

Serotonin syndrome

From Wikipedia, the free encyclopedia

Serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur following therapeutic drug use, inadvertent interactions between drugs, overdose of particular drugs, or the recreational use of certain drugs. Serotonin syndrome is not an idiosyncratic drug reaction; it is a predictable consequence of excess serotonergic activity at central nervous system (CNS) and peripheral serotonin receptors.^[1] For this reason, some experts strongly prefer the terms **serotonin toxicity** or **serotonin toxidrome** because these more accurately reflect the fact that it is a form of poisoning.^{[2][3]} It may also be called **serotonin sickness**, **serotonin storm**, **serotonin poisoning**, **hyperserotonemia**, or **serotonergic syndrome**.

The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects. The symptoms may range from barely perceptible to fatal.^[1] Numerous drugs and drug combinations have been reported to produce serotonin syndrome. Diagnosis of serotonin syndrome includes observing the symptoms produced and a thorough investigation of the patient's history. The syndrome has a characteristic picture but can be mistaken for other illnesses in some patients, particularly those with neuroleptic malignant syndrome. No laboratory tests can currently confirm the diagnosis.^[3]

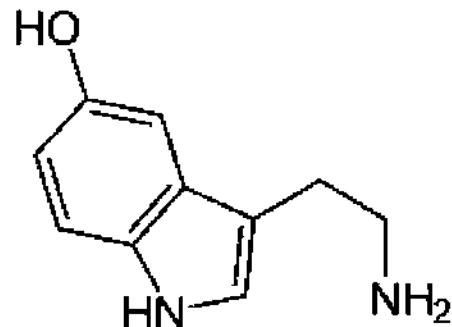
Treatment consists of discontinuing medications which may contribute and in moderate to severe cases administering a serotonin antagonist. An important adjunct treatment includes controlling agitation with benzodiazepine sedation. The high profile case of Libby Zion, who is generally accepted to have died from serotonin syndrome,^[1] resulted in changes to graduate medical education in New York State.^[4]

Contents

- 1 Signs and symptoms
- 2 Cause
- 3 Pathophysiology
- 4 Diagnosis
 - 4.1 Differential diagnosis
- 5 Management
 - 5.1 Agitation
 - 5.2 Hyperthermia
- 6 Prognosis
- 7 Epidemiology
- 8 Notable cases
- 9 References

Serotonin syndrome

Classification and external resources



Serotonin

ICD-9	333.99
DiseasesDB	30044
eMedicine	ped/2786
MeSH	<i>C21.613.276.720</i>

- 10 External links

Signs and symptoms

Symptom onset is usually rapid, often occurring within minutes. Serotonin syndrome encompasses a wide range of clinical findings. Mild symptoms may only consist of increased heart rate, shivering, sweating, dilated pupils, myoclonus (intermittent tremor or twitching), as well as overresponsive reflexes.^[1] Moderate intoxication includes additional abnormalities such as hyperactive bowel sounds, high blood pressure and hyperthermia; a temperature as high as 40 °C (104 °F) is common in moderate intoxication. The overactive reflexes and clonus in moderate cases may be greater in the lower limbs than in the upper limbs. Mental status changes include hypervigilance and agitation.^[1] Severe symptoms include severe increases in heart rate and blood pressure that may lead to shock. Temperature may rise to above 41.1 °C (106.0 °F) in life-threatening cases. Other abnormalities include metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation; these effects usually arise as a consequence of hyperthermia.^{[1][3]}

The symptoms are often described as a clinical triad of abnormalities:^{[1][5]}

- **Cognitive effects:** headache, agitation, hypomania, mental confusion, hallucinations, coma
- **Autonomic effects:** shivering, sweating, hyperthermia, hypertension, tachycardia, nausea, diarrhea.
- **Somatic effects:** myoclonus (muscle twitching), hyperreflexia (manifested by clonus), tremor.

Cause

A large number of medications either alone in high dose or in combination can produce serotonin syndrome.

