

Did Internet-purchased diet pills cause serotonin syndrome?

Phentermine also may have increased patient's neuroleptic malignant syndrome risk

Ms. G, age 28, presents to a tertiary care hospital with altered mental status. Six weeks ago she started taking phentermine, 37.5 mg/d, to lose weight. Her body mass index is 24 kg/m² (normal range), and she obtained the stimulant agent via the Internet. Her family reports Ms. G was very busy in the past week, staying up until 2 AM cleaning. They say she also was irritable with her 5-year-old son.

Two days ago, Ms. G complained of fatigue and nausea without emesis. She went to bed early and did not awaken the next morning. Her sister found her in bed, minimally responsive to verbal stimuli, and brought her to the hospital.

Patients have used phentermine as a weight-reducing agent since the FDA approved this amphetamine-like compound in 1960.¹ Phentermine's mechanism of action is thought to involve dopaminergic, noradrenergic, and serotonergic effects.² Stimulation of norepinephrine (NE) release is its most potent effect, followed by NE reuptake inhibition, stimulation of dopamine (DA) release, DA reuptake inhibition, stimulation of serotonin (5-HT) release, and 5-HT reuptake inhibition (weak).³

Because phentermine could in theory cause serotonin syndrome,⁴ its use is contraindicated with monoamine oxidase inhibitors (MAOIs) and not recommended with selective serotonin reuptake inhibitors (SSRIs).⁵ One case report describes an interaction between fluoxetine and phentermine that appears consistent with serotonin syndrome.⁶ We are aware of no case reports of serotonin syndrome caused by phentermine alone.

continued



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Serotonin syndrome

Clinical Point

We hypothesize that phentermine use may increase NMS risk through adverse drug events

Box 1

Serotonin syndrome: Excessive serotonin activity

Sternbach⁷ first summarized serotonin syndrome's clinical presentation in a review of 38 cases. The most frequent clinical features include changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor (*Table 1*).

The clinical syndrome varies in scope and intensity. Animal models suggest the pathophysiologic mechanism involves brainstem and spinal cord inundation with serotonin, acting on 5-HT_{1A} and 5-HT_{2A} receptors. Recent evidence supports a greater role for 5-HT_{2A} receptors.⁸

Primary treatment calls for discontinuing the suspected serotonergic agent and instituting supportive measures. Case reports also suggest using serotonin receptor antagonists—such as cyproheptadine, methysergide, chlorpromazine, or propranolol—to clinically manage serotonin syndrome, although empiric support is limited.⁹

The syndrome often improves within 24 hours of primary treatment, although confusion sometimes last for days and death has been reported.¹⁰

This article reports the case of Ms. G, who presented with probable serotonin syndrome associated with phentermine use and subsequently developed a rapid-onset, superimposed neuroleptic malignant syndrome (NMS). We hypothesize that phentermine use may increase NMS risk through adverse drug events and discuss potential pathophysiologic mechanisms and treatment implications.

Serotonin syndrome vs NMS

Serotonin syndrome is an infrequent and potentially life-threatening adverse drug reaction that presumably results from excess serotonin activity (*Box 1*).⁷⁻¹⁰ NMS also is an infrequent and potentially life-threatening neurologic emergency (*Box 2, page 70*).¹¹⁻¹⁸ Similarities between disorders of increased serotonergic activity and disorders of low dopaminergic activity (*Table 1*) suggest both may result from an imbalance

between the serotonergic and dopaminergic systems, which have reciprocal relationships in the CNS.¹⁹

Differentiating between serotonin syndrome and NMS is further complicated when both antipsychotics and serotonergic agents may be implicated.²⁰ Clinical trials are not feasible because NMS and serotonin syndrome rarely occur.

CASE CONTINUED

Fever follows haloperidol

Initial workup. Ms. G has no significant medical or psychiatric history. She has no history of seizures, head trauma, changes in mental status, recent travel, tick bites, or mosquito bites. Family history is relevant only for a maternal aunt with a history of 1 seizure. Ms. G is employed and lives with her husband and son. She is not taking other medications, herbal supplements, or vitamins and does not use tobacco, alcohol, caffeine, or illicit drugs.

On admission, she is somnolent and arousable only to painful stimuli. Temperature is 36.7°C, blood pressure 89/58 mm Hg, heart rate 73 bpm, and respirations 21/minute. She does not talk but is cooperative to physical examination, which is otherwise unremarkable.

