Letters to the Editor

Treatment of Kleine-Levin Syndrome: Melatonin on the Starting Block

Sir: Kleine-Levin syndrome (KLS) is complex and rare, primarily affects adolescent males, and is characterized by recurrent attacks of hypersomnia, excessive eating, and striking behavioral and psychiatric symptoms. It has been hypothesized that KLS is related to bipolar affective spectrum disorders.[1] Exogenous melatonin administration does not seem to improve patients with rapid-cycling bipolar disorder.[2] This treatment, however, has not yet been tested in KLS. We report a case of a man with persistent KLS symptoms that were alleviated after treatment with exogenous melatonin.

Case report. Mr. A, a 28-year-old man, first had KLS symptoms early, at the age of 9, consisting of periods of hypersomnia and bulimia combined with disinhibited attitudes. At age 16, Mr. A showed hypersexuality with compulsive masturbation during the recurrent attacks. KLS was only diagnosed during the fifth episode of his illness, at age 20. Mr. A mentioned that alcohol and physical exercise might have triggered acute episodes. Episodes occurred once a year, mostly during the winter season. Two episodes occurred during summers, at ages 20 and 27, probably owing to the jet lag accompanying transatlantic flights. Episodes had been treated with antidepressant drugs and antipsychotic drugs when needed. Despite those treatments, Mr. A continued to present with at least 1 episode per year, with serious negative consequences on his work and his social life. From when he was 20 years of age, he was treated with lithium and carbamazepine, which were maintained through the entire period of the study.

A sleep investigation was proposed because Mr. A complained of a delayed sleep pattern. We measured melatonin during 24 hours, sampling it every hour, to further assess the circadian pattern shift. Investigations demonstrated a 2-hour delay in the melatonin secretion pattern and a 90-minute delay in the sleep pattern. A dose of 5 mg of exogenous melatonin was given the 2 following nights at 8 p.m., and improvement in subjective mood and sleep was observed. Sleep data confirmed Mr. A's impression and were consistent with a normalized sleep: total sleep time and sleep efficiency index increased significantly, from 214 minutes and 55% at baseline to 379 minutes and 89% after treatment with 5 mg of melatonin. This improvement was mostly due to a sharp decrease in the frequency of intercurrent awakenings. Delta sleep ratio and REM sleep time remained unchanged. The use of 5 mg of melatonin was continued during the following 3 months. We then decreased the dosage of melatonin to 3 mg/day. Ten days later, Mr. A reported a mild relapse consisting of asthenia, depression, and paranoid ideas. Sleep parameters worsened except for delta sleep ratio and REM sleep time, with total sleep time dropping to 308 minutes and sleep efficiency index to 71%. Melatonin was again increased to 5 mg/day followed by a new clinical improvement.

In view of the disruption of the circadian cycle of sleep and wakefulness, it could be hypothesized that the syndrome described is associated with a dysfunction of the circadian system.[3] The effectiveness of our treatment may result from either melatonin alone or from the association of melatonin with mood stabilizers. To our knowledge, chronic treatment with carbamazepine does not significantly modify nocturnal sleep.[4]

Lithium, however, is known to shift melatonin phases forward.[5] Our patient displayed a melatonin phase delay with lithium treatment. We thus suggest that the effect of lithium alone was not sufficient to restore normal melatonin circadian cycle. The effect of combined exogenous melatonin and lithium could be synergistic and help move the displaced phases toward normalization.

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Multiple Rib Fractures Secondary to Severe Tardive Dystonia and Respiratory Dyskinesia

Sir: Szymanski et al.[1] reported rib factures as an unusual complication of severe tardive dystonia in 1993. An extensive MEDLINE search revealed no further cases reported in the English literature since. We now report an Asian patient who developed a similar complication and discuss the distinct features of the complication.

Case report. Mr. A, a 42-year-old divorced Chinese man with a 10-year history of psychotic depression, was admitted to

our unit in March 1996 for involuntary movements that he had experienced for 2 years. Medical history revealed treatment with benzodiazepines, β-blockers, neuroleptics, and tricyclic and selective serotonin reuptake inhibitor antidepressants before the development of the movement disorder. Mr. A's family history was negative for neurologic disease. Extensive blood screening, electroencephalogram, computed tomography, and brain magnetic resonance imaging all revealed normal findings. Clinical observation showed facial grimacing, coarse choreoathetosis over 4 limbs, marked cervical dystonia, severe trunk twisting and back arching, and severe grunting. Mental state examination revealed moderate anxiety and distress with no psychotic symptoms. Assessment with the Abnormal Involuntary Movement Scale (AIMS)[2] showed a global score of 4 (severe). A diagnosis of tardive dystonia with respiratory dyskinesia was made.

