

Letters to the Editor

A Cautionary Note When Using Zonisamide in Youths: A Case Report of Association With Toxic Epidermal Necrolysis

Sir: Zonisamide is a third-generation sulfonamide anticonvulsant indicated for treatment of partial seizures. As with other anticonvulsants, it has shown efficacy in treating bipolar disorder in adults¹ and, unlike other agents, does not appear to cause weight gain. Zonisamide is contraindicated in patients with known sulfa allergies due to the risk of developing a medically serious rash.

Case report. Ms. A, a 16-year-old white female with bipolar disorder, complained to her psychiatrist about weight gain during valproic acid and quetiapine treatment. Although she was psychiatrically stable, valproic acid was replaced with zonisamide in May 2003. The patient did not have a personal history of sulfonamide allergy and took no other medications. Her father had no drug allergies, and her mother reported being allergic to paroxetine and sulfa drugs.

After 2 weeks of zonisamide treatment, several "fever blisters" appeared on Ms. A's upper chest and zonisamide was stopped. However, a bright, erythematous rash soon covered her chest, back, and buttocks and extended onto her upper extremities bilaterally. The rash reddened and became painful, and on the third day bullae rapidly formed, causing large sheets of epidermis to be lost. Ms. A was admitted to an intensive care unit for fluid resuscitation, IV access, and management. Her temperature ranged from 39.0°C to 40.0°C (102°F to 104°F), and her white blood cell count reached a high of $15.3 \times 10^3/\mu\text{L}$, while her blood cultures remained negative. A biopsy taken within 36 hours of bullae formation showed extensive basal cell necrosis. In addition to extensive mucosal membrane involvement, she lost epidermis over an estimated 51% to 60% of her total body surface area. A diagnosis of toxic epidermal necrolysis was made.

By the end of the second week of hospitalization, she was able to take food and medicine orally. Treatment with quetiapine and valproic acid was restarted, and she was discharged home.

Allergies to sulfonamide antibiotics occur in approximately 3% of the general population.² Recent data suggest that nearly 1 in 10 of those with allergies to sulfonamide antibiotics will develop an allergic reaction when taking sulfonamide non-antibiotics.³ Interestingly, the same data suggest that a history of penicillin allergy produces an even greater likelihood of developing an allergic reaction to sulfonamide non-antibiotics, despite the clear chemical dissimilarities.³ In prescribing sulfonamides, the fact that a patient has any history of drug allergy may be more important than the specific allergy reported.

Special caution must be taken when prescribing sulfa medicines for children and adolescents, as their allergy status may

not yet be known. One should obtain a personal and family history of any drug allergies and give clear instructions to discontinue medication in case of rash. Unfortunately, discontinuing the medication does not always minimize the progression of the rash. This may be particularly true with medicines that have a long half-life, such as zonisamide ($T_{1/2} = 63$ hours). Early clinical studies show promise for zonisamide in the treatment of the symptoms of bipolar disorder. This case provides a cautionary note to clinicians considering the use of zonisamide in younger patients.

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**Kevin D. Majeres, M.D.
Trisha Suppes, M.D., Ph.D.**
Department of Psychiatry
University of Texas Southwestern Medical Center
Dallas, Texas

Two Cases of Acneiform Eruption Associated With Lamotrigine

Sir: Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an anticonvulsant commonly used for the treatment of epilepsy. More recently, it has also become widely used in psychiatry for the treatment of bipolar disorder.¹ It is generally well tolerated. Benign skin reactions such as morbilliform, urticarial, or maculopapular rash occur in approximately 10% of patients.² In addition, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.^{3,4} However, the risk of these serious reactions can be kept low (at approximately 0.1% of cases) when a low starting dose and a slow titration schedule are used. Acneiform eruptions, characterized by papules and

pustules on the face, chest, and upper back, have been reported with corticosteroids and psychotropics such as lithium, aminopine, chlorpromazine, and maprotiline,⁵ but to our knowledge there have been no published cases implicating lamotrigine as the cause of acne. Here we report 2 cases of lamotrigine-associated acneiform eruption.

