

Letters to the Editor

Fatal Body Dysmorphic Disorder by Proxy

Sir: Body dysmorphic disorder (BDD) is an underrecognized disorder characterized by a distressing or impairing preoccupation with an imagined or slight defect in one's appearance.¹ Several cases of "BDD by proxy" have been described in which an individual is overly concerned about the appearance of another person who looks normal.²⁻⁵ We describe a case of BDD by proxy that resulted in suicide. To our knowledge, this is the first report of a fatal outcome resulting from this variant of BDD.

Case report. Mr. A, a 63-year-old man, presented with a chief complaint of repetitive intrusive thoughts that he had caused his daughter's hair to thin. He stated that he thought about his daughter's hair "all the time." He had previously been active, but as a result of this preoccupation, he became withdrawn and was unable to sleep or engage in his usual activities. He denied having current concerns about his own appearance, although in the past his excessive concerns about how he looked had led to cosmetic surgery. Mr. A's preoccupation with his daughter's hair had become so distressing that he stated that he had thoughts of killing himself.

Mr. A had no past psychiatric history and had never attempted suicide. Results from laboratory tests and head computed tomography were normal. Neuropsychological testing was ordered, but the patient was guarded owing to his shame about causing his daughter's hair to thin, and the interview data and test results were considered invalid.

Mr. A was hospitalized; he was very guarded with the hospital staff and would not discuss his concerns about his daughter's hair in a group setting. While in the hospital, he constantly obsessed about his daughter's hair and in a pressured manner frequently sought reassurance from the staff, asking, for example, "Do you think it's possible that I gave her the thinning hair?" and "Do you think it was because of me?" He brought in photographs of his daughter and commented to the staff on how thin her hair was. In reality, his daughter's hair looked normal. Mr. A reported extreme distress and guilt, which he attributed entirely to these thoughts. Although he had depressive symptoms, he did not meet full criteria for major depression or any other psychiatric disorder.

Mr. A was initially treated with paroxetine, which was poorly tolerated, and was switched to sertraline, 100 mg/day; the patient stated that he was taking the sertraline as prescribed. He was also treated with clonazepam and then lorazepam. After 5 weeks of treatment in a partial hospital setting, he was discharged after stating that he was feeling improved, did not desire additional treatment, and did not have any suicidal thoughts. Several weeks later he committed suicide by shooting himself.

This case of BDD by proxy is notable for the patient's feelings of shame, severe distress, and impaired functioning—which are common characteristics of BDD^{1,4}—as well as its fatal outcome. Although BDD appears to be relatively com-

mon,^{4,6} only a few cases of BDD by proxy have been reported.²⁻⁵ It is not known how common this BDD variant is, but it may be more common than is recognized.

Available data suggest that serotonin reuptake inhibitors^{4,7,8} and cognitive-behavioral therapy^{4,9} are often effective for BDD; however, the treatment of the "by proxy" variant of BDD has not been studied. In 1 reported case,² exposure and response prevention led to improvement in BDD by proxy symptoms. In another case,² the patient's BDD symptoms that focused on his own appearance partially improved with behavior therapy and a number of pharmacotherapy trials (fluoxetine, sertraline, paroxetine, clomipramine, phenelzine, and fluoxetine plus pimozide), but none of these treatments improved his BDD by proxy (i.e., his concern about his children's appearance).

Because of his prominent obsessions, Mr. A was initially diagnosed with obsessive-compulsive disorder (OCD) according to DSM-IV criteria. However, BDD is a more accurate diagnosis because his obsessions focused only on appearance. BDD and OCD have many similarities and are probably closely related disorders,^{10,11} although they also appear to have some clinically important differences, including a higher rate of depression and suicide attempts in BDD.¹¹ The patient's delusional thinking and prominent guilt raise the question of whether he had psychotic depression. However, Mr. A did not meet full criteria for major depression, and his obsessions and compulsive behaviors were the most prominent symptoms, with his depressive features appearing secondary to these symptoms. Prominent guilt and depressive symptoms often accompany BDD^{4,12} and often appear secondary to the BDD symptoms.¹² BDD's treatment response appears more similar to that of OCD than depression or psychotic depression,^{12,13} although treatment data on BDD remain limited at this time. Investigation of what constitutes effective treatment for BDD, including its "by proxy" variant, is greatly needed; as this case demonstrates, BDD by proxy can be unusually distressing, impairing, and potentially fatal.