Neurologic exam also is unremarkable, with no evidence of meningeal irritation, abnormal reflexes, or muscle tone. Serum ammonia (51 $\mu\text{mol/L}$; normal range 7 to 42 $\mu\text{mol/L}$) is slightly elevated. Liver function tests, electrolytes, blood urea nitrogen, creatinine, complete blood counts, urinalysis, urine culture, and blood cultures are unremarkable. Ethanol, salicylate, and acetaminophen levels are negative. Evaluation reveals a positive urine drug screen only for amphetamines, attributed to use of phentermine. Chest radiography and head CT are unremarkable.

Electroencephalography (EEG) 17 hours after admission reveals left anterior temporal spikes suggestive of seizure activity lasting 50 seconds. The patient is described as stuporous but arousable during EEG, and diffuse delta slow waves are superimposed on an alpha rhythm with intermittent diffuse delta bursts. Brain MRI is unremarkable.

Despite no clinical evidence of seizure, Ms. G is transferred to the cardiac telemetry ward to monitor for potential side effects from IV phenytoin loading, at which time (24 hours

Table 1

Signs and symptoms of NMS vs serotonin syndrome

	NMS	Serotonin syndrome
Onset	Insidious, days to weeks	Acute (minutes to hours)
Resolution	Slow, often >1 week	Improvement or resolution often within 24 hours
Autonomic	Fever, <i>tachycardia</i> , diaphoresis, <i>elevated or labile blood pressure</i> , sialorrhea, tachypnea, incontinence	<i>Diaphoresis, shivering, fever, tachycardia, hypertension</i> , mydriasis
Gastrointestinal	Dysphagia, elevated transaminases	<i>Diarrhea</i> , nausea, vomiting, elevated ammonia and transaminases
Neuromuscular	<i>Rigidity</i> , bradykinesia, dysarthria, dyskinesias, coarse tremor, ataxia, opisthotonos, oculogyric crisis, rhabdomyolysis	Clonus, <i>myoclonus, hyperreflexia</i> , ataxia, incoordination, rigidity, <i>tremor</i>
Psychiatric	<i>Altered mental status</i> , stupor, somnolence, mutism	<i>Altered mental status</i> , agitation, hypomania, hyperactivity, <i>restlessness</i> , somnolence (less common)
Other	Leukocytosis, elevated creatine kinase (significant), elevated serum creatinine, proteinuria, renal failure, disseminated intravascular coagulation	Leukocytosis (rarely >20K cells/mm ³), elevated creatine kinase (less common), disseminated intravascular coagulation, metabolic acidosis

NMS: neuroleptic malignant syndrome
Note: Classically reported symptoms are italicized

Clinical Point

Differentiating between serotonin syndrome and NMS is difficult when both antipsychotics and serotonergic agents may be implicated

after admission) she is found to have intermittent sinus tachycardia ≤140 bpm.

Antipsychotic therapy. Thirty hours after admission—after phenytoin loading and normalized EEG—Ms. G shows periodic episodes of sudden startling, with repetitive leg shaking. Continuous ankle clonus is present bilaterally. She complains of severe paresthesias in her legs and is unable to urinate on her own.

Because of her altered mental status and prominent lower extremity neurologic signs, MRI of the spine and lumbar puncture are ordered to rule out epidural abscess, meningitis, and/or encephalitis. Results are normal. Because her agitation interfered with these examinations, she was given IV haloperidol, a total 12 mg this day.

NMS signs emerge. Forty-eight hours after admission, Ms. G becomes febrile (38.3°C) and shows tachycardia, with heart rate consistently >130 bpm. Her vital signs did not normalize before the fever developed. She remains somnolent and continues to have spastic lower leg and ankle clonus. She shows no seizure activity on video EEG monitoring during later episodes of repetitive leg shaking, approximately 60 hours after admission.

Ms. G receives empiric vancomycin, ceftriaxone, ampicillin, and acyclovir for possible infectious encephalitis, and lumbar puncture is done emergently. Further laboratory tests reveal creatine kinase (CK) elevation (17,282 U/L, from 270 on admission), leukocytosis (white blood cell count 16.1K/mm³, from 7.2K on admission), and elevated transaminases (AST 199 U/L, up from 21 on admission; ALT 84 U/L, up from 19 on admission).

Promising New Investigator Kyoung Bin Im, MD

This paper was among those entered in the 2007 Promising New Investigators competition sponsored by the Neuroleptic Malignant Syndrome Information Service (NMSIS). The theme of this year's competition was "New insights on psychotropic drug safety and side effects."

