



**Department of Veterans Affairs
Office of Inspector General**

Office of Healthcare Inspections

Report No. 15-02131-471

Healthcare Inspection

Unexpected Death of a Patient During Treatment with Multiple Medications Tomah VA Medical Center Tomah, Wisconsin

August 6, 2015

Washington, DC 20420

To Report Suspected Wrongdoing in VA Programs and Operations:

Telephone: 1-800-488-8244

E-Mail: vaoighotline@va.gov

Web site: www.va.gov/oig

Table of Contents

Purpose	1
Background	1
Scope and Methodology	1
Case Summary	3
Inspection Results	8
I. Mixed Drug Toxicity	8
II. Other Areas of Concern	10
<i>Documenting Patient’s Consent for Treatment</i>	10
<i>Cardiopulmonary Arrest Management</i>	11
Conclusions	13
Recommendations	13
 Appendixes	
A. Medications Administered August 28 through August 30, 2014	14
B. Consultant Forensic Toxicologist Report.....	16
C. Acting VISN Director Comments	24
D. Acting Facility Director Comments	25
E. OIG Contact and Staff Acknowledgments	29
F. Report Distribution.....	30

Executive Summary

The VA Office of Inspector General (OIG) Office of Healthcare Inspections (OHI) conducted an inspection at the request of Senator Tammy Baldwin and Senator Ron Johnson to assess the merit of an allegation made to OHI by a father after his son died unexpectedly during the course of treatment for mental health (MH) problems at the Tomah VA Medical Center (facility), Tomah, WI. The father alleged that his son (patient) died from an overdose of medications administered while receiving treatment at the facility.

The medical examiner concluded that the patient's cause of death was mixed drug toxicity. We enlisted the services of a non-VA forensic toxicologist to serve as a consultant and subject matter expert. The consultant agreed with the medical examiner's conclusion.

We determined that the patient died in the facility and that he was prescribed medications with potential for respiratory depression. Among the medications the patient received, the additive respiratory depressant effects of buprenorphine and its metabolite norbuprenorphine, along with diazepam and its metabolites, were the plausible mechanism of action for a fatal outcome. These drugs were prescribed by the treating psychiatrists at the facility. However, the consultant forensic toxicologist noted the following, "the possibility that the decedent received additional drug (Suboxone® [buprenorphine/naloxone]) in some form or fashion, cannot be excluded."

We also found deficiencies in the informed consent process and cardiopulmonary resuscitation efforts. The Veterans Health Administration requires written informed consent when administering hazardous drugs, including buprenorphine. We did not find evidence of written informed consent for buprenorphine treatment. Both psychiatrists involved in the ordering of buprenorphine acknowledged they did not discuss the risks inherent in off-label use of the drug with the patient.

Cardiopulmonary resuscitation deficiencies we identified included role confusion (between unit staff and facility firefighters who responded to the medical emergency) as well as delays in initiating cardiopulmonary resuscitation, calling for medical emergency assistance both within the unit and from facility emergency response staff, and applying defibrillator pads to determine cardiac rhythm for possible intervention. Further, certain medications used in emergency situations to reverse effects of possible drug overdose (naloxone and flumazenil) were not available on the unit.

We recommended that the Acting Veterans Integrated Service Network Director review the care of the patient who is the subject of this report and confer with the Office of Human Resources and the Office of General Counsel to determine the appropriate administrative action to take, if any.

We also recommended that the Acting Facility Director ensure compliance with Veterans Health Administration Handbook 1004.01, *Informed Consent for Clinical Treatments and Procedures*, as it relates to medication administration; review all elements needed to respond effectively to medical emergencies, including staff training,

equipment, and other resources at both the unit and the facility level and take any appropriate actions; and review and evaluate medications currently available on emergency crash carts, including but not limited to, reversal agents for narcotic and/or benzodiazepine toxicity, and make changes as appropriate.

Comments

The Acting Veterans Integrated Service Network and Facility Directors concurred with the report. (See Appendixes C and D, pages 24–28 for the Directors' comments.) We consider recommendation 4 closed. We will follow up on the planned actions for the open recommendations until they are completed.



JOHN D. DAIGH, JR., M.D.
Assistant Inspector General for
Healthcare Inspections

Purpose

The VA Office of Inspector General (OIG) Office of Healthcare Inspections (OHI) conducted an inspection at the request of Senator Tammy Baldwin and Senator Ron Johnson to assess the merit of an allegation made to OHI by a father after his son (patient) died unexpectedly during the course of treatment for mental health (MH) problems at the Tomah VA Medical Center (facility), Tomah, WI.

Background

Located on a 173-acre campus in west-central Wisconsin, the facility provides primary care, MH services, and nursing home care. It has a 4-bed Urgent Care Clinic, 180 Community Living Center (CLC) long-term care beds,¹ 35 Residential Rehabilitation Treatment Program (RRTP) beds, 21 acute care medical beds, and 10 vocational and social rehabilitation beds. The facility is part of Veterans Integrated Service Network (VISN) 12.

Inpatient programs include acute medicine, acute and long-term psychiatry, vocational and social rehabilitation, psycho-geriatric care, Alzheimer's assessment and management, residential substance abuse treatment, post-traumatic stress disorder (PTSD) residential treatment, and compensated work therapy/transitional residency.

The inpatient programs are augmented by an active outpatient component, including a mental hygiene clinic and MH intensive care management program. Outpatient care services are also provided at community based outpatient clinics (CBOCs) located in La Crosse, Owen, Wausau, and Wisconsin Rapids, WI.

Allegation: The complainant contacted the OIG Hotline and stated that his son died from an overdose of a cocktail of drugs administered while an inpatient on the Mental Health ward at VAMC Tomah, WI.

Scope and Methodology

This report focuses on the events surrounding the death of a patient on August 30, 2014, and the care he received at VA prior to his last admission at the facility. The period of our review was February 11–June 11, 2015. We conducted site visits February 11–12 and February 18–20. We interviewed the patient's surviving spouse and father. We interviewed the pathologist who performed the patient's autopsy. During our site visits, we interviewed facility leadership, managers, clinical caregivers, and other individuals knowledgeable about the events discussed in this report. We also interviewed individuals who contacted us to volunteer additional information and conducted phone interviews based on the need for additional information.

¹ Tomah WI Medical Center Memorandum. *Community Living Center Policy*. NO. PCS-EC-06. October 11, 2013 (Review Date: October 11, 2016). Tomah CLC provides an array of services including Short Stay Mental Health Recovery designed to provide evaluation and management such as medication adjustment for patients with exacerbations of medical and/or behavioral symptoms that can be managed in a non-psychiatric inpatient setting.

We reviewed relevant Veterans Health Administration (VHA) and facility policies and procedures, incident reports, and peer reviews. We reviewed the patient's VA electronic health records (EHR) and non-VA health care information. We reviewed the patient's forensic autopsy report, certificate of death, and postmortem toxicology report. We reviewed the patient's inpatient medication administration and outpatient medication prescription history. We also enlisted the services of a non-VA forensic toxicologist to serve as a consultant and subject matter expert. A copy of the consultant forensic toxicologist's report is appended to this report. (See Appendix B.)

We created a table of medications the patient received between 12:01 a.m. August 28 and the time he was found unresponsive at approximately 2:45 p.m. August 30, 2014, which is found in Appendix A of this report.

We conducted the inspection in accordance with *Quality Standards for Inspection and Evaluation* published by the Council of the Inspectors General on Integrity and Efficiency.

Case Summary

The patient was in his mid-20s when he first presented to a Tomah CBOC in 2003 to establish care at the VA. His only complaints at that time were nicotine dependence and over-the-counter ephedrine use. The patient did not return to the VA for care until 2005.

The patient continued his care at VA as well as non-VA facilities intermittently until his death in 2014. There were no VA visits between June 2009 and August 2010.

In 2005, approximately 2 years after his first 2003 VA evaluation, the patient reported to a VA primary care provider (PCP) that he was taking oxycodone obtained from a friend to relieve low back pain. Less than 2 weeks later, he presented to the PCP and requested treatment for oxycodone addiction; he was referred for the first time to the MH service at the Tomah VAMC. He was seen by the Tomah MH service the next day but declined admission, preferring to detox at home with the support of his parents. He agreed to return as needed. VA staff contacted the patient by phone 2 days later and documented that the patient was feeling much better and felt no urgency to begin treatment, but he would think it over.