REFERENCES

1. Phillips KA. Body dysmorphic disorder: the distress of imagined ugliness. *Am J Psychiatry* 1991;148:1138-1149
2. Josephson SC, Hollander E. Body dysmorphic disorder by proxy [letter]. *J Clin Psychiatry* 1997;58:86-87
3. Laugharne R, Upex T, Palazidou E. Dysmorphophobia by proxy. *J R Soc Med* 1998;91:266
4. Phillips KA. *The Broken Mirror: Understanding and Treating Body Dysmorphic Disorder*. New York, NY: Oxford University Press; 1996
5. Godden D. Body dysmorphic disorder by proxy [letter]. *Br J Oral Maxillofac Surg* 1999;37:331
6. Simeon D, Hollander E, Stein DJ, et al. Body dysmorphic disorder in the DSM-IV Field Trial for obsessive compulsive disorder. *Am J Psychiatry* 1995;152:1207-1209
7. Phillips KA, Dwight MM, McElroy SL. Efficacy and safety of fluvoxamine in body dysmorphic disorder. *J Clin Psychiatry* 1998;59:165-171
8. Hollander E, Allen A, Kwon J, et al. Clomipramine vs desipramine crossover trial in body dysmorphic disorder: selective efficacy of a

- serotonin reuptake inhibitor in imagined ugliness. *Arch Gen Psychiatry* 1999;56:1033-1039
9. Veale D, Gournay K, Dryden W, et al. Body dysmorphic disorder: a cognitive behavioral model and pilot randomized controlled trial. *Behav Res Ther* 1996;34:717-729
 10. McElroy SL, Phillips KA, Keck PE Jr. Obsessive compulsive spectrum disorder. *J Clin Psychiatry* 1994;55(10, suppl):33-53
 11. Phillips KA, Gunderson CG, Mallya G, et al. A comparison study of body dysmorphic disorder and obsessive-compulsive disorder. *J Clin Psychiatry* 1998;59:568-575
 12. Phillips KA. Body dysmorphic disorder and depression: theoretical considerations and treatment strategies. *Psychiatr Q* 1999;70:313-331
 13. Phillips KA. Pharmacologic treatment of body dysmorphic disorder: a review of empirical data and a proposed treatment algorithm. *Psychiatr Clin North Am* 2000;7:59-82

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Treatment of Refractory Major Depression With Tramadol Monotherapy

Sir: Recent reports describe treatment of patients with refractory major depression using augmentation with the μ -opioid agonists oxycodone and oxymorphone and the partial agonist buprenorphine.^{1,2} We report a patient with refractory major depression who responded to tramadol hydrochloride monotherapy.

Case report. Mr. A, a 64-year-old white man, was diagnosed with chronic major depressive disorder with melancholic features (DSM-IV criteria). His first episode occurred around 1984, and since being diagnosed in 1986, he has failed adequate medication trials of the following antidepressants: amitriptyline, oxmapipine, bupropion, clomipramine, doxepin, fluoxetine, fluvoxamine, imipramine, maprotiline, mirtazapine, nefazodone, paroxetine, phenelzine, sertraline, tranylcypromine, and venlafaxine. Furthermore, he has failed augmentation trials with bupropion, lithium, and methylphenidate. In addition to antidepressant medications, several anxiolytic medications were tried unsuccessfully, including alprazolam, buspirone, clonazepam, lorazepam, and temazepam. Neither supportive nor insight-oriented psychotherapy was helpful, and Mr. A has declined electroconvulsive therapy. He experienced mild relief with nortriptyline for approximately 2 years.

In 1998, Mr. A developed facial pain secondary to a salivary stone. At that time, he was taking no psychiatric medications and received tramadol for the pain. Tramadol improved the pain slightly, and ultimately the pain resolved. However, on tramadol treatment, Mr. A noticed immediately that his depressive symptoms improved 60% to 70%. Since 1998, he has continued taking 100 mg of tramadol 3 to 4 times daily. He finds that if he awakens to take a dose at 4:00 a.m., he will wake without depressive symptoms. He describes feeling the effect of tramadol within 30 minutes, but if he misses several doses, he will feel no effect for hours.