Case 1. Mr. A, a 23-year-old white man, was admitted for the first time to a psychiatric hospital in November 2001 due to a manic episode. He had suffered from milder mood symptoms since 1995, but he had never received psychotropic drugs. He had no somatic illness and no history of skin diseases. At admission, antimanic treatment with olanzapine was initiated with a final dose of 20 mg/day. Adjunctive clonazepam and zolpidem were also given. After 3 weeks, lithium was added as an antimanic in doses leading to serum levels up to 1.1 mmol/L. One week later, lamotrigine was initiated as a long-term mood stabilizer at 25 mg/day for 2 weeks. Subsequently, the dose was increased to 50 mg/day for the next 2 weeks and to 100 mg/day for the following week. Thereafter, the daily dose of lamotrigine was increased by 100 mg every week until a dose of 400 mg/day was reached. At this dose, the patient's steady-state serum level of lamotrigine was 4.61 µg/mL.

After remission of the manic episode, Mr. A was discharged (in February 2002) and both olanzapine and lithium were gradually tapered off. In May 2002, Mr. A received only lamotrigine 400 mg/day and had a serum level of 2.82 µg/mL. During Mr. A's visit to the outpatient clinic 1 month later, i.e., 6 months after the beginning of lamotrigine therapy and 1 month after all other drugs had been discontinued, clinical examination revealed acneiform eruptions on his back. Mr. A reported that these had developed over the last weeks. One month later, he was seen by a dermatologist, who confirmed the acneiform eruptions located on the back and dorsal aspects of the shoulders; the upper half of the back was most severely affected. At that time, the lesions were numerous small pustules and closed comedones. In addition, a few small cysts were seen.

After a few months of observation, in which the eruptions continued, lamotrigine was discontinued and replaced with valproic acid 1600 mg/day (in September 2002). Over the following weeks, the number of eruptions decreased without treatment, and after a few months there were no signs of acne except for redness corresponding to previous lesions. Mr. A is still followed in the clinic, and at this point in time (April 2004) there has been no recurrence of the acneiform eruptions.

Case 2. Mr. B, a 22-year-old white man with no previous skin diseases or somatic illness, was admitted for the first time to a psychiatric hospital in October 2001. At that time, he suffered from a manic episode with psychotic symptoms. Three years before, he had experienced a depressive episode, but he had never received psychotropic drugs. The patient's condition deteriorated into a delirious manic state, which was treated sequentially with haloperidol, zuclopentixol, and olanzapine and finally with electroconvulsive therapy (ECT). After 3 weeks, Mr. B's symptoms were under control.

Immediately after ECT was stopped, lithium was added as an antimanic in doses leading to serum levels up to 0.8 mmol/L. At the same time, the antipsychotics were tapered off due to emergent depressive symptoms, and a few weeks later, treatment with lamotrigine for prophylaxis was initiated using the same dosing schedule as was used in the case of Mr. A. When remitted, Mr. B was discharged in December 2001. In February 2002, the final lamotrigine dose of 400 mg/day was reached, leading to a steady-state serum level of 7.42 µg/mL. Lithium was then gradually tapered off and finally discontinued in March 2002. During Mr. B's visit to the outpatient clinic in June

2002, i.e., 6 months after lamotrigine had been initiated and 3 months after the discontinuation of all other drugs, inspection revealed numerous pustules, comedones, and cysts widespread on his back. He reported that these elements had been present during the prior month. At this time, the patient's serum level of lamotrigine was 4.81 µg/mL. As in the case of Mr. A, the patient's dermatologic condition was confirmed by a dermatologist shortly after.

During the following months, the eruptions continued, albeit with a reduced intensity. Although Mr. B was provided with an explanation that the skin reactions seemingly were related to lamotrigine, he was reluctant about discontinuing the drug. Therefore, he was continued on the same dose, and in October 2002, his serum drug level was 4.86 µg/mL. However, in November 2002, during a manic recurrence, lamotrigine was replaced with valproic acid 1500 mg/day. During the following few months, the eruptions stopped without dermatologic treatment, leaving only redness corresponding to previous lesions. At follow-up in April 2004, there was still no recurrence of the dermal symptoms.

