

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 21, 2000 APR 21 2000

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TO: Karen Midthun, M.D., Director  
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SUBJECT: OPDRA Postmarketing Safety Review (PID #: *D000248* D000210)  
Drug : Tramadol (Ultram®, NDA-20281)  
Reaction : Deaths associated with use.

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EXECUTIVE SUMMARY

This document was written in response to a request from Maria L. Villalba, M.D., Division of Antiinflammatory and Ophthalmic Drug Products, for information on deaths associated with Ultram® (tramadol). In this document, the cause of deaths and the risk factors (age, sex, dose and duration of treatment, concomitant medications and underlying diseases) were evaluated. There were a total of 322 unduplicated death reports in the Adverse Event Reporting System (AERS) database. Of those, 172 reports were excluded from further analysis. We evaluated 150 deaths that were temporally associated with tramadol use. There were 79 females, 61 males and 10 reports with an unknown gender. The cases were summarized under the following categories: **unintentional and intentional overdose** (63.3 %; single and multiple drug overdose-46.7%; drug abuse-10.6%, therapeutic error 6%), **adverse events** 34.7% and **drug interactions** 2%.

There were 95 death cases (intentional or unintentional) that were associated with tramadol overdose as either a single suspect agent (29) or co-suspect in combination with other drugs (66), primarily antidepressants. The ages were generally younger in the multiple drug overdose or drug abuse cases than in overdoses resulting from tramadol alone. There was no significant gender differences noted in any of the overdose cases. Approximately 30% of the overdoses were possibly secondary to a drug interaction between tramadol and selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). One overdose case involved a malicious intent. Sixteen overdoses occurred in patients with a history of drug abuse or dependency. Although the proportion of drug abuse overdose cases was smaller, the possibility of potential drug abuse in most overdose cases could not be ignored. In the majority of the cases, the dose,

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duration, and frequency of tramadol were not available but the patient's history, pill count, and toxicology results established overdose as possible cause of death. The ultimate causes of death related to overdose were due to respiratory depression, cardiac arrhythmias, hypotension, bradycardia, cardiac arrest, seizure, serotonin syndrome, hepatitis, and pneumonia.

Nine overdose deaths resulted from a possible therapeutic error. The majority of the cases were foreign. In seven cases, tramadol was used in pregnant and pediatric patients resulting in maternal death (3), stillbirth (1), and death in three children. These primarily occurred with dosage forms (injectable, suppository, and drops) that are not available in the U.S. There were two domestic cases involving two debilitated young HIV patients where the therapeutic dose was higher than recommended.

Fifty-two cases resulted from an adverse event occurring with the normal, prescribed, or labeled dose of tramadol, as opposed to an overdose, misuse or abuse. The patients were mostly elderly (70 to 80 years old). Concomitant multiple drugs (as many as 50), old age, and history of chronic concomitant illnesses might also have contributed to death in these patients. The events involved the cardiovascular, central nervous, digestive, skin, and immune systems. The events were cardiac arrest (3), convulsion (6), hepatic failure (5), pancreatitis (1), GI hemorrhages (3), bowel obstruction/ischemia (2), Steven-Johnson syndrome and/or toxic epidermal necrolysis (27), and anaphylactoid/ allergic reaction (5). Except for pancreatitis and bowel ischemia and obstruction, the remaining adverse events are in the product label.

Three deaths may have resulted from a drug interaction between tramadol and another medication (warfarin, flecainide, and selegiline). Two patients appeared to have received labeled doses of tramadol and either developed coagulopathy or arrhythmia when used in combination with warfarin or flecainide. One case reported a possible drug interaction between selegiline (MAOI) and tramadol. Due to known drug interactions between tramadol and warfarin or selegiline, two of the cases indicated a possible association between fatalities and drug toxicities. The other case was a possible unlabeled flecainide-tramadol interaction resulting in a fatal arrhythmia.

In summary, we have described 150 fatalities temporally related to the use of tramadol. By and large, most cases were the result of an unintentional or intentional overdose of tramadol alone as a single agent, as a multiple drug overdose, drug abuse, or therapeutic error. Fifty-two deaths occurred as a result of an adverse event associated with the recommended dose of tramadol. It is imperative for practitioners to be aware of the risks associated with Ultram® to include the potential for overdose, misuse, and abuse of this product.

## **PRODUCT INFORMATION AND LABELING**

Tramadol was approved on March 3, 1995 and is presently marketed by Ortho-McNeil Pharmaceuticals for the management of moderate to moderately severe pain. A combination product with acetaminophen, a sustained release formulation, and pediatric use is currently being evaluated in the U.S. Tramadol is a centrally acting analgesic that is not derived from natural sources nor is it chemically related to opiates. Although its mode of action is not completely

understood from animal tests, at least two complementary mechanisms appear applicable: binding to  $\mu$ -opioid receptors and inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to  $\mu$ -opioid receptors. In animal models, M1 is more potent than tramadol in producing analgesia and binding to  $\mu$ -opioid receptors. The human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol is extensively metabolized in the liver by the CYP2D6 P-450 isoenzyme. Therefore, concomitant administration CYP2D6 inhibitors, such as fluoxetine, paroxetine, and amitriptyline or inducers such as carbamazepine could result in change of tramadol metabolism. Approximately 30% of the dose is excreted in the urine as unchanged drug and 60% of the dose is excreted as metabolites.

There are several **Warnings** in the labeling, including *Seizure risk, Anaphylactoid Reactions, Avoidance of Use in Opioid-dependent Patients, Use with CNS Depressants, and Use with MAO Inhibitors.*

There are **Precautions** regarding *Respiratory Depression, Increased Intracranial Pressure or Head trauma, Acute Abdominal conditions, Patients Physically dependent on Opioids, Drug Interactions, Use in Labor and Delivery, Pediatric Population and Use in Renal and Hepatic Disease.*

The **Drug Interactions** section of the labeling indicates that concomitant administration with inhibitors of CYP2D6 such as *fluoxetine, paroxetine, and amitriptyline* could result in some inhibition of the metabolism of tramadol. Interactions with *MAO Inhibitors*, due to interference with detoxification mechanism, have been mentioned in this section and also under the warnings section. Post-marketing findings such as, alterations of *warfarin* effect, including elevation of prothrombin time was stated.