In 2006, the patient presented to his VA PCP with complaints of anxiety and reported he was being followed at a non-VA methadone clinic. The VA PCP prescribed lorazepam and referred the patient to the facility's MH service. His treatment for addiction by the non-VA clinic continued into 2007, and he was intermittently treated at VA for his psychiatric complaints. His psychiatric diagnoses included PTSD, bipolar I disorder, generalized anxiety disorder, attention deficit/hyperactivity disorder (ADHD), panic disorder, opioid dependence, and alcohol and benzodiazepine abuse. VA records indicated that he was treated for his addiction again in 2010 at a non-VA facility.

While the patient's VA EHR problem list did not include chronic pain, he occasionally presented with intermittent complaints of pain and, at times, providers prescribed pain relief medications as needed. According to the patient's VA outpatient medication prescription history record, no VA provider prescribed the patient oxycodone or other Schedule II opioid analgesic.²

When seen at the VA during 2006–2014, the patient's VA providers prescribed medications to treat his severe and complex MH issues, which included suicidal ideation and threats of harm to self and others. Records reflected the patient frequently adjusted and/or discontinued medications on his own, reported taking medications that were not prescribed for him, and misused certain of his medications by taking excessive

²United States Drug Enforcement Administration. "Drugs, substances, and certain chemicals used to make drugs are classified into five (5) distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychological and/or physical dependence. As the drug schedule changes-- Schedule II, Schedule III, etc., so does the abuse potential-- Schedule V drugs represents the least potential for abuse." <http://www.dea.gov/druginfo/ds.shtml>. Accessed August 4, 2015.

amounts. He also reported obtaining oxycodone and other drugs “off the street” and that he was treated for overdoses at non-VA facilities on several occasions. VA records show that the patient took medications as prescribed and functioned better when the medications were managed by his father.

On July 29, 2014, the patient was evaluated in the Tomah MH clinic by a MH Nurse Practitioner. Medications renewed by the MH Nurse Practitioner are listed below.

- Clonidine patch, 0.2 mg/24 hour
- Diazepam, 20 milligrams (mg) three times per day
- Diphenhydramine, 50 mg at bedtime as needed for allergies or itching
- Duloxetine, 60 mg two times per day
- Hydroxyzine, 50 mg two times per day as needed for itching
- Omeprazole, 20 mg/day
- Quetiapine, 50 mg two times per day and 100 mg at bedtime as needed for mood
- Temazepam, 30 mg at bedtime
- Tramadol, 50 mg four times per day as needed for pain

Although atomoxetine 60 mg every day is noted in the MH Nurse Practitioner’s plan, it is not listed in the EHR’s “Active Outpatient Medications” list.

On August 10, the patient presented to the facility’s UCC with suicidal ideation and was admitted to the acute psychiatric unit by Psychiatrist 1 (the inpatient attending). On August 14, he was transferred to the Short Stay Mental Health Recovery unit in the CLC where several medication changes were made. Quetiapine continued to be prescribed on an as needed basis. No other mood stabilizer was prescribed. On August 22, the patient met with Psychiatrist 2 who recommended no change in medications.

On August 25, Psychiatrist 1 initiated a trial of ziprasidone at a dose lower than a previous trial attempted in July, 2014. On August 27, Psychiatrist 1 documented the following:

Nursing reports that [name] is saying that he is having increased anxiety and restlessness since going back on the ziprasidone at 20 mg each night. He wrote a note for this provider stating "yesterday was one of my worst days ever. I being serious. I struggled from after 12-8 when I take my night medications. I have so much anxiety inside me that my body just cannot relax. That they dollars was missing to call me down. I laid my room all day just trying to sleep. That is when I would you before he came in the hospital. I would be struggling inside the bad that is why I would always take my night medications at 5 PM. The Geodon [ziprasidone] is not for me. It took me over an hour to fall asleep then I woke up throughout the night at least a dozen times. Then woke up for good at 4 AM. I am not going to suggest anything but please help me this morning. Please I can't take another day like yesterday. Please I'm miserable. Thanks [name]" I spoke with [the patient] briefly on the unit and indicated that I would discontinue the

*ziprasidone and restart him on the quetiapine. His father is coming for a family meeting tomorrow and we can discuss options in more detail at that meeting.*³

Ziprasidone was discontinued, and the patient was changed back to quetiapine on August 27. On that date, Psychiatrist 1 documented in a progress note, "He [the patient] will continue to have independent off unit privileges for two hours up to three times daily."

On August 28, Psychiatrist 1 documented a meeting she attended with the patient, his father, and a team social worker that afternoon. Psychiatrist 1 recommended a reduction of atomoxetine to 40 mg/day and noted:

I also recommended that we look at restarting Suboxone. I spoke with his outpatient psychiatrist, [Psychiatrist 2] earlier today and he agrees with starting Suboxone at 8 mg twice daily...At the end of the meeting, [the patient] indicates that he would like to try the Suboxone. He was told that likely it would be available to start tomorrow.

Under the "Plan" section of her note, Psychiatrist 1 stated:

He [the patient] indicates that he would like to go back on Suboxone in hopes that that it will help alleviate his chronic pain and potentially decrease his overall level of anxiety without having the potential for addiction as had been a problem for him previously.

The EHR does not contain documentation that the patient was informed this was an off label use of the drug⁴ or that he was informed of the risks of initiating Suboxone® treatment.⁵

On the morning of August 29, a social worker documented that the patient's thought process was "clear,"⁶ and a nursing assessment noted, "Resident is oriented to person, oriented to place, oriented to time, oriented to situation...Resident is alert...Resident exhibits appropriate behaviors."

Suboxone® was ordered. The initial order was for buprenorphine 8 mg/naloxone 2 mg, one sublingual (under the tongue) tablet 2 times daily. According to Bar Code

³This quotation as cited is an accurate copy of the original note.

⁴ Off-label drug use involves prescribing medications for indications (that is, specific medical conditions), or using a dose or dosage that have not been approved by the US Food and Drug Administration. Off-label drug use is relatively common in psychiatric practice. Suboxone is FDA-approved to treat patients with opioid dependence. This patient was not, at this time, dependent on opioids. The standard initiating recommended dose for treating patients with opioid dependence should not exceed buprenorphine 8 mg/naloxone 2mg on day 1. This patient received 2 doses of buprenorphine 8 mg/naloxone 2mg on day 1 and 1 dose of buprenorphine 8 mg/naloxone 2mg on day 2. All 3 doses were taken within a 24 hour period.

⁵ VA providers documented that the patient reported receiving outpatient Suboxone® treatment on at least two prior occasions by non-VA providers in 2007 and 2010; he was also prescribed Suboxone® by VA providers in April 2014. The VA EHR also shows that he requested Suboxone® in May 2012.

⁶ Although this note is dated and timed in the morning of August 29, OHI inspectors believe, based on an interview with the social worker, that its content refers to a meeting that the social worker attended the previous afternoon with the patient, his family, and his psychiatrist.

Medication Administration (BCMA) records, the tablet form was not available when the nurse attempted to administer the first dose on the morning of August 29. The nurse filed a “missing dose” report in BCMA.

Per the pharmacist’s interview, after approval from Psychiatrist 1, the pharmacist changed the order from sublingual tablet to sublingual film with no change in the dose or frequency.⁷ The nurse administered the first dose at 9:50 a.m. When the provider initiated Suboxone®, no dose adjustments were made to the patient’s other sedating medications. The EHR lists Psychiatrist 2 as the ordering provider. No note was entered into the EHR by Psychiatrist 2.

The second dose of Suboxone® was administered on August 29, at 8:36 p.m., and a third dose was administered on August 30, at 8:09 a.m.