Class	Drugs
Antidepressants	Monoamine oxidase inhibitors (MAOIs), ^[1] TCAs, ^[1] SSRIs, ^[1] SNRIs, ^[1] bupropion, ^[6] nefazodone, ^[7] trazodone ^[7]
Opioids	tramadol, ^[1] pethidine, ^[1] fentanyl, ^[1] pentazocine, ^[1] buprenorphine ^[8] oxycodone, ^[9] hydrocodone ^[9]
CNS stimulants	MDMA, ^[1] MDA, ^[1] phentermine, ^[10] diethylpropion, ^[10] amphetamine, ^{[3][10]} sibutramine, ^[1] methylphenidate, ^[10] methamphetamine, ^[11] cocaine ^[10]
5-HT ₁ agonists	triptans ^{[1][10]}
Psychedelics	5-Methoxy-diisopropyltryptamine, ^[1] LSD ^{[12][13]}
Herbs	St John's Wort, ^[1] Syrian rue, ^[1] Panax ginseng, ^[1] Nutmeg, ^[14] Yohimbe ^[15]
Others	tryptophan, ^[1] L-Dopa, ^[16] valproate, ^[1] buspirone, ^[1] lithium, ^[1] linezolid, ^{[1][17]} dextromethorphan, ^[1] 5-hydroxytryptophan, ^[7] chlorpheniramine, ^[10] risperidone, ^[18] olanzapine, ^[19] ondansetron, ^[1] granisetron, ^[1] metoclopramide, ^[1] ritonavir ^[1]

Many cases of serotonin toxicity occur in patients who have ingested drug combinations that

synergistically increase synaptic serotonin.^[5] It may also occur in patients following an overdose of a single serotonergic agent.^[20] The combination of MAOIs and other serotonin agonists or precursors pose a particularly severe risk of a life-threatening serotonin syndrome.^[21] Many MAOIs inhibit monoamine oxidase irreversibly, so that the enzyme cannot function until it has been replaced by the body, which can take at least four weeks.^[22]

Many medications may have been incorrectly thought to cause serotonin syndrome. For example, some case reports have implicated atypical antipsychotics in serotonin syndrome, but it appears based on their pharmacology that they are unlikely to cause the syndrome.^[23] It has also been suggested that mirtazapine has no significant serotonergic effects, and is therefore not a dual action drug.^[24] Bupropion has also been suggested to cause serotonin syndrome,^{[6][25]} although as there is no evidence that it has any significant serotonergic activity, it is thought unlikely to produce the syndrome.^[26] In 2006 the United States Food and Drug Administration issued an alert suggesting that the combined use of SSRIs or SNRIs and triptan medications or sibutramine could potentially lead to severe cases of serotonin syndrome.^[27] This has been disputed by other researchers as none of the cases reported by the FDA met the Hunter criteria for serotonin syndrome.^{[27][28]} The condition has however occurred in surprising clinical situations, and because of phenotypic variations among individuals, it has been associated with unexpected drugs, including mirtazapine.^{[29][30]}

The relative risk and severity of serotonergic side effects and serotonin toxicity, with individual drugs and combinations, is complex. Serotonin syndrome has been reported in patients of all ages, including the elderly, children, and even newborn infants due to in utero exposure.^{[31][32][33][34]} The serotonergic toxicity of SSRIs increases with dose, but even in over-dose it is insufficient to cause fatalities from serotonin syndrome in healthy adults.^{[35][36]} Elevations of central nervous system serotonin will typically only reach potentially fatal levels when drugs with different mechanisms of action are mixed together.^[3] Various drugs, other than SSRIs, also have clinically significant potency as serotonin reuptake inhibitors, (e.g. tramadol, amphetamine, and MDMA) and are associated with severe cases of the syndrome.^{[1][37]}

Pathophysiology

Serotonin is a neurotransmitter involved in multiple states including aggression, pain, sleep, appetite, anxiety, depression, migraine, and vomiting.^[5] In humans the effects of excess serotonin were first noted in 1960 in patients receiving a monoamine oxidase inhibitor (MAOI) and tryptophan.^[38] The syndrome is caused by increased serotonin in the central nervous system.^[1] It was originally suspected that agonism of 5-HT_{1A} receptors in central grey nuclei and the medulla was responsible for the development of the syndrome.^[39] Further study has determined that overstimulation of primarily the 5-HT_{2A} receptors appears to contribute substantially to the condition.^[39] The 5-HT_{1A} receptor may still contribute through a pharmacodynamic interaction in which increased synaptic concentrations of a serotonin agonist saturate all receptor subtypes.^[1] Additionally, noradrenergic CNS hyperactivity may play a role as CNS norepinephrine concentrations are increased in serotonin syndrome and levels appear to correlate with the clinical outcome. Other neurotransmitters may also play a role; NMDA receptor antagonists and GABA have been suggested as affecting the development of the syndrome.^[1] Serotonin toxicity is more pronounced following supra-therapeutic doses and overdoses, and they merge in a continuum with the toxic effects of overdose.^{[35][40]}