There are also several relevant **Adverse Reactions** in the labeling. They are *Body as a Whole-Anaphylaxis, Allergic reaction; Cardiovascular-myocardial infarction, syncope, hypotension; Respiratory-dyspnea; CNS-Seizures; Gastrointestinal-GI Bleeding; Skin-Stevens-Johnson syndrome/ Toxic epidermal necrolysis; and Lab Abnormalities-Elevated liver enzymes.*

The **Drug abuse and dependence** section of the labeling indicates that Ultram has *a potential to cause psychic and physical dependence of the morphine-type ( $\mu$ -opioid).* The drug has been associated with *craving, drug-seeking behavior and tolerance development.* Cases of abuse and dependence have been reported and it should not be used in opioid-dependent patients.

The **Overdosage** section includes the following statements. Cases of *overdose* with tramadol have been reported. The lowest dose reported to be associated with fatality was possibly between 500 and 1000mg. Serious potential consequences of overdosage are respiratory depression and seizure.

## DRUG USE

### LITERATURE

The Medline database was searched from 1995 to 2000 for any citations indexed to tramadol. A total of 299 citations were identified, 35 of which pertained to possible safety issues including abuse, overdose, drug dependence, toxic dermatitis, respiratory depression, drug interactions, and fatalities. The majority of these were issues previously known to occur during the use of tramadol. However, seven articles were related to fatalities. Three fatalities were ascribed to the action of tramadol alone.<sup>2,3,5</sup> In three articles, deaths were attributed to multiple-drug overdose.<sup>1,4,6</sup> Two articles were pharmacokinetic studies of tramadol in postmortem cases.<sup>6,7</sup>

### SELECTION AND SUMMARY OF CASES

As of 3/2/2000, there were a total of 4182 reports (foreign and domestic) for tramadol in AERS of which 1811 were serious, 375 had a fatal outcome. Counts of most frequently reported PT terms from the total 4182 cases were:

CONVULSIONS NOS	389
DRUG WITHDRAWAL SYNDROME	337
DRUG DEPENDENCE	326
GRAND MAL CONVULSION	155
NON-ACCIDENTAL OVERDOSE	142
TREMOR NOS	138
DRUG INTERACTION NOS	131
DYSPNOEA NOS	112
OVERDOSE	98
HALLUCINATION NOS	96
DRUG ABUSE	93
DRUG LEVEL NOS ABOVE THERAPEUTIC	70
DEPRESSION	69
AMNESIA	63
EPIDERMAL NECROLYSIS	56
HYPERTENSION	53
HYPOTENSION	52
THINKING ABNORMAL	51
GASTROINTESTINAL HAEMORRHAGE NOS	36

It is noted that convulsions and drug abuse/withdrawal/dependence related events constituted a large number of the total reports.

Counts of most frequently reported and "relevant" PT terms from the total of 375 death reports are listed below. The total number of events exceeds 375 because one report may contain more than one event.

DRUG LEVEL NOS ABOVE THERAPEUTIC	51
EPIDERMAL NECROLYSIS	48
OVERDOSE NOS	39
NON-ACCIDENTAL OVERDOSE	31
COMPLETED SUICIDE	26
DEATH	23
CONVULSIONS NOS	20
STEVENS JOHNSON SYNDROME	20
CARDIAC ARREST	16
DRUG TOXICITY	15
DRUG INTERACTION NOS	12
CARDIAC FAILURE	10
HEPATIC FAILURE	6
ASPHYXIA	5

Elevated drug levels, epidermal necrolysis, and overdoses constituted a large number of the total death reports.

After duplicate cases were accounted for, there were 322 cases with a fatal outcome and 172 were excluded from further analysis for the following reasons:

- Insufficient data (77) to establish causality
- Underlying disease (72): The majority were from a Pharmacovigilance Study in Latin America (via Germany) where the cancer patients received tramadol for a variety of conditions and died from their primary disease, cancer.
- Poor temporal relationship to tramadol (2)
- Single or multiple drug overdoses due to doxepin, acetaminophen, and narcotics (7)
- Deaths unrelated to tramadol use (accidental injury such as drowning, asphyxia, trauma and murder) (14)

The remaining 150 cases with a fatal outcome were temporally associated with tramadol use. Seventy-five were foreign and 75 were domestic source. Seventy-nine were female and 61 were male, and 10 did not report the gender. The distribution of reports in years is as follows.

1994	1
1995	13
1996	21
1997	26

1998	42
1999	43
2000	4

The higher numbers in 1998 and 1999 may reflect more events

The age distribution for the remaining 150 deaths are as follows.

0-9	5
10-20	3
20-29	12
<b>30-39</b>	<b>30</b>
40-49	21
50-59	17
60-69	9
<b>70-79</b>	<b>21</b>
<b>80-120</b>	<b>24</b>
null age	8

The age distribution was mostly in mid-age adult and the elderly. The 150 cases were categorized as follows (See attachments):

- Overdose- **95 cases; 63.3%**- these cases included those with a tramadol intake greater than recommended dose or tramadol levels were greater than normal range.
  - **Unintentional**
    - Single or multiple drug overdose (30 cases)
    - Therapeutic Error- Deaths occurred as result of possible inappropriate uses or use in unlabeled patient population (9 cases)
  - **Intentional**
    - Single or multiple drug overdose (40 cases)
    - Drug abuse and dependency (16 cases)
- Adverse events- **52 cases; 34.7%**- Deaths occurred from an adverse event associated with tramadol at normal or labeled doses.
- Drug Interactions- **3 cases; 2%**- these were deaths as a result of a potential drug interaction between tramadol and another drug.

## I. OVERDOSES

### A. UNINTENTIONAL- 39 cases

There were 39 deaths that resulted from an unintentional deviation of the proper therapeutic regimen of tramadol.

1. Unintentional single overdose- Eleven cases appeared to be fatalities occurring in association with an overdose of tramadol alone. The ages ranged from 31 to 84 years old (mean 60). Four were females, five were males, and the gender of two was unknown. The indication was for pain control in four patients and unknown in the others. Five patients had a significant history of depression, mental illness or alcoholism that might have contributed to overdose, but it did not appear to be intentional from these reports. The duration of tramadol therapy was not reported but the dose, frequency, route was available in five patients. Although four reported a recommended daily dose (200-400mg/day), one was likely a toxic dose (0.4 grams IV x 2) in an ICU setting. Post-mortem toxic tramadol levels values ( $> 700\text{ng/ml}$ ) were reported in seven patients. The remaining four cases had high, positive or toxic levels from autopsy findings. The cause of death was reported in six patients as respiratory depression, fatal car accident due to increased therapeutic response, sudden death, cardiac arrhythmia, and seizure. Summary of two cases is as follows. Therapeutic drug levels are shown in parenthesis were applicable.