Mr. A was treated with various medications together with intensive physical and behavioral therapy that included symptom charting, neck support, relaxation exercise, and anxiety control. The trifluoperazine and clomipramine that he had been receiving in the previous 6 months were gradually discontinued over 2 weeks' time and replaced with sulpiride, with little improvement. Tetrabenazine was subsequently added, followed by clonazepam and clozapine. Mr. A's condition was finally stabilized on treatment with clozapine, 325 mg/day; clonazepam, 9 mg/day; diazepam, 15 mg/day; and tetrabenazine, 50 mg/day, for more than 1 year before new complications emerged. During that 1-year interval, he continued to experience acute exacerbations of tardive dystonia.

In January 1998, a radiograph taken in response to right chest pain revealed multiple displaced fractures of the right 5th, 6th, 8th, 9th, and 10th ribs and recent fractures with callus formation over the right 4th to 7th ribs and left 5th and 6th ribs. No pneumothorax was found. Physical examination revealed mild tenderness over the right side of the back but no signs of external injury. Repeated rating with the AIMS showed scores similar to those from 1996. Mental state examination revealed satisfactory remission of his psychotic illness. No history of trauma to chest was known to the nurses or Mr. A himself. Skeletal survey excluded osteoporosis. Results of chest films taken in June 1997 were normal. The orthopedic surgeon diagnosed rib fractures caused by violent involuntary movements. Mr. A was closely observed, and the fractures were managed conservatively since there was no sign of cardiopulmonary decompensation. The neurologist added sodium valproate, which produced limited but clinically significant improvement. Repeated local injections of botulinum toxin were tried, but proved not to be useful because multiple muscle groups were involved.

Yassa and Jones[3] reviewed the complications of tardive dyskinesia and concluded that respiratory and gastrointestinal difficulties were the most serious outcomes of this disorder. The current report is the first of its kind among people of color. The scarcity of such reports could be attributed to uncommon occurrence of severe tardive dystonia and respiratory dyskinesia[4] as well as to underdetection of the complication. Our case included extensive rib involvement, which, together with the features of severe grunting and truncal twitching, suggests that the fractures most likely resulted from severe incoordinated contraction of the respiratory and axial muscles. The break probably occurred at the location where the serratus muscle and costal slips of the latissimus dorsi interdigitate with fibers of the external oblique.[5] Since there was no change in drug therapy during the period when fracture was supposed to have occurred, the natural fluctuating course of the dystonic/dyskinetic movements were probably responsible for the rib pathology instead of medication adjustment as in the case reported by Szymanski et al.[1] This finding should alert clinicians to obtain regular chest radiographs for patients with severe tardive dystonia and respiratory dyskinesia, even in asymptomatic cases.

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Nefazodone-Associated Subjective Complaints of Burning Sensations

Sir: Nefazodone is a relatively new antidepressant drug. Preclinical data suggest that it has potent antagonistic effects on postsynaptic serotonin-2 (5-HT_2) receptors and moderate presynaptic serotonin and norepinephrine reuptake inhibiting properties while demonstrating low affinity for other receptor types (including other 5-HT receptors and cholinergic, α-adrenergic, dopaminergic, and histaminergic receptors).[1] It has to date been shown to be safe and well tolerated,[2,3] with clinical efficacy comparable to that of selective serotonin reuptake inhibitors (SSRIs).[3–5]

Our attention was drawn to a recurrent complaint apparently associated with nefazodone. We report here 3 cases of patients who each complained of burning sensations in various parts of their bodies, not precisely related to organ systems, which appeared while they were treated with nefazodone and were alleviated by its withdrawal. To the best of our knowledge, this is the first report associating nefazodone therapy with complaints such as these.

Case 1. Mr. A, a 43-year-old man without somatic or neurologic problems, first saw a psychiatrist because of depressed mood, fatigue, diminished interest, listlessness, insomnia, and anxiety and a decrease in appetite and occupational and social functioning. He was diagnosed with major depression according to DSM-IV and was treated with fluoxetine, 20 mg/day. After a month, the treatment was stopped owing to complaints of sexual dysfunction (changes in libido and delayed ejaculation). After a washout period of 1 week, a regimen of nefazodone was started at 100 mg twice daily, the higher initial dose recommended by the manufacturer, because of the severity of the subjective suffering.

