JB&JS OPEN ACCESS

Found Down Extremity Compartment Syndrome Secondary to Substance Use

An Observational Multicenter Study

Richard D.J. Smith, MD, DPhil, Sharri J. Mortensen, MD, Dafang Zhang, MD, Malcolm R. Smith, MD, Michael J. Weaver, MD, and Arvind G. von Keudell, MD

Investigation performed at Massachusetts General Hospital and Brigham and Women's Hospital, Boston, Massachusetts

Background: With the worsening opioid epidemic in America, more patients are developing found down extremity compartment syndrome (FDECS). The purpose of this study was to describe this patient population, including their presenting symptoms, laboratory test results, and clinical outcomes.

Methods: We performed a 2-center retrospective review of adult patients who developed FDECS secondary to substance use from January 2006 to December 2019. Patients were managed operatively or nonoperatively at the surgeon's discretion. Data on patient demographic characteristics, laboratory values, hospital course, and clinical outcomes were collected from electronic medical records.

Results: In this study, 91 patients were included: 85 patients were managed operatively, and 6 patients were managed nonoperatively. Most patients were male, and the mean patient age (and standard deviation) was 37 ± 11 years. Opioids were the most common substance used. Patients managed operatively underwent a mean of 4 ± 3 surgical procedures, 44% received a skin graft, 25% developed a wound infection, and 11% underwent limb amputation. Patients managed nonoperatively did not undergo a subsequent fasciotomy or amputation. At a mean follow-up of 2.3 years, persistent weakness (66%), pain (78%), persistent sensory deficits (53%), and contractures (18%) were common.

Conclusions: Patients who develop FDECS secondary to substance use have high surgical complication rates and poor clinical outcomes. We found high rates of wound infection, revision surgical procedures, and amputation, often leaving young adults with lifelong disability.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Acute extremity compartment syndrome (AECS) is an orthopaedic emergency. Increasing pressure within a compartment impedes blood flow and subsequently damages tissues. Although AECS is commonly associated with high-energy trauma, non-traumatic causes also exist, such as found down extremity compartment syndrome (FDECS) secondary to substance use[1]. Patients often develop substance-related FDECS by intoxication leading to prolonged immobilization in a position that reduces blood flow to a particular muscular compartment. The ensuing compartment syndrome or rhabdomyolysis can irreversibly damage tissues and threaten the limb and life. Unfortunately, as the opioid epidemic has spread across America[2], FDECS secondary to substance use has become a problem more frequently encountered by orthopaedic surgeons[3].

AECS is often a clinical diagnosis that is made on the basis of symptoms and serial physical examinations[4]. However, it can be challenging to make the diagnosis in patients who develop FDECS secondary to substance use because many are obtunded at the time of presentation[3]. Objective data such as creatine kinase[5] and intracompartmental pressure can be used as adjuncts to help to inform clinical decisions.

An expeditious surgical fasciotomy is the preferred management option for patients with AECS. Increased time to surgical intervention has been associated with increased rates of tissue necrosis[6], amputation[7], and death[8]. However, most prior studies have focused on traumatic AECS or have had a smaller patient population at a single institution[3]. It is unclear if the conclusions would be the same for larger populations with non-traumatic etiologies of AECS. We hypothesized that patients diagnosed with FDECS have poor clinical outcomes.

Therefore, the primary aim of this study was to comprehensively describe the patient population who

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A321).

