exposition. Furthermore, we specifically did not want the words *sudden death* to be associated with one of the first published clinical trials of ziprasidone in children.

Thus, we acknowledge that our findings are based on a prematurely terminated study and an incomplete dataset. We regret not having been more explicit about our trial's "premature discontinuation" (Blair et al., 2005, p. 78). Despite our study's limitations, we believed that our preliminary data warranted publication to provide information about QTc prolongation in children treated with ziprasidone. We look forward with interest to the complete findings from DelBello and colleagues' preliminary work (2005). Certainly a larger, well-controlled set of ECGs in a pediatric sample will be an important contribution.

Until this and similar studies are completed and presented to the clinical community, however, we stand by our earlier recommendations: careful ECG monitoring seems warranted when using ziprasidone in children. Given the relative absence of efficacy data in the pediatric population, ziprasidone should be considered a second-line option in this age group. Finally, in light of the poor reliability of automated QTc readings that we and others have documented, we recommend that manual measurements of this critical parameter be done instead, and ideally by a pediatric cardiologist.

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NEUROLEPTIC MALIGNANT SYNDROME AND ARIPIPRAZOLE

To the Editor:

Neuroleptic malignant syndrome (NMS) may represent the extreme end of a continuum of extrapyramidal and catatonic side effects associated primarily with antipsychotic drugs possessing high affinity for the D2-dopamine receptor. As a result, second-generation antipsychotic agents (SGAs) may reduce the risk of NMS. Nevertheless, sporadic case reports indicate that NMS may occur in high-risk individuals even with SGAs (Caroff et al., 2000).

A related question is whether NMS induced by SGAs is milder or atypical compared with conventional antipsychotics. This question is difficult to answer, given that the presentation of NMS has historically been heterogeneous. In addition, clinicians are more aware of NMS, enabling diagnosis of incipient cases before full-blown symptoms emerge. However, it is important not to overlook this diagnosis, even if standardized criteria are not completely met.

Aripiprazole is a recently marketed SGA with an incidence of extrapyramidal side effects no higher than that with placebo in controlled trials (Marder et al.,

2003). There are only two NMS cases cited by the manufacturer in premarketing data and three published reports implicating aripiprazole in the development of NMS-like symptoms (Chakraborty and Johnston, 2004; Duggal and Kithas, 2005; Spalding et al., 2004). We report an additional case of a severe extrapyramidal syndrome with confusion and rhabdomyolysis occurring in a young girl who received low-dose aripiprazole and discuss these findings in relationship to the diagnosis of NMS.

CASE REPORT

A 14-year-old girl with a history of depression with psychotic features and mental retardation had received olanzapine and risperidone during past hospitalizations without adverse extrapyramidal reactions. Recently, she received quetiapine 300 mg daily without side effects, but that medication was discontinued because of a lack of efficacy 2 weeks before switching to aripiprazole 5 mg daily.

Within 48 hours after initiating aripiprazole, she was admitted with tremors, drooling, cogwheel rigidity, unsteady gait, incontinence, and increasing agitation. The patient was afebrile (37.1°C), with blood pressure of 118/57 mmHg, pulse of 131 bpm, and respiratory rate of 31/rpm. Neurological examination revealed intermittent disorientation, slurred and incoherent speech, tremor, fluctuating consciousness, and extreme cogwheel rigidity in all extremities. Laboratory findings included an elevated serum creatine phosphokinase (CPK) peaking at 23,340 IU, without myoglobinuria. An EEG and head computed tomography scan were normal. Her white blood cell count was 9,300/mm^3, and a urine toxicology screen was negative.

Psychiatric consultation was obtained noting delirium complicated by extrapyramidal symptoms associated with aripiprazole. NMS was considered less likely given the lack of autonomic instability and fever. Nevertheless, supportive measures were instituted with close monitoring and treatment. Sodium bicarbonate was used to alkalinize her urine, and she was treated with 2 mg lorazepam every 4 hours, which improved her tremors and agitation. After 2 days, the serum CPK level fell to 6,157 IU and continued to normalize. Lorazepam was tapered, and the patient returned to baseline.

DISCUSSION

In this patient, low-dose aripiprazole was associated with extrapyramidal symptoms, confusion, and rhabdomyolysis. This syndrome is similar to observations reported previously (Chakraborty and Johnston, 2004; Duggal and Kithas, 2005; Spalding et al., 2004). In these cases, patients who had tolerated other antipsychotics without adverse effects developed extrapyramidal symptoms, mental status changes including catatonic signs, and CPK elevations 2 to 14 days after starting aripiprazole. Complete recovery ensued within 1 week after supportive care and administration of lorazepam and/or benztropine. Hypermetabolic symptoms (hyperthermia, autonomic instability) were absent or minimal.

The scarcity of such reports supports the notion that the liability of NMS is reduced with aripiprazole, but susceptible patients may still be at risk. Potential risk factors illustrated by our patient are mental retardation and the history of recent switching between antipsychotics (Boyd, 1993; Caroff et al., 2000). In all four case reports, antipsychotic drugs were switched before the introduction of aripiprazole and the ensuing NMS-like reaction. Pretreatment followed by discontinuation of other antipsychotics may sensitize patients or produce perturbations in dopamine systems, increasing the risk of NMS (Duggal and Kithas, 2005; Spalding et al., 2004).

These cases also illustrate the possibility of milder episodes of NMS associated with SGAs. Although rigidity, tremor, mental status changes, and rhabdomyolysis were present in all four cases, hypermetabolic features were not prominent. Whether this reflects early diagnoses, a milder *forme fruste* of NMS, examples of the clinical heterogeneity of NMS, or a unique property of aripiprazole in sparing the thermoregulatory system, is unknown. The partial dopamine agonist activity and serotonergic properties (partial 5-HT1A receptor agonist and 5-HT2A receptor antagonist) of aripiprazole may modify the effects of D2-receptor blockade and thereby protect against extreme hyperthermia and extrapyramidal dysfunction during NMS.

In conclusion, this case provides additional evidence that aripiprazole can be associated rarely with a severe extrapyramidal, catatonic, or partial NMS syndrome in certain susceptible patients. Future research may corroborate clinical or pharmacogenetic factors that could predict increased risk of NMS among patients receiving

antipsychotics. Until then, it is worth emphasizing that clinicians should consider the diagnosis of NMS, even in patients treated with SGAs who develop an incomplete symptom picture.

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