Also on August 30, at 7:38 a.m., the patient was given tramadol for complaints of a headache. The nurse documented in the 7:38 a.m. EHR vital signs report that the patient’s pain was “10”⁸ and the “worst imaginable pain.” At 8:30 a.m., when documenting effectiveness of the tramadol administered at 7:38 a.m., the nurse noted, “reported little effect for his migraine” and entered a “9” in reference to the patient’s headache in the EHR vital signs report. Nursing staff contacted the medical officer of the day (MOD) who ordered Fioricet® (acetaminophen, butalbital, and caffeine), “1 tablet now po [by mouth],” which was administered at 8:59 a.m. A nursing note entered at 7:10 p.m. that summarized events of August 30 stated in part:

At approximately 0800 this writer arrived on shift. Veteran approached the nurse’s station at approximately 0820 and had complaints of a migraine headache, and troubles urinating. He was asked when the last time he urinated was, to which his response was “I was just able to urinate; I’m good now.” Veteran was alert and oriented, but shielding his eyes from the light. Another veteran walked behind him and talked loudly, of which he seemed irritated by. Veteran was told that the MOD would be notified, and that a PRN [as needed] medication for migraine headaches would be requested, and brought to him in his room so that he could rest. At approximately 0830 the MOD was notified and Fioricet was ordered. This writer obtained the order and was verified at 0855. Medication was scanned out as administered at 0859. This writer went to his room and requested he sit up to take the medication for safety reasons. The veteran responded appropriately, and sat up, complaining that his right arm was stiff. He was asked if it was because he was just laying on it, and he replied “yeah probably.” Veteran laid back down requesting the door be shut behind him because the light was too bright. The veteran’s family was waiting to visit with him, to drop off belongings, and had spoken with him around 0930. Veteran was left to recover from his pain.

An EHR note entered at 4:19 p.m. stated that at approximately 1:10 p.m., a nursing staff member checked on the patient and noted the following:

⁷ The pharmacist informed OHI that as a matter of practice, the facility has opted to use sublingual films rather than sublingual tablets.

⁸ VHA uses a 1–10 pain scale with 10 being the worst and 1 being the least.

Veteran was checked on by undersigned around 1310 [1:10 p.m.] as he did not get up for lunch or for his noon medications. After knocking at veteran's door, undersigned then entered and at that time, veteran was asleep and snoring. He was lying on his side facing the door.

Another EHR note entered at 4:16 p.m. stated that at approximately 2:45 p.m., a nursing staff member found the patient unresponsive:

This writer went into vet's room approximately 1445 [2:45 p.m.] and found vet unresponsive. This writer then went to notify RN and called 911 for medical emergency.⁹ CPR [cardiopulmonary resuscitation] was initiated until fire department relieved.

An EHR entry timed 5:14 p.m., written by a physician who responded to the emergency, stated that at approximately 3:05 p.m. responders arrived to administer emergency resuscitation.

Resuscitation efforts were unsuccessful. The EHR Resuscitation Note documents that the patient expired at 3:39 p.m. The Medical Emergency/Code Worksheet, a handwritten document that is recorded simultaneous with events, stated that cardiopulmonary resuscitation (CPR) was initiated at 1455 (2:55 p.m.), an overhead page sounded at 1500 (3:00 p.m.), the code team arrived at 1505 (3:05 p.m.), and the patient expired at 1539 (3:39 p.m.).

The case was referred to the Monroe County Medical Examiner's Office, which arranged to have a forensic autopsy performed in Madison, WI. According to a State of Wisconsin Certificate of Death issued on September 10, 2014, the "Immediate Cause" of death was "Mixed Drug Toxicity [sic]." No "Due to or as a consequence of" causes are listed. The manner of death is listed as "Accident."

During the last 48 hours of his life, the patient received multiple regularly scheduled and "as needed" medications. All drugs administered from 12:01 a.m. August 28, until the patient was found in an unresponsive state at approximately 2:45 p.m. on August 30 are listed in Table 1, Appendix A.

⁹911 is the facility's internal emergency number and does not summon community Emergency Medical Services.

Inspection Results

I. Mixed Drug Toxicity

Our inspection's findings were consistent with the medical examiner's conclusion that the patient's cause of death was mixed drug toxicity.

The forensic autopsy report under the section "Findings and Diagnoses" states that the patient had "mixed drug toxicity (tramadol, diazepam, diphenhydramine and buprenorphine)." In his report, the consultant forensic toxicologist (see Appendix B) stated that "subclavian blood concentration of drugs as stated in the final toxicology report, in the context of a complete medico-legal autopsy and death investigation, are sufficient to concluding the cause of death to be due to mixed drug toxicity."

The consultant forensic toxicologist also cautioned in his report that there are limitations on relying on post-mortem blood levels:

Correlating a dose of a drug or amount ingested with a postmortem blood concentration cannot be performed with any level of confidence, accuracy or scientific reliability.¹⁰

The forensic autopsy report notes that the mixed drug toxicity occurred in a context in which no competing cause of death or acute injuries were identified. Thus, as the pathologist explained in an interview, the diagnosis of mixed drug toxicity is one of exclusion. The pathologist in his report specified four drugs contributing to the mixed drug toxicity. In subsequent interviews, he indicated that these drugs were specified based on either their postmortem blood levels as were measured and found to be elevated or in the high end of the therapeutic range; or on the availability of published cases of fatality. He stated that no individual drug stood out as being lethal. He further stated that several other drugs were excluded because a therapeutic range had not been established or because they were not known to be involved in drug-related deaths. The autopsy report also noted in the Natural Disease section mild to moderate atherosclerotic cardiovascular disease, mild aortic atherosclerosis, and mild fatty liver. The pathologist stated in an interview with OHI inspectors that none of these medical conditions were of sufficient severity to have been a cause of death.

The consultant forensic toxicologist agreed that the findings in this case were sufficient to conclude that the cause of death was mixed drug toxicity. He stated in his report that the additive respiratory depressant effects of buprenorphine and its metabolite

¹⁰ Consultant forensic toxicologist's report (Appendix B).

norbuprenorphine, along with diazepam and its metabolites, are the plausible mechanism of action for a fatal outcome.¹¹

However, he also discussed a study of blood plasma concentrations of buprenorphine and its metabolite norbuprenorphine over time and noted that the post-mortem concentrations of buprenorphine and norbuprenorphine seemed considerably contrary to the reported C_{max} (average peak plasma concentration) data noted in the study. The consultant forensic toxicologist stated that

It is impossible to state how the dosing regimen applied correlates to the postmortem blood concentration observed. Similarly, the possibility that the decedent received additional drug (Suboxone®), in some form or fashion, cannot be excluded.¹²

When we interviewed Psychiatrists 1 and 2, they both hypothesized that the patient obtained additional quantities of his prescribed medications on his own and ingested them, thus precipitating the mixed drug toxicity. It was pointed out that the patient had privileges to leave the unit several times a day in an effort to help him re-integrate into the community.

The consultant forensic toxicologist also pointed out that virtually all of the other drugs detected in the postmortem blood sample are capable of producing sedation. Specifically, he noted this applies to tramadol and its metabolite nortramadol, duloxetine, diphenhydramine, hydroxyzine, and quetiapine. The consciousness-altering effects of these drugs are additive and may have contributed to the patient's obtunded posture and breathing difficulty. Review of the patient's EHR confirmed that all of these drugs were being prescribed by his providers at the facility.¹³

¹¹ Buprenorphine and its metabolite norbuprenorphine bind to a specific subtype of opioid receptor in the brain which results in diminished sensitivity to changes in oxygen and carbon dioxide outside normal ranges. The net effect is to diminish the magnitude of the central nervous system response to increased carbon dioxide, reducing the depth and frequency of breathing. In contrast, diazepam and its metabolites affect the neurotransmitter gamma-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the brain. These drugs enhance the inhibitory actions of GABA by binding to specific receptors. The centers in the brain that control breathing contain high densities of GABA receptors, and therefore are subject to these inhibitory actions. Thus, buprenorphine and diazepam, along with their various metabolites, affect respiration through two separate mechanisms that together can produce a fatal outcome.

¹² Consultant forensic toxicologist's report (Appendix B).

¹³ When we entered the patient's complete medication regimen (including two additional drugs, omeprazole and clonidine, that were not tested for in the postmortem analysis) into a standard drug interaction reference, we found a total of 32 warnings about potential drug interactions, 29 of which cited an increased risk of central nervous system depression (sedation). Five of these latter warnings also cited an increased risk of respiratory depression (buprenorphine with diazepam, buprenorphine with tramadol, buprenorphine with temazepam, diazepam with tramadol, and temazepam with tramadol). Most of the warnings advised caution or to monitor/modify treatment, but the warning for diazepam with omeprazole advised to avoid the combination and use an alternative, or lower the dose of diazepam due to increased blood levels of diazepam as a result of inhibited metabolism by omeprazole.

II. Other Areas of Concern

We identified the following areas of concern—the need for written informed consent in the setting of hazardous medication management and staff response to the patient’s cardiopulmonary emergency.