JBJS Open Access • 2021:e21.00038. openaccess.jbjs.org 2

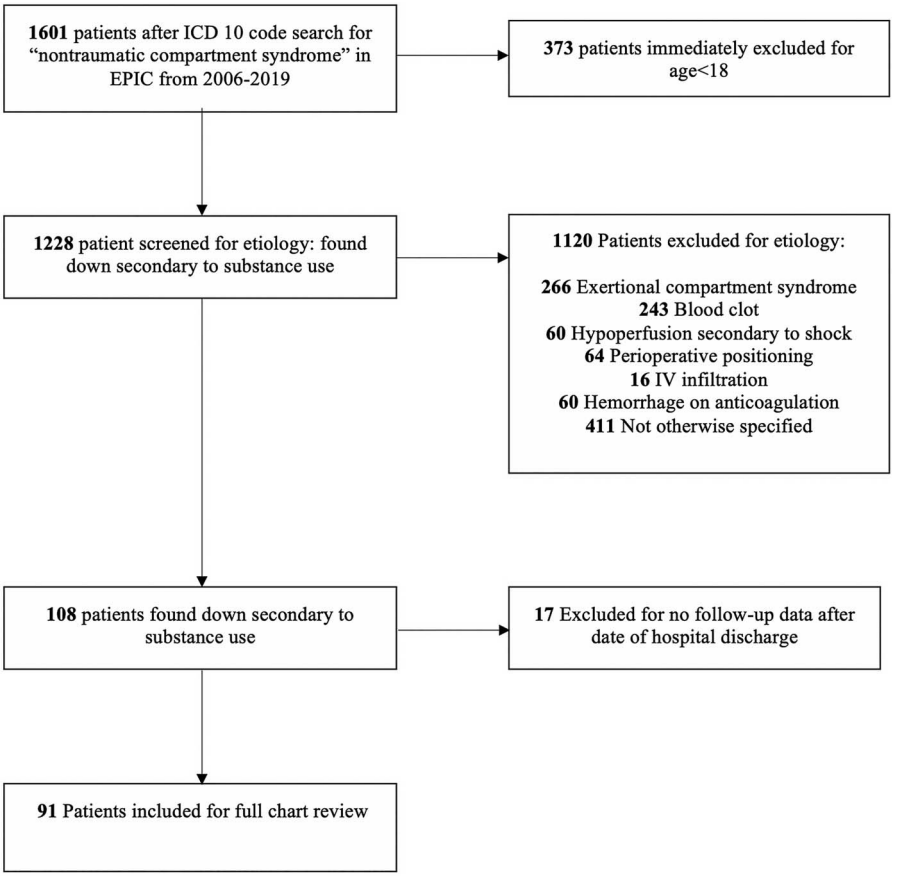

Fig. 1

Flow diagram of patient selection. EPIC = electronic medical records system, and IV = intravenous.

developed substance-related FDECS and report their presenting symptoms, laboratory test results, and clinical outcomes.

Materials and Methods

This was an institutional review board-approved retrospective review of the electronic medical records of patients who developed FDECS secondary to substance use at 2 level-II trauma centers. The Research Patient Data Registry (RPDR) system was queried using the International Classification of Diseases (ICD) codes for "non-traumatic compartment syndrome" of the upper and lower extremities from January 2006 to December 2019.

Only patients who developed FDECS after being in a position for a prolonged period of time (found down) secondary to substance use were included in this study (Fig. 1). Patients were excluded if they were younger than 18 years of age, the etiology was not secondary to substance use, or the patient did not have any documented clinical follow-up after being discharged from the hospital.

Outcome measures assessed by retrospective chart review included limb amputation, persistent pain, persistent weakness, persistent sensory deficits, and contracture at the final follow-up. The laboratory test results at presentation to the hospitals were also extracted.

Source of Funding

No external funding was received for this investigation.

Results

Demographic Characteristics

This study identified 91 patients who developed FDECS secondary to substance use (Table I). There were 85 patients treated with fasciotomy and 6 patients treated nonoperatively. The mean age was 37 years, and there were 67 male patients (74%) in this cohort. Substance use disorder was present in 76 patients (84%). Alcohol use disorder, major depressive disorder, generalized anxiety disorder, and hepatitis C were the other most common comorbidities (Table I).

Substances of Intoxication and Site of Compartment Syndrome

On average, there were 2 different substances used per patient. The most common substance used was opioids, in 59 patients (65%). Other commonly used substances included benzodiazepines, cocaine, cannabinoids, and alcohol (Table II).

