Case Report

Probable Tapentadol-Associated Serotonin Syndrome After Overdose

Heather Walczyk, PharmD, CPh, BCPS, CGP^{*}; Cheuk H. (Michael) Liu, PharmD, BCCCP, BCNSP, BCPS[†]; Antonia Alafiris, BS, PharmD, CGP[‡]; and Henry Cohen, MS, PharmD, FCCM, BCPP, CGP[§]

ABSTRACT

Purpose: Drug-induced serotonin syndrome is a potentially life-threatening condition. An Ovid MEDLINE, and PubMed search from 1950 to October 2015 revealed one published case report of suspected tapentadol-induced serotonin syndrome. We report a probable case of tapentadol-induced serotonin syndrome after overdose.

Case Summary: A 48-year-old male was found unresponsive after a witnessed overdose of medications including tapentadol. After administration of naloxone by emergency medical services, the patient became combative and presented with altered mental status. He was managed with physical and pharmacologic restraints in the emergency department. Other medications that could be implicated in the patient's presentation include duloxetine and amitriptyline. It was suspected that the opioid properties of tapentadol were masking the patient's signs and symptoms of serotonin syndrome. The patient was admitted to the medical intensive care unit, remained stable, and was discharged 2 days later. Currently, there is one published case report of suspected tapentadol-induced serotonin syndrome after an overdose. The manufacturer of tapentadol reported no cases of serotonin syndrome during clinical trials, but there have been postmarketing cases reported with co-administration of other serotonergic drugs.

Conclusion: We report a probable case of tapentadol-induced serotonin syndrome after overdose. Further research is needed to better understand the pharmacology and incidence behind this adverse event.

Key Words—serotonin syndrome, tapentadol

Hosp Pharm—2016;51:320-327

Tapentadol, a centrally acting analgesic, is thought to inhibit the reuptake of norepinephrine, a biogenic amine, while also acting predominantly as a mu (μ)-opioid receptor agonist. This dual action results in an opiate-sparing effect that has been shown to slow the development of tolerance when compared with morphine.¹ Tapentadol is currently US Food and Drug Administration (FDA)-indicated for the treatment of moderate to severe acute pain in adults with the initial dosing ranging from 50 to 100 mg

by mouth every 4 to 6 hours; doses greater than 700 mg on the initial day of therapy and greater than 600 mg on subsequent days have not been studied.² Tapentadol extended release oral tablets are FDA-approved for severe chronic pain where alternative treatment options are not deemed adequate and for diabetic peripheral neuropathy in adults.³ Dosing for the extended release formulation is 50 mg by mouth every 12 hours in opioid-naïve patients, with the maximum daily dose of 500 mg/day.³

^{*}SeaView Research, Miami, Florida; [†]Department of Pharmacy, Yale-New Haven Hospital, New Haven, Connecticut; [‡]Department of Pharmacy, St. Barnabas Hospital, Bronx, New York; [§]Department of Pharmacy Services, Kingsbrook Jewish Medical Center and Arnold & Marie Schwartz College of Pharmacy & Health Sciences of Long Island University, Division of Pharmacy Practice, Brooklyn, New York. Corresponding author: Cheuk H. (Michael) Liu, PharmD, BCCCP, BCNSP, BCPS, Department of Pharmacy, Yale-New Haven Hospital, 20 York Street, New Haven, CT 06510; phone: 203-688-5517; e-mail: cheukheimichael.liu@ynhh.org

Tapentadol is known *in vitro* to be a weak serotonin and norepinephrine reuptake inhibitor and is associated with a greater incidence of respiratory depression, coma, drowsiness, slurred speech, hallucination, and confusion when compared with tramadol.^{4,5} Postmarketing surveillance of tapentadol has revealed the potential for the development of serotonin syndrome with the concomitant use of serotonergic drugs. These drugs include serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and triptans.² The clinical manifestations of serotonin syndrome usually appear rapidly after ingestion of the offending agent(s) and can include agitation, shivering, diaphoresis, mydriasis, tachycardia, hypertension, hyperthermia, diarrhea, tremor, and hyperreflexia.⁶

Although there are limited data involving an overdose of tapentadol, it would be expected that miosis, vomiting, cardiovascular collapse, convulsions, and respiratory depression could develop due to the μ -opioid agonist activity.^{2,3,6}

We present a case of a patient who may have developed serotonin syndrome from an intentional tapentadol overdose.