Documenting Patient Consent for Treatment

In modern evidenced-based medicine, treatment providers approach therapeutic decision making through a process of risk-benefit analysis. Providers must balance the anticipated benefits of a particular treatment against the potential risks posed by that treatment, taking into account the relative risks and benefits of alternative treatments or no treatment, the perspective of the patient on the suffering and disability caused by the illness being treated, and the degree of risk that the patient is inclined to accept.

VHA Handbook 1004.01, *Informed Consent for Clinical Treatments and Procedures*, dated August 14, 2009, similarly states the following:

*In VHA, patients have the right to accept or refuse any medical treatment or procedure recommended to them. Except as otherwise provided in this Handbook, all [emphasis in original document] treatments and procedures require the prior, voluntary informed consent of the patient...*¹⁴

This Handbook further states that such consent must describe “the expected benefits and known risks associated with the recommended treatment or procedure...”¹⁵ Such consent, whether oral or written, must be documented in the EHR.¹⁶ Additionally, written informed consent is required when administering hazardous drugs; the Handbook specifically cites buprenorphine as one of several hazardous drug examples.¹⁷

We found no evidence of written informed consent in the EHR. However, absent VHA’s specific requirement to obtain written informed consent for buprenorphine whenever ordered, the circumstances of this case would have required practitioners to discuss and document the discussion of the relative risks and benefits of this patient’s medication management under general informed consent principles embodied within the Handbook. The use of a high dose of diazepam¹⁸ concomitant with a second benzodiazepine (temazepam), as well as another drug that elevates diazepam levels (omeprazole), the seriousness of the potential drug interactions between benzodiazepines and buprenorphine, and the use of buprenorphine above the labeled starting dose and in the absence of opioid tolerance (both of which constitute off-label

¹⁴ VHA Handbook *Informed Consent for Clinical Treatments and Procedures* 1004.01, p. 3. This Handbook was scheduled for recertification on or before the last working day of August 2014 but has not yet been recertified.

¹⁵ VHA Handbook 1004.01, p. 7.

¹⁶ VHA Handbook 1004.01, p. 10.

¹⁷ *Ibid*, Appendix A, p. A-2.

¹⁸ The upper boundary of the recommended dose for diazepam is 40 mg/day, whereas the patient was taking 60 mg/day.

use) placed this patient at even a higher risk than when buprenorphine is ordered under more usual circumstances.¹⁹

Psychiatrist 1 acknowledged that when she discussed initiating buprenorphine treatment with the patient, she did not obtain informed consent, either verbally or in writing. Two witnesses who were present at the time Psychiatrist 1 discussed buprenorphine with the patient confirmed that the patient was not informed of the risks of taking buprenorphine along with his existing drug regimen. Psychiatrist 1 stated that she is not an authorized prescriber for buprenorphine because she has not had the requisite training,²⁰ and so this drug was prescribed by Psychiatrist 2 who collaborated in the treatment. Psychiatrist 1 stated she entered the order for buprenorphine into the EHR as a courtesy to Psychiatrist 2, but the order required his signature before the drug could be dispensed. Thus, Psychiatrist 1 believed she did not have responsibility for obtaining informed consent.

Psychiatrist 1 had primary medical responsibility for this patient because the patient was an inpatient and she was his attending psychiatrist. She prescribed the benzodiazepines (diazepam and temazepam), as well as other drugs that were elements in the mixed drug toxicity.

Psychiatrist 2 had an appointment with the patient 8 days before he died. The EHR note from that appointment states, “No Change” to the medication regimen and makes no mention of buprenorphine. Psychiatrist 2 told us in an interview that Psychiatrist 1 sought his consultation 2 days before the patient died, and they reached a consensus to begin buprenorphine treatment. He did not meet with the patient subsequent to this conversation and did not inform the patient regarding the risks of treatment. Upon questioning, Psychiatrist 2 indicated that he believed it was Psychiatrist 1’s responsibility as the attending psychiatrist to obtain informed consent for the treatment.

Cardiopulmonary Arrest Management

We determined that facility staff did not respond appropriately after finding the patient unresponsive.

Unit staff did not immediately assess the patient and determine the need for cardiopulmonary resuscitation (CPR) upon finding the patient unresponsive. The American Heart Association states that high-quality CPR includes starting chest

¹⁹ This patient died within 29 hours of starting buprenorphine while he was on a high dose of diazepam. For the formulation of buprenorphine used (Suboxone® sublingual film), the recommended starting dose for day 1 of treatment for FDA approved uses contains 8 mg buprenorphine, whereas the patient was given 16 mg buprenorphine on day 1. Furthermore, this recommended dose as specified in the drug labeling is intended for use in patients who are dependent on and therefore have tolerance to opioid drugs, and the first dose should be started only when objective signs of moderate withdrawal appear. Since the patient was not in a state of opioid dependence or tolerance at the time, he would have had relatively greater sensitivity to the effects of buprenorphine.

²⁰ Physicians who prescribe buprenorphine must first meet several qualifications and obtain a waiver from the Substance Abuse and Mental Health Administration (SAMHSA) and an identification number from the Drug Enforcement Administration (DEA). - http://buprenorphine.samhsa.gov/waiver_qualifications.html. Accessed June 12, 2015.

compressions, a key component of CPR, immediately.²¹ Because the patient's cardiac status at the time he was found unresponsive is unknown, it cannot be determined with any degree of certainty whether resuscitative efforts would have been successful.

The unit staff who first discovered the patient unresponsive did not use the in-room emergency call system.²² At the time of our review, not all unit staff were aware of this system. Additionally, the unit breakroom intercom system was turned off, and staff in that room could not hear a facility overhead call for emergency assistance.

The second nurse staff member on the scene documented the following:

This writer was having difficulty processing what to do, so it was delegated to staff to initiate a medical emergency and obtain the crash-cart, as no life-saving procedures were being implemented. This writer rushed into the room, got the veteran onto his back, and began forceful compressions.

No staff in the building where the patient was located at the time he was found unresponsive were certified to perform more than basic life support. The CLC Short Stay Mental Health Recovery had an automatic external defibrillator. When responding to a medical emergency, staff must apply defibrillation pads as soon as possible in order to determine cardiac activity and administer defibrillation (electric shock) if indicated. Early defibrillation is critical, and delayed defibrillation is associated with a lower chance of survival.

Unit staff did not quickly place defibrillation pads on the patient to assess cardiac activity. As a result, the patient's initial cardiac rhythm is unknown. At the time the pads were placed, there was no cardiac activity (asystole).

Furthermore, through interviews, we learned unit staff stopped CPR efforts when facility firefighters arrived in response to the medical emergency, and facility staff believed the firefighters were then expected to take over the CPR efforts. However, firefighters at the facility are not designated as first line staff to provide hands-on emergency care and are not paramedics or emergency medical technicians.

Emergency reversal agents may be used for the management of benzodiazepine overdose (flumazenil) and opioid overdose (naloxone). Flumazenil and naloxone were not available on the emergency crash carts that were brought to the patient's room. A facility staff member was tasked to run to the UCC to obtain flumazenil, which was administered 33 minutes after the patient was found unresponsive. Emergency response staff did not administer naloxone.

²¹http://www.heart.org/HEARTORG/CPRAndECC/WhatIsCPR/CPRFactsandStats/CPR-Statistics_UCM_307542_Article.jsp

²²Staff in patient rooms who require emergency assistance push a button labeled "CODE" in patient rooms, which electronically alerts unit staff at the central nursing of the room number where emergency assistance is required.

Conclusions

Our inspection's findings were consistent with the medical examiner's conclusion that the patient's cause of death was mixed drug toxicity. Additionally, we found deficiencies in the informed consent process and cardiopulmonary resuscitation efforts.

Among the medications the patient received, the additive respiratory depressant effects of buprenorphine and its metabolite norbuprenorphine, along with diazepam and its metabolites, were the plausible mechanism of action for a fatal outcome. These drugs were prescribed by the treating psychiatrists at the facility. However, we cannot exclude the possibility that the patient self-administered additional doses of any of the medications.

VHA requires written informed consent when administering hazardous drugs including buprenorphine. We did not find evidence of written informed consent for buprenorphine treatment. Both psychiatrists involved in the ordering of buprenorphine acknowledged they did not discuss the risks inherent in off-label use of the drug with the patient.

CPR deficiencies we identified included role confusion (between unit staff and facility firefighters who responded to the medical emergency) as well as delays in initiating CPR, calling for medical emergency assistance within the unit and from facility emergency response staff, and applying defibrillator pads to determine cardiac rhythm for possible intervention. Furthermore, certain medications used in emergency situations to reverse effects of possible drug overdose (naloxone and flumazenil) were not readily available.

