Hypokalemia Secondary to Bupropion Sustained Release Overdose

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Chief Complaint and Presenting Problem

J. WAS A 17-YEAR-OLD AFRICAN AMERICAN GIRL who was admitted to a public crisis stabilization unit with a diagnosis of major depressive disorder (MDD) after making a suicide attempt by overdose. J. was living in a relative foster home with her aunt and was a senior in high school.

History of Present Illness

J. had been struggling with depressive symptoms for nearly 3 years. J. had experienced onset of decreased appetite, poor hygiene, poor sleep, decreased social interaction, listlessness, apathetic affect, and anhedonia at age 14, and she was subsequently diagnosed with major depressive disorder at age 15. She was treated with medication management by an outpatient psychiatrist. Stressors over the past 2 years had included felony fraud charges related to stealing family credit card numbers and an associated 2 week sentence at the local county jail. J. experienced a second major depressive episode following release from jail. She also had experienced significant social stressors including out-of-home placement, conflicts with friends, domestic violence in her home, and declining academic performance.

J. had been hospitalized in the past for a suicide attempt on an unknown quantity of 40 mg capsules of fluoxetine without serious medical complications. The suicide attempt was triggered by ongoing relationship conflicts with mother and was precipitated when her mother took away her phone privileges. J. had not been able to maintain her previous level of academic performance; as a result of worsening depressive symptoms and psychiatric hospitalizations, her grades were declining.

J. had an extended history of oppositional defiant behavior, including disobedience and verbal aggression directed toward her mother, but no reported suspensions or expulsions.

J. had been admitted to a pediatric hospital earlier in the year of the suicide attempt discussed here, after being struck by her mother with a mirror and trophy on her head, right arm, and right leg. This led to a Child Protective Services (CPS) referral and J.'s aunt was given custody following two group home placements.

Prior to the current admission, J. had been asked to clean her room by her aunt and told she could not visit with her mother until this was finished. J. made a suicide attempt by ingesting ~30

150 mg tablets of sustained-release bupropion. J.'s aunt was alerted when she heard a loud thumping sound upstairs where J. was found unresponsive on the floor. J.'s aunt called 911, and J. was transported to the local emergency department, where she had a seizure.

According to hospital records, J.'s seizure lasted 1 minute and was characterized by extremity jerking for a few seconds, fixed eye deviation to one side, and foaming at the mouth. She was administered lorazepam in the emergency department and the seizures stopped. Initial evaluation revealed a nongapped hypokalemic, hyperchloremic metabolic acidosis, hypocalcemia, and hypoglycemia. J. was administered ondansetron, ranitidine, potassium chloride and D5 ½ normal saline. Cardiac monitoring was uneventful; J. was reported to be hemodynamically and neurologically stable and was transferred to the pediatric intensive care unit.

Past Psychiatric History

J. had been hospitalized twice in the past; the first admission was for a suicide attempt by overdose on fluoxetine and the second for verbal and physical aggression toward her mother.

Developmental History

J. was the product of a full-term pregnancy without prenatal or perinatal complications. She was born by normal vaginal delivery at 40 weeks. She started walking at 9 months of age and achieved other developmental milestones at appropriate ages. There is no history of any significant losses or traumas.

Educational History

J. was in the 12th grade and reportedly had performed well academically in the past. She was previously in advanced classes, but her grades had declined as a result of her depression in the year of the suicide attempt discussed here. She had recently failed four classes and was reported to possibly not be able to graduate on time.

Social History

J. had been living in a relative foster home with her aunt, as a result of substantiated physical abuse by her mother in the context of J.'s defiant behavior. J. had been admitted to a pediatric hospital with multiple bruises within the previous year, and CPS had been

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notified and took custody. J. was initially placed in a group home and then moved to live with her aunt after running away from previous group home placements. J.'s uncle and three cousins were also in the home. J. desires to reside with her mother in the future; as of this writing, the mother is complying with the case plan initiated by CPS that requires parenting and physical abuse classes.

J.'s father had never been involved in her life; as of this writing J. has no current contact with him and is apathetic about his lack of involvement. J. does not have any siblings.

There is no history of alcohol or illicit drug use. J. denied being sexually active or having had any boyfriend or girlfriend in the past.

J. has a past legal history related to stealing and identity fraud. She reportedly created false identities and used them to purchase items online. When her cell phone was taken by her mother, she stole her mother's credit card to buy another cell phone.

Family History

J. and her aunt both denied any known family history of psychosis, antisocial behavior, or psychiatric illness, although little is known about J.'s father's history.

Medical History

J. had experienced episodes of vertigo several years previously. Medical workup, including an MRI, did not yield any organic etiology. She also has a history of iron-deficiency anemia, which had been treated with oral iron supplements. J. does not have any other chronic medical problems or any surgical history at the time of this writing.

J.'s menarche occurred at 12 years of age and menstrual cycles have been regular. There was no reported change in mood coinciding with her menses.

