

Phen/Fen

and the

Serotonin Syndrome

The coming of age of the new diet drug **Phen/Fen** has been hailed in news reports as everything from the latest in the series of popular pharmacological treatments for obesity to the outrageous claim of “wonder drug without side effects.” Public demand for the drug is high, if statistics from one state are any indication. In Utah alone roughly one-third—32%—of controlled substance prescriptions filled between Sept. 1 and Dec. 31, 1996 were for phentermine and fenfluramine, the two drugs that make up Phen/Fen. It is only lately, however, that the drugs have been linked with what has come to be known as the **serotonin syndrome**.

by Bruce H. Woolley, Pharm.D.

The

serotonin syndrome occurs when brain synapses are flooded by high levels of serotonin. Although it may be exacerbated by inherited or acquired factors, it is virtually always induced by medicines, and it can progress to a coma and even be fatal.

CASE STUDY

A 37-year-old Caucasian woman traveled to California to visit her parents over a holiday weekend. The previous year she had been treated with fluoxetine for depression. She had a Body Mass Index of about 30 and had been placed on the Phen/Fen diet.

While at her parents' house she developed an upper respiratory tract infection for which her physician prescribed an antibiotic. She later developed a cough, and a pharmacist recommended a cough medicine with dextromethorphan (like Robitussin DM). She returned to her parents' house and took a single recommended dose of 10-20 mg.

Within an hour she began to feel dizzy, nauseated, and dazed, and she developed the characteristic severe frontal headache. She became quite frightened, began to cry uncontrollably, and rapidly became unresponsive. She soon started to shiver and developed involuntary jerks of her legs. Her family called the paramedics, and she was transported to the hospital.

In the ER evaluation she was minimally responsive to pain stimuli. She had severe myoclonus, rigidity, and opisthotonos. Her vital signs were reported as temperature 38°C, pulse 74, blood pressure 156/94. She had warm, flushed skin. Her pupils were minimally reactive, but with significant hyperlacrimation. She also had hyperactive bowel sounds.

The patient became comatose and was intubated. She remained comatose with severe myoclonus and hyperreflexia. Her respirations were ventilator dependent.

She was admitted to the intensive care unit with a preliminary diagnosis of toxic shock syndrome, where she remained for three days. Lorazepam was administered for her rigidity and myoclonus. Forty-two hours after admission she became conscious and was extubated. She appeared to have continuous improvement for three days when she was discharged.

Although still present, her rigidity and myoclonus were greatly reduced at the time of discharge; however, she reported significant sustained ankle clonus and deep tendon reflexes in her legs.

A CLEARER PICTURE OF THE SYNDROME

To understand serotonin syndrome better, we need to review first what serotonin is and then how it works on the seven various 5HT receptors. (The 5HT stands for 5-hydroxytryptamine, the scientific name for serotonin.) It was previously believed that the neurotransmitter serotonin was confined solely to the central nervous system; we know now that this isn't the case. A person has approximately 10 mg of serotonin in storage at any one time. Of that 10 mg, 90% is found in the platelets and gastrointestinal tract. Only 10% actually exists in the central nervous system. This neurotransmitter does not cross the blood-brain barrier, and cannot simply be administered and expected to go into the brain. That's one reason why many health food stores tried—unsuccessfully—to sell L-tryptophan (from which serotonin is synthesized) to enhance serotonin as an antidepressant.

It is now becoming clearer that instead of serotonin working on just one receptor, there are at least seven different serotonin receptors. Four of them have been cloned, isolated, and evaluated in some depth. Three of these receptors have not yet been evaluated because they have only been cloned. Researchers know they exist, but very little is known about them. The ones that have been identified are labeled 5HT₁ through 5HT₄. They occur in different areas in the anatomy and each has a unique action. 5HT₁, ₂, and ₄ are G-protein linked receptors. The G-protein in 5HT₁ is adenylyclase, and the G-protein in 5HT₂ is phospholipase C, so they can be differentiated. 5HT₃ is a ligand-gated ion channel very similar to the calcium channels. Each receptor corresponds to a different set of symptoms (see *Table I* and *Table II*).

Almost without exception, serotonin syndrome is an iatrogenic condition. It occurs when a patient takes two or more serotonergic drugs that cause serotonin hyperstimulation in the postsynaptic serotonergic receptors. A key point is that there must be more than one receptor stimulated by more than one drug to trigger the syndrome. Reynolds wrote, "It should be underscored that serotonin syndrome is almost always caused by an interaction between two drugs that have different serotonergic

TABLE I: RECEPTOR DESCRIPTION

5HT ₁	5HT ₂	5HT ₃	5HT ₄	5HT ₅ , 5HT ₆ , 5HT ₇
G-protein linked	G-protein linked	ligand-gate ion channel	G-protein linked	Cloning suggests existence
(A) CNS depression	(A)	(A)	CNS/heart/GI	
(B) rodents 5HT _{1D}	(B)	(B)	inc. cAMP NT rel. activation	
(C) renamed 5HT _{2C} →	(C)	(C)	Agonists invoke gastric prokinetic activity	
(D) inhibit NT rel., migraine	vascular smooth muscle	peripheral & central neurons		
(E) cardiovascular	platelets/CNS/lung/GI	pain, emesis reflex, anxiolytic		
(F) insomnia, sexual function	potential antipsychotics			

