Neuroleptic malignant syndrome: a case responding to electroconvulsive therapy plus bupropion

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Abstract
Neuroleptic malignant syndrome (NMS) is a severe motor syndrome occurring as a consequence of neuroleptic treatment. We present a case of a 67-year-old Caucasian woman with a history of a major depressive disorder with psychotic features. During her third hospital admission, symptoms of autonomic instability, hyperpyrexia, severe extrapyramidal side effects, and delirium appeared, suggesting NMS due to concomitant treatment with risperidone and quetiapine, among other drugs. Despite several consecutive pharmacological treatments (lorazepam, bromocriptine and amantadine) and prompt initiation of electroconvulsive therapy (ECT), clinical improvement was observed only after combining bupropion with ECT. The symptoms that had motivated the admission gradually remitted and the patient was discharged home. Bupropion increases dopaminergic activity in both the nucleus accumbens and the prefrontal cortex. Therefore, from a physiopathological standpoint, bupropion has a potential role in treating NMS. However, there is scarce evidence supporting this approach and therefore future cases should be carefully considered.

Introduction
Neuroleptic malignant syndrome (NMS) is a severe motor syndrome with an estimated prevalence of 0.9 cases per thousand patients exposed to neuroleptics.1 The classic presentation consisted of autonomic instability, hyperpyrexia, severe extrapyramidal symptoms, and delirium.2 However, it is heterogeneous in onset, presentation, progression and outcome, and has a 6% mortality risk.3,4 The physiopathological mechanisms are associated with the blockade of dopamine receptors in the anterior hypothalamus, corpus striatum, and basal ganglia.3 Differential diagnosis, especially between NMS and catatonia, presents a challenge for clinicians, but exposure to a neuroleptic drug could be decisive.4 From 1985 to date, various attempts have been made to establish uniform diagnostic criteria, without reaching a clear consensus.6 We present the case of a 67-year-old Caucasian woman with a history of a major depressive disorder with psychotic features who developed a NMS.

Case Report
Since January 2016, a 67-year-old, single, Caucasian female patient had been followed up at our outpatient psychiatry practice for a depressive disorder. She has no previous psychiatric history and has never taken any psychotropic medications. She initially responded to an antidepressant drug (Citalopram 20 mg orally per day). On 20 May 2016, she presented to the Emergency Department with a symptomatology of a decrease in activities of daily living, nonspecific fears, weight loss, irritability, anhedonia, and lack of energy; therefore she was hospitalized. The eldest of five siblings, she has been living with her brother and his family. After working all her life in a textile factory, she retired 10 years ago. Her family described her as a very caring person, hard-working, pessimistic, and inflexible. She has not been pre-existing functional limitation of Activities of Daily Living.

In the acute ward, she presented with ideas of reference and persecutory delusions. She was started on clomipramine (225 mg orally per day) and olanzapine (30 mg orally per day), with no response. Subsequently, risperidone (6 mg orally per day) was initiated with no remission of symptoms. Treatment with ECT had to be started due to active delusional ideas and the appearance of visual and auditory hallucinations. After 14 sessions had been administered, the patient experienced a clinical improvement and was discharged home with follow-up in the outpatient clinic with the following treatment: clomipramine (225 mg orally per day) and risperidone (6 mg orally per day). On 4 November 2016, the patient was admitted to hospital again after two weeks of mood worsening and recurrence of psychotic symptoms. A new cycle of ECT was administered but was suspended after twenty-one sessions due to lack of clinical response. Lithium (400 mg orally per day) and quetiapine (100 mg orally per day) were added to the risperidone treatment. On 10 March 2017, Parkinsonian gait and bradykinesia were observed and risperidone was suspended. After 12 days, an episode of fever (up to 38°C) began, with diaphoresis, tachycardia (105 beats per minute), high blood pressure (195/115 mmHg), and leukocytosis (16,100 wbc/ml). Moreover, stiffness of the extremities, poverty of speech, stupor, mutism, negativism, and mannerism were noted. Following an assessment by the Internal Medicine doctor, the patient was transferred to the Intensive Care Unit. A cranial computed tomography scan, a lumbar puncture and blood tests were performed, without revealing any abnormality. Except for an episode of paroxysmal supraventricular tachycardia, the patient had no other medical issues and therefore was transferred to the Internal Medicine department after three days. She maintained high temperature (up to 38°C) during four days. A trial with lorazepam (6 mg per day) was not successful and the dose was not increased due to excessive somnolence. ECT was started again. Furthermore, we started bromocriptine, which had to be stopped because of hypotension, and amantadine, which yielded no clinical improve-
Discussion and Conclusions

We reported a case of an older woman who developed NMS after treatment with risperidone, combined withquetiapine during a period of time. These two neuroleptics were prescribed as part of the treatment for her major depressive disorder with psychotic features.

During the course of the disorder, we used drugs commonly proposed in the guidelines,7 apart from dantrolene, which we considered ICU treatment and this case was not being considered during the UCI stay. First, we tested a benzodiazepine, lorazepam at moderate doses, as excessive sedation precluded use of the higher doses (8-24 mg/day) recommended in these cases.8 Secondly, the well-established recommendation of ECT in NMS was tried, although with no established clinical evidence. The lack of response led us to test bromocriptine, but an intense episode of hypotension forced withdrawal. As a fourth option, amantadine was prescribed and withdrawn after no response. Finally, treatment with bupropion was started. This antidepressant inhibits the reuptake of norepinephrine and dopamine in humans without affecting the release or transport of other neurotransmitters and without binding to other neurotransmitter receptors. It also increases dopamine neurotransmission in both the nucleus accumbens and the prefrontal cortex.9

The patient achieved partial remission by the fourth week of treatment, a result similar to the one described by Liu et al. in a case of refractory depression with catatonic features.10 However, we cannot know the exact causes of the response, and it is difficult to ascertain the role of bupropion in the clinical improvement. A late response to ECT, as described in the literature, could also be possible.

This case triggered a clinical dilemma in our department; some colleagues considered that the patient had developed a malignant catatonia in the context of a severe depression, whereas others considered it NMS. The relationship between NMS and catatonia has been discussed since the 1990s,11 and remains controversial. Some authors argue that catatonic symptoms appearing before autonomic symptoms help to distinguish malignant catatonia from NMS,12 whereas others consider both as belonging to the same spectrum of illness.13 Nonetheless, in this case we considered the simultaneous use of two neuroleptics to be a potential trigger of the NMS. A case of concomitant use ofquetiapine and risperidone has been reported in the literature.14 Clinicians have to keep in mind that NMS could appear with all antipsychotics, including the newest. Furthermore, in some second generation antipsychotics atypical features would be observed as fewer intense extrapyramidal symptoms or with less fever making the diagnosis more difficult.15

To our knowledge, this is the first reported case of bupropion treatment in NMS. However, taking into account the cases of NMS described with this antidepressant,16 it should be administered with caution. In our opinion, further clinical trials could be considered to determine its efficacy.

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