Case Reports of Postmarketing Adverse Event Experiences With Olanzapine Intramuscular Treatment in Patients With Agitation

Stephen R. Marder, MD; Sebastian Sorsaburu, MD; Eduardo Dunayevich, MD; Jamie L. Karagianis, MD; Ian C. Dawe, MD, MHSc; Deborah M. Falk, BS; Mary Anne Dellva, MS; Janice L. Carlson, PhD; Patrizia A. Cavazzoni, MD; and Robert W. Baker, MD

Objective: Agitation is a medical emergency with increased risk for poor outcome. Successful treatment often requires intramuscular (IM) psychotropics. Safety data from the first 21 months of olanzapine IM, approved in the United States for the treatment of agitation associated with schizophrenia and bipolar disorder, are presented.

Method: A Lilly-maintained safety database was searched for all spontaneous adverse events (AEs) reported in temporal association with olanzapine IM treatment.

Results: The estimated worldwide patient exposure to olanzapine IM from January 1, 2004, through September 30, 2005, was 539,000; 160 cases containing AEs were reported from patients with schizophrenia (30%), bipolar disorder (21%), unspecified psychosis (10%), dementia (8%), and depression (5%). Many reported concomitant treatment with benzodiazepines (39%) or other antipsychotics (54%). The most frequently reported events involved the following organ systems: central nervous (21%), cardiac (12%), respiratory (6%), vascular (6%), and psychiatric (5%). Eighty-three cases were considered serious, including 29 fatalities. In these fatalities, concomitant benzodiazepines or other antipsychotics were reported in 66% and 76% of cases, respectively. The most frequently reported events in the fatal cases involved the following organ systems: cardiovascular (41%), respiratory (21%), general (17%), and central nervous (10%). The majority of fatal cases (76%) included comorbid conditions and potentially clinically significant risk factors for AEs.

Conclusions: Clinicians should use care when treating agitated patients, especially when they present with concurrent medical conditions and are treated with multiple medications, which may increase the risk of poor or even fatal outcomes. Clinicians should use caution when using olanzapine IM and parenteral benzodiazepines simultaneously.

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Corresponding author: *Stephen R. Marder, MD, Building 210, Room 130, West Los Angeles VA Healthcare Center, 11301 Wilshire Blvd, Los Angeles, CA 90073 (marder@UCLA.edu).*

Agitation is a nonspecific behavioral state with diverse medical causes, including general medical conditions, toxic states, and neurologic and neuropsychiatric disorders. The appropriate treatment is highly dependent on the underlying cause of agitation. Yet, identifying the underlying cause of agitation in the acute treatment setting may prove especially challenging: patients are typically confused and uncooperative, making it difficult to obtain an accurate medical history, perform adequate examinations, and determine underlying medical conditions and current prescribed medications or drug use. Many of the disease states that can lead to agitation (eg, delirium, schizophrenia, dementia) are associated with an increased risk for poor treatment outcomes.[1] Moreover, successful treatment of agitation may require polypharmacy[2] and physical restraints,[3,4] which may increase the risk of adverse events and sudden, unexplained deaths. Finally, the state of agitation itself is associated with an increased risk for adverse events.[5]

Successful treatments of agitation should address the behavioral and physiologic manifestations of agitation, as well as the underlying cause[6,7]; when agitation is associated with a psychiatric illness, antipsychotics can alleviate both. Intramuscular (IM) treatments are often used in treating agitation, as there may be an urgent need to calm uncooperative patients. The safety and tolerability of olanzapine IM in patients with schizophrenia and bipolar I mania have been established in randomized, placebo- and active treatment–controlled clinical trials[8–10] that included a total of 552 patients. Currently, olanzapine IM is approved in the United States to treat agitation associated with schizophrenia and bipolar disorder.

Postmarketing pharmacovigilance data from adverse events observed in general clinical practice can be a useful complement to clinical trial data, as they typically involve a much greater number of exposures to a much broader population of patients. However, the data may be confounded

because of underreporting, biases in the nature of adverse events reported, incomplete reports, and the unavailability of an exact number of patient exposures. Yet, these data are a useful guide to pharmaceutical companies and regulatory agencies to detect safety signals that may not be evident in the smaller, restrictive populations in clinical trials. These data and clinical trial data help to inform regulatory agencies regarding the necessity of changes to the product labeling (eg, black box warnings, medical letters). In this article, we present postmarketing safety data on olanzapine IM for the first 21 months of worldwide use (January 1, 2004, to September 30, 2005), with an emphasis on serious adverse events.

METHOD

Database

Eli Lilly and Company maintains a worldwide safety database of all spontaneously reported adverse events occurring in temporal proximity of treatment with Lilly products (1983–present). It contains all spontaneous adverse events (both serious and nonserious) reported with olanzapine IM use. The database also includes data from published literature and regulatory agency reports and serious adverse events from clinical trials and postmarketing studies. Cases are entered into the database regardless of the event reporter (eg, health care professional, patient, family member), the presence of concomitant treatments or medical comorbidities, or consideration of the potential relationship between olanzapine IM treatment and the adverse event. The adverse events contained in each case are mapped to terms in the Medical Dictionary for Regulatory Activities (MedDRA) to identify events and affected system organ classes.