TABLE II: MOST FREQUENT CLINICAL FEATURES AND RECEPTOR ACTION

SYMPTOM	FREQUENCY	SEROTONIN RECEPTOR ACTION
Changes in mental status (confusion/hypomania)	45%	5-HT _{1A} insufficient to explain 5-HT _{1D} agonists produce anxiety 5-HT _{1D} and ₂ precipitate acute confusional state 5-HT modulates vascular tone (peripheral/central) Cerebrovascular vasoconstriction associated with some anxiety states
Restlessness/agitation	45%	Poorly described in Serotonin Syndrome Resembles akathisia Understood as feature of anxiety or hypomania
Myoclonus	34%	5-HT regulates motor activity in two ways: • Brainstem raphe nuclei generates repetitive behaviors (e.g. chewing) • Depresses posthyperpolarization of CNS neurons (ongoing activity) 5-HT activity in Serotonin Syndrome increases discharge, duration, and frequency of these neurons Manifested as myoclonus/tremor/hyperreflexia
Hyperreflexia	29%	<i>See myoclonus</i>
Diaphoresis/fever	25%	CNS 5-HT ₂ stimulation causes hyperthermia CNS 5-HT _{1A} activation causes hypothermia May imply 5-HT ₂ predominance
Shivering/tremor (masseter)	25%	<i>See myoclonus</i>
Diarrhea, nausea, and/or abdominal pain	16%	May be due to activation of chloride pumps (regulated by gut 5-HT ₃) CNS 5-HT ₃ involved in diarrhea Peripheral 5-HT ₂ and 5-HT ₄ also prokinetic
Incoordination	13%	Incoordination reflects a deficit in cerebellar function 5-HT ₂ located in molecular and granular layers of the cerebellum and in the dentate nucleus
Dyspnea		5-HT ₂ stimulation of vascular and airway smooth muscle leads to bronchospasm Activation of medullary 5-HT _{1A} increases respiratory rate Associated anxiety may also contribute
Hypertension and EKG changes		Medullary 5-HT _{1A} stimulation decreases heart rate and blood pressure CNS 5-HT ₂ stimulation opposite effect May be that CNS 5-HT ₂ predominates in Serotonin Syndrome
Disseminated Intravascular Coagulation		Platelets have 5HT ₂ receptors Stores 5HT in dense granules 5HT ₂ stimulation causes platelet aggregation and degranulation Unbound 5HT degraded by enzymatic activity Enzymatic degradation blocked by many agents that induce Serotonin Syndrome

Adapted from Brown, Skop, Mareth: The Annals of Pharmacotherapy 1996; 30:527-533

mechanisms of action. It must be assumed that altering normal serotonin pathways at one step can be therapeutic, but interfering with two steps creates a problem.”

What are these mechanisms of action? There are generally six major mechanisms that can increase the concentration of serotonin in brain synapses:

1. By increasing the synthesis of serotonin
2. By stimulating 5HT release from the presynaptic vesicles
3. By inhibiting 5HT reuptake
4. By reducing 5HT degradation either in the synapse or after uptake into the presynaptic nerve
5. Through direct post-synaptic agonist action
6. Through nonspecific increases in the activity of serotonin

WATCHING OUT FOR ENEMY AGENTS

Table III lists commonly reported serotonin agents and their mechanisms of action. If serotonin agents affecting more than one mechanism are administered at the same time, patients have a greater risk of developing serotonin syndrome.

Two common agents that increase serotonin synthesis are L-tryptophan and alcohol. Although L-tryptophan has been withdrawn from the commercial market, it is still found in fairly significant amounts in white turkey meat. Of all the alcoholic beverages, those that seem to be most often implicated in serotonin syndrome are beer and red wine; this may be due to some of the pharmacological actions of the other compounds they contain.

The release of serotonergic drugs can be stimulated by certain kinds of phenylethylamines like amphetamines. Cocaine is a profound stimulator for the release of serotonin. The fenfluramines also stimulate 5HT release, as do rauwolfia and the common herbal product valerian root.

Melatonin is also serotonergic and has been implicated in many cases of serotonin syndrome. Angel Dust (phencyclidine), sumatriptan, and valerian root are other agents that also fit into this category.

Lithium is an example of a drug that works through nonspecific increases in the activity of serotonin. Electroconvulsive therapy also achieves the same ends.

THREE CATEGORIES OF RISK FACTORS

Factors that should alert physicians to the possibility a patient may be predisposed to the serotonin syndrome fit into the three basic risk factor categories detailed in *Table IV*: inherited, acquired, and iatrogenic.

Patients with low endogenous monoamine oxidase activity or a reduced ability to secrete endothelium-derived nitric oxide (an endothelial disease susceptibility marker) display inherited risk factors that could increase their chances of falling prey to the syndrome.