1. AERS# 3065938 (Foreign, 1997)

A 77-year-old female patient, who received tramadol 100 mg four times daily for a severe lower back pain, was found dead in her bedroom. The patient had a history of severe back pain, arthritis, depression, and petit mal fits. Concomitant medications included nitrazepam, promethazine, gabapentin, valproate, and paroxetine. Post-mortem blood samples revealed 1.8 mcg/ml (0.22-0.77 mcg/ml) of tramadol. No other drug levels were reported. The cause of death was confluent bronchopneumonia.

2. AERS# 3137843 (Foreign, 1998)

A 56-year-old male with a history of severe alcohol abuse for the past 5 years was admitted to the hospital for bilateral humerus fractures. During the hospitalization, he developed alcohol withdrawal symptoms, including cramping, sweating, cyanosis, and rapid atrial tachycardia with heart block. No renal and hepatic insufficiency was noted. He received atenolol 50 mg x 1 dose, diazepam (rectal and IM, unknown dose) with ketoprofen 100mg IM during withdrawal. Concomitant short-term medications were ibuprofen, oral tramadol 100mg tid, lorazepam and haloperidol. Five days after initiation of tramadol therapy, the patient suddenly died. The cause of death was suspected to be secondary to a cardiac arrhythmia. Autopsy showed an elevated tramadol blood level of 1.9mcg/ml (0.22-0.77 mcg/ml). All other drugs were within the therapeutic range.

2. Unintentional multiple drug overdoses - Nineteen deaths were most likely due to an unintentional multiple drug overdose. There was no indication of any history of drug or tramadol abuse. The ages ranged from 25 to 86 years old (mean 52). There were ten females and nine males. The tramadol dose was reported in three patients ranging from 100 to 400mg/day, and not known in the others. Two reported serious underlying medical

conditions such renal insufficiency or hepatic/renal disorder that might have contributed to their deaths.

Eighteen patients received one or more of the following concomitant medications: amitriptyline, nortriptyline, alprazolam, hydrocodone, methadone, sertraline, fluoxetine, paroxetine, doxepin, meprobamate, or propoxyphene for treatment of arthritis, back pain, fibromyalgia, orthopedic fusion, and depression. One reported concomitant alcohol use.

In the majority of the cases, dose and duration of tramadol was not available. Multiple drug use was determined from post-mortem blood samples. Fifteen reported toxic tramadol blood levels (ranged from 1000-6000ng/ml), and one reported a very high level of the tramadol metabolite, O-desmethyltramadol (ODT). Ten patients also reported toxic levels of amitriptyline, nortriptyline, alprazolam, temazepam, fluoxetine, doxepin, propoxyphene. Eight of those had concomitant toxic tramadol levels suggesting a possible drug interaction between tramadol and SSRIs and tricyclic antidepressants

It was unclear from many reports whether the deaths were directly related to tramadol overdose alone or combined drug levels. Although there was no history of drug abuse, the possibility of potential drug abuse in some cases could not be excluded because of the use of multiple psychoactive drugs for underlying conditions that were mentioned in the reports. The ultimate cause of death was reported in several cases as cardiac arrest, convulsions, tramadol intoxication, asphyxia from drowning, and pulmonary edema. The summary of three cases is as follows:

1. AERS# 3275733 (Foreign, 1999)

An 84-year-old female with heart failure, hypertension, IDDM, rheumatoid arthritis, hepatic disorder, renal stenosis, and a recent hip fracture received tramadol 200mg po daily (50 mg four times a day) for about one month for an post-op orthopedic pain. Concomitant medications included doxepin 100mg qd, furosemide 20 mg daily, methotrexate 5 mg daily, ketoprofen 300 mg daily, amoxicillin 1500 mg daily, doxycycline 150 mg daily, temazepam (unknown), and insulin 38 units. During hospitalization, she also received antibiotics for wound infection. CXR revealed a decompensated heart and no signs of pulmonary infection. The patient was found dead during hospitalization. Autopsy was performed and drug levels revealed high tramadol 4.4mcg/ml (0.3-0.6 mcg/ml), and doxepin 0.7 mcg/ml (0.03-0.15 mcg/ml) levels. Tramadol intoxication was considered the immediate cause of death.

2. AERS# 5269266 (Domestic, 1995)

A 53-year-old female with a history of aortic and mitral valve replacement, cerebral aneurysm, and previous suicide attempt was found dead in her home. Fourteen days before the patient's death, she received samples and a prescription for tramadol (50mg every 4-6 hours) for an unknown indication. Concomitant long-term medications included amitriptyline 100 mg qhs, digoxin, and coumadin (unknown dose, duration). Post-mortem blood samples indicated elevated levels of amitriptyline (0.5 mg/L), nortriptyline (1.7 mg/L), and tramadol (2.5 mg/L). This was not felt to be a suicide attempt. The medical examiner indicated that the cause of death was an overdose from combined action of tricyclic antidepressants and tramadol.

3. AERS# 3024881 (U.S., 1998)

A 36-year-old male patient was found dead in a parked motor vehicle with Ambien (zolpidem) on the passenger seat. The patient had a history of back pain. No history of drug abuse was reported. Concomitant meds included alprazolam, and propoxyphene. Post-mortem drug levels included; tramadol of 0.16 mg/L (0.23-0.77 mg/L), ODT (metabolite) 1.84 mg/L (extremely high), alprazolam 0.11 mg/L (0.02-0.04 mg/L), and propoxyphene 1.9 mg/L (0.05-0.75 mg/L). The reporter felt that although the tramadol level was low, the ODT (metabolite) was extremely high and the likely explanation was ingestion of a large but not fatal dose of tramadol at an earlier time. Acute drug intoxication was reported as the cause of death because of elevated levels of alprazolam, propoxyphene, and tramadol metabolite.

**3. Therapeutic Error** - Nine deaths were related to tramadol use in special or vulnerable patient populations (children, pregnant women, and AIDS) where the drug is not recommended or it is recommended to use with caution (according to US labeling).