Recommendations

1. We recommended that the Acting Veterans Integrated Service Network Director review the care of the patient who is the subject of this report and confer with the Office of Human Resources and the Office of General Counsel to determine the appropriate administrative action to take, if any.
2. We recommended that the Acting Facility Director ensure compliance with VHA Handbook 1004.01, *Informed Consent for Clinical Treatments and Procedures* as it relates to medication administration.
3. We recommended that the Acting Facility Director review all elements needed to respond effectively to medical emergencies including staff training, equipment, and other resources at both the unit and the facility level and take any appropriate actions.
4. We recommended that the Acting Facility Director review and evaluate medications currently available on emergency crash carts, including but not limited to, reversal agents for narcotic and/or benzodiazepine toxicity and make changes as appropriate.

Table 1. Medications Administered August 28–30, 2014

Date	Time ²³	Drug	Dose	PRN (Y)es (N)o	PRN Reason
August 28					
	4:41	Quetiapine	50mg	Y	Anxiety
	7:39	Diazepam	20mg	N	
	7:39	Omeprazole	20mg	N	
	7:39	Atomoxetine	80mg	N	
	7:39	Duloxetine	60mg	N	
	7:40	Hydroxyzine	50mg	Y	Anxiety
	7:40	Tramadol	50mg	Y	Pain Level #6
	7:44	Nicotine Resin	2mg	Y	Withdrawals
	11:36	Diazepam	20mg	N	
	11:36	Cholecalciferol	1000Unit	N	
	11:37	Nicotine Resin	2mg	Y	Withdrawals
	11:39	Quetiapine	50mg	Y	Agitation
	11:39	Tramadol	50mg	Y	Pain Level #6
	17:16	Nicotine Resin	2mg	Y	Withdrawals
	17:16	Quetiapine	50mg	Y	Agitation
	19:58	Duloxetine	30mg	N	
	19:59	Diphenhydramine	50mg	Y	Insomnia
	19:59	Tramadol	50mg	Y	Pain Level #6
	19:59	Quetiapine	100mg	Y	Insomnia
	19:59	Temazepam	30mg	N	
	19:59	Diazepam	20mg	N	
August 29					
	2:19	Tramadol	50mg	Y	Pain Level #6
	2:19	Quetiapine	50mg	Y	Anxiety
	7:06	Omeprazole	20mg	N	
	7:06	Diazepam	20mg	N	
	7:08	Tramadol	50mg	Y	Pain Level #6
	7:09	Nicotine Resin	2mg	Y	Withdrawals
	9:03	Duloxetine	60mg	N	

²³ For this table, times are shown in military time (or the 24-hour clock).

Appendix A

Date	Time	Drug	Dose	PRN (Y)es (N)o	PRN Reason
August 29 Cont'd					
	9:50	Suboxone	8mg/2mg	N	
	9:52	Atomoxetine	40mg	N	
	12:25	Cholecalciferol	1000Unit	N	
	12:25	Diazepam	20mg	N	
	12:27	Nicotine Resin	2mg	Y	Withdrawals
	12:29	Tramadol	50mg	Y	Pain Level #6
	12:30	Hydroxyzine	50mg	Y	Anxiety
	18:51	Nicotine Resin	2mg	Y	Withdrawals
	18:55	Hydroxyzine	50mg	Y	Anxiety
	18:56	Quetiapine	50mg	Y	Agitation
	20:32	Diazepam	20mg	N	
	20:34	Duloxetine	30mg	N	
	20:36	Temazepam	30mg	N	
	20:36	Suboxone	8mg/2mg	N	
	20:41	Tramadol	50mg	Y	Pain Level #6
	20:41	Quetiapine	100mg	Y	Agitation
	22:20	TB Skin Test	0.1 ml (5TU)	N	
August 30					
	0:56	Diphenhydramine	50mg	Y	Insomnia
	0:56	Quetiapine	50mg	Y	Agitation
	0:57	Nicotine Resin	2mg	Y	Withdrawal
	0:58	Tramadol	50mg	Y	Pain Level #7
	7:35	Diazepam	20mg	N	
	7:36	Duloxetine	60mg	N	
	7:36	Omeprazole	20mg	N	
	7:38	Tramadol	50mg	Y	Headache
	8:09	Suboxone	8mg/2mg	N	
	8:59	Fioricet	1 Tablet	N	

Source: OIG Analysis of VHA Data

Consultant Forensic Toxicologist Report
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June 12, 2015

Alan G. Mallinger, MD
 Senior Physician, Medical Consultation and Review
 Office of Inspector General
 Department of Veterans Affairs
 801 I Street, NW
 Washington, DC 20001

Dear Dr. Mallinger,

Thank you for the opportunity to provide consultative assistance in the matter at hand as it relates to decedent [REDACTED]. My opinion in this matter is predicated upon my formal education, training and experience as a forensic toxicologist, together with the toxicology report summarized below. I possess nearly 17 years of experience with the analyses and result interpretation of drugs and other poisons in death investigation and human performance cases. My highest earned academic degree is the Ph.D. in pharmacology and toxicology from St. John's University, Queens, New York in 1997. I am board certified as a Fellow by the American Board of Forensic Toxicology (F-ABFT). My curriculum vitae is available by request.

Autopsy specimens submitted for toxicological analyses were accessioned by AIT Laboratories on August 31, 2014. The specimens included: Subclavian blood (#40439158), urine (#40439160), and vitreous humor (#40439163). The toxicology report issued September 17, 2014 did not include the results for additional testing requested by the client medical examiner (ketamine). The amended report (February 10, 2015) indicates the test results for ketamine.

Relevant toxicological findings

Subclavian Blood	Concentration
Diazepam	897 ng/mL
Nordiazepam	1,388 ng/mL
Temazepam	81.6 ng/mL
Tramadol	827 ng/mL
Nortramadol	171 ng/mL
Buprenorphine	10.9 ng/mL
Norbuprenorphine	2.5 ng/mL
Duloxetine	386 ng/mL
Diphenhydramine	211 ng/mL
Hydroxyzine	221 ng/mL
Quetiapine	179 ng/mL
Amiodarone	Qualitative Positive (unconfirmed)

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Relevant toxicological findings-continued

Subclavian Blood	Concentration
Caffeine	Presumptive positive (unconfirmed)
Urine	
	Concentration
Temazepam	> 2,500 ng/mL
Nordiazepam	2,321 ng/mL
Oxazepam	> 2,500 ng/mL
Buprenorphine	152 ng/mL
Norbuprenorphine	186 ng/mL
Tramadol	> 10,000 ng/mL
Nortramadol	7,819 ng/mL

Request for Consultation/ Written Report/Opinion (March 10, 2015)

Toxicology consultation and written report/opinion contractor order with respect to the case review of decedent [REDACTED] between AIT Laboratories, Indianapolis, IN and the Department of Veterans Affairs, Office of Inspector General, Washington, DC. Order number VA101-15-P-0037.

Materials Reviewed re: [REDACTED], Date of Death August 30, 2014

- Standard Form 1449 (Solicitation/Contractor/Order for Commercial Items) with Medical Independent Contractor Statement of Work, effective date March 10, 2015
- Case Review (redacted and non-redacted versions)-provided by Alan G. Mallinger, MD
- Interrogatories (7)-provided by Alan G. Mallinger, MD
- State of Wisconsin-Certificate of Death
- University of Wisconsin Hospital and Clinics/Anatomic Pathology Laboratory Forensic Autopsy Report, Dr. Robert Corliss
- ECG Tracings-May 27, July 11 and July 15, 2015
- AIT Laboratories Toxicology Report, case # 2780504, decedent [REDACTED], date of death August 30, 2014, initial report September 17, 2014 and amended report February 10, 2105 (additional test results-ketamine).
- Relevant toxicological and technical references (annotated in References section of this written report)

Background

Mr. [REDACTED] was discovered to be unresponsive in a patient room at a Veterans Administration facility at approximately 1445 hours on August 30, 2014. Resuscitative (CPR) measures commenced contemporaneous to a 911 call for medical emergency. CPR measures continued through the relief by fire department personnel. Code Blue procedures were initiated at or around 1505 hours; however, CPR was discontinued between 1540-1545 hours. Mr. [REDACTED] medical history was remarkable for past psychiatric problems of PTSD, bipolar disorder, generalized anxiety disorder, attention deficit/hyperactivity disorder; additionally, a past history of opioid dependence with alcohol and benzodiazepine abuse was noted. In sum, sixteen psychiatric admissions were recorded between January 2011 and Mr. [REDACTED] date of death. Throughout his lengthy medical course, Mr. [REDACTED] was prescribed a number of medications which included antidepressant, anxiolytic, analgesic and opioid agents. His prescription history for August 29 and 30, 2014 was notable for two doses of Suboxone® (8 milligrams or mg) at 0950 and 2036 hours (August 29, 2014), one dose of Suboxone® (8 mg) at 0809 hours (August 30, 2014), 4 doses of diazepam 20 mg (three being August 29 and one on August 30, 2014), six doses of tramadol 50 mg (4 on August 29, and 2 on August 30, 2014), one dose of diphenhydramine (August 30, 2014) and two doses of hydroxyzine (both August 29, 2014). Fioricet® (butalbital in combination with acetaminophen) was administered the morning of August 30, 2014.

