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Dietary Supplement-Drug Interaction-Induced Serotonin Syndrome Progressing to Acute Compartment Syndrome

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Study Design A
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Data Interpretation D
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Patient: Male, 28
Final Diagnosis: Serotonin syndrome/acute compartment syndrome
Symptoms: Muscle pain
Medication: Sertraline
Clinical Procedure: Fasciotomy
Specialty: Critical Care Medicine

Objective: Rare co-existence of disease or pathology





Background: Dietary supplements have been associated with an increase in emergency intervention as a result of unexpected adverse events. Limited resources and information on significant drug-drug interactions with dietary supplements and prescription medications have contributed to associated complications and unexpected events. We present the case of a patient who consumed multiple prescription medications and dietary supplements which resulted in significant complications.

Case Report: A 28-year-old man presented to the Emergency Department complaining of severe calf pain after exercising. In addition to his prescription medications, which included sertraline, he also consumed dietary supplements prior to his workout. He developed serotonin syndrome with rhabdomyolysis, which rapidly progressed to acute compartment syndrome. An emergency bilateral four-compartment double-incision lower extremity and forearm fasciotomy was performed, with complete recovery.

Conclusions: Drug-drug interactions involving dietary supplements are frequently overlooked in most healthcare settings, especially in the Emergency Department. Health care providers should be cognizant of the potential drug-drug interactions resulting in serotonin syndrome to prevent the progression to acute compartment syndrome and associated complications. Pharmacists play a key role in recognizing drug-dietary supplement interactions and adverse effects.

MeSH Keywords: Abnormalities, Drug-Induced • Compartment Syndromes • Dietary Supplements • Herb-Drug Interactions • Rhabdomyolysis • Serotonin Syndrome

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Background

Serotonin syndrome is a known adverse effect of antidepressants, particularly, selective serotonin reuptake inhibitors (SSRI) when used alone or with other serotonergic agents [1]. The ability to diagnose serotonin syndrome is challenging due to its inconsistent nature, in which the signs and symptoms present depending on the severity, and due to the unavailability of specific confirmatory laboratory tests. Clinically, serotonin syndrome can lead to mental-status, autonomic, and neuromuscular abnormalities, such as hyperreflexia, and myoclonus. To our knowledge this is the first reported case of rhabdomyolysis related to serotonin syndrome caused by a drug interaction between an SSRI and a dietary supplement that led to acute compartment syndrome.

In the United States, 23 000 visits to the Emergency Department (ED) are estimated to occur annually due to the use of dietary supplements [2]. There is no single test that can confirm a serotonin syndrome diagnosis. A number of conditions can cause or mimic symptoms similar to serotonin syndrome; therefore, the importance of the patient's medical history, including pharmacotherapy and physical examination, are major components to guide the clinician in affirming the diagnosis of serotonin syndrome. The importance of soliciting information on the use of all prescription drugs, non-prescription drugs, illicit substances, and dietary supplements for the purposes of ruling out any potential drug interactions should be stressed and conveyed to patients at initial admission encounters by clinicians. As the dietary supplement market, both within the United States and globally, continues to expand, recognizing drug-dietary supplement interactions is vital to preventing morbidity and mortality due to adverse reactions.

Case Report

A 28-year-old man presented to the Emergency Department with spontaneous, extreme, sudden, and sharp anterolateral bilateral leg cramping with stiffness and calf pain of 10 out of 10 affecting his ambulation following vigorous jogging for 5 minutes at a high speed on an inclined treadmill. The decision to jog again after a 4-month hiatus from exercising was part of his self-identified plan to implement a healthier lifestyle, which also included lifting weights and the using dietary supplements. He did not report any recent falls or trauma related to the pain. He self-treated the pain with warm compresses, a sitz bath, and over-the-counter (OTC) pain relievers (i.e., ibuprofen and naproxen), with no relief prior to arriving to the ED.

His medical history was significant for bipolar disorder, post-traumatic stress disorder, alcohol abuse, arthroscopic surgeries for right and left shoulder dislocations, torn rotator cuffs, and

Table 1. Patient's home medications.