Seven cases were from foreign sources. They included four pediatric cases and three pregnant adults. All seven patients received an injection, a suspension, or a suppository form of tramadol. These formulations are not available in the U.S. Postmortem tramadol levels were very high in five patients (ranging from 1430 to 4100 ng/ml). The cause of death, where known, was respiratory depression, cerebral edema, and sudden death.

Of the four pediatric cases, one child (21 month old) inadvertently received a tramadol 100mg **suppository** instead of Tylenol®, and died from respiratory depression. Two children (5 month and 12 month old) inadvertently received high doses of tramadol **drops** and died of respiratory depression or cerebral edema. All three pregnant females received a single dose of 100-mg tramadol **injection** (IM-1, IV-2) during labor resulting in maternal death. The outcome of the fetus (the 4<sup>th</sup> pediatric case) was stillbirth in one, and was unknown in the other two.

The remaining two domestic cases involved young male patients with AIDS and wasting syndrome who developed toxic tramadol levels (ranging from 1430-4100ng/ml) with a recommended maximum dose of 400mg/day for an unknown duration. Hepatic or renal function tests were not available to determine the appropriateness of the dose. However, due to post-mortem toxic tramadol levels, the possibility of inappropriate tramadol dosing can not be excluded in these two patients. The summaries of two cases follow.

1. AERS# 5510885 (Foreign, 1999)

A 23-year-old female at 38 weeks gestation received tramadol 100 mg IM injection for labor pain. Approximately 10 minutes later, she was gasping (normal BP and pulse). Nalorphine and oxygen was given, but she died 20 minutes later of respiratory failure. The outcome for the fetus was not reported.

2. AERS# 5429434 (Foreign, 1996)

A one-year-old male received tramadol at an estimated dose of 10 drops (25mg=2.8 mg/kg) for post-operative pain. The recommended single dose in children is 1-2 mg/kg according to the reporter from Germany. Six hours after the dose, the child was admitted to hospital with somnolence and irritability. He died seven hours later. Autopsy findings reported cerebral edema and a tramadol level of 750 ng/ml (200-

590ng/ml) which corresponded to a single dose of 15.6 mg/kg. The amount actually administered was unknown at the time of the report.

## **B. INTENTIONAL - 56 cases (37.3 %)**

This category is used to capture the cases of intentional overdose and suicide, or victims of another person's intent to harm them (malicious intent).

**1. Intentional single overdoses** - Nine deaths resulted from an intentional overdose of tramadol alone. Four were females, four were males and the gender in one patient was unknown. The ages ranged from 11 days to 72 years old (mean age of 38). In the majority of the cases, the dose, duration, and indication of tramadol were unknown. Four reported post-mortem toxic tramadol levels (range 7090-80,000ng/ml). In most cases, tramadol overdose was established from empty pill bottles. In some cases, suicides were accomplished by ingestion of as many as 30 to 60 tablets of tramadol. Three patients had a significant past medical history of intentional overdose, personality disorder and migraine headaches that might have contributed to overdose. One patient (AERS case # 3023738) was the victim of malicious intent. An 11-day-old male infant died from a tramadol overdose. His mother admitted intentionally mixing five tramadol tablets (total dose 250mg) into his infant formula. Two hours later, the infant was found unresponsive and died in the hospital. Autopsy results indicated high, fatal tramadol levels in the infant.

### **1. AERS # 3152374 ( Foreign, 1998)**

A 49-year-old male with a history of previous suicide attempt was found dead in the back seat of a car. At the scene, a number of black capsules were found which later were identified as valerian, passion flower, and hops extracts. The dose, indication, and duration of tramadol and concomitant flunitrazepam was not available. The autopsy results revealed a tramadol level of 13mg/L (0.23-0.77 mg/L). O- desmethyl-tramadol (ODT), aminoflunitrazepam, opiates, barbiturates, cannabinoids, and tricyclic antidepressants were not detected. The cause of death was established as pulmonary edema due to high concentrations of tramadol.

### **2. AERS # 3113116 (Domestic, 1997)**

A 30-year-old female with a history of multiple herniated discs from spinal injuries received tramadol 50 mg oral three times a day for an unknown duration. The reporter (mother) stated that her daughter suffered from chest pains, psychosomatic symptoms, and suicidal tendencies. Autopsy findings indicated pulmonary edema and agonal aspiration of gastric contents. A blood tramadol level was 80,000 ng/ml and ODT metabolite was 7,200 ng/ml. The cause of death was tramadol overdose.

**2. Intentional multiple drug overdose** - Thirty-one cases of death were most likely due to intentional multiple drug overdoses. The ages ranged from 20 to 72 years (mean age was 42). There were 18 females, nine males, and four did not report the gender. In the majority of the cases, the dose, frequency, and indication of tramadol therapy were not reported. Six reported the use of tramadol for pain control. These patients used tramadol for reasons other than an analgesic effect with the intent to harm themselves (suicide or suicide attempt).

Most of the reports gave no indication that the patients had a history of drug or tramadol abuse. In two cases alcohol or drug abuse was in question. Fourteen patients reported a history of chronic back pain or a psychiatric history including, depression, bipolar disorder, anxiety or previous suicide attempts.

In all cases the patients had taken an overdose of tramadol in addition to one or more concomitant centrally acting agents including antidepressants, anxiolytics, sedatives, and opioids. Eighteen reported excessive psychoactive drug levels during a routine death investigation. Concomitant medications include Fiorinal®, clomipramine, amitriptyline, desipramine, alprazolam, zolpidem, fluoxetine, risperidone, codeine, hydrocodone, trazadone, klonopin, and morphine. The majority of these cases reported chronic use of benzodiazepines (10), narcotics (5), SSRIs (3), TCAs (4) and barbiturates (3).