There were 142 anatomic sites of FDECS in the 91 included patients. The forearm was the most commonly affected compartment in the operative group, in 38 patients (27%), followed by the leg in 33 patients (23%), the hand in 24 patients (17%), the

JBJS Open Access • 2021:e21.00038. openaccess.jbjs.org

TABLE I Demographic Characteristics of Patients with FDECS (N = 91)

Age* *(yr)*	37 ± 11
Sex†	
Male	67 (74%)
Female	24 (26%)
Medical history†	
Substance use disorder	76 (84%)
Alcohol use disorder	23 (25%)
Major depressive disorder	27 (30%)
Generalized anxiety disorder	20 (22%)
Bipolar disorder	15 (16%)
Hepatitis C	34 (37%)
Smoking	18 (20%)
Hypertension	18 (20%)
Homeless	8 (9%)
Posttraumatic stress disorder	8 (9%)
Chronic pain syndrome	7 (8%)
Asthma	5 (5%)
Hyperlipidemia	5 (5%)
Diabetes	5 (5%)
Obesity	3 (4%)
Hypothyroidism	3 (4%)
Other psychiatric disorders	9 (10%)
Other somatic comorbidities	26 (29%)

*The values are given as the mean and the standard deviation.
†The values are given as the number of patients, with the percentage in parentheses.

gluteal region in 19 patients (13%), the thigh in 19 patients (13%), and the arm in 9 patients (6%) (Table II).

Clinical Findings

The most common clinical finding at the time of presentation was a swollen or tense muscle compartment, which was found in 75 patients (82%). Pain was present in 72 patients (79%), muscle weakness was found in 55 patients (60%), decreased sensation was found in 50 patients (55%), skin discoloration was seen in 26 patients (29%), skin blisters were present in 18 patients (20%), paresthesias were found in 15 patients (16%), a pale and cold extremity was observed in 14 patients (15%), a decreased pulse was found in 8 patients (9%), and the pulse was absent in 8 patients (9%) (Table II). Decreased pulses and absent pulses were only seen in patients who were treated operatively. Intracompartmental pressure was measured in 42 patients (46%), yielding a mean of 48 ± 26 mm Hg. The vital signs at presentation are outlined in Table II.

Laboratory Test Results

On average, the white blood-cell count (WBC), C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) were increased. Other abnormal mean results included elevated spot glucose (141 ± 68 mg/dL), blood urea nitrogen (BUN) (26 ± 19 mg/dL), creatinine (2.2 ± 1.8 mg/dL), creatine kinase (50,604 ± 49,289 U/L), peak creatine kinase (75,940 ± 156,203 U/L), creatine kinase-myocardial band (CK-MB) (448 ± 510 ng/mL), troponin (3.4 ± 19 ng/mL), amylase (367 ± 977 U/

TABLE II Substances of Intoxication, Site of Compartment Syndrome, and Presenting Symptoms of Patients with FDECS (N = 91)

Substances used*	2 ± 1
Opioids†	59 (65%)
Benzodiazepines†	35 (38%)
Cocaine†	28 (31%)
Cannabinoids†	21 (23%)
Alcohol†	19 (21%)
Amphetamine†	10 (11%)
Antidepressant†	3 (3%)
Antipsychotic†	1 (1%)
Hallucinogen†	1 (1%)
Body site of FDECS* (n = 142)	1.6 ± 0.6
Forearm†	38 (27%)
Leg†	33 (23%)
Hand†	24 (17%)
Gluteal†	19 (13%)
Thigh†	19 (13%)
Arm†	9 (6%)
Clinical symptoms†	
Swollen or tense muscle compartment	75 (82%)
Pain	72 (79%)
Muscle weakness	55 (60%)
Decreased sensation	50 (55%)
Skin discoloration	26 (29%)
Skin blisters	18 (20%)
Paresthesia	15 (16%)
Pale and cold extremity	14 (15%)
Decreased pulse	8 (9%)
Absent pulse	8 (9%)
Compartment pressures	
Patients measured†	42 (46%)
Reading* *(mm Hg)*	48 ± 26
Vital signs at presentation*	
Body temperature *(°C)*	37.1 ± 0.8
Heart rate *(beats/min)*	96 ± 18
Blood pressure *(mm Hg)*	130/75 ± 20/14
Respiratory rate *(breaths/min)*	19 ± 6.5
Oxygen saturation	97% ± 2.5%

*The values are given as the mean and the standard deviation.
†The values are given as the number of patients, with the percentage in parentheses.