CURRENT PSYCHIATRY is honored to publish this peer-reviewed, evidence-based article on a clinically important topic for practicing psychiatrists.



Serotonin syndrome

Clinical Point

Phentermine increases serotonin efflux in the rat hypothalamus to a greater degree than fluoxetine

Box 2

NMS: Disorder of low dopaminergic activity

Neuroleptic malignant syndrome (NMS)—characterized by fever, extrapyramidal rigidity, and disturbances of autonomic function and consciousness—was first described with the use of haloperidol.¹¹ Risk factors include catatonia, disorganized presentation, and dehydration.¹² NMS is thought to result from deficient compensatory mechanisms following blockade of dopaminergic regulation of muscle tone and autonomic function.¹³

Although possibly idiosyncratic, the reaction has been associated with:

- intramuscular, higher total dose, or abruptly increasing doses of antipsychotics¹⁴
- withdrawal of dopaminergic agents, such as those used to treat Parkinson's disease.¹⁵

Akin to serotonin syndrome, managing NMS focuses on removing the offending agent(s) and providing supportive care. Severe cases require intensive monitoring, aggressive IV hydration, and respiratory support. Dopaminergics such as bromocriptine¹⁶ and skeletal muscle relaxants such as dantrolene¹⁷ also have been used to manage NMS.

Unlike serotonin syndrome, NMS often resolves slowly (typically >1 week). NMS' mortality rate of 11% to 38% appears to be declining in recent years, perhaps because it is being recognized more rapidly.¹⁸

She is transferred to the ICU with a preliminary diagnosis of NMS. Again, continuous EEG monitoring does not show seizure activity. CSF specimen is negative for infection (negative cultures, negative herpes simplex virus PCR, protein 31 mg/dl, glucose 75 mg/dl). She is started on dantrolene, bromocriptine, and levodopa but shows no initial improvement.

Intubation. On hospital day 8, the patient is intubated to protect her airway and placed in a pentobarbital coma for 2 days, with no improvement. On hospital day 9, cyproheptadine, 24 mg/d, is added for possible serotonin syndrome, and continued for 9 days.

On day 11, the addition of IV diazepam, 10 mg per hour, is followed by gradual improvement in rigidity. Ms. G remains on continuous

EEG, with no evidence of seizure activity before diazepam was added or after it is tapered off by day 23.

Discharge. Ms. G is extubated on hospital day 18. On day 23 she can follow commands but is not fully oriented, and levodopa, phenytoin, bromocriptine, and dantrolene are tapered off. She is discharged to a rehabilitation facility, where she again requires phenytoin for a witnessed seizure, attributed to anticonvulsant withdrawal.

On follow-up phone interviews 4 and 18 months after hospitalization, Ms. G says she remains seizure-free without taking anticonvulsants. She reports a subjective, interval improvement in cognitive function, which has since returned to baseline.

Evidence for serotonin syndrome

This case involves a young woman with a several-week history of phentermine use for weight reduction who presented with confusion, sedation, mutism, and nausea. She was initially found to have an abnormal EEG, for which she was loaded with the anticonvulsant phenytoin. However, she continued to exhibit altered mental status, myoclonus, and hyperreflexia along with autonomic dysregulation—such as urinary retention and tachycardia—despite a negative EEG on continuous monitoring.

On retrospective review, we believe she likely was experiencing serotonin toxicity from phentermine. She later developed NMS within several hours of receiving the antipsychotic haloperidol.

Seizure has been reported with Fen-Phen (fenfluramine and phentermine),²¹ but not to date with phentermine monotherapy. On the other hand, seizure—often generalized, tonic-clonic in nature—has been reported with serotonin syndrome.²² Partial seizures might explain Ms. G's initial confusion. However, neuromuscular abnormalities persisted after a normalized EEG, further supporting the diagnosis of serotonin syndrome.

Even though phentermine is thought to have a relatively weak serotonergic effect,³ it has been shown to markedly increase serotonin efflux in the rat hypothalamus (to a greater degree than the SSRI fluoxetine).²³

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Although Ms. G did not report having consumed foods or supplements that could have interfered with phentermine's metabolism, such use could have contributed to or prolonged a serotonin syndrome.²⁰ Phentermine misuse also cannot be ruled out.

Excess phentermine or concomitant use of other serotonergic agents may have precipitated serotonin syndrome. Ms. G's hyperactivity a few days before she complained of fatigue and somnolence may represent:

- a sign of phentermine intoxication or overuse
- a harbinger of serotonin syndrome, because these symptoms were followed by overt serotonin syndrome signs such as confusion, disorientation, myoclonus, and autonomic dysfunction.