Interrogatory Responses/ Opinion

1. In establishing a cause of death (which carries the likelihood of being associated as drug-related), or contributing cause of death, the certifier directs attention and focus to the toxicological data provided for postmortem blood. It is in blood in which active drug or drug metabolite circulates and distributes to other compartments of the body, to include specific drug receptor sites (e.g. the mu receptors in the brain for opiates and opioids) and target effector organs where pharmacologic effects (both therapeutic and toxic) are realized. Urine toxicological data in postmortem cases exhibit limited value; specifically, drug or drug metabolite concentrations in urine cannot establish behavioral effect/impairment (e.g. alcohol), toxicity, or lethality in a decedent. The essential difference between postmortem blood drug concentrations versus postmortem urine drug concentrations resides in the relative temporal differences between the two specimen types in terms of detection times or windows for a given substance. Generally, blood provides a limited time snapshot (hours) of drug use by a decedent; in contrast, urine drug concentrations may represent a number of days previous to a subject's death. For example, benzoylecgonine which is the inactive metabolite of cocaine may be detected in urine 2-4 days after drug use. In a postmortem setting, this can affirm proximate use of cocaine by a decedent at/around time of demise, but it does not exclude a longer time frame of drug use measured by days. Urine toxicological data does possess utility for affirming postmortem blood findings (the detection of parent drug and metabolites which corroborate with blood findings), the detection of significant drug metabolites (e.g. 6-acetylmorphine or 6-AM in heroin intoxication), and providing wider surveillance of a decedent's drug use which may support or refute clinical and case history or investigative information. With respect to the toxicological data compiled for medico-legal purposes of cause of death determination, the blood and urine results are complete and offer valuable insight into the use of drugs at and around the time of Mr. [REDACTED] death. Notwithstanding, the toxicology results must be considered within the entire context of the case

which includes the elements of a thorough autopsy, an accurately chronicled depiction of surrounding circumstances of the death, and pertinent medical and clinical history of the decedent.

- a. The toxicology results revealed in subclavian blood are remarkably consistent given the prescription history and detail provided for drugs administered to Mr. ██████████ during the period August 29-30, 2014. Suboxone[®] (4:1 buprenorphine/naloxone), diazepam, tramadol, diphenhydramine and hydroxyzine were administered to Mr. ██████████ August 29-30, 2014. All of the aforementioned parent drugs, together with their respective metabolites (norbuprenorphine, nordiazepam, temazepam, tramadol and nortramadol), were identified in the subclavian blood specimen. Duloxetine and quetiapine, two drugs annotated as being prescribed at an earlier time point in the chronological medical history of Mr. ██████████, were also identified. Fioricet[®] (butalbital in combination with acetaminophen) was administered to Mr. ██████████ the morning of August 30, 2014. Butalbital and/or acetaminophen were not detected in the subclavian blood specimen. The screening cut-off concentration by Time-of-Fight (ToF) Mass Spectrometry at AIT Laboratories for butalbital is 1,000 ng/mL; the average peak plasma concentration (C_{Max}) for a single 50 mg oral dose of butalbital is 1,300 ng/mL at about one hour [1]. It is possible for butalbital to be present in the subclavian blood specimen, but at a concentration below the limit of detection for testing by ToF mass spectrometry at AIT. Reference was made in the prescription history as to the administration of clonidine by transdermal patch. Clonidine is not a drug included in the comprehensive drug testing panel offered by AIT Laboratories. Interest in testing for this particular drug would require referral testing to a laboratory as a send out from AIT Laboratories. In such instances, the medical examiner or forensic pathologist requests directed analyses for drugs which are not included in AIT's comprehensive blood panel.
2. Correlating a dose of a drug, or amount ingested, with a postmortem blood concentration cannot be performed with any level of confidence, accuracy or scientific reliability. There are several prohibiting reasons for this: The pharmacokinetic stage a decedent is at the time of death is rarely, if ever, known; that is, the subject may be in a pre-absorptive, absorptive or post-absorptive state with regard to the drug (e.g., the postmortem blood concentration observed can't be assumed to represent peak or C_{Max} , or alternatively, cannot be presumed to be descending at which elimination of the drug is beginning). Gastric content (volume and quantity) and gastric emptying are factors in this regard. Secondly, the various pharmacokinetic parameters (e.g. volume of distribution, V_d) required for calculation of a dose from a blood concentration have been assessed and determined through the numerous studies involving living, human subjects. The test matrix is whole blood, serum or plasma. Cadaveric "blood" is in stark contrast to optimal specimens procured from healthy, living human beings. There are many variables which influence the quality of a postmortem blood specimen; by way of some examples, changes in the hematocrit of the specimen which are accompanied by intracellular and extracellular fluid shifts (water content), and decreases in pH which can lead to conformational changes in plasma and serum proteins. These changes have significance for drugs which are protein bound (e.g. buprenorphine), in that protein-bound drug distributes into the free matrix of blood which in turn is included with the free form of drug quantitatively measured in a specimen. In sum, attempting to retrograde extrapolate to a dose from a postmortem blood concentration is fraught with numerous pitfalls and flaws. It cannot and should not be performed.
3. The subclavian blood concentrations of drugs as stated in the final toxicology report, in the context of a complete medico-legal autopsy and death investigation, are sufficient to concluding the cause of death to be due to mixed drug toxicity. Relative to a respiratory depressive mechanism of death, two drugs and their associated metabolites are significant: Buprenorphine (and metabolite, norbuprenorphine) and diazepam (and metabolites, nordiazepam, temazepam). Of the two parent drugs, buprenorphine is the more potent respiratory depressant. Tramadol,