TABLE III Laboratory Test Results*

Blood Test Results	
WBC† *(×10⁹/L)*	17 ± 8
CRP† *(mg/L)*	135 ± 115
ESR† *(mm/hr)*	34 ± 36
Hemoglobin *(g/dL)*	14 ± 2.5
Hematocrit *(%)*	41.5 ± 7
Platelets *(×10⁹/L)*	231 ± 89
Sodium *(mmol/L)*	136 ± 5.5
Potassium *(mmol/L)*	4.8 ± 1.4
Chloride *(mmol/L)*	99 ± 7
Glucose† *(mg/dL)*	141 ± 68
Bicarbonate *(mmol/L)*	22 ± 5
BUN† *(mg/dL)*	26 ± 19
Creatinine† *(mg/dL)*	2.2 ± 1.8
Creatine kinase† *(U/L)*	50,604 ± 49,289
Peak creatine kinase† *(U/L)*	75,940 ± 156,203
CK-MB† *(ng/mL)*	448 ± 510
Troponin† *(ng/mL)*	3.4 ± 19
Amylase† *(U/L)*	367 ± 977
Total bilirubin *(mg/dL)*	0.6 ± 0.5
ALT† *(IU/L)*	465 ± 1,070
AST† *(IU/L)*	874 ± 1,930
Prothrombin time† *(sec)*	15 ± 4
Partial thromboplastin time *(sec)*	34 ± 21
Lactate† *(mmol/L)*	2.9 ± 2.2
Anion gap† *(mEq/L)*	15 ± 6
pH‡	7.29 ± 0.15
Urinalysis	
pH	5.8 ± 0.7
Protein *(mg/dL)*	2.7 ± 6
Glucose *(mg/dL)*	2.5 ± 18.6
Leukocytes *(wbc/hpf)*	0.3 ± 0.6
Red blood cells† *(rbc/hpf)*	13.4 ± 33

*The values are given as the mean and the standard deviation. †This was an abnormal test result that was higher than the standard normal range. ‡This was an abnormal test result that was lower than the standard normal range.

L), aspartate aminotransferase (AST) (874 ± 1,930 IU/L), alanine transaminase (ALT) (465 ± 1,070 IU/L), prothrombin time (15 ± 4 seconds), partial thromboplastin time (34 ± 21 seconds), lactate (2.9 ± 2.2 mmol/L), anion gap (15 ± 6 mEq/L), and urine red blood cells (13.4 ± 33 red blood cells/high power field [rbc/hpf]). The blood pH was acidic at 7.29 ± 0.15 (Table III).

Course of Hospital Stay

Rhabdomyolysis and acute kidney injury were seen in 59 patients (65%), and hemodialysis was required for 26 patients (29%). Patients treated operatively underwent a mean of 4 surgical procedures during their hospitalization; of these patients, 37 (44%) required a skin graft and 21 (25%) developed a wound infection during their hospitalization (Table IV). The mean length of stay was 20 ± 13 days.

Outcomes

The mean length of clinical follow-up was 2.3 ± 3.2 years. Persistent weakness was seen in 60 patients (66%), persistent sensory deficit was seen in 48 patients (53%), persistent pain was seen in 71 patients (78%), contractures were present in 16 patients (18%), and 9 patients (10%) underwent an eventual limb amputation (Table IV). None of the patients treated nonoperatively required a subsequent operation. None of the patients in the study died.

Discussion

FDECS secondary to substance use is an increasingly common problem. The majority of the patients in this study were young men, which is consistent with the demographic characteristics of patients with traumatic AECS[9] and those with substance use disorder[10]. McQueen et al.[9] suggested that young men are more susceptible to AECS because they have a large volume of skeletal muscle relative to a fixed compartment size. Many patients had mental health disorders, which are also common among patients who have substance use disorder[11,12]. Hepatitis C, which is prevalent among patients who use injection drugs[13], was the most common infectious disease seen in the study patient population.

