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Letter to the Editors

Aripiprazole and the Neuroleptic Malignant Syndrome

Dear Editors,

Neuroleptic malignant syndrome (NMS) is difficult to diagnose given that the side effect profiles of many of the second-generation D_2 antagonists overlap considerably with NMS criteria (Hasan and Buckley, 1998). A recent report by Srephichit et al. (2006) of atypical NMS with aripiprazole as well as two previously published cases of "aripiprazole-induced NMS" further complicates this diagnostic conundrum. In these cases, a number of drug-specific, clinical factors and other diagnostic possibilities deserve significant consideration. The likelihood of NMS in these cases can be evaluated using highly sensitive scales for NMS (Sachdev, 2005) and operational criteria established in large case series (Pope et al., 1986).

The patient presented by Mr. Srephichit and colleagues had been treated with high-dose aripiprazole (30 mg/day) and developed a mild fever (100.8 °F), "mild muscle rigidity," diaphoresis and disorientation. This patient's creatine kinase concentration peaked at 866 U/L and she was diagnosed with a urinary tract infection of hospital day 2 (Srephichit et al., 2006). As the authors note, "this patient did not present with extreme hyperthermia, grossly elevated CPK, and 'lead-pipe' muscle rigidity, which would make the diagnosis of NMS unmistakable" (Srephichit et al., 2006). In other reports of presumed aripiprazole-induced NMS, patients failed to have significant elevations in temperature (99.8 °F), significant autonomic instability (blood pressure range: 137–148/89–99 mm Hg) or disturbances in level of consciousness (Duggal and Kithas, 2005). In a report of NMS in a 17-year-old black male the presentation was characterized by severe extrapyramidal symptoms which were improved with benztropine and were associated with a temperature of only 99 °F, blood pressure of 149/105, heart rate was 102 bpm and an elevated creatine kinase of 762 U/L (Spalding et al., 2004). These cases of possible NMS associated with aripiprazole are evaluated in Table 1 using highly sensitive scales for NMS (Sachdev, 2005) and operational criteria established retrospectively in large case series (Pope et al., 1986).

While any dopamine antagonist or withdrawal of a dopamine agonist may theoretically precipitate the development of NMS, it is possible that many of the "atypical" features of the cases described above actually represent extrapyramidal spectrum adverse effects of aripiprazole. Earlier multi-centered placebo-controlled randomized trials of aripiprazole (2–30 mg/day, mean dose 19.2 mg/day) in patients with schizophrenia and schizoaffective disorder suggested that the frequency of extrapyramidal symptoms (EPS) associated with aripiprazole did not differ significantly from placebo as assessed by Simpson–Angus Scale (SAS) scores and Barnes Akathisia scores (Marder et al., 2003). However, 2 of the 3 reports of putative NMS discussed above occurred in patients taking 30 mg of aripiprazole/day, the maximum FDA-approved dosage. Higher dosages of aripiprazole have been associated with small but significant increases in extrapyramidal symptoms. In a double-blind placebo-controlled trial in which acutely manic patients were started at 30 mg/day and permitted dose reduction to 15 mg/day for tolerability, SAS and Barnes Akathisia scores were significantly higher in the aripiprazole-treated patients in whom 86% received an average aripiprazole dose of 28 mg/day (Keck et al., 2003). Moreover, in the case reported by Spalding, the patient improved with anticholinergic medications (Spalding et al., 2004) which improve EPS and are thought to worsen NMS. Finally, akathisia and agitation are

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Table 1
Evaluation of aripiprazole-induced NMS cases by standardized criteria

Report	Age (years)	Dose (mg/day)	Sachdev criteria	Pope et al. criteria	Co-morbid infection
Srephichit et al., 2006	23	30	Possible (score 9–10)	Not met	UTI
Duggal and Kithas, 2005	43	30	Less likely (score 8–9)	No met	
Spalding et al., 2004	17	15	Less likely (score 15)	Not met	

clinically known to be associated with mild increases in creatine kinase concentrations.

The atypicality of the NMS cases described above is complicated by a high likelihood of extrapyramidal spectrum adverse effects, a possibility of agitation-related CK increases and the low scores assessed by both operational criteria evidence-based highly sensitive NMS scales. Consideration of these factors raises concern for the validity the NMS diagnosis in these patients treated with high-dose aripiprazole.

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Jeffrey R. Strawn*
University of Cincinnati College of Medicine, Department of Psychiatry, 231 Bethesda Avenue, ML 0559, Cincinnati, OH 45267-0559, United States
E-mail address: strawnjr@uc.edu.
*Tel.: +1 513 313 7657; fax: +1 513 487 6696.

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