recognized as being equipotent to codeine, is considered to cause less respiratory depression and carry less abuse potential [1]. Daily doses in adults range 100-400 mg per day; doses in excess of 800 mg may cause coma and respiratory depression. Postmortem femoral blood concentrations averaged 6,100 ng/mL (n = 5) in which death was exclusively attributed to tramadol poisoning [1]. In three deaths attributed to the combined use of tramadol and at least two other drugs, tramadol concentrations observed were 1,400, 2,500 and 23,000 ng/mL. In another postmortem study, deaths (n= 17) after the use or abuse of tramadol and other agents, exhibited femoral tramadol concentrations with a range 1,100-12,000 ng/mL (average 3,700 ng/mL) [1]. Concomitant administration of tricyclic antidepressants, selective serotonin re-uptake inhibitor drugs and monoamine oxidase inhibitors with tramadol may result in serotonin syndrome. Both buprenorphine and diazepam are categorized broadly as Central Nervous System (CNS) depressant drugs. Buprenorphine is a partial mu (μ) agonist; that is to say, the drug exhibits a "ceiling effect" with respect to the full agonist effects of other opioid drugs. Interactions produced at the μ receptor produce CNS depression which clinically manifest as supraspinal (μ_1) and spinal (μ_2) analgesia, respiratory depression, miosis, euphoria, reduced gastrointestinal motility, hypothermia, bradycardia, and physical tolerance and dependence. In contrast, benzodiazepines mediate CNS depressant effects through the neurotransmitter gamma-amino butyric acid or GABA. GABA, the major inhibitory neurotransmitter in the brain, has two associated sub-type receptors: GABA_A and GABA_B. Benzodiazepines bind to GABA_A receptors and potentiate the inhibitory action of GABA. While there are a number of neurotransmitters mediating the control of respiration, glutamate and GABA are the primary excitatory and inhibitory neurotransmitters, respectively [2]. Control of breathing is principally localized in the brain stem involving two primary populations of neurons known as the Dorsal Respiratory Group (DRG) and the Ventral Respiratory Group (VRG). GABA receptors are distributed in high density in both the DRG and VRG. With respect to opioid drugs such as buprenorphine, partial agonist activity at the μ receptor causes respiratory depression. Within the control of respiration, there are several sites at which opioid drugs like buprenorphine produce effects. The inhibitory activity of opioid drugs at chemoreceptors, principally mediated by μ receptors, results in diminished sensitivity to changes in oxygen and carbon dioxide outside normal concentration ranges; the net effect is to diminish the magnitude of the response to increased carbon dioxide. The overall effects on both tidal volume and respiratory frequency appear to be opioid-concentration dependent; that is, low concentrations appear to have effects mainly on tidal volume, while at higher concentrations, respiratory tidal volume and frequency both become affected. In a compendium of French cases of deaths involving buprenorphine, which included the Institute of Legal Medicine of Strasbourg and a second group culled from 13 other French centers, blood concentrations for buprenorphine were observed in a range of 0.5 to 51 ng/mL (mean 10.2 ng/mL) for Institute cases, and 0.1 to 76 ng/mL (mean 12.6) for the other centers [3]. The norbuprenorphine blood concentrations observed were 0.2 to 47.1 ng/mL (mean 8.2 ng/mL) for Institute cases, and < 0.1 to 65 ng/mL (mean 10.6 ng/mL) for the other centers. The major risk factors for such fatalities concluded from this study were: The propensity of intravenous injection of crushed buprenorphine tablets, concomitant use of other psychotropic drugs (notably benzodiazepines and neuroleptics) and the availability of the high dosage buprenorphine formulation. In an earlier study of buprenorphine-related deaths among drug addicts in France, blood concentration ranges for buprenorphine and norbuprenorphine were 1.1 to 29 ng/mL (mean 8.4 ng/mL) and 0.2 to 12.6 ng/mL (mean 2.6 ng/mL), respectively [4]. Notably, these cases were observed in abusive patterns of intravenous administration of buprenorphine doses intended for sublingual use. With respect to diazepam and its metabolites, the detection of benzodiazepines is relatively common in postmortem cases; however, few fatal intoxications are exclusively attributed to these drugs because of their relatively high therapeutic indices. In this specific case, the additive respiratory depressant effects for buprenorphine/norbuprenorphine, and diazepam and metabolites are the plausible mechanism of action for a fatal outcome. To

- emphasize, norbuprenorphine, nordiazepam, and temazepam are pharmacologically active metabolites. Virtually all of the other drugs detected in the subclavian blood specimen are capable of producing somnolence and/or drowsiness; from the perspective of toxic mechanisms of action, “but for” the buprenorphine, and its active metabolite (norbuprenorphine), and diazepam (and active metabolites of nordiazepam and temazepam in blood), life-threatening respiratory depression is not the likely cumulative toxicity of the other drug agents identified by toxicological analyses. Specifically, this refers to tramadol/nortramadol, duloxetine, diphenhydramine, hydroxyzine and quetiapine. However, the conscious-altering effects of all of these drugs are additive in combination and capable of contributing to an overall obtunded posture of the decedent. The clinical history for August 30, 2014 notes Mr. ████████ did not present himself for lunch or noon time medication administration. He was noted to be asleep and snoring at about 1310 hours, but at about 1445 hours was determined to be unresponsive. Event descriptions such as this are not uncommon for decedents intoxicated by CNS depressant and sedating drug agents. Snoring loudly, or “breathing funny” are common descriptions related by attendant witnesses to such circumstances. CNS depressant and sedating drugs may exacerbate underlying morbidities such as chronic obstructive pulmonary disease and obstructive sleep apnea.
4. Peak (C_{Max}) plasma concentrations of a single sublingual buprenorphine/naloxone (8 mg/ 2 mg) dose exhibit a mean of 3.00 ± 1.53 ng/mL; moreover, the mean time to peak (t_{Max}) was noted to be 1.01 ± 0.36 hours. For the same single sublingual dose of buprenorphine/naloxone, the norbuprenorphine mean C_{Max} was 1.48 ± 0.56 ng/mL, with a mean t_{Max} of 1.07 ± 0.48 hours [5]. The postmortem subclavian blood concentrations for buprenorphine and norbuprenorphine, 10.9 ng/mL and 2.5 ng/mL, respectively, seem considerably contrary to the reported C_{Max} data for the study described above. It is imperative to be mindful of two facts: Frist, steady-state blood concentrations were not achieved for the decedent (the time to achieve steady-state for Suboxone[®] is reportedly 7-10 days from the initiation of pharmacotherapy); steady-state defines the equilibrium achieved between the rates of drug administration and drug elimination. Secondly, the decedent received a total of 24 mg buprenorphine in a period of time just short of 24 hours. Dosage and administration guidelines for Suboxone[®] sublingual film indicate that on Day 1, for patients dependent on short-acting opioid products who are in opioid withdrawal, administer up to 8 mg/2 mg Suboxone[®] sublingual film (in divided doses) with up to 16 mg/4 mg sublingual film administered on Day 2 as a single dose [6]. It is impossible to state how the dosing regimen applied correlates to the postmortem blood concentration observed. Similarly, the possibility that the decedent received additional drug (Suboxone[®]), in some form or fashion, cannot be excluded.
 5. Additional comments and observations:
 - a. The postmortem blood and urine toxicology data available to this case provide good insight into the known prescription drug use by the decedent. I have no further recommendations for additional testing despite the clinical history of clonidine transdermal administration. Maximal plasma clonidine concentrations average 0.16 and 0.27 ng/mL for 4 and 8 mg transdermal patches at 66-72 hours post-application [1]. I am confident that clonidine quantitative analyses, if indeed the drug could be detected, will not materially change the overall interpretive conclusions drawn from the toxicology data put forth to date for this case.
 - b. Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation; this is mediated primarily by CYP3A4. Dose-reduction of CYP3A4 inhibitors (e.g. ketoconazole, erythromycin, and HIV protease inhibitors) may be required [6]. Although there are numerous reports of interactions between buprenorphine and benzodiazepines, diazepam is not considered to be an inhibitor of this enzyme [7].
 6. Limitations in the interpretation of postmortem toxicology data:
 - a. A phenomenon ever present in the interpretation of postmortem toxicology data for blood is the postmortem re-distribution (PMR) of drugs. Although widely recognized by

forensic toxicologists and forensic pathologists/medical examiners, it is an occurrence poorly understood. PMR refers to movement of drug and drug metabolite, which occurs after death, into the central compartment of blood from peripheral sites (fluid compartments and tissues). The exact mechanism by which this occurs is not well established. For example, one explanation attributes chemical changes in postmortem blood, such as pH, that promotes re-distribution. Generally, drugs which are characterized by a relatively wide Vd (≥ 3 L/Kg) are considered candidates to undergo PMR. Artifact of an elevated blood concentration can lead to misinterpretation and an incorrect conclusion in assessing the significance of a drug relative to cause or contributing cause of death. The effects of PMR can be minimized by collecting postmortem blood from peripheral anatomical sites such as iliac vein or femoral vein; conversely, blood that is collected from the heart or from cavity sites increase the likelihood for PMR to be a factor in assessing quantitative data. Subclavian blood, by most forensic pathologists and toxicologists, is considered intermediate to peripheral sites and central sites with respect to PMR.

- b. Caution must be exercised when assessing postmortem blood concentrations of a drug versus “therapeutic” drug concentrations as reported in peer-reviewed publications and tables. The physical quality of forensic postmortem blood specimens varies widely (e.g. lipid content, fluidity, water content, the presence of clots). Therapeutic drug concentrations are principally derived from studies in serum and plasma. In general, the concentration of a drug in plasma or serum is higher than in whole blood [8]. When the concentration of a drug in whole blood (forensic postmortem case) is compared to therapeutic concentrations for that drug reported in serum or plasma, one has to weigh the significance of the analytic result in terms of toxicity and lethality (overdose).