Seventeen cases had excessive tramadol levels, thirteen of which were on concomitant SSRIs or TCAs. However, it was unclear from the reports whether the deaths were directly due to overdose from tramadol alone or combined drug levels. The cause of death was not available in most cases however where known it was reported as respiratory depression, hypotension, bradycardia, cerebral edema, cerebral hemorrhage, hepatic failure, serotonin syndrome, and cardiac arrest. One case involved a 30-year-old male who took an overdose of tramadol and ethanol and committed suicide by a self-inflicted gunshot wound. Three representative cases are as follows:

1. AERS# 3264715 ( Foreign, 1999)

A 72-year-old female patient with a history of four spinal surgeries, heart attack, gastrectomy, depression due to severe pain, and recent h/o overdose (with temazepam/ imodium), was given tramadol 200 mg SR twice a day from 10/19/98 until 1/18/99 for an unknown indication. The patient was found dead in bed on 1/18/98 with a whole box of tramadol. Toxicology reported a very high tramadol level of 33.2 mg/L (0.3-0.6mg/L), and temazepam of 5.5 mg/L (1mg/L). The cause of death was respiratory depression from tramadol and temazepam overdose.

2. AERS# 3025162 (Domestic, 1998)

A 32-year-old male HIV patient died of a multiple drug overdose. His death was ruled a suicide. Concomitant medications included propranolol, desipramine, trazadone, klonopin, hydroxyzine, and lithium. He received tramadol for an unknown indication, dose, frequency, and duration. Blood samples revealed tramadol 22.59 mg/L (0.23-0.77 mg/L), propranolol 3.90 mg/L (0.01-0.26 mg/L), desipramine 1 mg/L (0.01-. 028 mg/L), and trazodone 3.7 mg/L (0.49-1.60 mg/L).

3. AERS# 5270812 (Foreign, 1995) Literature report

A 41-year-old was found dead in a hotel room with multiple containers of medication including tramadol. Multiple drugs were identified in the blood post-mortem. A fatal serotonin syndrome presumably developed as a result of moclobemide-clomipramine interaction with tramadol possibly having a synergistic effect. The forensic pathologist ruled that the cause of death possibly suicide with multiple drug intoxication resulting in serotonin syndrome. An accidental death from drug abuse could be an alternative

diagnosis. Toxicologic analysis of blood-moclobemide: 59.76 mg/L, clomipramine 1.69 mg/L, tramadol 10.89 mg/L, diazepam 2.08 mg/L, nordiazepam 0.82 mg/L, caffeine 9.64 mg/L.<sup>4</sup>

**3. Drug abuse or dependency** - Sixteen patients who committed suicide with tramadol overdose also had a known history of multiple substance abuse or dependency (cocaine, marijuana, morphine, methadone, antidepressants, and alcohol). Six patients had underlying medical conditions including sickle cell anemia, gun shot wound with paraplegia, compartmentation syndrome, chronic back pain, depression, or opiate addiction that might have contributed to drug abuse and dependency. Drug dependency was determined in the reports by the patient's drug-seeking behavior, multiple prescribers, increased frequency for the refills, and increasing doses of pain or withdrawal symptoms.

Nine were males, six females, from ages 24 to 54 (mean 34). The dose, frequency, and duration of tramadol therapy were not available in the reports, but eight reported excessive post-mortem tramadol levels (range 1900- 8100ng/ml) which suggested a possible drug misuse. Four reported high levels of amitriptyline (2), cocaine (3), and methadone (1) that were suggestive of multiple drug overdose and possible drug abuse. The summaries of two cases follow.

1. AERS # 3427933 (Foreign, 2000)

A 29-year-old man with a history of parenteral drug addiction was admitted with humoral thrombophlebitis and compartmentation syndrome. He developed pulmonary edema and died. The dose, duration and indications of tramadol were not documented. Post-mortem blood levels indicated tramadol of 4.96 mg/L and methadone of 1.42 mg/L (high).

2. AERS # 3113116 (Domestic, 1997)

A 41-year-old male with a history of manic depression, drug abuse, and back pain received tramadol prescription for 40 tablets on 5/14/97. Concomitant medications included propoxyphene, haloperidol, and Vicodin (dose and duration unknown). The patient died on 5/15/97 after he suffered a skull fracture, subdural hematoma, tongue lacerations, and contusion from a fall. From a pill count, it was estimated that 15 tramadol tablets were ingested in 24 hours. Autopsy findings revealed tramadol blood level of 8.1 mcg/ml (0.22- 0.77 mcg/ml), and tramadol urine level of 56.5 mcg/ml. The cause of death according to medical examiner was seizures and respiratory depression from tramadol overdose.

## II. ADVERSE EVENTS- 52 cases (34.7 %)

Fifty-two deaths resulted from an adverse event occurring with the *recommended prescribed dose of tramadol*, as opposed to overdose, misuse or abuse. They are categorized by BODYSYSTEM and are reviewed in the following section.

## **A. CARDIOVASCULAR SYSTEM**

### **1. Cardiac Arrest (3)**

There were three reports of cardiac arrest temporally related to tramadol use. All were foreign (France, Chile) and all patients were elderly males (65, 82, 87 years old) who received an IV form of tramadol.

Case # 3128321 involves a patient with a history of Torsades de Pointes, pacemaker, and hypertension received a single dose of tramadol 40-mg IV for post-surgical generalized pain. Shortly after receiving the tramadol, the patient experienced respiratory depression, cyanosis, apnea, and ventricular tachycardia with periods of Torsades de Pointes. He suffered anoxic brain damage and eventually died.

Case # 3040032 involves a patient with history of dementia, vascularitis [sic], and repetitive falls who received three doses of tramadol 100-mg IV infusion about 5 and 12 hours apart for arm pain after a fall. Near the end of third infusion, he developed a grand mal convulsion, bilateral myosis, and respiratory distress. He was treated with clonazepam, midazolam, naloxone, and glucose and died of cardiac arrest approximately 12 hours after the last tramadol injection.

Case # 3021064 involves a patient with a history of asthma, aortic regurgitation, and a small aortic-aneurysm who received 100-mg of tramadol for post-op pain related to knee surgery. Ten minutes after the fifth dose, the patient developed a violent jaw, neck pain, loss of consciousness, myclonus, bilateral areflexic mydriasis, and died. The cause of death was thought to be a massive myocardial infarct or aortic dissection.

All three patients were elderly with multiple medical problems and they received tramadol IV therapy for one day. Although no autopsies were performed to establish a clear etiology, the cases did indicate a possible association between tramadol and the cardiac (arrhythmia, myocardial infarction), respiratory (dyspnea) and central nervous system (convulsion) events resulting in cardiac arrest.