During the first week of therapy, Mr. A began to complain of an unpleasant burning sensation in alternating areas beneath the skin of his face, back, abdomen, and legs, which appeared sev-

eral times each day and continued for up to 30 minutes each time. These sensations were not accompanied by sweating or flushing, but were very worrying and distressful for him. Physical examination and laboratory analyses revealed no pathologic findings. Mr. A was not found to be taking any other medications or over-the-counter herbal products. Continued treatment with the same dosage, based on the assumption that the complaints might improve over the subsequent few days and on the lack of physical findings, aggravated the intensity of the distressful sensations. He refused to continue treatment after an overall period of 2 weeks. Discontinuation of nefazodone treatment resulted in prompt relief of the discomfort.

Case 2. Mr. B, a 28-year-old man, was first examined by a psychiatrist at the age of 28 years for depressed mood, sleep disorder (difficulty in falling asleep and early waking), decreased appetite with objective evidence of weight loss, and anhedonia with a concomitant decrease in libido and impotence and was diagnosed with nonpsychotic major depressive episode according to DSM-IV. Nefazodone was selected as the initial drug treatment, owing to the fact that it is reported to have fewer effects on sexual function.[3] The initial dosage of nefazodone was 100 mg b.i.d. After 7 days, the dose was increased to 150 mg b.i.d., and after a further 3 days, to 200 mg b.i.d., as recommended by the manufacturer. For 3 weeks, Mr. B was treated with this dosage without evidence of significant clinical improvement.

During this period, he increasingly complained of feelings of burning sensations, described as lasting about 30 minutes and occurring a number of times each day. These sensations were unrelated to the time of ingestion of the drug and were located over alternating areas of the body and within various organs or tissues with distinct discomfort, but not enough to disrupt daily activity. Again, physical and laboratory work-ups revealed no pathology, nor was he receiving any other substances. In spite of the mild discomfort, the daily dosage was increased to 600 mg/day after 3 weeks with Mr. B's agreement. This dose resulted in a gradual improvement of the depressive symptoms and the disappearance of complaints of sexual dysfunction. However, the burning sensations intensified. They appeared repeatedly during the day and caused considerable subjective discomfort and distress. Repeated physical examination and laboratory analyses did not reveal any pathology. The dosage of nefazodone was maintained for 4 weeks at Mr. B's insistence, as he "preferred to suffer the discomfort to the depression." Eventually, the subjective discomfort prevailed, and the dosage was cut back to 400 mg/day and then to 200 mg/day, at which time his discomfort was alleviated. Continued treatment with this dose eventually resulted in clinical improvement of the depression.

Case 3. Mr. C, a 63-year-old man with a 30-year history of recurrent depression, was admitted to our outpatient clinic because of a recurrence of symptoms fulfilling DSM-IV criteria for major depression. He had previously experienced an improvement in his depressive symptoms with tricyclic antidepressants. Over the last 8 years, he had been in remission without any psychopharmacologic treatment. During these years, he had developed a prostatic adenoma and ischemic heart disease. He was not taking medication for the former and used sublingual nitrates (isosorbide dinitrate) when he felt chest pains for the latter. Mr. C reported diminished libido and was concerned about experiencing sexual disturbances, as occurred during treatment with tricyclic antidepressants in the past. Because of his physical condition and to minimize adverse affects on sexual function, nefazodone was chosen.

Nefazodone was started at a low dose of 50 mg b.i.d.; however, after 3 days he began to complain of highly uncomfortable burning sensations all over his body, similar to those described by the first 2 patients, which were not associated with other somatic complaints. Repeated physical examinations, including an electrocardiogram, did not reveal any changes compared with the pretreatment assessment. Mr. C continued to take the same dose of nefazodone for another week, again based on the assumption that his complaints reflected a transient side effect. However, the burning in his abdomen and chest, although without any other complaints or symptoms and neither panic nor cardiorespiratory in origin, was accompanied by a fear of death and was of such intensity and frequency that he refused to continue treatment with nefazodone after a total of 10 days. The burning sensations disappeared immediately after cessation of nefazodone therapy. Mr. C was switched to treatment with trazodone, which improved his mental state, although he continued to complain of sexual dysfunction.

