increments of 25 mg/day in two divided doses, and discontinued intravenous clomipramine (also 25 mg/day); the patient also restarted taking olanzapine 10 mg/day.

After 10 more days of hospital stay, there was a progressive and substantial improvement of the clinical status; the depressive symptoms, delusional ideas of ruin, and nihilistic delusions concerning her own body were in remission. The patient was discharged and referred to psychiatric outpatient treatment maintaining oral clomipramine 150 mg/day and olanzapine 10 mg/day.

In our clinical experience, we found that intravenous clomipramine can be useful to treat resistant-depression and obsessive compulsive disorder when standard oral antidepressant treatment fails.<sup>1</sup> The limited available literature also suggests that it can promote an apparent faster clinical improvement compared with oral antidepressants.<sup>2-6</sup> The low demethylation that results from the avoidance of the first-pass effect on hepatic metabolism led to a higher ratio of serotonergic clomipramine vs. noradrenergic metabolite desmethylclomipramine<sup>5</sup>; therefore higher drug plasma levels promote more bioavailability and enhanced selective 5-HT potency when intravenous clomipramine is used instead of oral formulation.<sup>5</sup> Other hypotheses, such as the placebo effect of the intravenous route or allowing the response to oral antidepressants, have also been proposed.<sup>5</sup>

Usually, the starting dose is 25 mg diluted in 500 mL of NaCl 0.9%, administered by slow infusion over 90 minutes. This can be increased to 250-300 mg by

increments of 25 mg/day during 10-14 days. Monitoring of pulse, blood pressure, and electrocardiogram are essential due to potential cardiac toxicity. Other side effects present in oral formulation, such as nausea, sweating, abdominal distress or restlessness, are likewise common.

In spite of the previous period of a combined treatment with paroxetine and olanzapine, the rapid and substantial improvement after starting treatment with intravenous clomipramine may indicate the existence of a specific effect of intravenous clomipramine on Cotard's syndrome. As observed in cases of resistant-depression, this may indicate that Cotard's syndrome can be successfully treated with intravenous clomipramine, especially in situations where there is significant feed refusal and negativism. Additionally, it may be a more rapid and effective alternative to the standard oral antidepressant and antipsychotic treatment.

Despite some concerns about its side effects and toxicity, considering intravenous clomipramine as a very effective and rapid acting agent in treatment-resistant or severe cases of depression with psychotic features, such as Cotard's syndrome, raises much interest in clinical practice and needs more investigation.

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## Disclosure

The authors report no conflicts of interest.

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