Spectrum concept

A postulated 'spectrum concept' of serotonin toxicity emphasises the role that progressively increasing serotonin levels play in mediating the clinical picture as side effects merge into toxicity. The dose-effect relationship is the term used to describe the effects of progressive elevation of serotonin, either by raising the dose of one drug, or combining it with another serotonergic drug which may produce large elevations in serotonin levels.^[41]

Diagnosis

There is no laboratory test for serotonin syndrome, therefore diagnosis is by symptom observation and investigation of the patient's history.^[1] Several diagnostic criteria have been proposed. The first criteria that were rigorously evaluated were introduced in 1991 by Harvey Sternbach, a professor of psychiatry at UCLA.^{[1][22][42]} Researchers in Australia have later developed the Hunter Serotonin Toxicity Criteria, which has better sensitivity and specificity, 84% and respectively 97%.^{[1][5]} As of 2007, Sternbach's criteria were still the most commonly used.^[3]

The most important symptoms for diagnosing serotonin syndrome are tremor, akathisia, or clonus (spontaneous, inducible and ocular).^[5] Physical examination of the patient should include assessment of deep-tendon reflexes and muscle rigidity, the dryness of the oral mucosa, the size and reactivity of the pupils, the intensity of bowel sounds, skin color, and the presence or absence of sweating.^[1] The patient's history also plays an important role in diagnosis, investigations should include enquiries about the use of prescription and over-the-counter drugs, illicit substances, and dietary supplements, as all these agents have been implicated in the development of serotonin syndrome.^[1] The Hunter Serotonin Toxicity Criteria suggests serotonin syndrome if the patient has taken a serotonergic agent and has symptoms of:^[5]

- Spontaneous clonus, or
- Inducible clonus or ocular clonus with agitation or diaphoresis, or
- Tremor and hyperreflexia, or
- Hypertension and temperature > 38 °C (100 °F) and ocular clonus or inducible clonus

Differential diagnosis

Serotonin toxicity has a characteristic picture which is generally hard to confuse with other medical conditions, but in some situations it may go unrecognized because it may be mistaken for a viral illness, anxiety, neurological disorder, anticholinergic poisoning, sympathomimetic toxicity, or worsening psychiatric condition.^{[1][3][43]} The condition most often confused with serotonin syndrome is neuroleptic malignant syndrome (NMS).^[44] The clinical features of neuroleptic malignant syndrome and serotonin syndrome share some features which can make differentiating them difficult.^[45] In both conditions, autonomic dysfunction and altered mental status develop.^[39] However, they are actually very different conditions with different underlying dysfunction (serotonin excess vs dopamine blockade). Both the time course and the clinical features of NMS differ significantly from those of serotonin toxicity.^[5] Serotonin toxicity has a rapid onset after the administration of a serotonergic drug and responds to serotonin blockade such as drugs like chlorpromazine and cyproheptadine. Dopamine receptor blockade (NMS) has a slow onset and typically evolves over several days after administration of a neuroleptic drug and responds to dopamine agonists such as bromocriptine.^{[1][39]}

Differential diagnosis may become difficult in patients recently exposed to both serotonergic drugs and neuroleptic drugs. Features that are classically present in NMS, that are useful for differentiating the two, are bradykinesia and extrapyramidal "lead pipe" rigidity, whereas serotonin syndrome causes hyperkinesia and clonus.^{[16][46]}