Features such as slow progression to the full-blown signs and unclear medication history may obscure the clinical picture at presentation in this and similar cases.²⁴

Evidence for NMS

Ms. G received haloperidol because her agitation obstructed urgent evaluation. After several doses, she rapidly developed signs and symptoms highly consistent with NMS. Onset was rapid compared with the typically described, more insidious NMS evolution of 24 to 72 hours, however.²⁵ Rapid NMS onset may have been precipitated in 2 ways:

- dopaminergic (phentermine) withdrawal combined with dopamine antagonist challenge (haloperidol)^{25,26}
- background serotonin syndrome caused by amphetamine (phentermine) predisposing the patient to develop NMS.²⁷

For the first possibility, 1 case report has described a narcolepsy patient developing NMS after discontinuing dextroamphetamine, which he had been taking for 16 years.²⁸ NMS also has been observed during withdrawal of dopaminergic medications used in Parkinson's disease.²⁹ For the second possibility, Kline et al³⁰ reported a similar case of a 45-year-old woman with probable serotonin syndrome who developed NMS after a single neuroleptic dose.

Table 2 Serotonin syndrome or NMS? When in doubt, follow 4 management principles

Avoid serotonin agonists and dopamine antagonists when a patient presents with features of serotonin syndrome or neuroleptic malignant syndrome (NMS) and the diagnosis is unclear²⁰

Provide supportive care with monitoring, cooling blankets as needed, and hydration

Avoid using antipsychotics for agitation, when possible; benzodiazepines may be preferable, although their use in NMS is controversial²⁵

Avoid using bromocriptine, given its contraindication in serotonin syndrome, but consider cyproheptadine for the serotonin syndrome component and dantrolene for skeletal muscle rigidity²⁰

Although phentermine-induced sympathetic hyperactivity also could have predisposed Ms. G to NMS,³¹ we think this is unlikely because phentermine was discontinued 3 to 4 days before she developed NMS. Nonetheless, sympathetic hyperactivity secondary to phentermine or serotonin syndrome may increase the risk of developing NMS.

Treatment strategy

Because serotonin syndrome and NMS share many clinical findings, differentiating between the 2 syndromes may be difficult, especially when the patient's medication history does not implicate a specific agent. A detailed history and physical may help distinguish the syndromes. Clonus may be particularly specific and is important in the diagnosis of serotonin syndrome.³² If you are unable to differentiate between serotonin syndrome and NMS in a patient with this acute neurotoxic abnormal behavior syndrome,³³ consider a common treatment strategy (Table 2).^{19,25}

In Ms. G's case, she probably should not have received bromocriptine for NMS,²⁰ given the potential role of serotonin syndrome in precipitating her symptoms.

Case reports support our hypotheses of an increased predilection for NMS with

Clinical Point

Sympathetic hyperactivity from phentermine or serotonin syndrome may increase the risk of developing NMS



Serotonin syndrome

Clinical Point

Consider a common treatment strategy if you are unable to differentiate between serotonin syndrome and NMS in your patient

dopaminergic withdrawal or serotonin syndrome. Growing evidence supports the use of chlorpromazine for serotonin syndrome,³⁴ but consider its use contraindicated in patients with NMS.

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Related Resources

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- Neuroleptic Malignant Syndrome Information Service (NMSIS). www.nmsis.org. NMS hotline for medical professionals (toll-free 888-667-8367) handles calls on NMS, serotonin syndrome, heat stroke, malignant catatonia, and other drug-induced heat-related disorders.

Drug Brand Names

Acyclovir • Zovirax	Fluoxetine • Prozac
Ampicillin • various	Haloperidol • Haldol
Bromocriptine • Parlodel	Levodopa • various
Ceftriaxone • Rocephin	Methysergide • Sansert
Chlorpromazine • Thorazine	Pentobarbital • Nembutal
Cyproheptadine • Periactin	Phentermine • various
Dantrolene • Dantrium	Phenytoin • Dilantin
Diazepam • Valium	Propranolol • Inderal
Dextroamphetamine • Dexedrine	Vancomycin • various

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

Diagnosis of serotonin syndrome or neuroleptic malignant syndrome (NMS) is clinical because confirmatory tests do not exist. We cannot be certain this patient had serotonin syndrome followed by NMS, but this case suggests the possibility of increased NMS risk in patients with serotonin syndrome, perhaps mediated by sympathetic hyperactivity.