Definitions

A "case" represents a report of events in 1 patient. An "event" represents a clinical sign, symptom, or syndrome reported in that case. Therefore, 1 case may contain more than 1 event. Serious adverse events were defined as those events that resulted in death, were considered life-threatening, required a new or prolonged an existing hospitalization, resulted in persisting disability, resulted in a congenital anomaly/birth defect, or were considered serious by the reporter. Nonserious adverse events were defined as those events that did not qualify as serious.

Estimated postmarketing exposure of olanzapine IM was determined from multiple data sources; the data were combined and analyzed in a modeling methodology to estimate a range of values and an estimate for the total number of exposed patients. Prescribed overdose was a category defined by MedDRA, and it described any case in which the administered dose was greater than the doses recommended in the reporting geographic region, even if no adverse event occurred. Patients who had been or were being concurrently treated with other antipsychotics were classified as having a history of antipsychotic use.

Analysis

The safety database was searched for all adverse events reported in temporal association with olanzapine IM treatment occurring from January 1, 2004, through September 30, 2005. All serious spontaneous, nonserious spontaneous, and serious postmarketing study case reports were included. The data were categorized by patient demographics, adverse event severity (fatal, serious nonfatal, and nonserious), underlying psychiatric diagnosis, history of concurrent antipsychotic use, concomitant benzodiazepine use, general medical comorbidities (eg, cardiovascular conditions), and other concurrent medications. In addition, cardiovascular and respiratory events were examined more closely because of the substantial number of serious events classified as such.

RESULTS

Overview of the Adverse Event Case Reports

There were 160 case reports: 155 were spontaneously reported from general use; 5 were reported from postmarketing studies. There were 83 reports coded as serious, 29 of which were fatal, and 76 as nonserious. There was also 1 case of a patient who did not suffer an adverse event, but received olanzapine IM during pregnancy. The most commonly reported adverse events (coded as MedDRA preferred terms) in these 160 cases included pyrexia (14), drug ineffective (13), hypotension (11), syncope (10), neuroleptic malignant syndrome (NMS; 9), somnolence (9), cardiac arrest (8), agitation (8), blood creatine phosphokinase increased (8), and falls (7). There were 15 cases coded as "prescribed overdose," none of which were judged to be intentional or accidental overdoses.

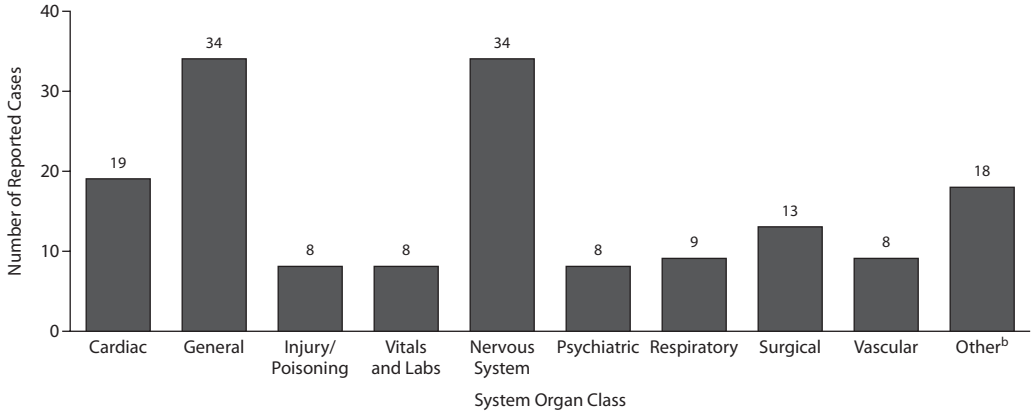
Patient Characteristics

For the first 21 months of olanzapine IM postmarketing use, the estimated exposure was 539,000 patients, and the rate of reported adverse event case reports was 0.03% (160/539,000); reports could have contained more than 1 adverse event. Patient age was reported in 133/160 cases, ranging from 11–98 years (mean age = 46.1 years). Sex was identified in 159/160 reports: males accounted for 56.6% (90/159) of the cases. The most frequently reported adverse events involved the nervous and general disorder organ classes (Figure 1). The underlying disease state of the agitated patients was identified in 113/160 reports; the most common included schizophrenia (34) and bipolar disorder (24; Figure 2).

Doses of Olanzapine and Proximity to Adverse Event Onset

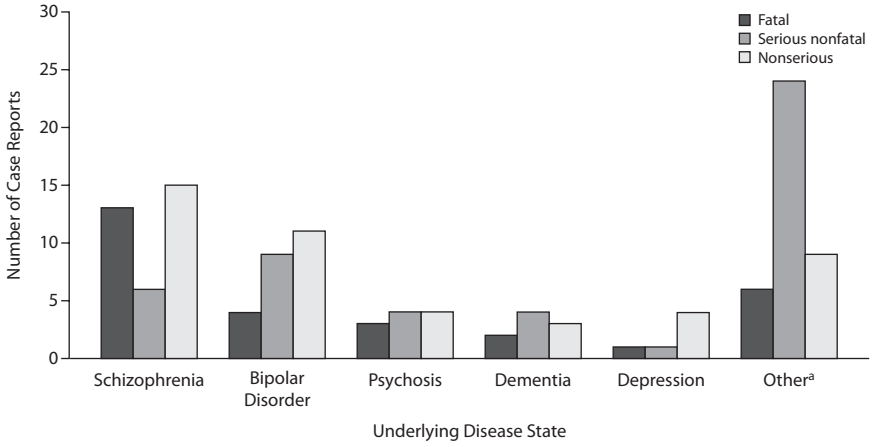
The time between olanzapine IM treatment and onset of the adverse event was reported in 82 cases; the serious cases

Figure 1. All Adverse Events (total = 160[a]) Presented by System Organ Class



[a]For this graph, N = 159, as one patient did not experience an adverse event but, rather, was treated with olanzapine IM during pregnancy.
[b]Includes blood/lymphatic, eye, gastrointestinal, hepatofibrillary, infections, metabolic, musculoskeletal, renal/urinary, reproductive, and skin.