There was no known history of any significant childhood illnesses and her vaccinations were up to date. J. had no known drug allergies.

Medication History

J. was initially treated with fluoxetine at age 15 for her first major depressive episode, starting at 10 mg and slowly titrated to 40 mg once daily. She took fluoxetine, with periods of non-adherence, for 1 year and reported moderate benefit. After an overdose on fluoxetine, she was hospitalized and was switched to aripiprazole; the dose was titrated to 15 mg once daily. J. reported that she did not like the way aripiprazole made her feel, and was non-adherent. She was off medications for 1 year before she was started on sustained-release bupropion 150 mg by her current outpatient psychiatrist. J. took the sustained-release bupropion for 1 day prior to her suicide attempt.

Hospital Course

Upon admission to the pediatric intensive care unit at a regional pediatric hospital, J. had an episode of bilious emesis. J. was subsequently placed on nothing per mouth, later advanced to a clear liquid diet, and eventually to a regular diet as she stabilized. Her intake and output were recorded and were not significant. Additional laboratory studies were obtained, which revealed a slightly low hemoglobin and hematocrit consistent with her documented history of iron deficiency anemia. Selected laboratory values at the time of admission and then again at discharge from the hospital are noted in Table 1. Urine drug screen; tests for alcohol, salicylate, and acetaminophen; urinalysis; and urine

TABLE 1. COMPLETE METABOLIC PANEL

<i>Component</i>	<i>Admission value</i>	<i>Discharge value</i>	<i>Normal range</i>
Glucose	49	83	70–110 (mg/dL)
Creatinine	0.4	0.7	0.4–0.9 (mg/dL)
Sodium	145	141	136–145 (mmol/L)
Potassium	2.4	4.6	3.5–5.6 (mmol/L)
Chloride	120	107	95–105 (mmol/L)
CO ₂	14	15	25–35 (mmol/L)
Calcium	4.8	9.0	8.8–10.7 (mg/dL)
Anion gap	13.4		5.0–18.0

pregnancy test were negative. No cultures were found, and no diagnostic studies were performed.

Once J. was medically stabilized, the psychiatry service was consulted.

Mental Status Examination

Upon examination by the consultation liaison team during hospitalization, J. appeared to look her stated age; she was lying in bed and was calm, but only somewhat cooperative. She was minimally engaged with the interviewer and was guarded with information about events preceding her admission.

At the time of admission to the crisis stabilization unit, J. was well groomed, with good hygiene, casually dressed, and well nourished. Psychomotor activity was within normal limits. Her muscle tone and strength were normal, and no abnormal movements were noted. Her gait, assessed at a later time, was within normal limits. Her mood was depressed with constricted range of affect. J.'s speech was spontaneous and normal in rate, tone, and volume. Her thought process was logical with tight associations, and her thought content contained ongoing suicidal ideation with a plan to kill herself by overdosing on medication. She reported ongoing depressed mood and stress as the cause of her suicidality. There was no indication of any hallucinations, illusions, or any perceptual disturbances. Assessment of her cognitive function revealed that she was awake; alert; and oriented to time, place, and person. Her immediate and remote memory was intact, but her recent memory was impaired. Her attention span was not formally assessed but was grossly intact, and her language and naming skills were intact. J.'s fund of knowledge seemed to be average for her age. She had good insight into her condition and was able to correlate the increasing stressors in her life with the worsening of her depression. She had poor judgment and poor impulse control.

Brief Formulation

In summary, J. was a 17-year-old African American adolescent girl with a history significant for adolescent onset, recurrent major depression, and a past history of physical abuse and oppositional defiant behavior, admitted for a suicide attempt by overdose. Her suicide attempt occurred in the context of worsening depression, anger, and poor impulse control. She had a history of significant behavioral and legal problems in temporal association with several psychosocial stressors, including physical abuse by her mother, culminating in placement outside the home. Biological factors included iron deficiency anemia, which may have rendered her more vulnerable to mood symptoms; there was no known family history

of psychiatric illness. Psychological factors included a history of trauma, legal issues, and conflicts with her mother resulting in placement outside the home. J.'s strengths included good intellectual capacity, fair insight into her condition, and adherence to the recommended treatment plan during the current treatment episode.

Multi-Axial Diagnoses

Axis I:	Major depressive disorder, severe, recurrent, without psychotic features Oppositional defiant disorder Physical abuse Parent-child relational problem
Axis II:	Deferred
Axis III:	Iron-deficiency anemia
Axis IV:	Status post-seizure secondary to overdose Severe: academic, primary support, and legal difficulties
Axis V:	Global Assessment of Functioning Score: 10

Discussion

Given widespread use of bupropion for depression and smoking cessation, and off-label use for attention-deficit/hyperactivity disorder (ADHD) and anxiety, electrolyte abnormalities and cardiotoxicity associated with overdose are of interest and importance to all prescribing clinicians.