Evaluation by the Structured Clinical Interview for DSM-IV³ revealed that he had had comorbid obsessive-compulsive disorder (OCD) since 1965 and panic disorder (in remission) since 1974. His OCD symptoms, including recurrent and intrusive fears of knives, led to avoidance of situations depicting violence. His OCD symptoms occur for approximately 1 hour/day, but were significantly worse prior to the start of tramadol treatment. His current score on the Yale-Brown Obsessive Compul-

sive Scale is 5. Mr. A describes depression in his mother and daughter, but he has no tics or family history of OCD or tics.

Mr. A's medical history includes rheumatic fever at age 5 years, knee surgery at ages 12 and 18 secondary to his rheumatic fever, tonsillectomy at age 6, appendectomy at age 8, cholecystectomy at age 49, total knee replacement at age 62, and 2 episodes of acute pancreatitis secondary to elevated triglycerides at ages 61 to 62. He has had a history of migraines and irritable bowel syndrome; both improved with tramadol treatment. Because of Mr. A's significant Axis III comorbidity, it is worth noting that an evaluation for somatoform and related disorders was negative.

Mr. A describes having periodically experienced chills, myalgias, pruritus, diarrhea, and yawning with rapid onset and resolution within 1 day without associated physical illness. These symptoms occurred between 1986 and 1998 during exacerbations of depression and are suggestive of opioid withdrawal even though Mr. A was not taking opioids during those times. He has not experienced these symptoms during treatment with tramadol. Mr. A stated that he first took an opioid medication during his painful acute pancreatitis episodes (meperidine) and then following his knee replacement (oxycodone). During both short-term exposures to opioids, he experienced improvement in his depressive symptoms. Additionally, there is no indication from Mr. A's history or collateral information that he has any covert history of opioid abuse.

Although Mr. A has a very unusual and complicated medical, psychiatric, and treatment history, his preferential response to opiates, as well as his symptoms of opioid withdrawal during periods of his life when he was opioid-free, suggests dysfunction of his endogenous opioid system. Furthermore, among recovering opiate addicts, depression rates are high.⁴ Recent research⁵ has demonstrated an increase in the number of endogenous opioid receptors in the central nervous system of depressed suicide victims. Tramadol is an atypical centrally acting analgesic with μ -receptor activity, and it also weakly inhibits norepinephrine and serotonin reuptake.⁶ Structurally, it is similar to the antidepressant venlafaxine.⁷ Tramadol has been shown to induce some antidepressant-type effects in mice, which appeared to be related to tramadol's noradrenergic activity,⁸ and has been reported effective in augmenting treatment in 12 patients with major depressive disorder who had a partial response to selective serotonin reuptake inhibitors.⁹ There are no published reports of tramadol as monotherapy for depression. Because Mr. A has comorbid OCD that improved on treatment with tramadol, it is interesting that tramadol has been shown to be efficacious in an open-label study of treatment-refractory OCD.¹⁰ Tramadol may represent an alternative to commonly used antidepressants in select treatment-refractory patients. More research is necessary to establish the antidepressant effect of opiates such as tramadol, as well as to determine if there is a distinct subset of depressed patients with endogenous opioid dysfunction.

REFERENCES

1. Stoll AL, Rueter S. Treatment augmentation with opiates in severe and refractory major depression [letter]. *Am J Psychiatry* 1999;156:2017
2. Bodkin JA, Zornberg GL, Lukas SE, et al. Buprenorphine treatment of refractory depression. *J Clin Psychopharmacol* 1994;15:49-57
3. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1995
4. Dackis CA, Gold MS. Opiate addiction and depression: cause or