Figure 2. Fatal (total = 29), Serious Nonfatal (total = 53), and Nonserious (total = 76) Adverse Event Reports Presented by Underlying Disease State



[a]Includes behavioral disorder, confusional state, mania, none, organic brain syndrome, paranoia, unspecified, unknown, and all other disorders.

onset ranged from immediately to 18 days after drug administration. The time to onset after the most recent dose of olanzapine IM was ≤ 1 day in 60% of all serious cases, with 51% of those occurring ≤ 12 hours. In the 29 fatalities in which time to onset was reported, the adverse event occurred ≤ 1 hour in 3 cases, > 1–12 hours in 4 cases, 13–24 hours in 8 cases, and > 24 hours in 11 cases (Table 1). Of the 54 nonfatal serious cases in which time to onset was reported, the adverse event occurred ≤ 1 hour in 8 cases, > 1–12 hours in 9 cases, 13–24 hours in 17 cases, and > 24 hours in 8 cases. In those fatal cases in which time from treatment to adverse event and olanzapine IM dose were reported, 3 patients were given more than 10 mg olanzapine IM within 12 hours (20 mg in 4 hours [cause of death, pulmonary embolism], 20 mg in 6 hours [cause of death, cardiac arrest], and 30 mg in 7.5 hours [cause of death, cardiac arrest]).

Concomitant Medications

A history of current or prior antipsychotic use was reported in 87.5% of the case reports. A majority of the fatal (24/29 [82.8%]) and serious nonfatal 29/54 [53.7%]) cases reported concurrent antipsychotic use (in the nonserious cases, 35/76 [46.1%]). Ninety-seven of the 160 cases provided information on benzodiazepine use; benzodiazepine treatment was administered in 63/97 of these cases. Benzodiazepine use was reported in a majority of the nonfatal serious cases (24/28 [85.7%]) and in half of the nonserious

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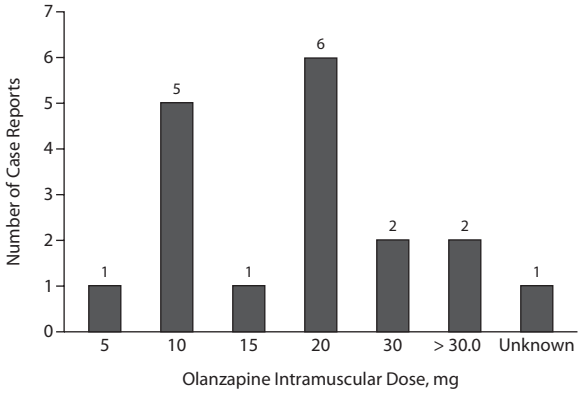
Table 1. A History of Current or Prior Antipsychotic and Benzodiazepine Use in the Fatal Cases in Which Multiple Medications Were Reported (24/29)

Medication	No. of cases
Antipsychotics	29
2	6
≥3	4
Benzodiazepines	15
Both antipsychotics and benzodiazepines	9

Figure 3. Number of Cardiac Adverse Event Case Reports in the Fatal Cases by Olanzapine IM Dose (total = 18)



cases (20/40 [50.0%]). Of the 29 fatal cases, 15 (51.7%) reported benzodiazepine use (oral, intravenous [IV], or IM), and 9 (31.0%) reported both antipsychotic and benzodiazepine use (Table 1).

Cardiovascular Events

Fifty-five of the 160 adverse event cases involved a possible cardiovascular event. Among cases with no history of prior antipsychotic treatment (10/55; 22 events), the most common adverse events included hypotension (5), bradycardia (3), falls (3), syncope (2), and loss of consciousness (2). Among all the cardiovascular adverse event cases with a known history of antipsychotic use (27/55; 48 events), the most common adverse events included cardiac arrest (8), syncope (7), changes in blood pressure (5), changes in heart rate (4), and hypotension (4). Eighteen of the 29 fatal cases experienced a cardiovascular adverse event; 14 of these patients died of cardiovascular events. In the fatal cases with cardiovascular events (18/29; 33 events), the most common adverse events were cardiac arrest (8), syncope (5), and hypotension (2). The number of fatal cases with a cardiac adverse event is presented by olanzapine IM dose in Figure 3.

Respiratory Adverse Events

Fifty-nine of the 160 cases reported respiratory adverse events, including 11 of the fatal cases. The most common respiratory adverse events included apnea (3), asthma (3), and Mendelson's syndrome (2; aka aspiration-related chemical pneumonitis; a pulmonary disorder that results from aspiration of stomach contents into the lungs). In the fatal cases in which the cause of death was known or suspected to be respiratory, 2 patients died of apnea; 1, from asphyxiation; and 1, from asthma.

