Serotonin syndrome

Stefan Alusik [1], Dagmar Kalatova [2], Zoltan Paluch [2,3]

1 Institute for Postgraduate Medical Education, Prague, Czech Republic
2 St. Elizabeth University of Health and Social Work, Bratislava, Slovakia, St. J. N. Neumann Institute Příbram, Czech Republic
3 First Faculty of Medicine, Institute of Pharmacology, Charles University Prague, Czech Republic

Correspondence to: Assoc. Prof. Zoltán Paluch, MD, PHD., MBA
First Faculty of Medicine, Institute of Pharmacology, Charles University Prague, Žitná 32, 120 00 Praha 2, Czech Republic.
TEL: +420 721737009; E-MAIL: Paluch.Z@seznam.cz

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Abstract

Serotonin syndrome is a potentially serious clinical condition. In this article, the authors put serotonin syndrome into historical context, discuss its pathophysiology, review in detail its clinical presentations, diagnostic criteria, differential diagnosis and treatment. Special attention is given to drugs that most often cause serotonin syndrome, and the gene polymorphisms involved in the metabolism of these drugs.

Serotonin syndrome is a potentially life-threatening condition developing through increased serotogernic activity in the central nervous system (Isbister *et al.* 2007; Boyer 2013; Gillman 2012; Hall *et al.* 2007; Hall *et al.* 2007). Some authors prefer the term serotonin toxicity or serotonin toxidrome instead of serotonin syndrome. Serotonin syndrome occurs in all age groups. Its incidence increased after the introduction of selective serotonin reuptake inhibitors (SSRI) into clinical practice. Serotonin syndrome developed in about 15% of patients receiving excessive doses of SSRIs (Isbister *et al.* 2004). In the USA, out of 48 204 cases of exposure to an SSRI in 2004, there were 8 187 reported cases of moderate and severe serotonin intoxication resulting in 103 deaths (Watson *et al.* 2005). In many cases, the effect of serotogernic medication is enhanced by drug interactions. Those developing serotonin syndrome require early diagnosis and initiation of therapy to make the prognosis favorable which means, in practice, that the patient should be both informed and aware of their condition. This is true particularly of first-line physicians. On the one hand, consumption of serotonergic drugs in the population continues to rise with a subsequent increase in the rate of drug interactions occurring due to polymedication; on the other hand, the awareness of physicians of potential side effects of drugs is still inadequate. In an earlier study, up to 85% of physicians were unaware of serotonin syndrome as a clinical diagnosis (Mackay *et al.* 1999).

HISTORY

Soon after the advent of tricyclic antidepressants and monoamine oxidase (MAO) inhibitors as therapies in the late 1950s, there were emerging reports about alterations in the behavior of not only experimental animals but, also, of treated patients. Presentations included increased physical activity, tremor, hyperexcitability, dilatation of the pupil, salivation, flush, tachypnea, hypertension, fever, myoclonus, and spasms (Bogdanski *et al.* 1958). In the 1970s, abnormal behavior of experimental animals treated with serotonin agonists was termed "serotonin behavioral syndrome" (Grahame-Smith 1971; Jacobs *et al.* 1975), this was further specified by Jacobs in 1976. The first to describe this response in humans was Mitchel in

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1955 in his report on a patient with tuberculosis treated with iproniazide and meperidine (pethidine). The patient died with the diagnosis of "fatal toxic encephalitis". Clinical manifestations related to excess serotonin levels in the central nervous system in man were first described by Oates and Sjostrand (1960) referring to "indolamine syndrome". These authors observed, in several hypertensive patients taking L-tryptophan (20–50 mg) while treated with a MAO inhibitor (beta-phenylisopropylhydrazine), impaired mental function, nervousness, sweating, myoclonus, ataxia, and hyperreflexia. The authors were the first to suggest the clinical manifestations of indolamine syndrome are due to increased serotonin and tryptamine levels. The author credited with coining the term serotonin syndrome in 1982 is Insel, although Gillman (1998), in his review, noted the clinical picture of serotonin syndrome and its etiology had been described earlier (Gerson *et al.* 1980). The first criteria of serotonin syndrome were developed and published by Sternbach in 1991 to be further specified by Radomski *et al.* in 2000, with new criteria (referred to as the Hunter Serotonin Toxicity Criteria) appearing in 2003 (Dunkley *et al.* 2003). Regarding treatment, a landmark study was an experimental one published in 1971 (Grahame-Smith 1971), documenting the inhibitory action of chlorpromazine on hyperactivity and hyperpyrexia induced by L-tryptophan in MAO inhibitor-treated rats.