## **B. CENTRAL NERVOUS SYSTEM**

### **1. Convulsions (6)**

There were seven unduplicated reports of convulsions with a fatal outcome related to tramadol use. However, one seizure report was excluded because although the patient suffered a seizure that was temporally related to tramadol, he died three days later from a pulmonary embolism. Five were domestic and one was foreign. There were four females and two males. The ages ranged from 34 to 88 years old (mean 49). The dose varied from 50 to 300mg/day in four, more than "standard" in one, and unknown in one. The onset of seizures, where known, was 30 min to 2 years after initiation of tramadol therapy. Two of

the patients received citalopram or venlafaxine (SSRIs), which are known to lower tramadol's seizure threshold. There was no other history of drug abuse in these cases.

Four reported either a history of seizures, head injury, or alcoholism that might have been a contributing factor for convulsions. In two cases (AERS# 3242374, #5483153), Ultram® misuse might have contributed to seizures and fatal outcome. However this was not evident from the reports. Summaries of the two best cases are as follows.

1. AERS# 5483153 (U.S., 1996)

A 51-year-old male took more than the recommended 50 mg qid of tramadol according to his wife and then started to seize in the bathroom hitting his head on the floor multiple times. He sustained intracerebral hemorrhages and a subdural hematoma. He was treated in an intensive care unit but eventually expired. Prednisone was taken concomitantly. His past medical history was negative for known allergies, smoking or drinking, HIV and RPR.

2. AERS# 5276830 (U.S., 1995)

An 82-year-old female had a drop in BP to 80 (?SBP, unclear from the report) within 30 minutes of taking first dose of Ultram® 50 mg. She was taken to ER and her BP responded to fluids. Nine hours after taking the Ultram®, she had a grand mal seizure and subsequently developed cardiac arrest and died. Her BP at the time of the seizure was 130 systolic. The patient had no history of seizures. She was allergic to coal tar and aspirin.

## C. DIGESTIVE SYSTEM (11)

### 1. Hepatic Failure (5)

There were five unduplicated cases of fatal liver failure associated with tramadol. There was no indication of any drug abuse or overdose of tramadol in any of the cases. Three were foreign, and two were domestic. The ages ranged from 58 to 95 (mean 74). Three were female and two males. The dose ranged from 50mg to 100mg a day. One patient received an IV dose, and the remaining patients were receiving oral therapy. The time to onset ranged from four days to four months. In two cases tramadol was the only suspect drug. Recent chemotherapy and history of alcoholism confounded one of these cases. In the remaining three cases, tramadol was a co-suspect drug along with acetaminophen and/or bromfenac (Duract®). The following is the summary of the best case:

1. AERS# 5434291 (U.S., 1996)

A 61-year-old male presented with jaundice and abdominal ascites 2 weeks after initiating tramadol 100 mg/day. He had a history of femoral popliteal bypass for peripheral vascular disease and no known allergies. He was not taking any other medications. He was admitted on 8/4/96, paracentesis was performed and resulted in 5100 cc's of straw colored ascites. The labs were significant for sodium: 118, albumin: 3.4, BUN: 95, creatinine: 4.4, total bilirubin: 41.6, alk phos: 414, alanine transaminase: 857, aspartate amino transferase: 178, PT: 28 sec, ammonia: 17, PLT: 61K, H/H: 8.5/52.1. The patient became encephalopathic. His clinical condition continued to deteriorate and he died on 8/12/96. Pathology report from liver biopsy revealed extensive parenchymal loss with features suggestive of submassive hepatic necrosis.

## 2. Pancreatitis (1)

There is one case of acute hemorrhagic pancreatitis/pancreatic pseudocyst in a 74-year-old female after receiving the recommended dose of tramadol (duration unknown). The patient died of respiratory failure, pneumonia and COPD, however, the pancreatic pseudocyst was considered contributory. Concomitant medications included prednisone, diltiazem, isosorbide dinitrate, Os-Cal, nizatidine, and Premarin, but therapy dates were unknown. The reporter felt that this was most likely a drug-induced pancreatitis with Ultram® being most suspected medication.

## 3. GI Hemorrhage (3)

There were three unduplicated cases of gastrointestinal hemorrhage in elderly females (71, 80, 81 years old) temporally associated with tramadol use. All reports were domestic. Duration of tramadol therapy varied from four to eleven months in two patients, and was unknown in one. The dose was 50 mg and 300 mg daily in two patients, and was unknown in one patient. The patients presented with melanic, black tarry stools and low hemoglobin values (7.4, 8.3, unknown). One female patient who received 300-mg per day was enrolled in a long-term open label study to evaluate the safety of a tramadol controlled-release formulation when event occurred.

All patients had multiple serious underlying illnesses such as aplastic anemia, diabetes, pulmonary embolism, gastritis, PUD (endoscopically confirmed), diverticulosis (CT scan confirmed), or concomitant bromfenac, indomethacin, diclofenac, ketorolac, aspirin, or prednisone that might have contributed to GI hemorrhages. Although concomitant medications were much more likely to be contributory, the role of tramadol cannot be completely excluded in these patients.

## 4. Bowel obstruction and ischemia (2)

There were two cases involving female patients (ages 77 and 80) who developed either bowel obstruction or bowel ischemia while they were on tramadol therapy. One case was poorly documented, but the reporting physician indicated that the patient with breast cancer was receiving Ultram 50 mg orally twice daily and died of an ischemic bowel. The other case, a diabetic patient with multiple cardiac and respiratory problems, was hospitalized for unknown reason and received tramadol 50 mg orally three times a day for one day. Soon after she developed delirium and confusion and bowel obstruction.

There were several confounding factors (cardio-respiratory decompensation, infection related to a lower limb ulcer, old age, malignancy, and poor health status of the patient) that might have contributed to the patients' death, but the role of tramadol cannot be excluded in these cases.

#### D. SKIN (27)

There were 27 unduplicated cases of fatal Stevens-Johnson syndrome and /or toxic epidermal necrolysis associated with tramadol. All were of foreign origin, mainly from a center in Germany, where a prospective study is being conducted on the incidence and drug etiology of severe skin reactions.

The patients ages ranged from 47 to 91 years old (mean 68.8). Sixteen were female and 11 were males. The daily dose of tramadol was within the recommended range. There was no indication of any tramadol overdose. The mean duration of tramadol therapy was 5 days (range 1-34 days). The onset of severe skin reactions, where known, was 1 to 20 days after initiation of tramadol therapy. All patients were receiving concomitant multiple medications (as many as 50), one reported autoimmune disorder, and seven reported drug allergies that might have contributed to the risk of developing a severe skin reaction. Nine patients received tramadol drops, one an injection, and one a suppository form that are not currently available in the US.