Fatal Cases

The mean age of the patients in the 29 fatal cases was 49.1 years, ranging from 20–82 years. In the fatal cases, the most commonly reported MedDRA-coded events included categories of cardiac (12), vascular (10), and respiratory (4). Six of these cases appeared to have no remarkable history or potential contributing factors, while 14 had ≥1 clinically relevant contributing factors, such as age ≥60 years (10); cardiac (10), respiratory (11), metabolic (8), or vascular (7) conditions; use of restraints (5); and/or dementia (2).

Summary of the Fatal Cases

Case 1. A 70-year-old male patient with schizophrenia was given 1 dose of 10 mg olanzapine IM. The patient's medical history included aortic aneurysms, arterial hypertension, chronic obstructive pulmonary disease, anemia, and smoking. The patient was taking antihypertensive medication, ferrous fumarate, 200 mg oral amisulpride 3 times/d, and 25 mg oral zotepine 3 times/d. The patient died of a rupture of an aortic aneurysm (not confirmed by autopsy) on the same day he received the injection of olanzapine IM.

Case 2. A 43-year-old female patient with chronic schizophrenia was given 1 dose of 10 mg olanzapine IM for severe agitation. She had a history of chronic schizophrenia and suicide attempts. The patient was taking 100 mg haloperidol deaconate IM biweekly, 5.0 mg oral haloperidol, and 1.0–2.5 mg oral lorazepam. The patient also ingested yew toxin. The patient did not receive either oral haloperidol or lorazepam on the day she died; she did receive her scheduled haloperidol deaconate IM injection that day. She became agitated and was given the injection of olanzapine. Approximately 4.5 hours after her injection, she experienced an episode of syncope (from which she recovered), followed by another episode of syncope, arrhythmic pulse, ventricular fibrillation, and asystole; death from cardiac arrest with ventricular fibrillation occurred approximately 5.5–6 hours later. An autopsy could not find evidence of a macroscopic event. A previous electrocardiogram (ECG) showed no irregularities, and the autopsy revealed no obvious cause of death but the presence of yew toxin in the organs.

Case 3. A 39-year-old male patient with schizoaffective disorder received a total of 40 mg olanzapine IM over a 12-day period (1 dose of 10 mg olanzapine IM on 4 separate days). He had a history of alcoholism, morbid obesity, hypertension, hyperuricemia, and hypercholesterolemia. The patient was taking several antipsychotic medications: 100

mg risperidone depot, oral risperidone, and haloperidol IM. The patient was also taking 6 mg oral clonazepam, 100 mg oral clorazepate, 500 mg oral valproate, and sustained-release biperiden. The day before he died, the patient was given 1 dose of 500 mg valproate, 2 doses of 6 mg clonazepam, 2 doses of oral risperidone, 1 dose of olanzapine IM, and possibly zuclopenthixol acuphase IM. The patient also had received 100 mg risperidone decanoate microspheres 2–3 days before he died, and he was restrained the day before he died. Approximately 10 hours after the last dose of olanzapine IM, he died of a suspected cardiac event; the autopsy revealed a previously unspecified cardiac hypertrophy, but the cause of death was not listed in the case report.

Case 4. A 31-year-old female patient with resistant schizophrenia was given 10 mg of olanzapine IM after refusing to take oral olanzapine. She had a history of suicide attempts, 1 just 7 days prior to her death, and aspiration-related chemical pneumonitis. This suicide attempt resulted in a head injury and subsequent neurosurgery. The patient was taking oral clozapine, 80 mg flupenthixol decanoate, and oral olanzapine. The patient died of asphyxia by pulmonary edema (confirmed by autopsy) approximately 75 minutes after receiving olanzapine IM.

Case 5. A 36-year-old male patient with schizophrenia received 10 mg olanzapine IM for psychomotor agitation. He was obese and had a history of nocturnal choking. The patient was not taking any medications in the month prior to receiving olanzapine IM but had taken quetiapine and olanzapine in the past without problems. Two hours before injection of olanzapine IM, he received promazine IM, lorazepam IM, and 200 mg quetiapine. The day following treatment with olanzapine IM, he experienced dyspnea and later died of suspected pulmonary edema. An autopsy stated the cause of death as ". . . a cardiocirculatory arrest following an acute dysrhythmia event in a patient suffering from chronic cardiopathy . . ."

Case 6. A 55-year-old female patient with bipolar disorder received a total of 30 mg olanzapine IM (3 doses of 10 mg 3.5–4 hours apart) for a manic episode. She had no remarkable medical history, and recent laboratory tests and an electroencephalogram (EEG) showed no abnormalities. The day before receiving olanzapine IM, the patient took the antipsychotics chlorpromazine, promazine, and promethazine; 4 hours after receiving olanzapine treatment, she received 4 mg lorazepam IM. She died 15 hours after receiving the last injection of olanzapine IM of suspected cardiocirculatory arrest (listed on death certificate; not confirmed by autopsy).

Case 7. A 25-year-old female patient with paranoid schizophrenia received a total of 90 mg olanzapine IM over a period of 4 days (3 doses of 10 mg the first day and 2 doses of 10 mg every day for 3 days). She had a history of suicidal ideation and attempts. She was previously treated with olanzapine with no notable difficulties. Her concomitant medications were cyclodol and reladorm (cyclobarbital and diazepam), and she was switched from olanzapine IM to 20 mg oral olanzapine for the 8 days following the IM treatment. The patient committed suicide 9 days after receiving the last olanzapine IM injection; it is not known if an autopsy was performed.