Management

Management is based primarily on stopping the usage of the precipitating drugs, the administration of serotonin antagonists such as cyproheptadine, and supportive care including the control of agitation, the control of autonomic instability, and the control of hyperthermia.^{[1][47]} Additionally, those who ingest large doses serotonergic agents may benefit from gastrointestinal decontamination with activated charcoal if it can be administered within an hour of overdose.^[3] The intensity of therapy depends on the severity of symptoms. If the symptoms are mild, treatment may only consist of discontinuation of the offending medication or medications, offering supportive measures, giving benzodiazepines for myoclonus, and waiting for the symptoms to resolve. Moderate cases should have all thermal and cardiorespiratory abnormalities corrected and can benefit from serotonin antagonists. The serotonin antagonist cyproheptadine is the recommended initial therapy, although there have been no controlled trials demonstrating its efficacy for serotonin syndrome.^{[3][48][49]} Despite the absence of controlled trials, there are a number of case reports detailing apparent improvement after patients have been administered cyproheptadine.^[3] Animal experiments also suggest a benefit from serotonin antagonists.^[50] Cyproheptadine is only available as tablets and therefore can only be administered orally or via a nasogastric tube; it is unlikely to be effective in patients administered activated charcoal and has limited use in severe cases.^[3] Additional pharmacological treatment for severe case includes administering atypical antipsychotic drugs with serotonin antagonist activity such as olanzapine.^[1] Critically ill patients should receive the above therapies as well as sedation or neuromuscular paralysis.^[1] Patient who have autonomic instability such as low blood pressure require treatment with direct-acting sympathomimetics such as epinephrine, norepinephrine, or phenylephrine.^[1] Conversely, hypertension or tachycardia can be treated with short-acting antihypertensive drugs such as nitroprusside or esmolol; longer acting drugs such as propranolol should be avoided as they may lead to hypotension and shock.^[1]

Agitation

Specific treatment for some symptoms may be required. One of the most important treatments is the control of agitation with benzodiazepines.^[1] Physical restraints are not recommended for agitation or delirium as they may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia. If physical restraints are necessary for severe agitation they must be rapidly replaced with pharmacological sedation.^[1]

Hyperthermia

Treatment for hyperthermia includes reducing muscle over-activity via sedation with a benzodiazepine. More severe cases may require muscular paralysis with vecuronium, intubation, and artificial ventilation.^{[1][3]} Succinylcholine is not recommended for muscular paralysis as it may increase the risk of cardiac dysrhythmia from hyperkalemia associated with rhabdomyolysis.^[1] Antipyretic agents are not recommended as the increase in body temperature is due to muscular activity not a hypothalamic

temperature set point abnormality.^[1]

Prognosis

Upon the discontinuation of serotonergic drugs, most cases of serotonin syndrome resolve within 24 hours,^{[1][3][51][52]} although in some cases delirium may persist for a number of days.^[22] Symptoms typically persist for a longer time frame in patients taking drugs which have a long elimination half-life, active metabolites, or a protracted duration of action.^[1]

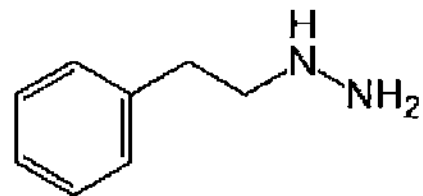
Cases have reported muscle pain and weakness persisting for months,^[53] and antidepressant discontinuation may contribute to ongoing features.^[54] Following appropriate medical management, serotonin syndrome is generally associated with a favorable prognosis.^[55]

Epidemiology

Epidemiological studies of serotonin syndrome are difficult as many physicians are unaware of the diagnosis or they may miss the syndrome due to its variable manifestations.^{[1][56]} In 1998 a survey conducted in England found that 85% of the general practitioners that had prescribed the antidepressant nefazodone were unaware of serotonin syndrome.^[32] The incidence may be increasing as a larger number of pro-serotonergic drugs (drugs which increase serotonin levels) are now being used in clinical practice.^[48] One post-marketing surveillance study identified an incidence of 0.4 cases per 1000 patient-months for patients who were taking nefazodone.^[32] Additionally, around 14 to 16 percent of persons who overdose on SSRIs are thought to develop serotonin syndrome.^[35]

Notable cases

The most widely recognized example of serotonin syndrome was the death of Libby Zion in 1984.^[57] Libby was a freshman at Bennington College at her death on March 5, 1984, at age 18. She died within 8 hours of her emergency admission to the New York Hospital Cornell Medical Center. She had an ongoing history of depression, and came to the Manhattan hospital on the evening of March 4, 1984, with a fever, agitation and "strange jerking motions" of her body. She also seemed disoriented at times. The emergency room physicians were unable to diagnose her condition definitively, but admitted her for hydration and observation. Her death was caused by a combination of pethidine (aka meperidine (Demerol)) and phenelzine.^[58] The doctor who prescribed the pethidine was a medical intern.^[59] The case had an impact on graduate medical education and residency work hours. Limits were set on working hours for medical post graduates, commonly referred to as interns or residents, in hospital training programs, and they also now require closer senior physician supervision.^[4]



Phenelzine is a MAOI which contributed to serotonin syndrome in the Libby Zion Case