- effect? *Drug Alcohol Abuse* 1983;11:105–109
5. Gross-Isseroff R, Dillon KA, Israeli M, et al. Regionally selective increases in opioid receptor density in the brains of suicide victims. *Brain Res* 1990;530:312–316
 6. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an “atypical” opioid analgesic. *J Pharmacol Exp Ther* 1992;260:275–285
 7. Markowitz JS, Patrick KS. Venlafaxine-tramadol similarities. *Med Hypotheses* 1998;51:167–168
 8. Rojas-Corralles MO, Gibert-Rahola J, Micó JA. Tramadol induces antidepressant-type effects in mice. *Life Sci* 1998;63:PL175–PL180
 9. Fanelli J, Montgomery C. Use of the analgesic tramadol in antidepressant potentiation [abstract]. *Psychopharmacol Bull* 1996;32:442
 10. Shapira NA, Keck PE, Goldsmith TD, et al. Open-label pilot study of tramadol hydrochloride in treatment-refractory obsessive-compulsive disorder. *Depress Anxiety* 1997;6:170–173

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Emergence of PTSD in Trauma Survivors With Dementia

Sir: Posttraumatic stress disorder (PTSD), a syndrome marked by reexperiencing, arousal, and avoidance symptoms, typically emerges soon after a traumatic event. However, some trauma survivors may experience the full-blown syndrome for the first time as they age. Several published cases involving World War II veterans describe the onset of PTSD after decades of living without symptoms.^{1–5} Explanations have included job retirement with loss of daily structure and social contact,^{6,7} increased exposure to death or other losses reminiscent of past trauma,^{3,8} and age-related weakening of psychological defenses.⁹ In a recent case series, Johnson⁵ described 3 World War II veterans in whom onset of dementia was heralded by an exacerbation of PTSD symptoms. In the present report, we extend this work and describe 3 additional patients who also experienced a marked increase in PTSD symptoms after onset of dementia. However, only 1 of these patients was a war veteran; one was a Holocaust survivor, and another, a passenger on the *Titanic*. Thus, the relationship between PTSD and dementia appears to extend beyond the trauma of combat and include a much larger group of elderly individuals who have been traumatized in the past.

Case 1. Ms. A, a widowed white woman, was admitted to a nursing home when she was 95 years old because of progressive deterioration of cognitive functions, including memory loss, apraxia, and agnosia consistent with Alzheimer’s disease (DSM-IV criteria). She no longer recognized family members, including her daughter. Workup of causes of reversible dementia was negative. Her use of language remained relatively intact.

Ms. A was 22 years old when she survived the sinking of the *Titanic*. Throughout her life, when asked about the event, she would ignore the question and move on to another topic. Her family could not recall significant reexperiencing or autonomic hyperactivity.

In the nursing home, Ms. A began to have periods of extreme psychomotor agitation, accompanied by vivid reexperiencing of

her earlier trauma. For example, when placed in the day room with other residents, she would become markedly distressed, calling out, “The water is coming up! Go to the lifeboats! Save the children! We’ll all be dead!”

Case 2. Mr. B, a 75-year-old World War II veteran, had seen combat in Iwo Jima and Saipan, where he witnessed the deaths of many servicemen and feared for his own life. After the war, his only trauma-related symptom was an occasional nightmare. He married, raised children, and ran a successful business. When asked about the war, he calmly answered questions, but never spontaneously volunteered information about his combat experiences.

Ten months prior to evaluation, Mr. B and his wife began to notice signs of cognitive impairment. He forgot names and numbers of clients, and could not remember his automated banking code number or how to balance his checkbook. A computed tomographic scan of the brain suggested multi-infarct dementia. Mr. B became progressively more anxious and began to startle more easily. Car horns caused him to jump dramatically, making it difficult for him to drive. He awakened from sleep physically fighting, and his wife described “rage attacks,” during which Mr. B yelled, threw objects, and slammed doors. In addition, he perseverated on war memories and wanted to talk about little else. He came to believe that, despite his Purple Heart, he had been a coward and was consumed with guilt.

Case 3. Ms. C, an 83-year-old widowed woman, had been traumatized during the Holocaust. Nazi soldiers had killed a pet in front of her family and told them they would return the next morning. The family fled but were placed in resettlement camps, where they feared for their lives.

Over the years, Ms. C experienced occasional intrusive memories with environmental cues, in addition to nightmares, startle responses, and suspiciousness. She functioned as a housewife and mother, but tended toward social isolation.