The cause of deaths, where known was listed as cardiac/circulatory failure (10), multiorgan failure (3), cardiogenic shock/ leukopenia/thrombocytopenia (1), septic shock (1), peritonitis (1), and sepsis/pneumonia (1).

#### E. IMMUNE SYSTEM

##### 1. Anaphylactoid/ Allergic reactions (5)

There were five unduplicated cases of fatal anaphylactoid/allergic reaction associated with tramadol. None of the patients had a history of drug allergies. Three were foreign and two were domestic. There were two females and three males. The ages ranged from 9 to 80 years old (mean 50). Four patients developed symptoms of respiratory distress associated with angioedema, cyanosis, and hypotension 10 to 60 minutes after taking oral tramadol. One patient might have also received concomitant ketoprofen 100mg IM. One case (# 5323281) involved a child who was given a single dose of tramadol 25mg and developed anaphylactic shock and died. No other details were given. Autopsy results confirming an anaphylactoid drug reaction was reported in two patients.

#### III. DRUG INTERACTIONS – 3 Cases (2%)

Three deaths were possibly due to a drug interaction between tramadol and another drug. One patient on concomitant long-term warfarin therapy was initiated on tramadol and subsequently developed prolonged prothrombin time. His INR was reported as “out of range” The patient died from purpura and hemorrhagic diathesis. No other information was available. This case is additionally supported by the labeled drug interaction between tramadol and warfarin.

One case (AERS# 3154328) reported a possible drug interaction between selegiline (MAOI) and tramadol. The dose and duration of tramadol was not available. The patient

also had Parkinson's disease and received concomitant apomorphine therapy for unknown dose and duration. No other information was available.

The remaining case (AERS# 3383041, Literature) involved a possible drug interaction between flecainide and tramadol. The patient was stable on flecainide and within 36 hours of commencing an unknown dose of tramadol developed arrhythmia and died. The authors postulated a possible drug-drug interaction between flecainide and tramadol and further studied their theory in healthy volunteers. Their results were published in the literature.<sup>9</sup>

Although a drug interaction was not suspected and objective data was not provided in the cases previously mentioned (see unintentional multiple drug overdose, page 7 and 8), the possible role of a drug interaction between tramadol and TCAs and SSRIs cannot be excluded.

## DISCUSSION AND CONCLUSION

In response to Dr. Maria L. Villalba's consult request, we evaluated a total of 322 unduplicated deaths reported with Ultram® (tramadol) use. One hundred seventy-two were not analyzed further due to insufficient information, underlying diseases, poor temporal relationship or other drugs or events unrelated to tramadol use. The remaining 150 deaths were possibly related to tramadol.

There were 95 death cases (intentional, unintentional) that were associated with tramadol overdose as either a single suspect agent or co-suspect in combination with other medications. In this case series, patients took generally higher than the recommended dose of tramadol and/or the co-suspect medications. These medications included primarily anti-depressants including TCAs and SSRIs. The ages were younger in the multiple overdose and drug abuse cases than in overdoses resulting from tramadol alone, therapeutic error, or drug interactions. In the majority of the cases, the dose, duration or frequency of tramadol was not available but based on the patient's history, a pill count, and a post-mortem toxicology analysis, overdose was established. The cause of death, where known, was respiratory depression, cardiac arrhythmia, hypotension, bradycardia, cardiac arrest seizure, hepatic failure, serotonin syndrome and pneumonia.

Therapeutic errors may have resulted in nine overdose deaths. The errors include incorrect dose, wrong drug, or use of tramadol for an unapproved U.S. indication. Seven cases were foreign where tramadol was used in pregnant and pediatric patients with formulations (suppository, injection and suspension) that are not available in U.S. The two domestic cases involved debilitated young HIV patients where the dose appeared to be higher than recommended for the patient's clinical condition.

Three deaths were attributed to a possible drug interaction between tramadol and another medication (warfarin, selegiline, and flecainide). Two patients appeared to have received labeled doses of tramadol and either developed coagulopathy, or an arrhythmia when

used in combination with warfarin or flecainide. One case reported a possible drug interaction between selegiline (MAOI) and tramadol. The dose and duration of selegiline therapy was not available. However, due to known drug interactions between tramadol, warfarin, and selegiline, two of the cases indicated a possible association between fatalities and drug toxicities. The other case was a possible flecainide-tramadol interaction where an interaction was not known.

Fifty-two deaths involved adverse events that occurred with the normal, prescribed, or labeled dose of tramadol, as opposed to overdose, misuse, or abuse. The patients were generally older (age range in 70-80s). Concomitant multiple drugs (as many as 50), old age, and history of chronic concomitant illnesses might also have contributed to death in these patients. The events involved the cardiovascular, central nervous, digestive, skin, and immune systems. The majority of the adverse events are in the product labeling except for pancreatitis and bowel obstruction/ischemia.

In summary, 150 deaths were temporally associated with tramadol use. The majority of the deaths were related to single or multiple drug overdose or adverse drug events with therapeutic doses. A history of drug abuse and concomitant use of antidepressive agents including TCAs and SSRIs were identified as possible risk factors in most overdoses. However, there were a large number of overdoses involving high doses of tramadol as a single agent. An increased awareness of tramadol's abuse and misuse may help to prevent future fatalities as new combination products or formulations may become available in the U.S.