CASE REPORT

A 48-year-old, African American, male substitute teacher was found unresponsive after sustaining a fall at the school where he worked. His coworkers stated that he was witnessed overdosing on unknown quantities of medications. At the scene of incident, emergency medical services (EMS) described the patient as having pinpoint pupils and being responsive only to pain. Vital signs obtained by EMS were blood pressure (BP) 119/80 mm Hg, heart rate (HR) 119 beats/min, and respiratory rate (RR) 8 breaths/min. No basal temperature was recorded and no overt signs of trauma were noted. A bottle containing a variety of different tablets was obtained from the patient's possessions. While in the ambulance, he was administered one dose of intramuscular naloxone 1 mg. He became agitated and restless and began thrashing and talking incoherently, requiring physical restraint by EMS personnel.

On emergency department (ED) admission, the patient was physically restrained by 6 hospital security personnel and was immediately placed on a vest restraint. Vital signs recorded at triage were BP 117/50 mm Hg, HR 133 beats/min, RR 46 breaths/min, and oxygen saturation (O_2 sat) of 100%; the

temporal temperature was not checked. The fingerstick glucose was 113 mg/dL. The ED clinical pharmacist was given the bottle of tablets; they were identified as tapentadol 75 mg immediate-release tablets, duloxetine 60 mg capsules, atenolol 25 mg tablet, and enalapril 5 mg tablet. No other medications or information on the patient's medication and medical histories were available. The ED physician evaluated the patient and documented a Glasgow Coma Score of 8 (normal range, 13-15), normal heart sounds, positive bowel sounds, tremor, and hyperreflexia. An electrocardiogram (EKG) was interpreted as sinus tachycardia with narrow QRS complexes and a QTc of 454 ms. Vital signs 35 minutes after ED arrival were BP 166/100 mm Hg, HR 123 beats/min, RR 27 breaths/min, O_2 sat 100%, and a temporal temperature of 100.2°F. Based on the available history and presentation, the ED physician suspected that the patient had developed serotonin syndrome that was initially suppressed by the opioid activity of tapentadol until naloxone was administered. While naloxone is known to antagonize primarily the μ -opioid receptor, it will be ineffective in reversing the serotonin reuptake effects of certain opioids such as dextromethorphan and meperidine.^{7,8} As a result, the Poison Control Center was contacted and recommended lorazepam 6 mg intravenous push and 2 mg intramuscularly, diphenhydramine 50 mg intravenous push, and 2 doses of haloperidol 5 mg intramuscularly. The patient became less agitated and his body temperature decreased without further intervention, indicating that his febrile state was most likely due to persistent agitation with muscle hyperactivity. Vital signs 1 hour after ED arrival were BP 152/91 mm Hg, HR 117 beats/min, RR 20 breaths/min, O_2 sat 100%, and a temporal temperature of 100.8°F. Laboratory orders and urine toxicology screening were obtained. The only significant finding was an elevated creatinine kinase level (Table 1). Since the patient's clinical signs and symptoms improved and remained stable, the ED physician did not order enteral cyproheptadine nor naloxone continuous intravenous infusion. Later that afternoon, the patient was admitted to the medical intensive care unit (MICU) for monitoring.

In the MICU on hospital day 1, the patient's mental status improved and his vital signs remained stable. The patient was administered oral tapentadol 50 mg 3 times a day due to his complaints of back pain and as recommended by the palliative care team. A medication history was obtained by the pharmacy team from the patient and his wife (Table 2). His past medical history is significant for major depressive disorder