The most common substance of intoxication in both study groups was opioids, consistent with the ongoing opioid epidemic[3]. The influx of illicitly manufactured fentanyl into America has been associated with increased rates of overdose and death[14]. Fentanyl can be 100 times stronger than morphine

TABLE IV Hospital Course and Clinical Outcomes of Patients with FDECS (N = 91)

Initial operative treatment*	85 (93%)
Hospital course	
Rhabdomyolysis*	59 (65%)
Acute kidney injury*	59 (65%)
Hemodialysis*	26 (29%)
Surgical procedures†	4 ± 3
Skin graft*	37 (41%)
Wound infection*	21 (23%)
Outcomes	
Length of follow-up† *(yr)*	2.3 ± 3.2
Persistent weakness*	60 (66%)
Persistent sensory deficit*	48 (53%)
Persistent pain*	71 (78%)
Contracture*	16 (18%)
Amputation*	9 (10%)

*The values are given as the number of patients, with the percentage in parentheses. †The values are given as the mean and the standard deviation.

and is often mixed with other opioids[14]. Users are often unaware of the increased strength, putting them at higher risk for overdose, prolonged immobilization, and subsequent FDECS.

The mean number of substances of intoxication per patient was 2 in both operatively and nonoperatively treated patients in the present study. When used in combination, opioids, benzodiazepines, and alcohol can also increase sedation and decrease respiratory drive[15]. The use of multiple substances also increases the risk of overdosing[16], which can also lead to prolonged immobilization and subsequent FDECS. Furthermore, opioids, benzodiazepines, and cannabinoids lower blood pressure[17-19], and opioids, benzodiazepines, and alcohol decrease respiratory drive[15]. A lower diastolic blood pressure means that even a small increase in intracompartmental pressure could compromise blood supply to a myofascial compartment. Similarly, a diminished respiratory drive can lower oxygen blood saturation and thus decrease oxygen delivery to bodily tissues. A lower blood pressure combined with reduced oxygen saturation may put patients at increased risk for FDECS.

Pain, muscle weakness, and decreased sensation were the most common presenting clinical symptoms. Some patients in this study presented with observable skin changes, including discoloration and blistering. Signs of skin damage may suggest prolonged immobilization and should prompt clinicians to consider FDECS in obtunded patients. Pallor of the extremity, diminished arterial pulsation, and pulselessness were infrequent and late signs of FDECS and should not be relied upon for initial diagnosis.

The laboratory test results of these patients at presentation indicated an increased inflammatory response with elevated inflammatory markers such as WBC, CRP, and ESR. BUN and creatinine were also elevated, indicating renal impairment. Creatine kinase and peak creatine kinase were elevated because of muscle damage. CK-MB was elevated, which usually suggests myocardial injury; however, due to the small quantity of CK-MB in the skeletal muscle, an increased CK-MB level may be present when substantial muscle damage occurs[20]. Likewise, serum troponin I has been found to be increased not only when myocardial damage is present but also when patients have rhabdomyolysis[21]. We also found elevated levels of amylase, AST, and ALT, which may be explained by the substances that were abused. Furthermore, AST and ALT can be elevated because of muscle release of these enzymes in conditions such as rhabdomyolysis[22]. Ongoing tissue necrosis was supported by our findings of elevated levels of serum lactate and the presence of metabolic acidosis, with low blood pH and a high anion gap.

Compartments of the distal upper and lower extremities were most commonly affected. The possible explanations for this include anatomically smaller compartments and the fact that distal extremities may be more easily trapped under the body when patients become intoxicated. Approximately half of the patients in this study developed FDECS in multiple compartments, illustrating the need to evaluate all extremity compartments during the initial evaluation of this patient population.