References

1. [^]^a^b^c^d^e^f^g^hⁱ^j^k^l^mⁿ^o^p^q^r^s^t^u^v^w^x^y^z ^{aa} ^{ab} ^{ac} ^{ad} ^{ae} ^{af} ^{ag} ^{ah} ^{ai} ^{aj} ^{ak} ^{al} ^{am} ^{an} ^{ao} ^{ap} ^{aq} ^{ar} ^{as} ^{at} ^{au} ^{av} ^{aw} ^{ax} ^{ay} ^{az} ^{ba} ^{bb} ^{bc} ^{bd} ^{be} Boyer EW, Shannon M (2005). "The serotonin syndrome". *N Engl J Med* **352** (11): 1112–20. doi:10.1056/NEJMra041867. PMID 15784664.
2. [^] Gillman PK (June 2006). "A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action". *Biol Psychiatry* **59** (11): 1046–51. doi:10.1016/j.biopsych.2005.11.016. PMID 16460699.
3. [^]^a^b^c^d^e^f^g^hⁱ^j^k^l^m Isbister GK, Buckley NA, Whyte IM (September 2007). "Serotonin toxicity: a practical approach to diagnosis and treatment". *Med J Aust* **187** (6): 361–5. PMID 17874986. http://www.mja.com.au/public/issues/187_06_170907/isb10375_fm.html.
4. [^]^a^b Brensilver JM, Smith L, Lyttle CS (1998). "Impact of the Libby Zion case on graduate medical education in internal medicine". *Mt Sinai J Med* **65** (4): 296–300. PMID 9757752.
5. [^]^a^b^c^d^e^f^g Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (September 2003). "The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity". *QJM* **96** (9): 635–42. doi:10.1093/qjmed/hcg109. PMID 12925718.
6. [^]^a^b Munhoz RP (2004). "Serotonin syndrome induced by a combination of bupropion and SSRIs". *Clin Neuropharmacol* **27** (5): 219–22. doi:10.1097/01.wnf.0000142754.46045.8c. PMID 15602102.
7. [^]^a^b^c Ener RA, Meglathery SB, Van Decker WA, Gallagher RM (March 2003). "Serotonin syndrome and other serotonergic disorders". *Pain Med* **4** (1): 63–74. doi:10.1046/j.1526-4637.2003.03005.x. PMID 12873279. <http://www3.interscience.wiley.com/resolve/openurl?genre=article&sid=nlm:pubmed&issn=1526-2375&date=2003&volume=4&issue=1&spage=63>.
8. [^] Isenberg D, Wong SC, Curtis JA (September 2008). "Serotonin syndrome triggered by a single dose of suboxone". *Am J Emerg Med* **26** (7): 840.e3–5. doi:10.1016/j.ajem.2008.01.039. PMID 18774063.
9. [^]^a^b Gnanadesigan N, Espinoza RT, Smith RL (June 2005). "The serotonin syndrome". *N Engl J Med* **352** (23): 2454–6; author reply 2454–6. doi:10.1056/NEJM200506093522320. PMID 15948273.
10. [^]^a^b^c^d^e^f^g "Prescribing Practice Review 32: Managing depression in primary care". National Prescribing Service Limited. 2005. http://www.nps.org.au/_data/assets/pdf_file/0006/16971/ppr32.pdf. Retrieved 16 July 2006.