PATHOPHYSIOLOGY

Although serotonin (5-hydroxytryptamine) was first isolated and got its name in 1948 (Rapport *et al.* 1948), its effects in the body are not yet fully understood (Amireault *et al.* 2013). In fact, the substance, identified 10 years before serotonin isolation, was referred to in the relevant literature as enteramine (Vialli *et al.* 1937) and it took some time before both were found to be actually identical (Erspamer *et al.* 1952). Serotonin is a neurotransmitter playing a crucial role in affecting numerous states such as aggression, pain, fear, sleep, appetite, migraine, and vomiting; more recently, it has been implicated in other processes such as bone metabolism, hemostasis, blood pressure control, anti-inflammatory action, and so on (Yadav *et al.* 2008; Tseng *et al.* 2013; Watts *et al.* 2012; Yu *et al.* 2008; Zhang *et al.* 2012; Beikmann *et al.* 2013). Serotonin is produced by hydroxylation and decarboxylation of L-tryptophan. Its chemical structure is similar to that of melatonin and belongs to the class of indolalkylamines. In the body, it is synthesized in brainstem neurons and in the gastrointestinal tract. The key enzyme involved in serotonin synthesis is tryptophan hydroxylase (Tph). A decade ago, Tph has been shown to have two isoforms, Tph1 and Tph2 (Walther *et al.* 2003). While the presence of Tph2 is limited to nerve cells, Tph1 occurs in the other non-neuronal tissues. Brain-synthesized serotonin affects attention, behavior, and thermoregulation. It is estimated that the serotonin produced in the brain accounts for 1–2% of the total amount of serotonin in the body. Up to 95% of serotonin is formed in the enterochromaffin cells of the gastrointestinal tract to subsequently enter blood circulation where it is eventually reuptaken by thrombocytes via specific transporters (Jedlitschki *et al.* 2012). A small fraction remains in the blood acting as a hormone and affecting, e.g., bone metabolism. The serotonin synthesized in the gastrointestinal tract has been shown to affect its motility, vasoconstriction, uterine contractions, and bronchoconstriction. Serotonin is metabolized predominantly by monoamine oxidase (MAO) and excreted into the urine as 5-hydroxyindolacetic acid.

A major breakthrough in our understanding of the action of serotonin came with the discovery of serotonin receptors. In their experiments with the guinea pig ileum, Gaddum and Picarelli identified two types of 5-HT receptors: the D receptor (for dibenziline) and the M receptor (for morphine) (Gaddum *et al.* 1957). The D receptors were later found to be akin to the 5-HT2 and M 5-HT3 receptors. It was as early as 1979 that Peroutka and Snyder identified two types of serotonin-binding receptors in the brain named 5-HT1 a 5-HT2; this group of receptors gradually expanded including as it was newcomer receptors. Today, serotonin receptors are divided into 7 groups with some of them split further into subgroups. The role of some novel receptors remains unknown (Pytliak *et al.* 2011) despite intensive research in this area (Wang *et al.* 2013; Wacker *et al.* 2013). The 5-HT1A receptor occurs predominantly in the brain, the peripheral one mainly in the plexus myentericus of the gastrointestinal tract (Hoyer *et al.* 2002). It is encoded by a gene localized on chromosome 5q11.2-q13. The receptor 5-HT2A gene is localized on chromosome 13q14-q21. In addition to the brain, the 5-HT2A receptor is relatively abundant in peripheral organs where it mediates the constrictive response of the smooth muscle (bronchi, uterus, urinary tract), vasoconstriction/vasodilation, platelet aggregation, and increases capillary permeability (Pytliak *et al.* 2011; Hoyer *et al.* 2002).