Case 8. A 59-year-old male patient with schizophrenia was given a total of 60 mg olanzapine IM over a period of 3 days (1 dose of 10 mg the first day, 2 doses of 10 mg on the second day, and 3 doses of 10 mg on the third day) for agitation and delirium. He had a history of arterial hypertonia, atherosclerosis, cardiomyopathy, hyperlipidemia, ischemic heart disease, obesity (body mass index [BMI] = 33.1), and smoking. The patient was given 50 mg chlorprothixine, clozapine, haloperidol, and levopromazine; he was also receiving cordiamin, trihexyphenidyl, and 50 mg tizercin. He developed constipation, and an ECG showed tachycardia; he was given zuclopenthixol decanoate. Olanzapine IM and chlorpromazine were discontinued. He developed urinary retention and was diagnosed with cardiomyopathy, ischemia, and arterial hypertension; he was given doxazosin, castor oil, an α-adrenomimetic, vitamins B1 and B6, and antibiotics; 5 L of urine were excreted. Later, he was given chlorpromazine and 400 mg zuclopenthixol decanoate; tizercin was discontinued. Twelve days after he received his final dose of olanzapine IM, he developed a tremor, became cyanotic, and died of reported pulmonary thromboembolism. Although no autopsy was performed, the attending physician considered his death to be the result of generalized chronic atherosclerosis and cardiac pathology.

Case 9. A 47-year-old male patient with schizophrenia was given a total of 20 mg olanzapine IM (2 doses of 10 mg 4 hours apart) for agitation. The patient was overweight (BMI = 29.5) and had a history of agitation. In the past, he had received promazine, propranolol, and valproic acid. The patient had to be restrained due to the severity of his agitation and was given 2 mg oral biperiden and 5 mg haloperidol. On the fifth day, he was given 2 mg oral biperiden, 10 mg oral haloperidol, and 2 mg clonazepam. The sixth day, he was given 15 mg midazolam and 2 injections of 10 mg olanzapine IM, in addition to the same drugs as the previous day. Fourteen hours after the last injection of olanzapine IM, the patient died of bilateral pulmonary embolism (confirmed by autopsy).

Case 10. An 82-year-old female patient with Alzheimer's disease and vascular dementia received 5 mg olanzapine IM for aggression and agitation. She had a history of atherosclerotic cardiovascular disease, mitral and tricuspid valve insufficiency, and stroke. The patient had a previous history of undisclosed antipsychotic treatment, and on the day before she died, she received 5 mg haloperidol IM and 2 mg lorazepam IM following the olanzapine injection. Forty-five minutes after receiving the injection of olanzapine, the patient fell from her wheelchair and suffered a head injury. The next day, she developed bilateral stroke

symptoms: weakness in her extremities, impaired motor abilities, changes in speech patterns, facial droop, drooling, and decreased levels of consciousness. Later that day, she died of a left parietal hemorrhagic stroke; it is not known if an autopsy was performed.

Case 11. A 64-year-old female patient with paranoid schizophrenia was treated with 1 injection of 20 mg olanzapine IM for acute psychomotor agitation. The patient was obese and had a history of hypertension and type 2 diabetes. In the past, she had been treated with levopromazine IM, thioridazine, and trifluphenazine. She was also receiving carbamazepine, diazepam, and both oral (10 mg) and IM (5 mg) formulations of haloperidol. She was given 10 mg oral haloperidol 3 hours after and 200 mg carbamazepine 4 hours after receiving olanzapine IM; 2 ampoules haloperidol IM (dose unknown) 6 hours after receiving the olanzapine injection; and 1 ampoule levopromazine IM 10 hours after receiving the olanzapine injection. She was then given 10 mg diazepam and a total of 400 mg carbamazepine in the evening. The patient died of reported sudden death, unknown cause, 4 days after receiving olanzapine IM treatment; no autopsy was performed.

Case 12. A 52-year-old male patient received 20 mg olanzapine IM over a period of 2 days for the treatment of schizoaffective psychosis. He had a history of severe sleep apnea with breathing interruptions and was obese (BMI = 30.4). He was treated with 15 mg oral fluphenazine, fluphenazine decanoate, 200 mg pipamerone, biperiden, levothyroxine, lorazepam, valproic acid, chlorprothixene, and restraints. He died of sleep apnea syndrome more than 1 day after the last olanzapine injection; an autopsy reported that he did not die of a macroscopic event.

Case 13. A 65-year-old male patient received 10 mg olanzapine IM for the treatment of mania. He had no remarkable medical history except bipolar disorder and was being treated with cyamemazine, clorazepate, and loxapine. He died of unreported reasons approximately 2 days after receiving olanzapine IM; no autopsy was performed.

Case 14. A 30-year-old male received 10 mg olanzapine IM for a delusional episode. He had a history of epilepsy, status epilecticus, cardiorespiratory arrest, and aspiration-related chemical pneumonitis leading to a pulmonary infection and was being treated with valproate, phenobarbital, and an unspecified benzodiazepine. He died of septicemia more than 10 days after receiving olanzapine IM; it is not known if an autopsy was performed.