Five years prior to evaluation, Ms. C began having difficulties with memory. Examination demonstrated memory loss, apraxia, and difficulty with executive functioning. No causes of reversible dementia could be found, and she was diagnosed with Alzheimer’s disease (DSM-IV criteria). As her dementia progressed, nursing home placement was sought. Shortly after admission, she began to have near-constant reexperiencing of her life in the camps and started speaking in German. She frequently reacted to her surroundings with extreme fear and agitation. For weeks at a time, she was combative with the nursing staff because she believed they were Nazis.

In the 3 cases presented, symptoms of PTSD worsened dramatically after the onset of dementia. With a decline in cognitive functioning, all 3 patients experienced a marked increase in daytime intrusive memories; 2 patients were plagued by flashbacks. All 3 patients demonstrated increased irritability and agitation, especially in response to their traumatic memories. For patient 2, startle response became so exaggerated he had difficulty driving, and for patient 3, hypervigilance and suspiciousness about “Nazi” nurses made interacting with nursing staff extremely frightening. Retirement from work or death of loved ones cannot account for symptom exacerbation, since none of the patients either retired from work or lost loved ones shortly before their increase in PTSD symptoms. Moreover, most research suggests that coping strategies do not decline in normal aging.

There are many possible explanations for an association between declining cognitive function and increasing PTSD symptoms. Environmental cues often serve as triggers for the reexperiencing of past traumas. These patients may have misinterpreted neutral sensory stimuli and experienced them as if

they were trauma related. It is further possible that a dementing process interferes with cognitive strategies or defense mechanisms that had previously been effective at warding off, or coping with, chronic memories of trauma. For example, avoidance is commonly viewed as a coping mechanism that decreases exposure to traumatic reminders. Individuals with dementia may become less capable of using avoidance strategies and more susceptible to the disruptive effects of these trauma-related triggers. Similarly, focusing on areas of life unrelated to past traumas, such as becoming absorbed in one's work, is a common way to deal with painful memories. Cognitively impaired individuals may have a compromised ability to actively focus their attention elsewhere.

There are a number of biological explanations to consider. A large body of evidence suggests that emotionally arousing events stimulate the release of stress-related hormones that facilitate the encoding and consolidation of memory.¹⁰ Thus, traumatic memories tend to be remembered better than neutral memories. It may be that traumatic memories are more resistant to the deleterious effects of dementia. Also, Alzheimer's disease tends to have a greater impact on short-term memory than long-term memory, which might lead to a relative increase in long-standing traumatic memories. Further, it is well known that the medial prefrontal cortex mediates fear, responding through inhibitory connections with the amygdala,¹¹ and it is possible that dementia-related cortical cell loss leads to a disinhibition of subcortical emotional memories.

Finally, some dementias damage the hippocampus. Recent studies in trauma survivors with PTSD have also reported hippocampal dysfunction and reduction in hippocampal volume.¹¹ The hippocampus is critically involved in memory, regulation of the hypothalamic-pituitary-adrenal axis, and contextual fear conditioning, all of which have been reported as abnormal in PTSD.¹¹

The present report has a number of limitations. Accounts of past history and symptom course were retrospective and thus susceptible to inaccurate recall. The report involves only 3 patients; it remains to be seen whether their experiences can be generalized to other traumatized people who develop dementia.

Dementia affects 5% of people over the age of 65 years and more than 20% of those over 80.¹² The lifetime prevalence of PTSD has been estimated between 5% and 10%.¹³ Given the high rates of PTSD and dementia, the present case reports highlight the importance of systematic epidemiologic research on the comorbidity of these disorders and further investigation of potential relationships between them.

REFERENCES

1. Christenson RM, Walker JI, Ross DR, et al. Reactivation of traumatic conflicts. *Am J Psychiatry* 1981;138:984-985
2. Hamilton JW. Unusual long-term sequelae of a traumatic war experience. *Bull Menninger Clin* 1982;46:539-541
3. van Dyke C, Zilberg NJ, McKinnon JA. Posttraumatic stress disorder: a thirty-year delay in a World War II veteran. *Am J Psychiatry* 1985; 142:1070-1073
4. Brockaway S. Case report: flashback as a post-traumatic stress disorder (PTSD) symptom in a World War II veteran. *Milit Med* 1988;153:372-373
5. Johnson D. A series of cases of dementia presenting with PTSD symptoms in World War II combat veterans. *J Am Geriatr Soc* 2000; 48:70-72
6. Van der Kolk BA, Ducey C. Clinical implications of the Rorschach in posttraumatic stress disorder. In: *Posttraumatic Stress Disorder: Psychological and Biological Sequelae*. Washington, DC: American Psychiatric Press; 1984:303-321
7. Kulman M, Suttrop O. Late onset posttraumatic spectrum disorders in survivors of Nazi terror: a retrospective study of 100 patients