11. [^] Schep LJ, Slaughter RJ, Beasley DM (August 2010). "The clinical toxicology of metamfetamine". *Clin Toxicol (Phila)* **48** (7): 675–94. doi:10.3109/15563650.2010.516752. PMID 20849327.
12. [^] Bijl D (October 2004). "The serotonin syndrome". *Neth J Med* **62** (9): 309–13. PMID 15635814. <http://www.zuidencomm.nl/njm/getarticle.php?v=62&i=9&p=309>.
13. [^] Francis B, Harchelroad F (1996). "LSD/Fluoxetine induced serotonin syndrome". *J Toxicol Clin Toxicol* **34** (5): 560. doi:10.3109/15563659609028019. <http://www.informaworld.com/smpp/content~content=a784519284~db=all~order=page>.
14. [^] U. Braun U, Kalbhen DA: (October 1973). "Evidence for the Biogenic Formation of Amphetamine Derivatives from Components of Nutmeg". *Pharmacology* **9** (5): 312–16. doi:10.1159/000136402. PMID 4737998. <http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract&ArtikelNr=000136402&Ausgabe=236741&ProduktNr=224274>.
15. [^] http://www.erowid.org/plants/yohimbe/yohimbe_info1.shtml
16. [^]^a^b Birmes P, Coppin D, Schmitt L, Lauque D (May 2003). "Serotonin syndrome: a brief review". *CMAJ* **168** (11): 1439–42. PMC 155963. PMID 12771076. <http://www.cmaj.ca/cgi/pmidlookup?view=long&pmid=12771076>.
17. [^] Steinberg M, Morin AK (January 2007). "Mild serotonin syndrome associated with concurrent linezolid and fluoxetine". *Am J Health Syst Pharm* **64** (1): 59–62. doi:10.2146/ajhp060227. PMID 17189581.
18. [^] Karki SD, Masood GR (2003). "Combination risperidone and SSRI-induced serotonin syndrome". *Ann Pharmacother* **37** (3): 388–91. doi:10.1345/aph.1C228. PMID 12639169.
19. [^] Verre M, Bossio F, Mammone A, *et al.* (2008). "Serotonin syndrome caused by olanzapine and clomipramine". *Minerva Anestesiol* **74** (1–2): 41–5. PMID 18004234. <http://www.minervamedica.it/index2.t?show=R02Y2008N01A0041>.
20. [^] Fraser J, South M (May 1999). "Life-threatening fluvoxamine overdose in a 4-year-old child". *Intensive Care Med* **25** (5): 548. doi:10.1007/PL00003776. PMID 10401959. <http://link.springer-ny.com/link/service/journals/00134/bibs/9025005/90250548.htm>.
21. [^] Sun-Edelstein C, Tepper SJ, Shapiro RE (September 2008). "Drug-induced serotonin syndrome: a review". *Expert Opin Drug Saf* **7** (5): 587–96. doi:10.1517/14740338.7.5.587. PMID 18759711.