Case 15. A 34-year-old male received 30 mg olanzapine IM within a 24-hour period for psychomotor agitation. He had a history of cocaine abuse, smoking, congestive heart failure, cardiac dilation, arterial hypertension, and multiple organ failure. He was being treated with 10 mg haloperidol, midazolam IV, diazepam IV, hydrocortisone, furosemide, heparin, vencuronium, fentanyl, flumacenil, methylprednisolone, omeprazole, metamizol, dopamine, and insulin. He died of cardiac failure, hypotension, and possible benzodiazepine intoxication an unspecified time after receiving olanzapine IM; no autopsy was performed.

Case 16. A 35-year-old female received 10 mg olanzapine IM for an unreported reason. She had a history of sleep apnea, which affected her cardiac output and rhythm, and was receiving oral and IM lorazepam, quetiapine, lithium, zopiclone, and oral olanzapine. She died of suspected sleep apnea approximately 42 hours after receiving olanzapine IM; an autopsy was performed but did not reveal anything further.

Case 17. A 35-year-old female with bipolar disorder received 10 mg olanzapine IM for agitation. The patient had a suspected history of sleep apnea and was receiving clonazepam. Approximately 1 hour after receiving olanzapine IM, she experienced cardiac arrest, gastrointestinal bleeding, and shock. She died of cardiac arrest and sleep apnea 6 days after receiving olanzapine IM; an autopsy was not performed.

Case 18. A 66-year-old male with psychotic depression received 20 mg of olanzapine IM over 6 hours. He was a former smoker, had a familial history of fatal heart disease, and was being treated with mirtazapine. He died 11.5 hours after receiving the second dose of olanzapine IM of cardiopulmonary arrest; it is unknown if an autopsy was performed.

Case 19. A male of unknown age received at least 10 mg of olanzapine IM for bipolar disorder. While in the hospital, he developed diabetes insipidus, kidney failure, and status epilepticus. The patient was treated with 1 mg alprazolam twice/d, 10 mg bisoprolol, oral olanzapine (5–15 mg), 100 mg lamotrigine twice/d, levothyroxine, and 450 mg lithium twice/d. The patient died of candida septicemia 18 days after being treated with olanzapine IM; it is unknown if an autopsy was performed.

Case 20. A 65-year-old female received an unknown dose of olanzapine IM over a 2-week period for inappropriate behavior associated with an unspecified mental illness. No data were provided on concomitant medications, but she was being treated alternately with oral and IM olanzapine and had, in the past, received electroconvulsive therapy. The patient died of a suspected pulmonary embolism approximately 90 minutes after receiving oral olanzapine; it is unknown if an autopsy was performed.

Case 21. A 25-year-old male with treatment-resistant schizophrenia received 10 mg olanzapine IM for agitation. He had a history of asthma, upper respiratory tract infections, self-injurious behavior, and weekly electroconvulsive therapy, which had recently been ceased due to his agitation. The patient was being treated with 75 mg oral chlorpromazine, an unspecified benzodiazepine, 2 mg oral clonazepam, phenoxymethylpenicillin benzathine, inhaled steroids, inhaled bronchodilators, oral corticosteroids, oral olanzapine, and restraints. He died of acute asthmatic symptoms within 30 minutes of receiving chlorpromazine and clonazepam and within minutes of receiving olanzapine IM; it is unknown if an autopsy was performed.

Case 22. A 70-year-old female received 20 mg olanzapine IM as 2 injections of 10 mg over a 9-hour period for dementia-related psychotic agitation. She had Alzheimer's dementia and was being treated with 30 mg mirtazapine, 50 mg zuclopenthixol acetate, depot zuclopenthixol, and 10 mg diazepam. She died of cardiopulmonary arrest approximately 12 hours after receiving the second dose of olanzapine IM; an autopsy was not performed.

Case 23. A 40-year-old male received 15 mg olanzapine IM over 6 hours for agitation associated with schizophrenia. He was receiving treatment with diazepam IV, 100 mg oral chlorpromazine twice/d, 2 mg lorazepam, 200 mg oral tramadol, 100 mg diclofenac, and 1.5 mg cefuroxime sodium IV. He had a history of myocardial infarction, severe infection, and sepsis. He died of myocardial infarction approximately 18 hours after receiving olanzapine IM; an autopsy was not performed.

Case 24. A 20-year-old female received 2 olanzapine IM treatments (the first dose was 5 mg, the second was unknown) for confusional states associated with anxiety disorder. She had a history of confusional states with vomiting and pseudocatatonia. The day before she died, she was intubated (because of hypoxia and confusion) and treated with ceftriaxone, amoxicillin, clonazepam, phenytoin, and acyclovir. After receiving olanzapine IM, the patient experienced corrected QT interval (QTc) prolongation, fever, and tonic-clonic episodes. The patient died of massive edema and severe anoxic encephalopathy (confirmed by autopsy) approximately 1 day after receiving the second injection of olanzapine IM.

Case 25. A 61-year-old male with agitated depression received 20 mg olanzapine IM over 36 hours. He had a history of asthma and was being treated with 100 mg zuclopenthixol IM, 100 mg haloperidol IM, 10 mg oral diazepam, 1 mg oral risperidone, and 7.5 mg midazolam and received electroconvulsive therapy between olanzapine IM treatments. He died of sudden cardiac death 2 days after receiving the last injection of olanzapine IM; an autopsy was not performed.