The 2 cases presented here are suggestive of induction of acne by lamotrigine. Acne developed in both cases within a few months after the target dose of lamotrigine had been reached and while the patient received no other drugs. The clinical presentation was a uniform picture with numerous small pustules, closed comedones, and to a lesser degree small cystic elements. Furthermore, the acne resolved without therapy when lamotrigine was discontinued, and after a follow-up period of more than 1 year, the patients still showed no symptoms or signs of recurrence of acne. In addition, in both cases there was no history of previous acne. However, no rechallenge was performed in these cases to further support any causal relationship. That the patients were actually taking lamotrigine was confirmed by their serum drug levels, which were within an acceptable range. It is well known that lithium treatment may lead to acne.⁶ However, in our cases the eruptions did not develop until 1 to 2 months after lithium was discontinued. In addition, lithium-induced acne most often develops within days or weeks after starting treatment and resolves when lithium is discontinued,⁷ meaning that both of our patients received lithium for a sufficient period of time to develop lithium-induced acne, had lithium been the causative agent. However, the possibility that the preceding treatment with lithium may be a related causative factor obviously cannot be ruled out.

Although overall health is not impaired, acne can produce numerous psychological problems for adolescents and adults.⁸ With the increasing use of lamotrigine, this potential adverse reaction to lamotrigine should be borne in mind.

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**Jannie Noernberg Nielsen, M.D.
Rasmus Wentzer Licht, M.D., Ph.D.**

Mood Disorders Research Unit
Aarhus University Psychiatric Hospital
Risskov, Denmark

Karsten Fogh, M.D., M.Sc.

Department of Dermatology
Aarhus University Hospital
Aarhus, Denmark

A Case of Hyponatremia Associated With Escitalopram

Sir: There have been several case reports of hyponatremia induced by selective serotonin reuptake inhibitors (SSRIs), including citalopram, secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).¹⁻³ A recent survey described 35 reports of hyponatremia associated with citalopram administration. Three quarters of the cases involved women. Elderly women were particularly vulnerable to citalopram-induced SIADH.⁴

We report the first case of escitalopram-induced hyponatremia secondary to SIADH. Escitalopram, the therapeutically active S-enantiomer of RS-citalopram, is a highly selective and potent SSRI that was only recently approved for the treatment of mood and anxiety disorders.

Case report. Ms. A, a 62-year-old woman, had a 10-year history of 2 major depressive episodes (DSM-IV-TR criteria). Her medical history included hypertension, osteoporosis, hypercholesterolemia, paroxysmal atrial fibrillation, and an episode of deep vein thrombosis years earlier due to activated C protein deficiency. She was well controlled on treatment with losartan, simvastatin, sotalol, warfarin, calcium and vitamin D preparation, and occasionally oxazepam.

Three weeks prior to her admission in June 2003, Ms. A developed her third major depressive episode. She was started on treatment with escitalopram, 5 mg/day, which was increased to 10 mg/day after 1 week. She was then admitted to a general hospital after a syncope and a fall with mild head trauma. This event had been preceded by mild headaches, nausea, fatigue, dry mouth, and lower abdominal discomfort. At admission, the patient's serum sodium level was 110 mmol/L, serum osmolality was 261 mmol/kg H₂O, urine sodium level was 53 mmol/L, and urine osmolality was 286 mmol/kg H₂O. Results of repeated electrocardiogram tracings were normal. The patient's coagulation panel results were within therapeutic range for warfarin treatment. Computed tomography of the head showed no evidence of brain abnormality. After a thorough investigation for possible causes of SIADH, no other etiology was identified apart from escitalopram. Escitalopram was discontinued, and the patient was treated with intravenous normal saline solution.