22. ^{^ a b c} Sternbach H (June 1991). "The serotonin syndrome". *Am J Psychiatry* **148** (6): 705–13. PMID 2035713. <http://ajp.psychiatryonline.org/cgi/pmidlookup?view=long&pmid=2035713>.
23. [^] Isbister GK, Downes F, Whyte IM (April 2003). "Olanzapine and serotonin toxicity". *Psychiatry Clin Neurosci* **57** (2): 241–2. doi:10.1046/j.1440-1819.2003.01110.x. PMID 12667176. <http://www.blackwell-synergy.com/openurl?genre=article&sid=nlm:pubmed&issn=1323-1316&date=2003&volume=57&issue=2&spage=241>.
24. [^] Gillman P (2006). "A systematic review of the serotonergic effects of mirtazapine in humans: implications for its dual action status". *Hum Psychopharmacol* **21** (2): 117–25. doi:10.1002/hup.750. PMID 16342227.
25. [^] Thorpe EL, Pizon AF, Lynch MJ, Boyer J (June 2010). "Bupropion induced serotonin syndrome: a case report". *J Med Toxicol* **6** (2): 168–71. doi:10.1007/s13181-010-0021-x. PMID 20238197.
26. [^] Gillman PK (June 2010). "Bupropion, bayesian logic and serotonin toxicity". *J Med Toxicol* **6** (2): 276–7. doi:10.1007/s13181-010-0084-8. PMID 20440594.
27. ^{^ a b} Evans RW (2007). "The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and Triptans: an analysis of the 29 case reports". *MedGenMed* **9** (3): 48. PMC 2100123. PMID 18092054. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2100123>.
28. [^] Wenzel RG, Tepper S, Korab WE, Freitag F (November 2008). "Serotonin syndrome risks when combining SSRI/SNRI drugs and triptans: is the FDA's alert warranted?". *Ann Pharmacother* **42** (11): 1692–6. doi:10.1345/aph.1L260. PMID 18957623.
29. [^] Duggal HS, Fetchko J (April 2002). "Serotonin syndrome and atypical antipsychotics". *Am J Psychiatry* **159** (4): 672–3. doi:10.1176/appi.ajp.159.4.672-a. PMID 11925312. <http://ajp.psychiatryonline.org/cgi/pmidlookup?view=long&pmid=11925312>. Retrieved 2009-02-15.
30. [^] Boyer and Shannon's reply to Gillman PK (June 2005). "The serotonin syndrome". *N Engl J Med* **352** (23): 2454–6; author reply 2454–6. doi:10.1056/NEJM200506093522320. PMID 15948272.
31. [^] Laine K, Heikkinen T, Ekblad U, Kero P (July 2003). "Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations". *Arch. Gen. Psychiatry* **60** (7): 720–6. doi:10.1001/archpsyc.60.7.720. PMID 12860776.
32. ^{^ a b c} Mackay FJ, Dunn NR, Mann RD (November 1999). "Antidepressants and the serotonin syndrome in general practice". *Br J Gen Pract* **49** (448): 871–4. PMC 1313555. PMID 10818650. <http://openurl.ingenta.com/content/nlm?genre=article&issn=0960-1643&volume=49&issue=448&spage=871&aulast=Mackay>.
33. [^] Isbister GK, Dawson A, Whyte IM, Prior FH, Clancy C, Smith AJ (September 2001). "Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome?". *Arch Dis Child Fetal Neonatal Ed* **85** (2): F147–8. doi:10.1136/fn.85.2.F145g. PMC 1721292. PMID 11561552. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1721292>.
34. [^] Gill M, LoVecchio F, Selden B (April 1999). "Serotonin syndrome in a child after a single dose of fluvoxamine". *Ann Emerg Med* **33** (4): 457–9. doi:10.1016/S0196-0644(99)70313-6. PMID 10092727.
35. ^{^ a b c} Isbister G, Bowe S, Dawson A, Whyte I (2004). "Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose". *J Toxicol Clin Toxicol* **42** (3): 277–85. doi:10.1081/CLT-120037428. PMID 15362595.
36. [^] Whyte IM, Dawson AH (2002). "Redefining the serotonin syndrome [abstract]". *J Toxicol Clin Toxicol* **40** (5): 668–9. doi:10.1081/CLT-120016859.
37. [^] Vuori E, Henry J, Ojanperä I, Nieminen R, Savolainen T, Wahlsten P, Jääntti M (2003). "Death following ingestion of MDMA (ecstasy) and moclobemide". *Addiction* **98** (3): 365–8. doi:10.1046/j.1360-0443.2003.00292.x. PMID 12603236.
38. [^] Oates JA, Sjoerdsma A (December 1960). "Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor". *Neurology* **10**: 1076–8. PMID 13730138.
39. ^{^ a b c d} Whyte, Ian M. (2004). "Serotonin Toxicity/Syndrome". *Medical Toxicology*. Philadelphia: Williams & Wilkins. pp. 103–6. ISBN 0-7817-2845-2.
40. [^] Whyte I, Dawson A, Buckley N (2003). "Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants". *QJM* **96** (5): 369–74. doi:10.1093/qjmed/hcg062. PMID 12702786.
41. [^] Gillman PK (June 2004). "The spectrum concept of serotonin toxicity". *Pain Med* **5** (2): 231–2. doi:10.1111/j.1526-4637.2004.04033.x. PMID 15209988.
42. [^] Hegerl U, Bottlender R, Gallinat J, Kuss HJ, Ackenheil M, Möller HJ (1998). "The serotonin syndrome scale: first results on validity". *Eur Arch Psychiatry Clin Neurosci* **248** (2): 96–103.