Sertraline 200 mg orally every morning
Divalproex ER 1000 mg orally twice daily
Bupropion XL 150 mg orally daily
Bupropion 100 mg orally every 12 hours
Prazosin 6 mg orally at bedtime
Hydroxyzine HCl 50 mg orally at bedtime
Sildenafil 100 mg orally as needed
Cyclobenzaprine orally*

* Dose and frequency unknown.

a right ankle surgery due to recurrent Achilles tendonitis. He denied recent illness and illicit drug use, including the use of cocaine or anabolic steroids, but his medical records stated a propensity for significant substance and alcohol abuse. Notably, he drank 2 to 3 beers daily, but he had abruptly stopped to pursue a healthier lifestyle. He reported being a former smoker during adolescence. A medication allergy to penicillin, which resulted in urticaria, was documented during a previous hospital admission. He self-reported non-adherence to long-term medications (Table 1), including sertraline 200 mg by mouth every morning that he self-titrated based on his mood.

On examination in the ED, he was afebrile with a blood pressure 149/54 mmHg, heart rate of 109 bpm, temperature 36.7°C, a normal sinus rhythm, with S1 and S2 heart sounds. No murmurs were identified. He had clear bilateral breath sounds with no wheezing or crackles upon auscultation of the lungs. He appeared moderately distressed with acute agitation. The musculoskeletal examination showed significant tenderness and pain in the proximal anterolateral calves with limited dorsiflexion bilaterally, and episodes of muscle spasms and clonus were observed while in the ED. The neurological examination did not show significant sensory or motor deficit; the lower extremities were intact. Dorsalis pedis and posterior tibial pulses were present without any loss of sensation or strength. Examination of the upper extremities was grossly unremarkable. Laboratory results were normal with the exception of an initial serial creatinine phosphokinase of 5038 units/L, BUN/Cr ratio (reference range 10: 1–20: 1) trending at less than 15: 1, and white blood cell count $20.3 \times 10^9/L$ (reference range $4.0\text{--}10.0 \times 10^9/L$) trending down (Table 2). Initial urinalysis was unremarkable for blood or myoglobin. The urine toxicology screen was positive for benzodiazepines and opioids; however, the source from which the patient obtained these drugs was unidentifiable. The x-rays of the lower extremities did not show any bilateral tibia or fibia fractures. The patient was admitted to the General Medicine Department.

Table 2. Laboratory values and blood chemistry during hospitalization.

Date	3/8	3/09	3/10	3/11	3/12	3/13	3/14	3/15	3/16	Normal range
Day	ER	2 nd	3 rd	4 th	*5 th	6 th	7 th	8 th	9 th	
CK (U/L)	5058	23752	15263	20880	25000	9297	8940	6941	5707	<150 U/L
AST (U/L)	–	–	466	576	535	390	282	239	228	0–35 U/L
ALT (U/L)	–	–	126	135	117	116	110	101	127	0–35 U/L
Lactate (mmol/L)	–	1.3	0.9	–	–	0.8	0.8	–	–	0.5–1 mmol/L
BUN (mg/dL)	14	12	8	6	5	5	7	9	8	8–20 mg/dL
Cr (mg/dL)	1.1	0.9	1	1	0.8	0.8	1	0.8	0.7	0.6–1.2 mg/dL
K (meq/L)	4.5	4.4	4.1	3.8	3.8	3.5	3.8	3.9	4.3	3.5–5 mEq/L
WBC (10 ⁹ /L)	20.8	–	15.3	21	19.7	21	18.74	19.12	18.15	4–11×10 ⁹ /L
Hb (g/dL)	16.1	–	5.5	7	7.5	10.2	10.1	10.1	10.1	14–18 g/dL
Platelet (×10 ⁹ /L)	263	–	132	168	194	235	317	358	450	150–450×10 ⁹ /L

Patient care-taker provided list of supplements (Table 3). CK – creatinine kinase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; BUN – blood urea nitrogen; Cr – serum creatinine; K – potassium; WBC – white blood cell; Hb – Hemoglobin. When CK levels start to rise again diagnosis of compartment syndrome is suspect.

After developing slight erythema and swelling bilaterally in the lower extremities, he was transferred to the Intensive Care Unit. He was started on early and aggressive fluid resuscitation, sodium bicarbonate, furosemide, and mannitol for extensive rhabdomyolysis. His pedis pulses diminished from +2/4 to +1/4. He developed pain on palpitation of the distal anterior aspect of right leg compared to left leg, with decreased sensation and inability to dorsiflex his feet. Despite receiving subcutaneous morphine, the pain in both calves continued to worsen. Due to worsening swelling and concern for vascular compromise, an emergency bilateral 4-compartment double-incision lower extremity fasciotomy was performed under general anesthesia. Following the procedure, the patient showed signs of hyperthermia, and experienced vigorous seizure-like activity. A second seizure-like episode with hypoxia required intubation and sedation with propofol. Within 24 hours, his right forearm became hard to the touch, swollen, tense with cyanosis, and was accompanied by right-hand numbness. An urgent forearm fasciotomy was performed. He continued to have rigid muscular movements and agitation.