Table 1. Laboratory results in the emergency department

Variable	Result	Reference range
<i>Serum</i>		
Sodium, mEq/L	144	135-145
Potassium, mEq/L	4.5	3.3-5
Chloride, mEq/L	102	96-106
Bicarbonate, mg/dL	25	22-30
Glucose, mg/dL	107	70-110
Blood urea nitrogen, mg/dL	11	10-20
Creatinine, mg/dL	1.3	0.5-1.3
Calcium, mg/dL	10.2	8.8-10.2
Total protein, g/dL	7.3	6-8.3
Albumin, g/dL	4.5	3.5-5
Aspartate aminotransferase, units/L	31	0-34
Alanine aminotransferase, units/L	31	0-34
Alkaline phosphatase, units/L	79	30-130
Creatinine kinase, units/L	1,922 ^a	38-174
Creatinine kinase-myocardial band, ng/mL	5.5	<6
Cardiac troponin I, ng/mL	0.010	<0.04
Ethanol, mg/dL	<5	<5
Salicylate, mcg/mL	<40	<40
Acetaminophen, mcg/mL	2	<15
<i>Urine toxicology screen</i>		
Barbiturates	Negative	Negative
Benzodiazepines	Negative	Negative
Cannabinoids	Negative	Negative
Cocaine	Negative	Negative
Opiates	Negative	Negative
Phencyclidine	Negative	Negative

^aAbove normal reference range.

(MDD), suicidal ideation, anxiety, hypertension, and gastroesophageal reflux disease (GERD). The patient denied smoking, illicit drug use, and any special diets, and he rarely consumed alcohol. His only known drug allergy was to penicillin, with which he experienced itching and swelling. The wife brought in the patient's prescribed medications from home, including a vial of tapentadol. For his home medications, the patient had been prescribed oral tapentadol 75 mg 3 times a day for chronic back pain, which is the recommended initial dosing for moderate to severe pain per the drug's prescribing information.² According to the patient and his wife, he received a bottle with

90 tablets of tapentadol 10 days prior to admission. Correcting for the days he should have taken the medication as prescribed, a total of 37 tablets were missing. The patient verbally confirmed that he overdosed primarily on tapentadol as a suicide attempt.

According to the patient and his wife, he had also been taking oral methadone 10 mg 3 times a day for chronic pain until a month prior to the day of incident when tapentadol was initiated. Oral oxycodone was also prescribed, but the dose, frequency, and duration were unknown. At the time of the case report, New York State had not yet implemented the Prescription Monitoring Program Registry when schedule II, III,

Table 2. Medication history

Generic name (<i>brand name</i>)	Dose, route, frequency, indication	Additional information
Tapentadol (<i>Nucynta</i>)	75 mg orally tid for chronic pain	Initiated several months prior to incident
Duloxetine (<i>Cymbalta</i>)	60 mg orally QAM or QHS for chronic pain	Initiated 1 year ago; sometimes nonadherent
Atenolol (<i>Tenormin</i>)	25 mg orally daily for hypertension	Initiated 1 year ago; sometimes nonadherent
Enalapril (<i>Vasotec</i>)	5 mg orally daily for hypertension	Initiated 1 year ago; sometimes nonadherent
Esomeprazole (<i>Nexium</i>)	40 mg orally daily for acid reflux	Initiated 1 year ago; does not take everyday
Amitriptyline (<i>Elavil</i>)	50 mg orally Q12H for major depressive disorder	Initiated 3-4 days prior to incident, and took 2-3 tablets the day before the incident, and 1 tablet the morning of the incident
Simvastatin (<i>Zocor</i>)	20 mg orally QHS for hyperlipidemia	Initiated 1 year ago, sometimes nonadherent
Methadone (<i>Methadose</i>)	10 mg orally tid for chronic pain	Stopped once tapentadol was initiated
Oxycodone (<i>OxyContin</i>)	Unknown	Took concomitantly with tapentadol for an extended period, unsure of timeline

Note: tid = twice daily; Q12H = every 12 hours; QAM = 09:00; QHS = 21:00.

and IV controlled substances are prescribed.⁹ Moreover, the patient was taking oral duloxetine 60 mg/day for the previous year. He also took 2 to 3 oral amitriptyline 50 mg tablets the day prior to the incident and one tablet on the day of the incident. The amitriptyline was self-medicated the day prior to the incident without consultation with a medical professional, as he found the medication in his home. The patient said that he was prescribed amitriptyline for his history of MDD and ingested 2 to 3 tablets of the medication in an attempt to “treat” the MDD the day before his suicide attempt and took 1 tablet on the morning of the suicide attempt (Table 2).