Ms. A's sodium levels normalized slowly, with a concomitant resolution of the somatic symptoms. She was discharged with a serum sodium level of 130 mmol/L. A week later, her serum sodium level stabilized at 135 mmol/L, and serum and urine osmolality also normalized. She was subsequently treated with mirtazapine, 30 mg/day, and experienced gradual improvement in her mood without recurrence of hyponatremia.

In this case, the diagnosis of escitalopram-induced SIADH was supported by the return of serum and urine electrolyte levels to normal values after escitalopram discontinuation. It seems that the risk for SIADH is not confined to racemic citalopram,³ but may occur also with the escitalopram enantiomer. Moreover, it is possible that citalopram-induced SIADH may be due to escitalopram and possibly not attributable to R-citalopram. Further studies are needed to elucidate the unique activity of escitalopram in iatrogenic SIADH.

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Eitan Nahshoni, M.Sc., M.D.

Abraham Weizman, M.D.

Geha Mental Health Center

Rabin Medical Center

Dafna Shefet, M.D.

Nimrod Pik, M.D.

Department of Internal Medicine E

Rabin Medical Center, Beilinson Campus

Petah Tikva, Israel

Catatonia Is a Risk Factor for Neuroleptic Malignant Syndrome

Sir: We read the article by Ananth et al.¹ on neuroleptic malignant syndrome (NMS) and atypical antipsychotic drugs with great interest. We thank them for their review of 68 cases drawn from the medical literature. They identified some of the major risk factors for NMS associated with atypical antipsychotics, including the male gender, diagnosis of schizophrenia and other psychoses, mental retardation, and concurrent physical illness. We feel that additional risk factors should be listed. They are catatonia, genetic predisposition, ambient heat, preexisting extrapyramidal signs (EPS) or parkinsonism, dehydration, agitation, previous episodes of NMS, and low serum iron level.² Since NMS is a rare phenomenon, these other factors must be considered in relative comparisons and should not be considered as contraindications to the use of antipsychotics for patients with disorders for which antipsychotics are warranted.²

Our research has focused on 3 possible subtypes of NMS: (1) catatonia exacerbated to NMS, (2) NMS with resultant catatonia, and (3) non-catatonic NMS. Preexisting catatonia has been shown to be a potent risk factor for the development of NMS.³ Furthermore, cases of NMS were found to exhibit catatonia in at least 1 study.⁴ On the basis of a prospective analysis of 14 episodes of NMS, Lee⁵ has proposed that non-catatonic NMS (1) is preceded by EPS and delirium, (2) has a poor response to benzodiazepines, (3) is associated with EPS nonresponsive to anticholinergics, (4) has a long and protracted course, (5) is associated with high creatine phosphokinase levels ($> 1000 \mu\text{g/mL}$), and, most importantly, (6) is associated with atypical antipsychotics and concomitant lithium therapy. The identification of the non-catatonic NMS subtype suggests that there may be different encephalopathic processes within the populations of patients who develop NMS.^{5,6}

Ananth et al.¹ did not assess the cases of NMS in their review for catatonia. We think that it would be helpful to analyze the 68 cases for the 3 possible NMS subtypes. We plan to obtain the articles from their reference list and apply the Lee-Carroll Scale⁷ to the cases. The Lee-Carroll Scale is a 7-item assessment tool that can be applied to reports of patients with a diagnosis of NMS. The score ranges from 0 to 14 with items to address each of the 6 points listed above. It is modeled after the Hynes-Vickar Scale for NMS.⁸ However, the Lee-Carroll Scale differs from this NMS scale because it requires determination of (1) whether catatonia or catatonic signs are present and (2) if present, whether catatonia preceded the development of NMS.

We have been able to identify the 3 NMS subtypes in cases drawn from the Neuroleptic Malignant Syndrome Information Service database.⁹ However, our cases were drawn from patients exposed to typical and atypical antipsychotics.^{9,10} We note that some investigators are examining ways to identify NMS early and even prevent NMS.^{9,11} We also hope to examine some of the other risk factors listed above, such as low baseline serum iron level. The study of NMS is difficult due to the paucity of prospective studies. We thank Ananth et al. for their efforts to improve our understanding of NMS.