After the procedure, the caretaker revealed that on the day of presentation to the ED, the patient had started taking “tons” of dietary supplements for weight loss and energy and had abruptly stopped drinking alcohol. Upon explaining the possible risks of drug-dietary supplement interactions, she bought in a list of dietary supplements (Table 3) that included 5-hydroxytryptophan (5-HTP). Lorazepam 1 mg intravenous push as needed for agitation was administered for the treatment of serotonin syndrome.

Table 3. Patient’s reported over-the-counter dietary supplements.

5-HTP (Natrol)	Ultimate Muscle
Burn 60	Pro-hormone X3
GAIN272	Lipro 6
Cycle armour	Craving Crush
Glutamine	Kre-alkalyn
T-boost	TestX180
Lean Muscle	Proiron
Malic Acid	AM/PM Burner
CLA	Jacked Muscle Extreme
CLA PM	Kyani Nitro FX
MASS	Quadra Lean
CLK	Get Ripped

The patient was discharged with a vascular and plastic surgery consultation for wound care. Sertraline was discontinued during the hospital course and reinitiated at a follow-up visit with a mental health care practitioner at a dose of 25 mg by mouth in every morning with a plan for titration.

Discussion

Serotonin syndrome is not always an obvious diagnosis and 85% of physicians fail to recognize the syndrome at the onset, leading to rapid progression and complications [1]. In this

case, the development of rhabdomyolysis-induced acute compartment syndrome (ACS) can be attributed to the presence of serotonin syndrome, which went unidentified in the patient at the time of presentation. The main challenge in identifying serotonin syndrome is the failure to recognize drug interactions caused by using dietary supplements. Limitations in obtaining necessary medication history, including the patient's reluctance to provide a complete drug and dietary supplement medication list, can delay appropriate treatment. A difficulty, in this case, was the patient's denial regarding the use of dietary supplements. After the fasciotomy, it was discovered that he was in possession of more than 21 different dietary supplement products, which enhanced fat burning, decreased appetite, and increased sexual function.

Acute compartment syndrome can be caused by rhabdomyolysis [3]. When ACS occurs secondary to rhabdomyolysis due to a delayed reaction to drug therapy, it is termed a "second wave phenomenon" because the symptoms of ACS are not obvious at initial presentation. Acute compartment syndrome is characterized by severe pain, swelling, and paresthesia due to increased pressure in the fascia, and can lead to the development of ischemia and necrosis [4,5]. The highest incidence of ACS occurs mostly in young men due to large muscle size and inadequate space for swelling after a muscle injury [6]. Early diagnosis, either by clinical presentation, as made in this patient, or by the measurement of intracompartmental pressure (ICP), is necessary to prevent long-term disability. An indication for a fasciotomy is an ICP differential (diastolic blood pressure – absolute compartment pressure) of less than 30 mmHg. Complications related to ACS are an infection, contracture, and amputation.

In severe cases of serotonin syndrome, laboratory abnormalities identified include rhabdomyolysis [1]. Sertraline has been reported to lead to the development of rhabdomyolysis in the literature [7,8]. There appear to have been no reported cases related to serotonin syndrome or rhabdomyolysis caused by a dietary supplement-drug interaction leading to the development of acute compartment syndrome. A case series discussed the use of sertraline and development of rhabdomyolysis, especially in the presence of overly strenuous exercise [8]. In this case, the development of severe leg pain 5 minutes into the vigorous exercise, as well as the use of 5-HTP and sertraline may have exacerbated the effect of the excessive serotonin, leading to severe rhabdomyolysis and culminating into ACS.

Natrol 5-HTP is a dietary supplement marketed to enhance mood and control appetite. It is available as a tablet formulation, which contains 100 mg of 5-HTP, with directions to take 1 tablet up to twice daily with a meal. While serotonin does not cross the blood-brain barrier, 5-HTP, a direct precursor of serotonin, does so freely [9]. Moreover, 5-HTP is not regulated by a

biochemical feedback mechanism, making it possible to achieve high levels of serotonin. The use of 5-HTP is contraindicated in depression due to an imbalance of dopamine and norepinephrine exacerbating the disease process. In addition, 5-HTP should not be used with antidepressants such as SSRIs and monoamine oxidase inhibitors (MAOIs) because of its known potential to cause serotonin syndrome. Co-administration of sertraline with serotonin precursors (e.g., 5-HTP) found in dietary supplements is not recommended [10].

