

Serotonin Syndrome Associated With High-dose Diphenhydramine Use Complicating Abdominoplasty and Mastopexy

Ashley E. Rosenberg, BS*
Richard Wang, BS*
Michael H. Rosenberg, MD†

Summary: Serotonin syndrome is a condition associated with increased serotonergic transmission in the central nervous system. Although shortfalls with diagnostic criteria have led to misleading associations with multiple medications, a possible precipitant is diphenhydramine. Documentation of such an association would prove important for physician practice, as diphenhydramine remains one of the most popular antihistamines available. We present a case of a 43-year-old woman who developed serotonin syndrome after bilateral mastopexy, miniabdominoplasty, and liposuction. The patient was on multiple serotonergic medications, including duloxetine, asenapine, and trazodone, in addition to high-dose diphenhydramine. Postoperatively, she developed tachycardia, leukocytosis, respiratory distress, and elevated lactate, initially leading to concerns of sepsis; however, further evaluation revealed the likely diagnosis of serotonin syndrome, triggered by the combination of serotonergic agents and intraoperative fentanyl. Management included an intensive care unit admission with discontinuation of serotonergic medications, administration of benzodiazepines, intravenous fluids, and norepinephrine for shock. The patient's condition improved for 36 hours, and she was discharged with adjustments to her psychiatric medications. This case contributes to the growing body of literature highlighting the risks of serotonin syndrome in patients on serotonergic polytherapy, particularly in the postoperative period. The interaction between our patient's chronic diphenhydramine abuse and multiple other serotonergic medications likely precipitated this condition. Preoperative medication reconciliation, early recognition of triggers and signs, and prompt intervention are key to preventing adverse outcomes in serotonin syndrome. (*Plast Reconstr Surg Glob Open* 2025;13:e6634; doi: 10.1097/GOX.00000000000006634; Published online 12 March 2025.)

Serotonin syndrome is a group of symptoms associated with serotonin toxicity caused by initiation, increasing dosage, or overdose of a serotonergic agent, or drug–drug interactions.¹ Manifestations begin within hours of medication administration with a triad of neuromuscular excitation, autonomic excitation, and altered mental status.^{1,2}

For documented precipitators, although selective serotonin reuptake inhibitors are the most commonly

implicated medications,³ serotonin-norepinephrine reuptake inhibitors have more potential to cause serotonin syndrome,⁴ and direct serotonin agonists such as fentanyl and triptans are less likely to cause classic or severe serotonin syndrome.¹ For medications that may induce serotonin syndrome, diphenhydramine has been shown in preclinical data to potentiate serotonin activity and has been linked to serotonin syndrome in combination with other precipitators.^{5,6} Understanding serotonin syndrome as a potential differential diagnosis may become increasingly crucial for surgeons, as its clinical presentation can easily mimic other perioperative complications requiring different management approaches.⁷

We report a case of serotonin syndrome in a patient following elective plastic surgery who was taking multiple serotonergic agents including high doses of diphenhydramine. Although the specific drug–drug interaction that caused her syndrome is unknown, diphenhydramine has remained one of the most popular antihistamines

From the *New York Medical College, Valhalla, NY; and †Department of Surgery, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Chappaqua, NY.

Received for publication October 2, 2024; accepted February 4, 2025.

Copyright © 2025 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the [Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 \(CCBY-NC-ND\)](#), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.00000000000006634

Disclosure statements are at the end of this article, following the correspondence information.

used due to familiarity,⁸ and as such, documentation of an association between diphenhydramine and serotonin syndrome would prove vital to safe prescribing practice. Furthermore, early recognition of symptoms of serotonin syndrome remains a point of education for providers.

CASE REPORT

The patient is a 43-year-old woman with a medication regimen including duloxetine for anxiety and depression, asenapine for mood stabilization, trazodone for insomnia, and diphenhydramine for insomnia. The patient underwent bilateral mastopexy, miniabdominoplasty, and liposuction of the buttocks and back. Intraoperatively, the surgeon noted muscle rigidity in the abdominal muscles, whereas the anesthesiologist observed tightness of the mandible. Otherwise, the procedure was uncomplicated. Postoperatively, the patient developed tachycardia, leukocytosis, respiratory distress, and lactic acidosis. She subsequently revealed a history of chronic diphenhydramine abuse, reporting nightly use of 300–500 mg as a sleep aid for over a year. A 50 mg intravenous dose was given for suspected withdrawal, with no improvement. The history of diphenhydramine use, combined with other chronic and perioperative serotonergic medications, and the presence of muscle rigidity, autonomic instability, and elevated lactate levels in the setting of a negative infectious workup, supported the diagnosis of serotonin syndrome. The patient was managed with discontinuation of serotonergic agents, benzodiazepines, intravenous fluids, and vasopressor support.

Over the following 36 hours, the patient's condition improved with supportive care. By postoperative day 3, she was hemodynamically stable and afebrile. The patient was eventually discharged with adjustments to her medication regimen and advised to follow-up with psychiatry for ongoing medication management.

DISCUSSION

The case presented involves a 43-year-old woman who developed serotonin syndrome following surgery in the setting of chronic and perioperative use of multiple serotonergic agents, including diphenhydramine at high doses. The development of serotonin syndrome in this context underscores understanding polypharmacy in the perioperative setting, especially with medications that modulate serotonin levels.