- (1973-1988). Presented at the Congress "Psychische Schaden alternder Uberlebenden des Nazi-Terror und ihrer Nachkommen"; October 11-14, 1989; Hanover, Federal Republic of Germany
8. Ruskin P, Talbot J. *Aging and Posttraumatic Stress Disorder*. Washington, DC: American Psychiatric Press; 1996
9. Lipton MI, Schaffer WR. Post-traumatic stress disorder in the older veteran. *Milit Med* 1986;151:522-524
10. McGaugh JL. Significance and remembrance: the role of neuromodulatory systems. *Psychol Sci* 1990;1:15-25
11. Charney DS, Grillon CG, Bremner DB. The neurobiological basis of anxiety and fear: circuits, mechanisms, and neurochemical interactions. *Neuroscientist* 1998;4:122-132
12. Caine ED, Lyness JM. Delirium, dementia, and amnesic and other cognitive disorders. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*. 7th ed. New York, NY: Lippincott, Williams, & Wilkins; 2000:894
13. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;52: 1048-1060

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Physical Restraints, Thromboembolism, and Death in 2 Patients

Sir: Thromboembolism has occurred in relation to stupor and catatonia¹ and to psychotropic medication.² I report 2 fatalities associated with physical restraints in which thromboembolism was the underlying cause of death.

Case 1. Mr. A, a 37-year-old man with chronic undifferentiated schizophrenia, was brought to a hospital emergency department by the police. His family had reported him missing for several days, and he had not taken his medication in over 2 weeks.

On examination, Mr. A was delirious, with a temperature of 99.4°F (37.5°C), dehydration, hallucinations, and disorientation to time and place. Laboratory testing results showed decreased blood levels of potassium (3.2 mmol/L) and CO₂ (19.4 mmol/L) and increased serum urea nitrogen (29 mg/dL) and creatinine (1.4 mg/dL) levels. His white blood cell (WBC) count was elevated at 20.5 × 10⁹/L. An electrocardiogram showed left ventricular hypertrophy. Chest x-ray, brain computed tomographic scan, urine drug screen, and cultures of blood, urine, and cerebrospinal fluid were negative. Thyrotropin level was normal.

Mr. A was treated with intravenous fluids and ceftriaxone sodium. He was restarted on his usual medication of haloperidol, 10 mg b.i.d.; olanzapine, 10 mg b.i.d.; divalproex sodium, 500 mg t.i.d.; and benztropine, 1 mg b.i.d. He was placed in 4-point leather restraints for combative behavior. His WBC count and creatinine level returned to normal after 3 days, but he remained psychotic.

Restraints were applied continuously throughout Mr. A's hospitalization. He was only able to turn and reposition himself. Mr. A never had significant range of motion and never was permitted to ambulate, exercise, or use the bathroom (a bedpan and indwelling urinary catheter were used instead).

Eight days after admission, following several failed attempts to arrange for psychiatric consultation, Mr. A was transferred by ambulance to a psychiatric hospital. He arrived at midnight, but there was no physician to examine him. Mr. A's vital signs were

checked and found to be normal, and he was placed in bed, without restraints, and observed every 15 minutes. At 6:10 a.m., Mr. A was found at the foot of the bed, unresponsive, with fixed and dilated pupils. There were no detectable breath sounds, heartbeat, or pulse. A call was placed to 911, and an emergency medical team pronounced him dead.

Autopsy findings revealed extensive bilateral pulmonary emboli. Blood clots present near the iliac vein and the inferior vena cava were thought to be the origin of the thrombi. The brain and other essential organs were normal.