Bupropion is a unique monocyclic antidepressant chemically unrelated to any other antidepressant. It is structurally related to amphetamines and has comparable efficacy to other antidepressants. Bupropion was developed by Nariman Mehta in 1969 and was granted United States patent in 1974 (Mehta 1969).

The United States Food and Drug Administration (FDA) gave approval for the use of bupropion as an antidepressant in 1985. However, it was withdrawn from the market in 1986 as a result of it putting patients at increased risk of seizures; it was reintroduced to the market in 1989 after the seizure risk was found to be dose dependent. Bupropion was marketed under the brand name of Wellbutrin and sustained-release (twice daily) and extended-release (once daily) preparations received subsequent approval as antidepressants. Bupropion also received FDA approval, and was marketed as Zyban for smoking cessation. Currently, the maximum recommended dose of sustained-release bupropion is 450 mg per day (FDA).

Bupropion induces the release and inhibits the reuptake of dopamine (DA) and norepinephrine (NE). Bupropion is also a non-competitive antagonist of several nicotinic acetylcholine receptors (AChRs). The pharmacologic effect of the drug may be the result of its stimulatory action on the DA and NE systems as well as its inhibitory action on AChRs (Arias 2009).

Some studies have shown that bupropion may be useful in patients with ADHD, which makes it a reasonable choice for children and adolescents who have comorbid symptoms of depression and ADHD (Wilens et al. 2005). It is interesting to speculate in J.'s case that bupropion was recommended as a result of her failure to respond to fluoxetine, and/or an attempt to address both her mood and disruptive behavior symptoms.

As with other antidepressants, bupropion has a black box warning related to an increased risk of suicidality in young patients <age 24 during initial treatment (Hammad et al. 2006). As J.'s suicide attempt by overdose occurred prior to initiation of treatment at the recommended dose, dose and association between bupropion and suicidal behavior cannot be made in this case.

Symptoms of bupropion overdose may include difficulty breathing or swallowing, dizziness, fainting, shakiness, sweating, confusion, blurred vision, seizure, hallucinations, loss of consciousness, rapid or pounding heartbeat, blurred vision, lightheadedness, confusion, lack of energy, upset stomach, and jitteriness (AHFS™ Consumer Medication Information 2012).

Bupropion has a narrow therapeutic margin. Observational studies have shown that bupropion causes increased risk of seizures at doses ≥ 600 mg. The risk for seizures is highly dose dependent; seizure activity occurred in 21% of patients with overdose (Spiller et al. 1994). Some studies have suggested that sustained-release and extended-release bupropion may have a delayed onset of seizures within 24 hours after ingestion. However, J.'s seizure occurred within a few hours of her overdose, which fortunately responded well to lorazepam, without recurrence (Starr et al. 2009).

Hypokalemia is not a commonly reported adverse effect associated with bupropion overdose. A PubMed search performed using keywords "hypokalemia" and both "Wellbutrin" and "bupropion" did not yield any results. Notably, a three-year, multicenter, retrospective analysis of bupropion overdose reported hypokalemia in three out of five patients in whom potassium levels were reported (Spiller et al. 1994). As J.'s hypokalemia was clearly significant, associated with cardiotoxicity, and, if untreated, could have been life threatening, it is fortunate that close monitoring took place. Given frequent use of bupropion in clinical practice with children and adolescents, increased vigilance regarding potential metabolic and cardiac toxicity is recommended.

Disclosures

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References

- AHFS™ Consumer Medication Information: Bupropion. Bethesda, MD: American Society of Health-System Pharmacists, Inc.; ©2012. Available from: www.nlm.nih.gov/medlineplus/druginfo/meds/a695033.html. Last accessed November 2012.
- Arias HR: Is the inhibition of nicotinic acetylcholine receptors by bupropion involved in its clinical actions? *Int J Biochem Cell Biol* 41:2098–2108, 2009.
- Hammad TA, Laughren T, Racoosin J: Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 63:332–339, 2006.
- Mehta NB (June 25, 1974). United States Patent 3,819,706: Metachloro substituted α -butylamino-propiphenones. United States Patent and Trademark Office. Retrieved June 2, 2008.
- Spiller HA, Ramoska EA, Krenzelok EP, Sheen SR, Borys DJ, Vilalobos D, Muir S, Jones-Easom L: Bupropion overdose: A 3-year multi-center retrospective analysis. *Am J Emerg Med* 12:43–45, 1994.

- Starr P, Klein-Schwartz W, Spiller H, Kern P, Ekleberry SE, Kunkel S : Incidence and onset of delayed seizures after overdoses of extended-release bupropion. *Am J Emerg Med* 27:911–915, 2009.
- Wilens TE, Haight BR, Horrigan JP, Hudziak JJ, Rosenthal NE, Connor DF, Hampton KD, Richard NE, Modell JG: Bupropion XL in adults with attention-deficit/hyperactivity disorder: A randomized, placebo-controlled study. *Biol Psychiatry* 57: 793–801, 2005.

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