The patient remained clinically stable without any incidents or naloxone therapy throughout his MICU stay and was discharged directly from the MICU on hospital day 2. The case was electronically reported to the FDA’s Adverse Event Reporting System on hospital day 2.

DISCUSSION

Opioid Intoxication: Pathophysiology, Clinical Presentation and Management

The clinical manifestations of opioid intoxication include mental status depression, hypoventilation, miosis, and hypoperistalsis.⁶ These effects can be attributed to the drug’s actions on various opioid receptors. For example, the μ receptors are responsible for analgesia, sedation, miosis, euphoria, respiratory depression, and decreased gastrointestinal motility. Opioid antagonists, such as naloxone, can be used to reverse most effects of opioid analgesics. Naloxone is most potent

at the μ -opioid receptor. Opioid withdrawal after administration of an opioid antagonist may occur, presenting with symptoms such as agitation, diaphoresis, mydriasis, vomiting, myalgias, mild elevations in both heart rate and blood pressure, and pulmonary edema.⁷ Resedation can occur; it is dependent on the duration of action of both the opioid antagonist and the opioid agonist and the patient’s ability to metabolize and eliminate these agents. The use of opioid antagonists may not reverse the nonopioid effects demonstrated by several opioids, such as seizures induced by tramadol.¹⁰ Similarly, the use of opioid antagonists may “unmask” any other concurrent underlying clinical condition. For instance, cocaine-induced cardiac dysrhythmias may develop after naloxone reverses the effects of heroin, an opioid, in a patient who has co-administered both heroin and cocaine.⁷

Tapentadol is a synthetic opioid that inhibits the reuptake of serotonin and norepinephrine and also binds to the human μ -opioid receptor.^{4,5} It has been shown in preclinical models that the μ -opioid activity of tapentadol is reversed through administration of opioid antagonists.^{2,3} Since tapentadol is known to be a weak serotonin and norepinephrine reuptake inhibitor similar to tramadol, it is unlikely that naloxone will reverse these effects.

Serotonin Syndrome: Pathophysiology, Clinical Presentation, and Management

Serotonin is synthesized in the presynaptic neuron via the decarboxylation and hydroxylation of L-tryptophan, and it is then incorporated into the

presynaptic vesicles.¹¹ Once released into the intrasynaptic space, presynaptic serotonin receptors inhibit further release of serotonin. The released serotonin binds to postsynaptic receptors and a reuptake mechanism returns the serotonin back to the presynaptic vesicles. Serotonin is then metabolized by monoamine oxidase (MAO) subtype A into hydroxyindoleacetic acid. Serotonin effects may be enhanced through several mechanisms including increased consumption of the serotonin precursor L-tryptophan, increased release of serotonin, inhibition of serotonin metabolism through the use of MAOIs, or prevention of serotonin reuptake back into the synapse by using SSRIs and SNRIs, such as duloxetine.

Symptomatic onset of serotonin syndrome is usually rapid and can occur within minutes of ingesting the offending agent. Mild cases of serotonin syndrome may present with tachycardia, shivering, diaphoresis, or mydriasis. Moderate cases may progress to hyperactive bowel sounds, hyperreflexia and clonus of the lower extremities, and mild agitation. Severe cases can present with severe hypertension and tachycardia, delirium, muscular rigidity and hypertonicity, rhabdomyolysis, and renal failure.¹¹ Diagnostic criteria for serotonin syndrome have been developed including the Hunter's criteria, with an 84% sensitivity and 97% specificity.¹² Fulfillment of Hunter's criteria include ingestion of a serotonergic agent within the past 5 weeks and presence of any of the following symptoms: (a) tremor and hyperreflexia; (b) muscle rigidity, core temperature greater than 38°C, and either inducible or ocular clonus; (c) ocular clonus with either diaphoresis or agitation; (d) inducible clonus with either agitation or diaphoresis; or (e) spontaneous clonus.¹¹

Initial management of serotonin syndrome is to remove the offending agent. For weak serotonin reuptake inhibitors such as tapentadol, discontinuation of the offending agent is most likely warranted in the event of either an overdose or ingestion of multiple serotonergic agents since usage of tapentadol at the FDA-labeled recommended dosing is unlikely to cause this syndrome. Many cases of serotonin syndrome will resolve within 24 hours, however, it is important to take into consideration the half-lives of the medications ingested as symptoms may persist. The administration of 5-HT_{2A} antagonists such as cyproheptadine may be considered, although patients with mild cases may be managed with supportive care (eg, intravenous fluids) and benzodiazepines to

control agitation.¹¹ Since cyproheptadine is available only in oral dosage forms, administration in moderate and severe cases is very difficult.