Patients in this study experienced a challenging hospital course that often included rhabdomyolysis, acute kidney injury, and hemodialysis. Over 90% of patients treated with fasciotomy underwent >1 surgical procedure during their initial hospitalization. In the operative treatment group, 40% of patients required a skin graft, almost one-quarter developed wound infections, and 1 in 10 underwent a limb amputation. No surgical procedures occurred in the 6 patients who were treated nonoperatively. The cumulative risks associated with multiple surgical procedures, which may include the need for skin grafts, development of perioperative infections, and need for amputations, should be weighed against the potential benefits to these patients. Bhattacharyya and Vrahas[23] investigated the medicolegal aspects of compartment syndrome and found that documentation of abnormal neurological findings but no action was associated with higher rates of successful malpractice claims against the surgeon. As many patients with FDECS present with neurological deficits, the idea of managing the patient nonoperatively may be uncomfortable for many orthopaedic surgeons. In a recent study, Parzych et al. suggested a role for nonoperative treatment of patients with FDECS who present with absent limb function[3]. However, that study only included 30 patients, with 5 patients treated nonoperatively, and thus was not sufficiently powered to draw reliable conclusions. Furthermore, they reported that laboratory values at the time of presentation did not correlate with the extent of muscle necrosis, but they only reported on creatine kinase, lactate, and creatinine. Our study differs with regard to a higher number of patients included and a more comprehensive description of this patient group.

This study was based on documentation in patients' electronic medical records, and it is possible that data were inconsistently reported. The study also excluded patients without documented clinical follow-up after discharge, and this group of patients may have had more barriers to accessing care or may have died. This study was performed over a long period of time and included the practice of many different surgeons, so limitations with regard to variation in surgeon practice should be considered. Despite these limitations, this study possesses several strengths. To our knowledge, this is the largest study analyzing patients who developed FDECS secondary to substance use. Furthermore, it is the first study with a comprehensive presentation of this patient group including their comorbidities and laboratory test results.

In conclusion, FDECS secondary to substance use is an increasingly common problem that can cause extensive morbidity in young adults. Many patients present to the hospital in an obtunded state after being found down for an unknown period of time. Clinical signs such as pain, motor and sensory deficits, and skin changes should prompt the consideration of FDECS. All extremity compartments should be examined because multiple compartments can be affected, particularly in the distal extremities. A small proportion of these patients are managed nonoperatively, but the precise criteria for the

utilization of nonoperative management remain unclear. Clinical outcomes such as persistent weakness, pain, reduced sensation, contractures, and rates of amputation were high in this patient population. Further research is warranted to better understand and improve treatments for this devastating orthopaedic condition. ■

Richard D.J. Smith, MD, DPhil[1,2]
Sharri J. Mortensen, MD[3,4]
Dafang Zhang, MD[2,5]
Malcolm R. Smith, MD[6]
Michael J. Weaver, MD[2,5]
Arvind G. von Keudell, MD[2,5]

[1]Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[2]Harvard Orthopaedic Trauma Initiative, Harvard Medical School, Boston, Massachusetts

[3]Harvard Medical School, Boston, Massachusetts

[4]Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, Boston, Massachusetts

[5]Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

[6]Department of Orthopaedic Surgery, UMass Memorial Medical Center, Worcester, Massachusetts

Email for corresponding author: rsmith21@partners.org

References

1. von Keudell AG, Weaver MJ, Appleton PT, Bae DS, Dyer GSM, Heng M, Jupiter JB, Vrahas MS. Diagnosis and treatment of acute extremity compartment syndrome. Lancet. 2015 Sep 26;386(10000):1299-310.

2. Seymour RB, Ring D, Higgins T, Hsu JR. Leading the way to solutions to the opioid epidemic: AOA Critical Issues. J Bone Joint Surg Am. 2017 Nov 1;99(21):e113.

3. Parzych L, Jo J, Diwan A, Swart E. "Found down" compartment syndrome: experience from the front lines of the opioid epidemic. J Bone Joint Surg Am. 2019 Sep 4; 101(17):1569-74.

4. Mortensen SJ, Vora MM, Mohamadi A, Wright CL, Hanna P, Lechtig A, Egan J, Williamson PM, Wixted JJ, Rutkove SB, Nazarian A. Diagnostic modalities for acute compartment syndrome of the extremities: a systematic review. JAMA Surg. 2019 Jul 1;154(7):655-65.