Serotonin syndrome occurs due to excess serotonin activity in the central nervous system and requires a plausible mechanism as well as characteristic signs for diagnosis.^{1,2} It is often precipitated by the combination serotonergic modulators, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and opioids with serotonergic activity.^{1,9} In this case, diphenhydramine, asenapine, trazodone, and duloxetine were likely precipitants of serotonin toxicity through drug–drug interactions, potentiated by perioperative medications including fentanyl.^{1,10} The muscle rigidity, tachycardia, and leukocytosis fit within the characteristic muscle

hyperactivity, autonomic excitation, and altered mental status of serotonin syndrome.⁷

The diagnosis of serotonin syndrome is clinical and requires ruling out other diagnoses such as neuroleptic malignant syndrome, malignant hyperthermia, and sedative-hypnotic withdrawal.^{1,10} The Hunter Serotonin Toxicity Criteria are regarded as the most sensitive diagnostic tool for serotonin syndrome. In this patient, muscle rigidity, tachycardia, and elevated lactate levels aligned with the criteria, assisting the team to arrive at the diagnosis. However, perioperative conditions such as malignant hyperthermia, neuroleptic malignant syndrome, and withdrawal from sedative-hypnotics can mimic serotonin syndrome in their autonomic hyperactivity. The serotonin syndrome can be distinguished by a history of multiple serotonergic medication usage and resolution upon discontinuation; its characteristic findings of neuromuscular hyperactivity, such as tremor and hyperreflexia; and a lack of response to treatments for differential diagnoses.²

The primary treatment for serotonin syndrome is the discontinuation of serotonergic agents, along with supportive care such as intravenous fluids and vasopressors for hypotension; benzodiazepines for agitation; and cyproheptadine, a serotonin antagonist, in severe cases.^{5,9} In this case, the patient was managed with discontinuation of her serotonergic medications, intravenous fluids and vasopressors, and benzodiazepines. Early recognition and intervention is important in serotonin syndrome, as symptoms resolve within 24–48 hours with appropriate management.^{5,10} The rapid improvement in our patient's condition was consistent with the expected timeline.⁹ For patients who do not improve with discontinuation of serotonergic agents and addition of benzodiazepines and supportive therapy, cyproheptadine is considered to be antidotal therapy through its serotonin antagonism, although its efficacy has not been established.²

Although diphenhydramine is recognized for its antihistamine and anticholinergic effects, at higher doses, it can inhibit presynaptic serotonin reuptake, contributing to elevated serotonin levels in the central nervous system.^{5,6} In this case, the use of high-dose diphenhydramine likely exacerbated the patient's risk for serotonin syndrome when combined with her other serotonergic medications. Due to the popular usage of serotonin-modulating medications for psychiatry and diphenhydramine as an antihistamine, this case highlights new widespread considerations in medication reconciliation.^{3,8}

This case underscores the need for awareness of serotonin syndrome, particularly in the perioperative period. Preoperative planning should involve a review of the patient's medications and, given the increasing use of serotonergic medication in psychiatry and continued widespread use of diphenhydramine, clinicians must remain vigilant for the signs of serotonin syndrome.⁷ In patients on chronic serotonergic therapy, alternative analgesics and sedatives that do not increase serotonin levels should be prioritized.¹ Future research should focus on management of serotonergic medication polytherapy, with consideration for medications administered perioperatively.

Michael H. Rosenberg, MD

Surgical Services, Northwell Health Northern
Westchester Hospital
480 Bedford Road, Suite D
Chappaqua, NY 10514
E-mail: mrosenberg2@northwell.edu

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. Chiew AL, Buckley NA. The serotonin toxidrome: shortfalls of current diagnostic criteria for related syndromes. *Clin Toxicol (Phila)*. 2022;60:143–158.
2. Boyer EW, Shannon M. The serotonin syndrome [published correction appears in *N Engl J Med*. 2007 Jun 7;356(23):2437] [published correction appears in *N Engl J Med*. 2009 Oct 22;361(17):1714]. *N Engl J Med*. 2005;352:1112–1120.
3. Gummin DD, Mowry JB, Beuhler MC, et al. 2022 annual report of the National Poison Data System® (NPDS) from America's Poison Centers®: 40th Annual Report. *Clin Toxicol (Phila)*. 2023;61:717–939.
4. Cooper J, Duffull SB, Isbister GK. Predicting serotonin toxicity in serotonin reuptake inhibitor overdose. *Clin Toxicol (Phila)*. 2023;61:22–28.
5. Khan S, Saud S, Khan I, et al. Serotonin syndrome presenting with concomitant tramadol and diphenhydramine use: a case report of an unlikely side-effect. *Cureus*. 2018;10:e2421.
6. Tanaka T, Takasu A, Yoshino A, et al. Diphenhydramine overdose mimicking serotonin syndrome. *Psychiatry Clin Neurosci*. 2011;65:534–534.
7. Schuch LG, Yip A, Nouri KF, et al. Serotonin syndrome following an uncomplicated orthopedic surgery in a patient with post-traumatic stress disorder. *Mil Med*. 2016;181:e1185–e1188.
8. Wolfson AR, Wong D, Abrams EM, et al. Diphenhydramine: time to move on? *J Allergy Clin Immunol Pract*. 2022;10:3124–3130.
9. Takata J, Arashi T, Abe A, et al. Serotonin syndrome triggered by postoperative administration of serotonin noradrenaline reuptake inhibitor (SNRI). *JA Clin Rep*. 2019;5:55.
10. Bartakke A, Corredor C, van Rensburg A. Serotonin syndrome in the perioperative period. *BJA Educ*. 2020;20:10–17.