Review of the Case and Literature Search

This patient was thought to have developed serotonin syndrome fulfilling Hunter's criteria after an overdose of unknown quantities of tapentadol, based on the ingestion of a serotonergic agent within the past 5 weeks and the presence of tremor and hyperreflexia.¹¹ The episode was initially suppressed by the opioid activity until naloxone was administered, at which point the symptomatic presentation of serotonin syndrome became evident. As mentioned, Hunter's criteria has both high sensitivity and specificity for serotonin syndrome. Although opioid withdrawal may be considered a differential diagnosis based on the patient's presentation, it is unlikely because altered mental status is typically not present in opioid withdrawal, the patient did not experience resedation as naloxone's half-life is relatively short, and the patient responded primarily to benzodiazepines, which is the treatment of choice for serotonin syndrome.^{11,13} Among all the medications the patient was taking, only duloxetine, amitriptyline, and tapentadol are associated with the development of serotonin syndrome.^{14,15} Application of the Naranjo adverse reaction probability nomogram (Table 3) yields a score of 7, indicating a *probable* temporal and causal relationship between tapentadol and serotonin syndrome.¹⁶

A comprehensive literature search was conducted using Ovid MEDLINE and PubMed (1950–October 2015). The search was limited to human cases and the following key words were used: tapentadol, Nucynta®, serotonin syndrome, serotonin. The search yielded one published case report of suspected tapentadol-induced serotonin syndrome.¹⁷ Although the case by Franco and colleagues did not confirm with certainty that the cause of death was due to serotonin syndrome and did not report the application of the Naranjo adverse reaction probability nomogram, the patient's clinical presentation and the presence of significantly elevated tapentadol concentration, more than 20 times the established therapeutic ranges, suggests it as a possible mechanism of death. The manufacturer of tapentadol, Janssen Pharmaceuticals, was contacted via telephone to inquire if any reports of serotonin syndrome related to the drug had ever been reported. The manufacturer's senior therapeutic specialist (M. Han, PharmD, November 2011) responded

Table 3. The Naranjo nomogram¹⁶ for causality assessment

	Yes	No	Don't Know	Score
1. Are there previous reports of this reaction? (If no, please provide documentation of search strategy)	+1	+0	+0	+1
2. Did the adverse drug event (ADE) appear after the suspected drug was administered?	+2	-1	+0	+2
3. Did the ADE improve when the drug was discontinued or a specific antagonist was administered?	+1	+0	+0	+1
4. Did the ADE reappear when the drug was readministered?	+2	-1	+0	-1
5. Are there alternative causes (other than the drug) that could, on their own, have caused the ADE?	-1	+2	+0	+2
6. Did the ADE reappear when a placebo was given?	-1	+1	+0	+0
7. Was the drug detected in the blood or other fluids in concentrations known to be toxic?	+1	+0	+0	+0
8. Was the ADE more severe when the dose was increased or less severe when the dose was decreased?	+1	+0	+0	+1
9. Did the patients have a similar reaction to the same or similar drugs in any other previous exposure?	+1	+0	+0	+0
10. Was the adverse event confirmed by any objective evidence?	+1	+0	+0	+1
Total score				Z

Note: Rating scale: 9 points = definite; 5-8 points = probable; 1-4 points = possible; ≤0 = doubtful.

on the phone and through a follow-up e-mail that no such incidence were reported in phase 2 and 3 clinical trials, however, there have been postmarketing reports of the syndrome in patients using tapentadol along with other serotonergic drugs. When asked for copies of these reports, we were told that they were deemed confidential and unable to be released for our review.