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Brendan T. Carroll, M.D.

Department of Psychiatry

University of Cincinnati

Chillicothe, Ohio

Joseph W. Y. Lee, M.R.C.Psych., F.R.A.N.Z.C.P.

School of Psychiatry and Clinical Neurosciences

University of Western Australia

Perth, Australia

Adjunctive Therapeutic Effects of Galantamine on Apathy in a Schizophrenia Patient

Sir: The limitations of the current medications used to treat schizophrenia have led to a search for adjunctive treatments that may better address the negative symptoms, cognitive deficits, and behavioral problems of the disorder. A promising strategy might be adopted from the current use of acetylcholinesterase inhibitors in the treatment of Alzheimer's disease.¹ Acetylcholinesterase inhibitors (e.g., tacrine, donepezil) improve general cognitive functioning and reduce apathy, anxiety, agitation, and other psychiatric symptoms in Alzheimer's patients. Galantamine has a dual mechanism of action that may offer particular benefits for individuals with schizophrenia. Like donepezil, it reversibly inhibits cholinesterase, increasing the quantity and lifetime of acetylcholine within the synaptic cleft. Unlike donepezil, galantamine also acts as a positive allosteric modulator of nicotinic acetylcholine receptor sites and, thereby, enhances signal strength.^{2,3}

Diminished expression of the α_7 subtype of nicotinic acetylcholine receptor has been reported in several brain regions in schizophrenia, including the hippocampus, frontal cortex, and thalamus.⁴ There are data to suggest that early central processing abnormalities, especially difficulties with sensory gating, may exist in patients with schizophrenia and be due, in part, to defective signal transduction by the α_7 nicotinic acetylcholine receptor.⁴ There are also data showing abnormal regulation of the density of high-affinity nicotinic acetylcholine receptors in schizophrenia.⁵ Because of its allosteric properties, galantamine may be able to improve the efficiency of acetylcholine signal transduction by both high- and low-affinity nicotinic acetylcholine receptors.⁶ We report a beneficial therapeutic effect of adjvant galantamine administration on apathy in 1 schizophrenia patient with persistent deficit symptoms.

Method. Galantamine was added in August 2002 on an open-label basis to the stable psychotropic medication regimens of 2 treatment-refractory male inpatients with a DSM-IV diagnosis of schizophrenia. Informed consent was obtained for this protocol, which was approved by the institutional review board of the University of Maryland Medical Center. (Treatment-refractory was defined as persistence of symptoms in spite of adequate trials of at least 3 classes of antipsychotic medications and inability to live independently and work competitively.) Patient 1, a 47-year-old heavy smoker, was maintained on a stable medication regimen of olanzapine, risperidone, and valproic acid. Patient 2, a 42-year-old non-smoker, was maintained on a stable medication regimen of olanzapine and citalopram. Both patients had histories of

Table 1. Marin Apathy Evaluation Scale (AES) Ratings in 2 Schizophrenia Patients Receiving Adjuvant Galantamine Treatment^a

AES Area	Baseline	End of Titration (at 3 mo)	Optimal Dose (for 4 wk)	Optimal Dose (for 8 wk)
Motivation^b				
Patient 1	3.3	3.3	2.0	2.0
Patient 2	4.0	3.7	4.0	3.7
Novelty^c				
Patient 1	4.0	4.0	2.0	2.0
Patient 2	4.0	4.0	4.0	4.0
Persistence^d				
Patient 1	3.5	4.0	1.5	1.5
Patient 2	4.0	4.0	3.5	3.5

^aThe values represent mean scores of pooled questions from the clinician-rated version of the Marin AES. Lower scores reflect improvement in targeted symptoms.

^bConsists of questions 1 ("S/he is interested in things"), 16 ("Getting things done during the day is important to him/her"), and 18 ("S/he has motivation").

^cConsists of questions 4 ("S/he is interested in having new experiences") and 5 ("S/he is interested in learning new things").