Rhabdomyolysis is also a known adverse reaction associated with 5-HTP [11]. The patient's home medications included cyclobenzaprine; however, the dose and frequency were unknown (Table 1). Cyclobenzaprine is structurally similar to amitriptyline, a tricyclic antidepressant; it can interact with 5-HTP to potentially cause serotonin syndrome and it has been associated with a case of rhabdomyolysis in an overdose [12]. In this case, based on the Naranjo Scale, the development of rhabdomyolysis was probably related to the serotonin syndrome caused by a dietary supplement-drug interaction between sertraline and Natrol 5-HTP.

Initially, exercise-induced rhabdomyolysis was considered the most likely diagnosis given the relationship between the onset of symptoms and the exercise-related activities performed. However, upon discovering the reported use of dietary supplementation and non-adherence with prescribed medications, serotonin syndrome was determined to be the cause of the patient's global presentation. During the initial examination in the ED, muscle spasms and clonus were observed, as well as tachycardia, limited dorsiflexion, agitation, and moderate distress; the patient later developed neuromuscular rigidity, hyperthermia, and seizures, which are all consistent with the clinical presentation of serotonin syndrome. Rhabdomyolysis can occur due to non-pharmacological causes (e.g., crush injuries and exercise) or due to pharmacological agents (e.g., SSRI and cocaine). Other drug-induced etiologies, NMS, and malignant hyperthermia, which are related to the observed laboratory abnormality associated with an increase in creatine kinase, were considered. Neuroleptic malignant syndrome was ruled out due to the time of onset of symptoms, and no known recent additions or changes of neuroleptics to chronic medications. Malignant hyperthermia was also ruled out since the rhabdomyolysis was present prior to the fasciotomy and administration of general anesthesia. Clinical pharmacists played a key role in identifying and researching all of the dietary supplements taken by the patient to check for drug interactions; this contributed significantly in helping the clinicians understand the etiology of the serotonin syndrome that developed in this patient.

Serotonin syndrome can manifest similarly to NMS, anti-cholinergic toxidrome, and malignant hyperthermia [1]. The patient was also prescribed bupropion, a weak dopamine and

norepinephrine inhibitor, which can cause NMS. NMS and serotonin syndrome are treated distinctively and it is critical to assess the more likely causative syndrome. The ACS was treated appropriately with a bilateral lower-leg 4-compartment double-incision fasciotomy and a right forearm fasciotomy. The rhabdomyolysis was addressed by utilizing fluid hydration, alkalization of the urine, and forced diuresis. The serotonin syndrome was treated with a benzodiazepine as recommended in practice. Fortunately, the patient did not develop acute kidney injury during hospitalization.

One limitation to our case is that the degree of synergy between sertraline and 5-HTP that led to the development of serotonin syndrome could not be appreciated due to the reluctance of the patient to provide additional information. The patient did report self-adjusting his sertraline dose. It is uncertain if the dose of sertraline was increased beyond the recommended 200 mg maximum daily dose at the time of presentation. At discharge, the patient was restarted on sertraline 25 mg by mouth daily with a planned titration. Although limited information is available, a rechallenge with sertraline is not a contraindication if the contributing factors leading to the development of serotonin syndrome are discontinued [13].

Conclusions

Based on this case and the rising use and proliferative marketing of serotonergic agents, weight loss, and exercise dietary supplements, we suggest that health care providers should be more vigilant and aware of potential drug-dietary supplement

interactions. Prompt review and recognition of patients at risk of developing serotonin syndrome due to drug-dietary supplement interactions is essential to avoid morbidity and mortality. Severe complications of serotonin syndrome, including rhabdomyolysis-induced compartment syndrome, should be identified early and treated appropriately. Serial ICP measurements can help with diagnosing compartment syndrome early rather than waiting and relying solely on clinical presentation [14]. Pharmacists can play a critical role in educating clinicians regarding potentially harmful drug-dietary supplement interactions, as well as by working together on interdisciplinary teams to identify such interactions. Similarly, educating patients on the importance of consulting with their healthcare providers prior to changing medication doses or adding dietary supplements, as well as providing an updated list of their medication regimen, can help identify, rectify, and prevent drug interactions and adverse reactions.

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Conflicts of interest

None.

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