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**/S/**

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Concurrence:

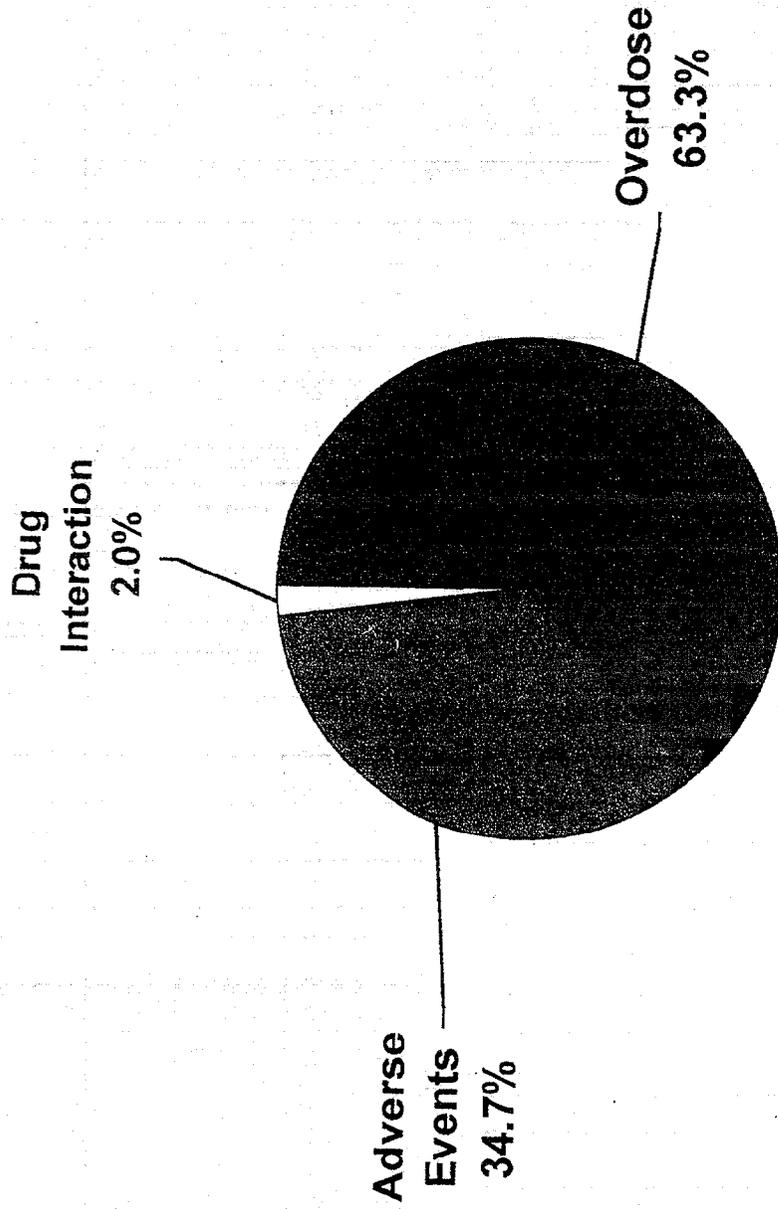
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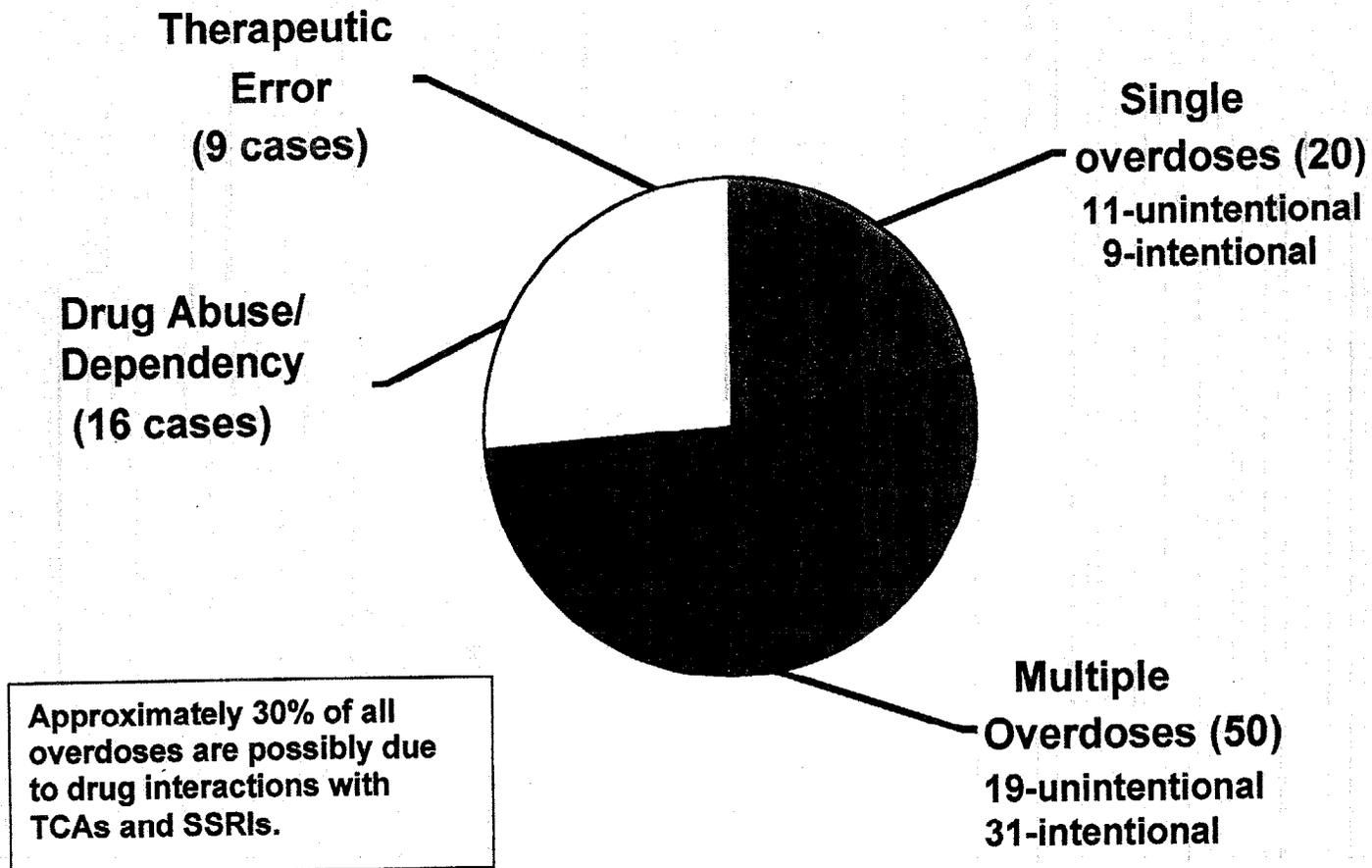
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# Deaths Associated with Ultram®



# Overdoses (95 cases)



## Deaths Associated with Ultram® Adverse Events