Patients may acquire a susceptibility to the syndrome if they have any one of four risk factors: liver disease, sub-

If serotonin agents affecting more than one mechanism are administered at the same time, patients have a greater risk of developing serotonin syndrome. Physicians who want to reduce their patients' risks should consider applicable inherited and acquired risk factors, then choose to use serotonergic agents that are selective for specific sites or receptors.

Agents whose actions inhibit 5HT reuptake include the tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), amphetamines, cocaine, dextromethorphan, fenfluramine [dex], and meperidine.

Agents that reduce degradation after reuptake include monoamine oxidase inhibitors. Herbal products include St. John's wort and yohimbe.

One agent with direct postsynaptic agonist action is buspirone. Some physicians put patients on buspirone because they want to avoid using a tricyclic antidepressant. Sometimes they don't realize that buspirone is every bit as serotonergic as tricyclics and LSD. An agent that seems to have become the drug of choice for insomniacs or frequent travelers who want to relieve "jet lag" is melatonin.

stance abuse, long-term use of amines, or an endothelial disease susceptibility marker (such as atherosclerosis, hypertension, hypercholesterolemia, damaged vascular or pulmonary epithelium, or diabetes).

While both of the above risk factor categories can make a patient vulnerable to developing the syndrome, it takes a stimulus for 5HT release (i.e., another serotonergic agent) to actually cause it.

Physicians who want to reduce their patients' risks should consider applicable inherited and acquired risk factors, then choose to use serotonergic agents that are selective for specific sites or receptors. By doing so, they can eliminate many of the adverse effects caused by agents which are non-selective to specific serotonin receptors.

TABLE III:
SEROTONERGIC DRUGS/HERBS IMPLICATED IN SEROTONIN SYNDROME

TYPE OF AGENT	SUBSTANCES IMPLICATED
Increase synthesis	L-tryptophan, alcohol
Stimulate release	Amphetamines, cocaine, fenfluramine, rauwolfia
Inhibit reuptake	TCA's, SSRIs, amphetamines, cocaine, dextromethorphan, fenfluramine [dex], meperidine, tramadol
Reduce degradation after reuptake	MAOI, St. John's wort, yohimbe
Direct postsynaptic agonist action	Buspirone, LSD, phencyclidine (angel dust), melatonin, valerian root
Nonspecific increase in activity	Lithium
Dopamine agonists	Amantadine, bromocriptine, bupropion, levodopa, phencyclidine, selegiline

DIAGNOSIS AND TREATMENT

What are the warning symptoms of this potentially serious syndrome? The typical picture is that of an agitated delirium in combination with generalized hyper-tonicity, seizures, hyperpyrexia, and variable elevation of heart and respiratory rates. The condition may or may not change, but can progress to a coma. *Table II* shows the most frequent clinical features in a study of 100 cases. Note that although the condition may worsen rapidly, the syndrome is not implicated in sudden death.

Symptoms can help point out the severity of the condition. In a mild case of the syndrome symptoms will include tremor, some confusion and incoordination. A moderate case would be characterized by agitation, hyper-reflexia, diaphoresis, and shivering. In a severe case the patient will exhibit fever, myoclonus, and diarrhea. Severe cases require hospitalization.

The primary treatment is to discontinue the causative agent or agents. Symptoms will generally resolve in about 24 hours for agents with a half-life of less than 10 hours. For agents with half-lives between 10 and 18 hours, symptoms generally take three to four days more to resolve. If the causative agent has a half-life of more than 18 hours, patients may take much longer to recover. If delirium is present, symptoms will take at least four days to resolve.

The first and most important supportive measure is to deal with the hyperthermia. It is imperative that body temperature first be controlled. (Surgical procedures requiring anesthesia should be postponed for this reason.) Cooling blankets can help bring down body temperature, and then other agents can be administered as supportive measures: IM chlorpromazine as an antipyretic/sedative, anticonvulsants for the seizures, clonazepam for the myoclonus, and amlodipine to counteract the hypertension. Other symptoms can be treated systematically.

TABLE IV:
PROPOSED PATHOPHYSIOLOGIC RISK FACTORS

Inherited

Low endogenous MAO activity

Acquired

Liver disease

*Atherosclerosis

*Hypertension

*Hypercholesterolemia

*Damaged vascular or pulmonary epithelium

Substance abuse

Long-term amine use

*Diabetes

Iatrogenic

Serotonergic agents

**Reduced ability to secrete endothelium-derived nitric oxide*

Adapted from Sternbach H: Am J Psych 1991; 140:705-713

In treating serotonin syndrome, blockade of 5HT₁ receptors is crucial; 5HT₂ antagonists do not stop symptomatology. One effective agent is propranolol, which is a 5HT_{1A} receptor antagonist. Other beta-blockers only inhibit the syndrome induced by L-tryptophan/tranylcypamine.

By knowing how serotonergic agents operate on different 5HT receptors, physicians already have a plan for avoiding the potential mine fields that conflicting agents can create for their patients. The strategy is to know the patient's background (inherited and acquired risk factors) and to choose only those serotonergic agents selected for specific receptor sites.

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