Nefazodone is an antidepressant with a chemical structure unrelated to that of SSRIs, tricyclics, tetracyclics, or monoamine oxidase inhibitors.[4] The most common adverse effects causing discontinuation of nefazodone therapy include nausea, headache, dizziness, asthenia, and insomnia.[6] In all 3 abovementioned cases, nefazodone was considered to be a reasonable clinical choice, based on its reported efficacy, safety, and conveniently mild side effect profile, including the reputed sparsity of drug-related sexual dysfunction.[3] However, in the above cases, we encountered complaints of troublesome subjective burning sensations associated with nefazodone therapy. These complaints were relatively uniform in character, began shortly after the introduction of monotherapy, and in 1 case (case 2) were quite clearly dose related. They were alleviated on reduction of dose or refusal to continue treatment. We are thus led to suspect that these complaints may represent a previously unreported adverse effect of nefazodone.

We are hesitant to propose possible mechanisms underlying the complaints at this time, since they would be based on only 3 cases. The intention of this report is to draw the attention of clinicians to the phenomenon, which may represent a heretofore unreported side effect of treatment with a relatively novel medication. Further systematic study would be warranted should a significant number of cases be reported.

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Metrifonate for Alzheimer's Disease Patients

Sir: Metrifonate, an organophosphate compound synthesized in the 1950s, is widely used as an insecticide for fruit and field crops, as an antiparasitic agent for domestic animals, and as a second-line antischistosomiasis agent in humans.[1–3] Because of the irreversible cholinesterase inhibitor properties of metrifonate, Becker and colleagues[4] proposed it for improving cognitive function in patients with Alzheimer's disease. Published and unpublished results of phase 3 clinical trials generally support metrifonate's essential cognitive efficacy.[5–7] Unfortunately, the results of one of these trials, undertaken by Raskind et al. (May 1999 issue),[7] have been reported in such a way as to make it difficult to appreciate metrifonate's clinical effects or safety.

Although the written protocol specified 2 primary outcomes (i.e., the Alzheimer's Disease Assessment Scale-Cognitive subscale [ADAS-Cog] and the Clinician Interview-Based Impression of Change with Caregiver Input [CIBIC-Plus]), the published report highlighted and discussed only 2 of many secondary outcomes, the Mini-Mental State Examination (MMSE) and the Neuropsychiatric Inventory (NPI). The essential and primary ADAS-Cog—the "gold standard" of efficacy in all definitive cholinesterase inhibitor trials—is reported merely as statistically significant with a p value, but without providing an appropriate statistic and the means and variances of the difference scores. Therefore, a reader cannot appreciate the drug's clinical or statistical effect, nor compare it with the other published metrifonate trials. By contrast, much was made of the importance and size of the MMSE score differences (larger in this metrifonate trial than in others) and the NPI differences.

Minimizing the significance of the adverse events, which were 4 to 5 times more common with metrifonate than placebo, and considering them as "peripheral" also undermine a reader's confidence in these results. That 8% of metrifonate patients compared with 2% of placebo patients developed agitation is contrary to the argument that metrifonate benefited behavioral disturbances (based on a very small mean difference on the NPI total score for the whole sample). The Bayer investigators should have specifically assessed these patients to see if the clinically observed agitation was accompanied by worsening as measured by scores on the NPI. A demonstration of convergence would have been informative.

Finally, there have been other adverse events associated with metrifonate—more serious than those enumerated in the publication—that in September 1998 led Bayer Corporation and the U.S. Food and Drug Administration to halt its development and to withdraw all patients from the medication. This important circumstance should have been mentioned.

Ideally, the Bayer personnel should have more completely represented the efficacy, safety, and current status of their potentially useful cholinesterase inhibitor for Alzheimer's disease.

Disclosure: Dr. Schneider has received honoraria, contracts, and/or consulting fees from the following developers of cholinesterase inhibitors: Pfizer, Eisai America, Novartis, Bayer, Parke-Davis, Forest, and Janssen. In addition, he has received similar support from several developers of other medications for Alzheimer's disease. Specifically, in the past, he has received support for writing reviews of tacrine, donepezil, and rivastigmine from the sponsor of these medications and most recently was commissioned by Bayer Corporation to review metrifonate.[2]

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Drs. Raskind and Cyrus Reply

Sir: We would like to respond to Dr. Schneider's comments on our article.[1] For regulatory reasons, the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC-Plus) are generally the primary outcome measures. It has become increasingly apparent that these primary efficacy variables do not describe the total symptomatic profile of Alzheimer's disease, and, therefore, the secondary outcomes were reported in our article with equal prominence to scores on the ADAS-Cog and the CIBIC-Plus. It is acknowledged that the exclusion of the actual treatment difference in ADAS-Cog scores did not provide a clear indication of the clinical effect size. This particular study had a treatment difference of 1.7. When reviewing the 2 other similar studies with metrifonate,[2,3] we found that the treatment difference for ADAS-Cog scores after 6 months was 2.9 in each case. Taken overall, the ADAS-Cog outcome therefore appears to be equivalent to those of other agents. Our study[1] also demonstrated statistically significant treatment differences for CIBIC-Plus, Mini-Mental State Examination (MMSE), Disability Assessment for Dementia scale, and Neuropsychiatric Inventory (NPI) scores.