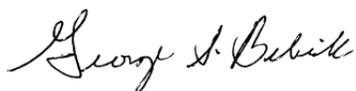
References:

- [1] Baselt RC. *Disposition of Toxic Drugs and Chemicals in Man*. 10th edition, Biomedical Publications, Seal Beach, CA; pp. 309,496; 2014
- [2] White JM and Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction* 1999; 94(7):961-972
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- [4] Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *Journal of Analytical Toxicology* 1998; 22: 430-434
- [5] Harris DS, Mendelson JE, Lin ET, Upton RA, Jones RT. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone. *Clinical Pharmacokinetics* 2004; 43(5):329-340
- [6] Full Prescribing Information for Suboxone® sublingual film (Revised April 2014), Reference ID: 3496928, Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA by electronic mail communication with Tony Tommasello, Ph.D., Medical Affairs Manager
- [7] Oechsler S and Skopp G. Buprenorphine and major metabolites in blood specimens collected for drug analysis in law enforcement purposes. *Forensic Science Int* 2010; 195:73-77

[8] Jones AW, Holmgren A and Kugelberg FC. Concentrations of scheduled prescription drugs in blood of impaired drivers: considerations for interpreting the results. *Therapeutic Drug Monitoring* 2007; 29(2):248-260

I am available to answer any questions you may have regarding this written opinion, or assist with any requests you may have for additional information at a time and means most convenient to you.

Sincerely,



George S. Behonick, Ph.D., F-ABFT
Manager, Forensic Business Unit/ Senior Forensic Toxicologist
gbehonick@aitlabs.com
(317) 627-9663

Acting VISN Director Comments

Department of Veterans Affairs

Memorandum

Date: July 10, 2015

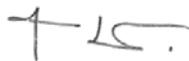
From: Acting Director, VISN 12 (10N12)

Subj: Healthcare Inspection—Unexpected Death of a Patient During Treatment with Multiple Medications, Tomah VA Medical Center, Tomah, WI

To: Director, Kansas City Office of Healthcare Inspections (54KC)
Director, Management Review Service (VHA 10AR MRS OIG Hotline)

1. I appreciate the OIG's in-depth investigation into the unexpected and tragic death of this young Veteran. VISN 12 took immediate and ongoing actions to address the recommendations identified in this report.
2. I concur with all the recommendations in the final draft report and will use them to improve the focus of our actions moving forward.
3. Attached are our specific responses to address the 4 recommendations contained in the report.

(signed memorandum attached.)



James Rice
Acting VISN 12 Network Director

Acting Facility Director Comments

**Department of
Veterans Affairs**

Memorandum

Date: July 10, 2015
From: Acting Director, Tomah VA Medical Center (676/00)
Subj: Healthcare Inspection—Unexpected Death of a Patient During Treatment with Multiple Medications, Tomah VA Medical Center, Tomah, WI
To: Director, VISN 12

1. Thank you for the opportunity to view the draft report of the Tomah Veterans Affairs Medical Center inspection. I have reviewed the document and concur with the recommendations.
2. Corrective action plans have been established with planned completion dates, as detailed in the attached report. If additional information is needed please contact my office at (608) 372-1777.



John J. Rohrer
Acting Medical Center Director

Comments to OIG's Report

The following Director's comments are submitted in response to the recommendations in the OIG report:

OIG Recommendations

Recommendation 1. We recommended that the Acting Veterans Integrated Service Network Director review the care of the patient who is the subject of this report and confer with the Office of Human Resources and the Office of General Counsel to determine the appropriate administrative action to take, if any.

Concur

Target date for completion: Pending completion of Administrative Action Proceedings

VISN 12 response:

We are deeply saddened by the tragic, unexpected, death of this Veteran. We are committed to learning from this event and making improvements in the care we provide.

Given that this was an unforeseen death, the facility initiated review of the death in advance of the autopsy findings. Upon receiving the autopsy results in October 2014, the facility determined that this patient's death was not due to natural causes and warranted further action. The death was immediately reported as a sentinel event to the Joint Commission in addition to initiating a Root Cause Analysis (RCA) and Peer Reviews. Facility Leadership reached out to the family and expressed sympathy for their son's death, shared the findings of the autopsy, and disclosed known clinical facts surrounding the Veteran's death.

Dialogue has been ongoing between the VISN, the facility, Human Resources, and General Counsel for several months regarding this case. The facility has initiated actions against both providers based on information that was developed prior to the release of this report. The information contained in this report may be used the support additional actions. As of July 10, 2015, Physician 1 no longer works for the Department of Veterans Affairs due to termination. Administrative proceedings for Physician 2 are in process. We are committed to ensuring due process and individual accountability.

Recommendation 2. We recommended that the Acting Facility Director ensure compliance with VHA Handbook 1004.01, *Informed Consent for Clinical Treatments and Procedures* as it relates to medication administration.

Concur

Target date for completion: October 2015

Facility response:

We respect and honor our patients' rights to make informed decisions about their health care. Ethical care dictates that patients are given the opportunity to consent to their care. Tomah VAMC's processes for obtaining and documenting informed consent as they relate to medication administration requires improvement.

The Acting Chief of Staff will send a memorandum to all prescribers regarding the requirements of VHA Handbook 1004.01 – *Informed Consent for Clinical Treatments and Procedures*. Under direction of the Acting Chief of Staff, all appropriate providers will be required to take relevant VHA training on informed consent, such as TMS modules or other modalities. These actions will reinforce requirements for using iMedConsent prior to initiating hazardous drugs, such as buprenorphine.

All (100%) of the patients currently on buprenorphine will be reviewed to ensure that consent has been obtained as required by VHA Directive. In addition, an ongoing monitor will be implemented and reported through the facility Pharmacy and Therapeutics Committee to review compliance with consent and identify any further opportunities for improvements.

Recommendation 3. We recommended that the Acting Facility Director review all elements needed to respond effectively to medical emergencies including staff training, equipment, and other resources at both the unit and the facility level and take any appropriate actions.

Concur

Target date for completion: November 30, 2015

Facility response:

The Tomah VAMC has taken several actions to address response to medical emergencies within the medical center. These include:

- Implemented unannounced mock codes during evening and night shifts when minimal emergency service back-up is available.
- Retrained all nursing staff who had not performed sufficiently in the emergency code response.
- Re-certified a pool of available Basic Life Support (BLS) instructors for the facility.
- Provided education at the recent annual Nursing Skills Fair (July 2015) on use of defibrillator and pads, crash cart set up, and BLS concepts. This education will be added to all future annual Nursing Skills Fairs.
- Added Flumazenil (a reversal agent) to the Fire Department medication bag in March 2015.

The Emergency Services Committee (ESC) will continue to work with key stakeholders from medical and nursing leadership to review medical emergency response at the Tomah VAMC and put processes in place to ensure all elements needed to respond effectively are present. Actions will include:

- Expanding the current mock code team to function as an interdisciplinary mock code team and conducting unannounced mock codes on all tours of duty, rotating to all patient care areas.
- Ensuring post-medical emergency debriefings with involved staff are held to determine what went well and identify concerns and areas for improvement.
- Debriefing review will assess whether adequate equipment is present for medical emergencies.
- Working with medical and nursing staff to implement the “First Five Minutes” competency program for clinical staff.
- Monitoring BLS and ACLS credentials on a monthly basis.

Monitoring mock code data to ensure at least 90 percent of mock codes have initiation of CPR within two minutes of the mock code being called. In addition, the ESC will review mock code debriefing sessions and monitor recommendations to closure.

Recommendation 4. We recommended that the Acting Facility Director review and evaluate medications currently available on emergency crash carts, including but not limited to, reversal agents for narcotic and/or benzodiazepine toxicity and make changes as appropriate.

Concur

Target date for completion: March 31, 2015

Facility response:

Through review of medical emergency responses, we identified that a need existed for flumazenil to be available for all medical emergencies. The Emergency Services Committee determined that the most appropriate process was to add Flumazenil to the medication bag brought to every medical emergency by the Fire Department.

On March 16, 2015, Flumazenil was added to the medication bag as well as to select medication distribution units throughout the facility. The reversal agent for narcotic toxicity, (i.e., Naloxone) is and continues to be present on the emergency crash carts. Medications available on emergency crash carts are reviewed in accordance with facility policy by the Emergency Services Committee.

Based on the submitted response we request closure of this recommendation.

OIG Contact and Staff Acknowledgments

Contact	For more information about this report, please contact the OIG at (202) 461-4720.
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Contributors	Alan Mallinger, MD Sheila Cooley, GNP, MSN Stephanie Hensel, RN, JD Terri Julian, PhD George Wesley, MD
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