In our case report, other than the sporadic use of amitriptyline, no other medications were added or changed during the patient's course of tapentadol therapy, including over-the-counter, herbals, or other alternative medications. In addition, alcohol and illicit substance use were unlikely to have contributed based on patient history and urine toxicology screen. The toxicology screen for opiates at our institution does not detect for oxycodone, meperidine, pentazocine, propoxyphene, and tapentadol.^{18,19} Although it is possible that oxycodone contributed to the patient's unconsciousness prior to admission, it is unlikely to have caused serotonin syndrome based on the drug's lack of affinity for any serotonin receptor.¹³

Typical clinical presentation of individuals who overdose on first-generation, tertiary-amine tricyclic antidepressants, such as amitriptyline, include hypotension, seizures, wide QRS complex tachyarrhythmias, and anticholinergic toxic effects such as

decreased bowel sounds, dry flushed skin, hallucination, and agitation.²⁰ The EKG and physical findings for our patient are not consistent with this typical presentation, therefore it is unlikely that amitriptyline played a major contributing role in the adverse event. Signs of significant overdose of duloxetine can range from confusion with nonspecific electrolyte abnormalities to reversible coma.^{21,22} Other than confusion, the patient did not exhibit any of these signs.

It is important to distinguish serotonin syndrome from the similar symptomatic presentations of neuroleptic malignant syndrome (NMS), anticholinergic toxicity, and malignant hyperthermia.¹¹ These differential diagnoses were ruled out in our case, as our patient's history was not significant for any medications associated with these conditions, with the exception of amitriptyline, which is a tertiary amine tricyclic antidepressant that possesses anticholinergic properties.²⁰ The clinical presentation is also inconsistent with these conditions. For example, our patient presented with altered mental status, positive bowel sounds, hyperreflexia, and tachypnea immediately after naloxone. These symptoms are consistent with serotonin syndrome and rule out similar conditions such as NMS (typically develops in 1-3 days as opposed to less than 12 hours), anticholinergic

toxicity (no decreased or absent bowel sounds), or malignant hyperthermia (no signs of decreased bowel sounds or hyporeflexia).

Potential Mechanism of Tapentadol-Induced Serotonin Syndrome

Although the exact mechanism for the development of serotonin syndrome from tapentadol is unknown, we suspect that it may be due to the reuptake of serotonin, leading to more serotonin being present in the synapse. Tramadol, a synthetic opioid, is similar to tapentadol in that it acts as a μ -opioid agonist and a weak inhibitor of norepinephrine and serotonin, although tapentadol's norepinephrine reuptake-inhibiting effect may play a significant role in its analgesic effects.^{5,13,23} Published case reports document the development of serotonin syndrome associated with tramadol.^{24,25} Given that the mechanism of tapentadol is similar to that of tramadol, the concomitant use of tapentadol with other serotonergic agents may increase the risk for serotonin syndrome.⁶

Limitations

Our case report has several limitations. First, the history was obtained from the patient and his wife, therefore recall bias is possible. Also, the history was not confirmed with the patient's community pharmacy, but the patient's medication vials corroborate the history given. Second, the patient's presentation could have been hypertensive crisis as tapentadol and duloxetine both inhibit norepinephrine reuptake. This is unlikely, however, as his symptoms improved without any antihypertensive agents and his blood pressure readings are consistent with the definition of hypertensive crisis, where the systolic blood pressure is 180 mm Hg or greater and/or diastolic blood pressure 110 mm Hg or greater.^{26,27} Furthermore, we did not obtain a serum duloxetine level as reported elsewhere.²¹ Third, we did not obtain a serum TCA immunoassay for the presence of amitriptyline. As mentioned previously, the EKG and physical findings are not consistent with TCA overdose. Last, the urine toxicology screen for opioids was negative, but the assay used does not detect for tapentadol and his initial symptomatic presentation was consistent with opioid intoxication.¹⁹

CONCLUSIONS

To our knowledge, we present the second case of tapentadol-associated serotonin syndrome secondary to an overdose. We recommend that clinicians and

patients be cognizant of the risk of developing serotonin syndrome with this agent. Further investigation on the mechanism and risk is warranted.

ACKNOWLEDGMENTS

The authors have no funding or conflicts of interest to disclose. The authors thank Elizabeth Tencza for reviewing the content of the manuscript.