- doi:10.1007/s004060050024. PMID 9684919.
<http://link.springer.de/link/service/journals/00406/bibs/8248002/82480096.htm>.
43. ^ Fennell J, Hussain M (2005). "Serotonin syndrome: case report and current concepts". *Ir Med J* **98** (5): 143–4. PMID 16010782.
 44. ^ Nisijima K, Shioda K, Iwamura T (2007). "Neuroleptic malignant syndrome and serotonin syndrome". *Prog Brain Res* **162**: 81–104. doi:10.1016/S0079-6123(06)62006-2. PMID 17645916.
 45. ^ Christensen V, Glenthøj B (2001). "[Malignant neuroleptic syndrome or serotonergic syndrome]". *Ugeskr Laeger* **163** (3): 301–2. PMID 11219110.
 46. ^ Isbister GK, Dawson A, Whyte IM (September 2001). "Citalopram overdose, serotonin toxicity, or neuroleptic malignant syndrome?". *Can J Psychiatry* **46** (7): 657–9. PMID 11582830.
 47. ^ Sporer K (1995). "The serotonin syndrome. Implicated drugs, pathophysiology and management". *Drug Saf* **13** (2): 94–104. doi:10.2165/00002018-199513020-00004. PMID 7576268.
 48. ^ ^a ^b Graudins A, Stearman A, Chan B (1998). "Treatment of the serotonin syndrome with cyproheptadine". *J Emerg Med* **16** (4): 615–9. doi:10.1016/S0736-4679(98)00057-2. PMID 9696181.
<http://linkinghub.elsevier.com/retrieve/pii/S0736467998000572>.
 49. ^ Gillman PK (1999). "The serotonin syndrome and its treatment". *J Psychopharmacol (Oxford)* **13** (1): 100–9. doi:10.1177/026988119901300111. PMID 10221364.
 50. ^ Nisijima K, Yoshino T, Yui K, Katoh S (January 2001). "Potent serotonin (5-HT)_{2A} receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome". *Brain Res*. **890** (1): 23–31. doi:10.1016/S0006-8993(00)03020-1. PMID 11164765.
 51. ^ Prator B (2006). "Serotonin syndrome". *J Neurosci Nurs* **38** (2): 102–5. doi:10.1097/01376517-200604000-00005. PMID 16681290.
 52. ^ Jaunay E, Gaillac V, Guelfi J (2001). "[Serotonin syndrome. Which treatment and when?]". *Presse Med* **30** (34): 1695–700. PMID 11760601.
 53. ^ Chechani V (February 2002). "Serotonin syndrome presenting as hypotonic coma and apnea: potentially fatal complications of selective serotonin receptor inhibitor therapy". *Crit Care Med* **30** (2): 473–6. doi:10.1097/00003246-200202000-00033. PMID 11889332. <http://meta.wkhealth.com/pt/pt-core/template-journal/lwwgateway/media/landingpage.htm?issn=0090-3493&volume=30&issue=2&spage=473>.
 54. ^ Haddad PM (2001). "Antidepressant discontinuation syndromes". *Drug Saf* **24** (3): 183–97. doi:10.2165/00002018-200124030-00003. PMID 11347722.
 55. ^ Mason PJ, Morris VA, Balcezak TJ (July 2000). "Serotonin syndrome. Presentation of 2 cases and review of the literature". *Medicine (Baltimore)* **79** (4): 201–9. doi:10.1097/00005792-200007000-00001. PMID 10941349. <http://meta.wkhealth.com/pt/pt-core/template-journal/lwwgateway/media/landingpage.htm?issn=0025-7974&volume=79&issue=4&spage=201>.
 56. ^ Sampson E, Warner JP (November 1999). "Serotonin syndrome: potentially fatal but difficult to recognize". *Br J Gen Pract* **49** (448): 867–8. PMC 1313553. PMID 10818648. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1313553>.
 57. ^ Brody, Jane (February 27, 2007). "A Mix of Medicines That Can Be Lethal". *New York Times*. <http://www.nytimes.com/2007/02/27/health/27brody.html?n=Top/News/Health/Diseases,%20Conditions,%20and%20Health%20Topics/Antidepressants>. Retrieved 2009-02-13. "The death of Libby Zion, an 18-year-old college student, in a New York hospital on March 5, 1984, led to a highly publicized court battle and created a cause célèbre over the lack of supervision of inexperienced and overworked young doctors. But only much later did experts zero in on the preventable disorder that apparently led to Ms. Zion's death: a form of drug poisoning called serotonin syndrome."
 58. ^ Asch DA, Parker RM (March 1988). "The Libby Zion case. One step forward or two steps backward?". *N Engl J Med* **318** (12): 771–5. doi:10.1056/NEJM198803243181209. PMID 3347226.
 59. ^ Jan Hoffman (January 1, 1995). "Doctors' Accounts Vary In Death of Libby Zion". *The New York Times*. <http://query.nytimes.com/gst/fullpage.html?sec=health&res=990CE4DC1230F932A35752C0A963958260>. Retrieved 2008-12-08.

External links

- Image demonstrating findings in moderately severe serotonin syndrome from Boyer EW, Shannon M (2005). "The serotonin syndrome". *N Engl J Med* **352** (11): 1112–20. doi:10.1056/NEJMra041867. PMID 15784664.

Retrieved from "http://en.wikipedia.org/w/index.php?title=Serotonin_syndrome&oldid=487649921"

Categories: Pharmacology | Syndromes

- This page was last modified on 16 April 2012 at 11:24.
- Text is available under the Creative Commons Attribution-ShareAlike License; additional terms may apply. See Terms of use for details.
Wikipedia® is a registered trademark of the Wikimedia Foundation, Inc., a non-profit organization.