In the brain, serotonin is produced by presynaptic neurons, mainly in the pons and upper section of the brainstem. If bound to post-synaptic receptors, it remains active until it is removed by reuptake pumps or degraded by MAO. The cause of serotonin syndrome is overstimulation of post-synaptic serotonin receptors in the CNS. In experimental animals, a role in the symptomatology of serotonin syndrome is played by post-synaptic 5-HT receptors in the region of so-called raphe nuclei distributed near the midline of the brainstem along its rostro-caudal extension, and divided into 9 anatomical-functional groups (B1–B9) (Frazer *et al.* 1999). As serotonin does not cross the blood-brain barrier, increased peripheral serotonin levels, such as those found in carcinoid patients, do not get reflected in the CNS (Gillman 2012). As regards serotonin syn-

drome, the receptors playing a crucial role are 5-HT 1A and 5-HT2A. In terms of clinical symptomatology, 5-HT1A overstimulation has been implicated in conditions such as hyperactivity, hyperreflexia, and anxiety, while 5-HT2A overstimulation has been suggested to cause hyperthermia, poor coordination, and neuromuscular irritability. While, in the past, 5-HT1A receptors were believed to play a more important role in the pathogenesis of serotonin syndrome, today, such a role is generally attributed to the 5-HT2A receptors. In animal experiments, post-synaptic 5-HT2A receptor blockade prevented death of animals from hyperpyrexia whereas 5-HTA1 receptor blockade failed to have this effect (Nisijima *et al.* 2000; Nisijima *et al.* 2001; Nisijima *et al.* 2003; Nisijima *et al.* 2004). Also, experiments have demonstrated high noradrenaline levels in the hypothalamus; noradrenaline has also been implicated in the manifestations of serotonin syndrome. While dopamine, gamma-aminobutyric acid, and other factors including other receptors have also been suggested to be involved in the development of serotonin syndrome (Diaz *et al.* 2011), their contribution has not been conclusively documented. Despite several similarities between serotonin behavioral syndrome in animal experiments and serotonin syndrome in man, some experts call for caution when interpreting findings in individual groups and caution against generalization (Isbister *et al.* 2005; Izumi *et al.* 2006). Recently, there has been an effort at standardizing animal models using even modern genetic methods to allow for a more detailed insight into the pathogenesis of serotonin syndrome and more effective use of these models in preclinical testing of drugs (Haberzettel *et al.* 2013).

Potential therapeutic options are focused on at least 4 mechanisms of action resulting in excess activation of serotonin receptors (Iqbal *et al.* 2012):

- decreasing serotonin breakdown (MAO inhibitors, linezolid)
- decreasing serotonin reuptake (SSRIs, tricyclic antidepressants, tramadol, fentanyl, cocaine, amphetamine, etc.)
- increasing serotonin precursors or agonists (L-tryptophan, antimigraine drugs, buspirone, etc.)
- increasing serotonin release (amphetamine, cocaine, buspirone, lithium)

CLINICAL PICTURE

The clinical picture of serotonin syndrome is characterized by three types of presentations (Table 1): 1) increased neuromuscular irritability, 2) increased activity of the autonomic nervous system, 3) impaired mental status (Isbister *et al.* 2007; Boyer 2013; Boyer *et al.* 2005; Ables *et al.* 2010; Gillman 2005; Walsh 2010; Buckley *et al.* 2014). Some authors have even separated gastrointestinal manifestations (diarrhea, abdominal spasms, hyperactive bowel sounds) from the second group to refer to an entity useful in the differential diagnosis of serotonin syndrome (Hall *et al.* 2007).

Manifestations involving the neuromuscular system include the most frequent ones in serotonin syndrome. Up to 50% of serotonin syndrome patients show manifestations related to increased neuromuscular activity, primarily tremor, hyperreflexia, and hypertonia (more intensive in the lower limbs), bilateral Babinski sign, bruxism, myoclonus, ataxia, nystagmus, and pyramidal rigidity involving also trunk muscles.

Presentations related to the autonomic nervous system can be encountered in up to 40% of serotonin syndrome patients. These include dilated unresponsive pupils, tachycardia, tachypnea, diarrhea, abdominal pain, flush, profuse sweating, elevated temperature, hypertension or hypotension.

Mental disorders include a wide range of conditions, from mild ones to unconsciousness: agitation, excitation, restlessness, hyperactivity, fear, disorientation, lethargy, hallucinations, delirium, and coma occurring in close to 40% of serotonin syndrome patients (Iqbal *et al.* 2012). Summarizing data of a group of 168 patients identified in literature reports, Keck *et al.* found mental disorders including mood swings in up to 85% of these patients (Keck *et al.* 2000).

Importantly, patients with serotonin syndrome may not necessarily show symptoms of all of the three above categories, but just one. The key finding for establishing the diagnosis of serotonin syndrome is increased neuromuscular excitability. New-onset tremor, clonus, muscular rigidity, and brisk reflexes should invariably make the physician consider serotonin syndrome in the differential diagnosis (Lawrence 2013).