REFERENCES

1. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (TapentadolHCl): A novel μ -opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323(1):265-276.
2. *Nucynta* (tapentadol) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc.; September 2013.
3. *Nucynta ER* (tapentadol) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc.; April 2014.
4. Tsutaoka BT, Ho RY, Fung SM, et al. Comparative toxicity of tapentadol and tramadol utilizing data reported to the national poison data system [published online ahead of print September 14, 2015]. *Ann Pharmacother*.
5. Ramaswamy S, Chang S, Mehta V. Tapentadol - the evidence so far [editorial]. *Anaesthesia*. 2015;70(5):518-522.
6. Helm S, Trescot AM, Colson J, Sehgal N, Silverman S. Opioid antagonists, partial agonists, and agonists/antagonists: The role of office-based detoxification. *Pain Physician*. 2008;11(2):225-235.
7. Nelson LS, Howland M. Antidotes in depth: Opioid antagonists. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR. Hoffman R.S., Howland M, Lewin N.A., Nelson L.S., Goldfrank L.R. Eds. Robert S. Hoffman, et al.eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York: McGraw-Hill; 2015. <http://accessemergencymedicine.mhmedical.com/content.aspx?bookid=1163&Sectionid=65086999>. Accessed October 23, 2015.
8. Linn KA, Long MT, Pagel PS. "Robo-tripping": Dextromethorphan abuse and its anesthetic implications. *Anesth Pain Med*. 2014;4(5):e20990.
9. Prescription Monitoring Program Registry. New York State Department of Health website. https://www.health.ny.gov/professionals/narcotic/prescription_monitoring/. Accessed October 26, 2015.
10. Spiller HA, Gorman SE, Villalobos D, et al. Prospective multi-center evaluation of tramadol exposure. *J Toxicol Clin Toxicol*. 1997;35(4):361-364.
11. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
12. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: Simple and accu-

rate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642.

13. Nelson LS, Olsen D. Opioids. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR, eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York: McGraw-Hill; 2015. <http://accessemergencymedicine.mhmedical.com/content.aspx?bookid=1163&Sectionid=65093560>. Accessed October 23, 2015.
14. Dougherty JA, Young H, Shafi T. Serotonin syndrome induced by amitriptyline, meperidine, and venlafaxine. *Ann Pharmacother*. 2002;36(10):1647-1648.
15. Gelener P, Gorgulu U, Kutlu G, Ucler S, Inan LE. Serotonin syndrome due to duloxetine. *Clin Neuropharmacol*. 2011;34(3):127-128.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
17. Franco DM, Ali Z, Levine B, Middleberg RA, Fowler DR. Case report of a fatal intoxication by Nucynta. *Am J Forensic Med Pathol*. 2014;35(4):234-236.
18. Chyka PA. Substance abuse and toxicological tests. In: Lee M, ed. *Basic Skills in Interpreting Laboratory Data*. 3rd ed. Bethesda, MD: American Society of Health-Systems Pharmacists; 2004:91-116.
19. Herring C, Muzyk AJ, Johnston C. Interferences with urine drug screens. *J Pharm Pract*. 2011;24(1):102-108.
20. Liebelt EL. Cyclic antidepressants. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR, eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York: McGraw-Hill; 2015. <http://accessemergencymedicine.mhmedical.com/content.aspx?bookid=1163&Sectionid=65097419>. Accessed October 23, 2015.
21. Kruithof MK, Bruins NA, van Roon EN. Coma after overdose with duloxetine. *Ann Pharmacother*. 2011;45(1):e5.
22. Menchetti M, Gozzi BF, Saracino MA, Mercolini L, Petio C, Raggi MA. Non-fatal overdose of duloxetine in combination with other antidepressants and benzodiazepines. *World J Biol Psychiatry*. 2009;10(4 Pt 2):385-389.
23. *Ultram* (Tramadol hydrochloride) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc.; July 2014.
24. Peacock LE, Wright F. Serotonin syndrome secondary to tramadol and citalopram. *Age Ageing*. 2011;40(4):528.
25. Vizcaychipi MP, Walker S, Palazzo M. Serotonin syndrome triggered by tramadol. *Br J Anaesth*. 2007;99(6):919.
26. Marik PE, Varon J. Hypertensive crises. *Chest*. 2007; 131(6):1949-1962.
27. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation. *Hypertension*. 2003;42(6):1206-1252. ■