5. Valdez C, Schroeder E, Amdur R, Pascual J, Sarani B. Serum creatine kinase levels are associated with extremity compartment syndrome. J Trauma Acute Care Surg. 2013 Feb;74(2):441-5, discussion 445-7.

6. Sheridan GW, Matsen FA 3rd. Fasciotomy in the treatment of the acute compartment syndrome. J Bone Joint Surg Am. 1976 Jan;58(1):112-5.

7. Finkelstein JA, Hunter GA, Hu RW. Lower limb compartment syndrome: course after delayed fasciotomy. J Trauma. 1996 Mar;40(3):342-4.

8. Ritenour AE, Dorlac WC, Fang R, Woods T, Jenkins DH, Flaherty SF, Wade CE, Holcomb JB. Complications after fasciotomy revision and delayed compartment release in combat patients. J Trauma. 2008 Feb;64(2)(Suppl):S153-61, discussion S161-2.

9. McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome. Who is at risk? J Bone Joint Surg Br. 2000 Mar;82(2):200-3.

10. Steingrímsson S, Carlsen HK, Sigfússon S, Magnússon A. The changing gender gap in substance use disorder: a total population-based study of psychiatric in-patients. Addiction. 2012 Nov;107(11):1957-62.

11. Compton WM, Conway KP, Stinson FS, Grant BF. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991-1992 and 2001-2002. Am J Psychiatry. 2006 Dec;163(12):2141-7.

12. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. Sci Pract Perspect. 2005 Dec;3(1):13-21.

13. Bruneau J, Roy E, Arruda N, Zang G, Jutras-Aswad D. The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users. Addiction. 2012 Jul;107(7):1318-27.

14. Somerville NJ, O'Donnell J, Gladden RM, Zibbell JE, Green TC, Younkin M, Ruiz S, Babakhanlou-Chase H, Chan M, Callis BP, Kuramoto-Crawford J, Nields HM, Walley AY. Characteristics of fentanyl overdose — Massachusetts, 2014–2016. MMWR Morb Mortal Wkly Rep. 2017 Apr 14;66(14):382-6.

15. Lindsey WT, Stewart D, Childress D. Drug interactions between common illicit drugs and prescription therapies. Am J Drug Alcohol Abuse. 2012 Jul;38(4):334-43.

16. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999 Jul; 94(7):961-72.

17. Lang RE, Brückner UB, Kempf B, Rascher W, Sturm V, Unger T, Speck G, Ganten D. Opioid peptides and blood pressure regulation. Clin Exp Hypertens A. 1982;4(1-2):249-69.

18. Robson P. Therapeutic aspects of cannabis and cannabinoids. Br J Psychiatry. 2001 Feb;178:107-15.

19. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abu-AjAj M, Wolak A, Shalev H, Wolak T. Benzodiazepine consumption is associated with lower blood pressure in ambulatory blood pressure monitoring (ABPM): retrospective analysis of 4938 ABPMs. Am J Hypertens. 2018 Mar 10;31(4):431-7.

20. Wu AHB, Wang XM, Gornet TG, Ordóñez-Llanos J. Creatine kinase MB isoforms in patients with skeletal muscle injury: ramifications for early detection of acute myocardial infarction. Clin Chem. 1992 Dec;38(12):2396-400.

21. Punukollu G, Gowda RM, Khan IA, Mehta NJ, Navarro V, Vasavada BC, Sacchi TJ. Elevated serum cardiac troponin I in rhabdomyolysis. Int J Cardiol. 2004 Jul;96(1):35-40.

22. Lim AKH. Abnormal liver function tests associated with severe rhabdomyolysis. World J Gastroenterol. 2020 Mar 14;26(10):1020-8.

23. Bhattacharyya T, Vrahas MS. The medical-legal aspects of compartment syndrome. J Bone Joint Surg Am. 2004 Apr;86(4):864-8.