Case 2. Ms. B, a 70-year-old woman with bipolar disorder and hypothyroidism, was brought to the hospital emergency department by her husband following an acute exacerbation of psychosis. Medications were lithium, 300 mg t.i.d.; nortriptyline, 75 mg h.s.; olanzapine, 2.5 mg b.i.d.; levothyroxine, 50 µg/day; simvastatin, 10 mg/day; hydrochlorothiazide, 25 mg/triamterene, 37.5 mg/day; and lorazepam, 0.5 mg t.i.d. as needed.

On examination, Ms. B was delirious, with a temperature of 99.7°F (37.6°C), dehydration, and delusions. She was hostile and would not answer questions related to orientation and memory. Laboratory testing results showed decreased chloride (100 mmol/L) and increased serum urea nitrogen (42 mg/dL), and creatinine (1.9 mg/dL) levels. WBC count and serum lithium level were elevated at $20.5 \times 10^9/L$ and 2.1 mEq/L, respectively. Chest x-ray, blood cultures, and arterial blood gas results were normal.

Ms. B received fluids intravenously. All psychotropic medication was resumed except lithium. Her temperature returned to normal on the second day, and she was transferred to the psychiatric unit. Soft 4-point restraints were applied owing to agitation and impulsive behavior. Ms. B's serum lithium level was 0.9 mEq/L on the third day, and her restraints were removed. On the fourth day, at 8:45 p.m., she went to the bathroom to have a bowel movement, but was unsuccessful. Staff escorted Ms. B to bed, whereupon her eyes suddenly rolled up and she became unresponsive. Cardiopulmonary resuscitation was unsuccessful.

Autopsy results revealed pulmonary thromboemboli due to venous stasis in the lower extremities.

An investigation by the *Hartford Courant* between 1988 and 1998³ attributed 142 deaths in 30 states to inappropriate use of restraints. Among the confirmed causes of death in 125 cases, 33% of patients died of asphyxia and 26% died from cardiac-related causes. Two patients died from acute pulmonary thromboembolism—1 patient was in a restraint chair for 30 of the last 36 hours of life.

A MEDLINE search revealed only 1 other restraint-related death due to thromboembolism. In that report,⁴ a patient without hematologic predisposition to coagulopathy developed deep vein thrombosis and pulmonary embolism following immobilization in restraints. Prolonged immobilization is a well-known risk factor for thromboembolism, yet the occurrence of restraint-related deaths due to thromboembolism appears to be underrecognized. This may be due, in part, to a delay between removing the restraints and the actual time of death (approximately 6 hours in the case of Mr. A and 24 hours in the case of Ms. B) and the fact that ambulation or other type of movement after restraints are removed may activate clots and obscure the sequential relationship between restraints, immobilization, and death.

The inappropriate use of restraints has been uncovered in psychiatric hospitals, group homes, residential treatment facilities, and nursing homes. This tragic problem has received less attention in general hospitals, although new federal regulations should change this.⁵ Despite guidelines⁶ for the use of re-

straints, further restraint reduction initiatives and alternatives to restraints are clearly necessary. Staff education, use of specially trained personnel and the patient's family as treatment partners, and a variety of de-escalation techniques, including one-on-one discussions, use of peer advisers, walking the grounds, and voluntary return to the patient's living quarters, have proven effective.⁷

REFERENCES

- O'Brien PD. Thromboembolism complicating psychiatric stupor [letter]. *J Clin Psychiatry* 1991;52:137-138
- Pantel J, Schroder J, Eysenbach K, et al. Two cases of deep vein thrombosis associated with a combined paroxetine and zotepine therapy. *Pharmacopsychiatry* 1997;30:109-111
- Deadly restraint: a Hartford Courant investigative report. Available at: <http://courant.ctnow.com/projects/restraint/reform.stm>. Accessed November 8, 2000
- Hem E, Opjordsmoen S, Sandset PM. Venous thromboembolism in connection with physical restraint [in Norwegian]. *Tidsskr Nor Laegeforen* 1998;118:2156-2157
- Annas GJ. The last resort: the use of physical restraints in medical emergencies. *N Engl J Med* 1999;341:1408-1412
- Zusman J. *Restraint and Seclusion: Improving Practice and Maintaining JCAHO Compliance*. 2nd ed. Marblehead, Mass: Opus Communications; 1999
- Ross EC. Death by restraint: horror stories continue, but best practices are also being identified. *Behav Healthc Tomorrow* 1999;8:21-23