^dConsists of questions 8 ("Seeing a job through is important to him/her") and 9 ("S/he spends time doing things that interest him/her").

multiple psychiatric hospitalizations with durations of illness of greater than 20 years.

The patients were evaluated at baseline, at the end of the 3-month galantamine titration schedule, and after 1 and 2 months on "high-dose" (24 mg/day) adjuvant galantamine treatment with a battery of measures that included the Marin Apathy Evaluation Scale (AES).⁷ The effect of adjuvant galantamine administration on the construct of apathy was assessed objectively with the pooling of specific questions from the Marin AES that changed from baseline; these questions related to the areas of motivation (questions 1, 16, and 18), novelty (questions 4 and 5), and persistence (questions 8 and 9). The scores for the areas of motivation, novelty, and persistence on the Marin AES reflect the mean of the scores for the individual questions within each of these areas (Table 1).

Results. Patient 1 showed a dramatic response to galantamine, while patient 2 was essentially a nonresponder. The global improvement of apathy in patient 1 was reflected in the increase in his total score on the Marin AES. Patient 1 also showed improvements on formal ratings of affective nonresponsivity, anergia, and ability to enjoy sexual interests and activities.

This initial finding suggests that galantamine may be a useful adjunctive agent for the treatment of apathy, which may be an important therapeutic target, in at least some medication-resistant patients with schizophrenia. Importantly, galantamine was well tolerated, with no reported or observed side effects (such as nausea, vomiting, diarrhea, anorexia, or headache). Of interest, the patient who showed response to treatment has elected to continue to receive galantamine.

Conceivably, galantamine's greatest therapeutic benefit will be observed in schizophrenia patients with diminished expression of nicotinic acetylcholine receptors in selected regions of the brain. Abnormal variants of the promoter region for the α_7 nicotinic acetylcholine receptor located on chromosome 15 may be a mechanism for its diminished expression in selected brain areas.⁸ Diminished expression of normal receptor protein would encourage exploration of strategies to improve the transduction of the acetylcholine signal, such as galantamine use. Of course, only future double-blind, placebo-controlled trials can substantiate the suggestions of therapeutic efficacy of adjuvant galantamine administration, especially for such targets as negative

symptoms, apathy, and mood.⁹ It might be informative to randomize subjects in these future controlled studies according to smoking status and genetic profiles of promoter variants that regulate expression of the α_7 nicotinic acetylcholine receptor subunit. It is possible that the smoking status of the patient who responded contributed to his therapeutic response to galantamine.

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David S. Arnold, M.D.
Richard B. Rosse, M.D.
Dwight Dickinson, Ph.D.
Rhonda Benham, R.N.
Stephen I. Deutsch, M.D., Ph.D.
VISN 5 Mental Health Service Line
Department of Veterans Affairs
Linthicum, Maryland

Matthew W. Nelson, Pharm.D.
Maryland Psychiatric Research Center
Baltimore, Maryland

Rhabdomyolysis and Coma Associated With Amisulpride: A Probable Atypical Presentation of Neuroleptic Malignant Syndrome

Sir: Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse reaction, generally associated with typical neuroleptics. Levenson criteria¹ for the diagnosis of NMS require the 3 major (fever, rigidity, elevated creatine kinase [CK]) or 2 of the major and 4 of the minor (tachycardia, diaphoresis, tachypnea, abnormal blood pressure, altered consciousness, leukocytosis) manifestations. The following case report describes a patient who developed a comatose state accompanied by CK elevation after 5 days of treatment with amisulpride, a selective D₂/D₃ antagonist. To our knowledge, this is the first report asso-

ciating a probable atypical presentation of NMS with amisulpride monotherapy.²

Case report. Ms. A, a 41-year-old woman with a 22-year history of DSM-IV disorganized schizophrenia and no history of NMS, drug/alcohol use, or other medical illness, was admitted with an acute exacerbation. She had been completely medication-free for several months. Amisulpride was initiated at 400 mg/day, to be increased to 600 mg/day 2 days later.