Case 26. A 36-year-old female received 5 mg olanzapine IM to treat her first known psychotic episode. She had no history of psychiatric illness, but did have a history of mild asthma. The patient was antipsychotic-naïve and restrained. The patient died 40 minutes after receiving olanzapine IM. The cause of death was reported as pulmonary embolism and thrombophlebitis (confirmed by autopsy). There was also evidence of aortic stenosis, but there was no indication that the aortic stenosis played a role in her death.

Case 27. A 70-year-old female with organic brain syndrome received 20 mg olanzapine IM over 12 hours. She had a history of alcohol abuse (withdrawal began 1 month prior to olanzapine IM treatment); she was hospitalized for hyponatremia. She was treated with 500 mg valproic acid IV, 0.25 oral clonazepam twice/d, and vitamin B. The patient experienced delirium and a probable seizure and died of suspected cardiorespiratory failure 30 minutes after receiving the last dose of olanzapine IM; an autopsy was not performed.

Case 28. A 59-year-old female with acute mania disorder received 10 mg olanzapine IM for psychomotor agitation. She was obese and had type 2 diabetes. She was restrained and treated with 300 mg oral lithium and oral olanzapine. She died of an acute myocardial infarction and thrombophlebitis an unspecified time after receiving olanzapine IM; no autopsy results were available to confirm the cause of death.

Case 29. A 61-year-old female with schizophrenia received 20 mg olanzapine IM over 21 hours. She had a history of hypertension and a family history of cardiac problems. She was overweight (209 pounds) and had gained 39 pounds in the 8 days preceding her death. She was being treated with 2 mg oral risperidone, fluphenazine decanoate, and benztropine. The patient died of atherosclerotic heart disease (confirmed by autopsy) less than 4 hours after receiving the last injection of olanzapine IM.

DISCUSSION

To our knowledge, this is the first published review of postmarketing safety data of an IM antipsychotic. The most common spontaneous adverse events reported occurring in temporal proximity to olanzapine IM treatment included pyrexia, drug ineffective, hypotension, syncope, neuroleptic malignant syndrome, somnolence, cardiac arrest, agitation, blood creatine phosphokinase increased, and falls. Based on the estimated patient exposure of olanzapine IM, adverse events were reported in less than 1% of the estimated number of patients receiving olanzapine IM treatment. However, with postmarketing safety data, there is always the potential for underreporting.

Use of multiple antipsychotics was common in the fatal cases. Different adverse events have been reported during treatment with each of these agents and are part of their safety profile; therefore, it is difficult to determine a potential causal relationship between any of the treatments and the adverse event. Although polypharmacy may be potentially associated with an increased risk for adverse events,[2,6] it is common in the treatment of agitation,[6,11] due to the immediate need to calm these patients, and may be a marker for potentially severe or treatment-refractory symptoms. Though polypharmacy with various psychotropics is common among olanzapine IM adverse event reports, it is not possible to discern whether or how much the polypharmacy contributed to unfavorable outcomes. In clinical trials, olanzapine IM has been shown to be effective without addition of benzodiazepines.[8-10,12] Based on the data presented here, concurrent olanzapine IM and parenteral benzodiazepine use is not recommended, as it has not been studied prospectively. This is especially true for the elderly: benzodiazepines were administered in 7/9 fatal case reports of elderly patients in this analysis. Adverse events have been reported during

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treatment with benzodiazepines,[13,14] and elderly patients, in particular, are especially sensitive to adverse events during benzodiazepine treatment.[6,11]

The state of agitation is, itself, associated with adverse events, some of which can be serious. Agitated patients are often restrained, and the use of physical restraints is also associated with an increased risk for adverse events, including mortality.[4] The risk of mortality is also increased in mental health patients over the age of 45[1]; the mean age of the patients in the fatal cases was 49.1 years. Twenty-four percent of the fatal cases also had metabolic conditions (ie, obesity, diabetes, hyperlipidemia), and 75% of these were treated with multiple medications. These factors may have affected the treatment outcome of the patients in these case reports.

The presence of underlying medical conditions may potentially increase the risk for adverse events—including mortality—in patients receiving parenteral antipsychotics.[1,2] Among the cases in the database, a large proportion presented with underlying medical conditions. Patients afflicted with severe mental illnesses have increased difficulties in recognizing and reporting symptoms of general medical disorders,[15] which can negatively affect treatment outcomes and worsen health.[16] These findings underscore the need to obtain complete medical histories whenever possible to ensure that medical conditions are not overlooked. They also emphasize the need to take caution when treating patients with unstable medical conditions with olanzapine IM.

An important factor to consider when interpreting these data is that the patient population potentially differs from the population in the olanzapine IM clinical trials. In clinical practice, the population treated with olanzapine IM is likely to be more severely agitated compared with the patients enrolled in clinical trials. Patients in the olanzapine IM trials were required to sign consent forms, implying a certain degree of lucidity, whereas the patients in this analysis were markedly agitated, as evidenced by the common use of multiple medications and restraints. Also, the olanzapine IM clinical trials excluded patients treated with depot medications, benzodiazepines within 4 hours,[9,10] and other psychoactive drugs.[12] The majority of cases in this dataset were treated with these medications. Finally, patients with comorbid medical disorders were excluded in clinical trials, whereas comorbid medical conditions were common in the patients in this dataset. Comorbid medical problems were likely to have contributed to agitation in some of the patients in the current analysis, through delirium, discomfort, or other factors. Though the patients with spontaneously reported adverse events appear overall more complex than the clinical trial population—in terms of concomitant illness, polypharmacy, and other risk factors—these are representative of challenges that are encountered in clinical practice.