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Lithium Intoxication After Administration of AT₁ Blockers

Sir: Candesartan is one of the new antihypertensive agents targeting the AT₁ subtype of the angiotensin II receptor. Apart from candesartan, the AT₁ receptor agents available in the United States are losartan, telmisartan, irbesartan, and valsartan. Candesartan exerts its antihypertensive effect by a selective blockade of the angiotensin II receptor, whereas angiotensin-converting enzyme (ACE) inhibitors, another class of antihypertensive agents, act through decreasing the production of angiotensin II and aldosterone by inhibiting the conversion of angiotensin I to angiotensin II. Whereas to our knowledge no interaction between the AT₁ blocker candesartan and lithium has been reported to date, cases of lithium intoxication have been observed during concomitant therapy of lithium with ACE inhibitors¹ and with the angiotensin II receptor blockers losartan² and valsartan.³ It has been shown that simultaneous administration of ACE inhibitors and lithium can elevate lithium levels from 1.7- to 5-fold.¹

Case report. Ms. A, a 58-year-old female patient, had suffered from bipolar disorder (DSM-IV criteria) since the age of 33 years. She had had no additional depressive or manic episode in the last 18 years, during which time she began treatment with lithium. She had arterial hypertension, which had been treated with calcium antagonists for several years. Because of a deterioration of hypertension 2 months before hospitalization, the AT₁ blocker candesartan was added at a daily dose of 16 mg. At that time, Ms. A's serum lithium level was stable between 0.6 and 0.7 mmol/L on a daily lithium carbonate dose of 900 mg. Serum creatinine and creatinine clearance were normal as well.

Eight weeks later, after a 10-day history of ataxia and increasing confusion, disorientation, and agitation, Ms. A was hospitalized. At the time of hospitalization, her serum lithium concentration was 3.25 mmol/L. All other laboratory test results were within normal limits, and an electrocardiogram and magnetic resonance imaging results showed no abnormalities. She was treated for 4 days at an intensive care unit, during which time candesartan and lithium treatment were stopped immediately. After a 7-day drug-free interval, antihypertensive therapy was switched to the α_1 -antagonist urapidil, and lithium prophylaxis was restarted without further problems. A serum lithium level of 0.7 mmol/L was achieved again on a daily lithium carbonate dose of 900 mg.

ACE inhibitors decrease the production of angiotensin II, which in turn leads to a decreased production of aldosterone. Blockade of the AT₁ subtype of the angiotensin II receptor reduces aldosterone release as well. Reduced aldosterone levels may be responsible for an increased renal serum flow, glomerular filtration rate, and sodium excretion, with elevated serum lithium levels and possible side effects as consequences. However, in view of inconsistencies in various preclinical studies, the mechanism that determines how AT₁ blockers increase lithium concentrations remains speculative at present.

This case report provides further evidence that administration of AT₁ blockers as antihypertensive medications together with lithium bears the potential risk of lithium intoxication because of the inherent mechanism of action of AT₁ blockers. Thus, this combination should be avoided as far as possible. If AT₁ blockers are truly necessary as antihypertensive medications, serum lithium levels must be monitored closely, and the respective lithium dose must be adjusted.

REFERENCES

1. Teitelbaum M. A significant increase of lithium levels after concomitant ACE inhibitor administration. *Psychosomatics* 1993;34:450–453
2. Blanche P, Raynaud E, Kerob D, et al. Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* 1997;52:501
3. Leung M, Remick RA. Potential drug interaction between lithium and valsartan [letter]. *J Clin Psychopharmacol* 2000;20:392–393

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Corrections

In the article “Intramuscular Ziprasidone, 2 mg Versus 10 mg, in the Short-Term Management of Agitated Psychotic Patients” by Michael D. Lesem, M.D., et al. (January 2001 issue, pp. 12–18), the Clinical Global Impressions-Severity of Illness scale (CGI-S) served as a primary efficacy variable. The CGI-S was incorrectly cited as a secondary efficacy variable on page 14 (first paragraph, first line).

The review of *Coping With Trauma: A Guide to Self-Understanding* by Melvyn M. Nizny, M.D. (December 2000 issue, pp. 953–954), does not reflect the opinions of the American Board of Psychiatry and Neurology.