On the fifth day of her treatment, she developed clouding of consciousness that progressed to coma in 6 hours. She maintained spontaneous respiration but was unable to localize painful stimuli. She had no rigidity. Electrocardiogram findings and blood pressure were within normal limits. Ms. A's body temperature was slightly elevated (100°F). Tachypnea, tachycardia, and diaphoresis were absent. Electroencephalogram revealed generalized slowing. Other findings included hyponatremia (120.4 mmol/L), hypokalemia (3.0 mmol/L), leukocytosis (20,100/mm³), and elevated levels of aspartate aminotransferase (114 U/L) and CK (10,137 U/L) on the first day of the coma. Blood and urine cultures were negative.

Acyclovir 40 mg/kg/day was started and amisulpride was discontinued with the tentative diagnosis of viral encephalitis or NMS. Ms. A's coma resolved in 2 days with no other specific intervention. Acyclovir was discontinued 7 days later, when viral encephalitis was ruled out with normal findings on cranial magnetic resonance imaging and cerebrospinal fluid examination, including negative cultures for all possible infectious agents. The patient's leukocyte count and CK levels started to decrease on the third day and were completely normalized on the fifteenth day after amisulpride was discontinued. Partial remission of psychosis was later achieved with clozapine 450 mg/day.

With the presence of 2 major and 2 minor manifestations, this case does not fulfill the Levenson criteria¹ for NMS. However, since other possible causes of coma accompanied by rhabdomyolysis were ruled out, an atypical mild presentation and a forerunner of the full syndrome are the most probable diagnoses. These diagnoses are supported by the rapid resolution of coma and normalization of laboratory findings following the discontinuation of amisulpride. Furthermore, atypical presentations lacking 1 or more of the classical symptoms and findings have previously been described, especially with the use of novel antipsychotics.³⁻⁵

Some authors have associated the atypicality of presentation with the broader receptor profile of novel antipsychotics.³ In the case of amisulpride, the presynaptic activity at the dopamine D₂/D₃ receptors that increases dopaminergic transmission at lower doses might have compensated for the strong postsynaptic dopamine D₂ blockade at higher doses. The rapid increase in the dose of amisulpride is another conceivable explanation for this case. Since our pharmacologic armamentarium is expanding with new antipsychotics that have broader receptor profiles, the mild and atypical forms of NMS might be expected to increase. When the equally strict interventions that the mild cases require are taken into account, the diagnostic criteria for NMS might need to be reviewed to include atypical forms.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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E. Cem Atbasoglu, M.D.
Halise Devrimci Ozguven, M.D.
Meram Can Saka, M.D.
Ceren Goker, M.D.

Department of Psychiatry
Ankara University School of Medicine
Ankara, Turkey

Correction

The below reply should have accompanied the Letter to the Editor by Timothy R. Berigan, M.D.,¹ that was published in the January 2004 issue of the *Journal* (2004;65:133). The staff regrets the oversight.

Dr. Makela Replies to Dr. Berigan¹

Sir: When used concomitantly, medications having the potential to cause sedation may produce additive sedative effects. Certainly this may have occurred in our patients² as a result of divalproex administration. Importantly, however, at the time of modafinil initiation our patients were stable and sedation was their primary complaint. Thus, regardless of serum levels, it would not have been prudent to decrease the dosage of divalproex in order to minimize the existing sedation at the risk of symptom decompensation.

Interestingly, a recent research report³ suggests the potential usefulness of modafinil in the treatment of patients with major depressive disorder and symptoms of sleepiness or fatigue. In an open-label study, 20 patients received modafinil 200 mg/day and fluoxetine or paroxetine 20 mg/day. Fatigue and wakefulness were significantly improved after 1 week of treatment and improvement continued through week 6. Thus, evidence is accumulating that modafinil may have beneficial effects for fatigue/sedation associated with medical conditions or adverse effects of medications.

Dr. Makela has no financial affiliation or other relationship relevant to the subject matter of this letter.

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Eugene H. Makela, Pharm.D., B.C.P.P.
Schools of Pharmacy and Medicine
West Virginia University
Morgantown, West Virginia