There are several limitations to spontaneously reported data (http://www.fda.gov/medwatch/articles/medcont/postrep.htm). In clinical practice and emergency settings, physicians may be less likely to report adverse events that are not unusual or serious in nature. Additionally, because these are not prospectively collected data, the case reports are typically missing key information, such as age (missing in ~ 16% of the reports), concurrent treatments, relevant medical history, and confirmation of the cause of death. This analysis included all cases reported, without regard to a potential causal relationship between olanzapine IM treatment and the event. Finally, spontaneous data are not adequate information upon which to base conclusions regarding causation.

To our knowledge, this is the first published analysis of postmarketing safety data in an IM antipsychotic; therefore the data regarding olanzapine IM cannot be compared with other similar data from other treatments of agitation. A comparison would help to better define the safety profiles of these agents in clinical practice and provide guidelines for safely treating these patients. On the basis of Lilly clinical trial data[8–10,12] and the data presented in this analysis, we make the following recommendations to clinicians when using olanzapine IM in patients with agitation: (1) bear in mind that agitation can be a manifestation of underlying physical decompensation or drug/substance toxicity, even in patients with established psychiatric disorders; (2) concomitant administration of olanzapine IM and parenteral benzodiazepines has not been studied and, therefore, is not recommended, especially in the elderly; (3) if the need arises for concomitant parenteral benzodiazepine use, clinicians should assess these patients for signs of excessive sedation and cardiorespiratory depression, as coadministration of lorazepam IM and olanzapine IM may add to the somnolence observed with either drug alone; (4) if, nevertheless, patients receive concomitant parenteral benzodiazepine and olanzapine IM, they should be monitored for signs of excessive sedation and cardiorespiratory depression, as coadministration of lorazepam IM and olanzapine IM may add to the somnolence observed with either drug alone and as co-occurring bradycardia and hypotension have been reported during treatment with olanzapine in this analysis and in the literature[17–19]; (5) hypotension and/or bradycardia has been observed during olanzapine IM treatment, so patients should remain recumbent if drowsy or dizzy after injection until clinicians determine that patients are not experiencing hypotension, postural hypotension, bradycardia, and/or hypoventilation; (6) in view of the possibility of bradycardia and/or hypotension, caution should be considered in patients with serious cardiovascular disease when the occurrence of syncope or hypotension and/or bradycardia might put the patient at increased medical risk; (7) caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, or respiratory or central nervous system depression; and (8) olanzapine IM should be used in accordance with product labeling.

A recent update with 30 additional months of data and almost 1.5 million patient exposures (vs ~ 500,000 in this

article) were provided to regulatory agencies and confirmed the findings presented here, particularly those surrounding the fatal cases: most were treated with benzodiazepines and other antipsychotics; most had risk factors, such as polypharmacy and medical comorbidities; and the most common causes of death were cardiac or cardiorespiratory. Olanzapine IM exposure has tripled since the cutoff used in this article, but the incidence of fatalities has decreased from 0.005% in this analysis to 0.004%. Every effort should be made to use antipsychotics in the safest possible manner, particularly in the vulnerable agitated patient population who may be concomitantly treated with antipsychotics and other medications. Bearing these important limitations in mind, this analysis will provide additional insight on the key safety findings from almost 2 years of postmarketing olanzapine IM use.

Drug names: acyclovir (Zovirax and others), alprazolam (Xanax, Niravam, and others), amoxicillin (Trimox, Amoxil, and others), benztropine (Cogentin and others), biperiden (Akineton), bisoprolol (Zebeta and others), carbamazepine (Carbatrol, Equetro, and others), ceftriaxone (Rocephin and others), cefuroxime (Ceftin, Zinacef, and others), clonazepam (Klonopin and others), clorazepate (Gen-xene, Tranxene, and others), clozapine (FazaClo, Clozaril, and others), diazepam (Diastat, Valium, and others), diclofenac (Flector, Zipsor, and others), doxazosin (Cardura and others), fentanyl (Duragesic, Onsolis, and others), furosemide (Lasix and others), haloperidol (Haldol and others), hydrocortisone (Hi-cor, Ala-cort, and others), insulin (Novolog, Levemir, and others), lamotrigine (Lamictal and others), levothyroxine (Synthroid, Levo-T, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), methylprednisolone (Medrol, Depo-Medrol, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), phenytoin (Dilantin, Phenytek, and others), promethazine (Promethegan, Promethacon, and others), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel), risperidone (Risperdal and others), tramadol (Ultram, Ryzolt, and others), valproate (Depacon and others), valproic acid (Stavzor, Depakene, and others), zopiclone (Lunesta).

Author affiliations: Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (UCLA); Los Angeles Veterans Administration (Dr Marder); and Orexigen Therapeutics, La Jolla (Dr Dunayevich), California; Lilly Research Laboratories, Eli Lilly, Lilly Corporate Center, Indianapolis, Indiana (Drs Sorsaburu, Carlson, Cavazzoni, and Baker and Mss Falk and Dellva); Eli Lilly, (Dr Karagianis) and Department of Psychiatry, St. Michael's Hospital, University of Toronto (Dr Dawe), Toronto, Ontario, Canada.

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