Adverse events in this study have to be put into perspective. For patients discontinuing the study owing to adverse events, the rates were very similar, with 11% for metrifonate and 9% for placebo. We reported in the article only those adverse events that differed from placebo by more than 5%. Of those, the rates of these mild or moderate adverse events were 4 to 5 times higher than the placebo rate, ranging from 8% to 10%. They were predominantly mild in nature and were not unusual for the acetylcholinesterase class of drugs.

The analysis suggested by Dr. Schneider to further evaluate those patients who demonstrated agitation as an adverse event is interesting, and it may be important to incorporate that into future studies. To do this appropriately, it will be critical to define the exact behavior being measured to distinguish between aggression and agitation, which may not be possible with the current scales of the NPI.

In September 1998, well after completion of the trial reported here, Bayer Corporation took the precautionary decision to place all clinical trials with metrifonate on hold so that no

patient would be put at unnecessary risk and to evaluate a possible association of muscle weakness and metrifonate use. At this time, Bayer has determined that there was a dose-related association with muscle weakness, but this association was predominantly evident at doses exceeding 1.25 mg/kg. In theory, this pharmacologic effect due to excessive doses is possible for all acetylcholinesterase inhibitors. The dose administered in our trial was well below this range, and no cases of muscle weakness were observed and no serious adverse event has been omitted. At the time of publication of the article, the outcome of the clinical data review was not complete, and it was considered that an unclear statement on safety from other studies should not be added.

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Urinary Incontinence With Risperidone

Sir: Urinary incontinence has been reported to occur in about 1% of individuals receiving the atypical antipsychotic clozapine.[1] One study reported that at least 28% of patients developed transient urinary incontinence after initiation of risperidone treatment.[2] Despite this substantially high reported incidence, urinary incontinence with risperidone treatment has been little studied and rarely reported in literature. This report describes 2 patients who developed incontinence when started on risperidone treatment.

Case 1. Ms. A, a 48-year-old woman, was diagnosed with paranoid schizophrenia for 5 years. She was receiving injections of fluphenazine decanoate, 25 mg every 2 weeks, with trihexyphenidyl, 4 mg/day. Because of exacerbation of symptoms, risperidone, up to 4 mg/day, was added. After about 3 weeks, Ms. A developed urinary incontinence, which led to poor compliance: she was continent on days when she skipped a dose of risperidone. Her dose was decreased to 2 mg/day, but she continued to experience incontinence. Her risperidone was stopped since the family requested to change the drug because of the incontinence. After discontinuation of risperidone, Ms. A's incontinence stopped. Results of gynecologic examination and urinalysis were normal.

Case 2. Mr. B, a 46-year-old man, had been diagnosed as having chronic undifferentiated schizophrenia at the age of 30 years. His treatment was gradually switched from haloperidol to risperidone, 4 mg/day, because of prominent negative symptoms. After about 4 weeks, he developed urgency for micturition during the daytime and urinary incontinence at night. The frequency of urinary incontinence gradually increased. Results of urinalysis were normal. Risperidone was discontinued since Mr. B refused to take it because of incontinence. After discontinuation of risperidone, his incontinence gradually stopped.

In both cases, incontinence is clearly temporally correlated with risperidone treatment. Adrenergic blockade is commonly proposed as a mechanism for clozapine-induced urinary incontinence.[3] Adrenergic blockade may cause urinary incontinence as it decreases the tone of the internal bladder neck sphincter.[4] Risperidone also may cause urinary incontinence because of adrenergic blockade since it has high affinity for α_1 receptors (almost double that of clozapine).[5] Alternatively, urinary incontinence may also occur with risperidone because of reduced dopamine transmission leading to secondary noradrenergic hypoactivity in basal ganglia, especially when risperidone is combined with a classical neuroleptic.[6] However, there is a need to study the characteristics of urinary incontinence with risperidone and measures to control it, because urinary incontinence is an embarrassing side effect and may lead to poor compliance with medication.

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