Serotonin syndrome is associated with a wide spectrum of clinical manifestations ranging from mild forms to fatal ones (Frank 2008). Depending on their severity, the manifestations are divided into three groups, mild, moderate, and severe (Radomski *et al.* 2000). Mild forms may occur even if serotonergic therapy remains within the therapeutic range. Mild manifestations of toxicity include restlessness, intermittent tremor, sweating, mydriasis, and so on. Moderate forms are associated with tachycardia, hypertension, hyperthermia, hyperreflexia/clonus, sweating, and mental disorders such as restlessness, mild agitation, and hypervigilance. Patients with moderate presenta-

Tab. 1. Clinical features of serotonin toxicity (Isbister *et al.* 2007).

Neuromuscular effects	Autonomic effects	Mental state changes
Hyperreflexia	Hyperthermia:	Agitation
Clonus	mild: below 38.5 °C	Hypomania
Myoclonus	severe: over 38.5 °C	Anxiety
Shivering	Tachycardia	Confusion
Tremor	Diaphoresis	
Hypertonia/rigidity	Flushing	
	Mydriasis	

tions will usually require symptomatic management. Those with full-blown and toxic forms experience generalized tonic-clonic spasms, variable blood pressure levels (hypertension or hypotension), muscle rigidity, delirium, and coma. Elevated temperature is frequently in excess of 40 °C; the patient may develop rhabdomyolysis, renal failure, metabolic acidosis or less often, disseminated intravascular coagulopathy. Increased muscle tone, clonus, and hyperthermia, which may be high as 41 °C, invariably suggest a serious, life-threatening course, eventually progressing – if left untreated – to multiple organ failure within several hours. These most severe forms are encountered in patients taking combinations of drugs targeted at different sites, most often MAO inhibitors and SSRIs (Gillman 2006).

Tab. 2. Sternbach´s criteria for serotonin syndrome (Sternbach 1991).

1.	Requires serotonergic agent started or increased
2.	At least of 3 of the following clinical features are present: • Agitation • Diaphoresis • Diarrhea • Fever • Hyperreflexia • Incoordination • Mental state changes (confusion, hypomania) • Myoclonus • Shivering • Tremor
3.	Other causes ruled out
4.	A neuroleptic had not been started or increased in dosage

Tab. 3. Radomski´s revised diagnostic criteria for serotonin syndrome (Radomski 2000).

1.	Requires serotonergic agent started or increased
2.	Presence of 4 of the following major symptoms or 3 major and 2 of the following minor symptoms: • Major symptoms: diaphoressis, elevated mood, fever, hyperreflexia, impaired consciousness, myoclonus, rigidity, semicoma/coma, shivering, tremor • Minor symptoms: akathisia, diarrhea, dilated pupils, hypertension or hypotension, incoordination, insomnia, restlessness, tachycardia, tachypnea or dyspnea
3.	Symptoms not related to preexisting psychiatric disorders or better explained by another process (eg. infection, change in neuroleptic medication)

Tab. 4. The Hunter Serotonin Toxicity Criteria (Dunkley 2003).

To fulfill the Hunter criteria, a patient had to take a serotonergic agent and meet one of the following conditions:
- Spontaneous clonus
- Inducible clonus plus agitations or diaphoresis
- Ocular clonus plus agitation or diaphoresis
- Tremor plus hyperreflexia
- Hypertonia plus temperature above 38 °C plus ocular clonus or inducible clonus

The onset of symptoms is rapid; they will usually appear within 6 hours of increasing dosage or adding another serotogernic drug (Sternbach 1991; Iqbal *et al.* 2012) and will in most cases wane within 24 hours of discontinuing therapy; clinical presentations may persist longer after the administration of drugs with long half-life (Boyer 2013; Watson *et al.* 2005). Development of Serotonin syndrome may also be triggered by initiation of another type of serotonergic therapy within 5 weeks of SSRI discontinuation.

The risk for developing Serotonin syndrome is increased with elderly patients because of their lower ability to metabolize drugs and concurrent use of various types of drugs. A combination associated with a particular risk is one of antidepressants and analgesics. The risk is also increased by renal dysfunction, a condition frequently found in the elderly, and involving excretion rates.

DIAGNOSIS

The diagnosis of Serotonin syndrome is based exclusively on physical examination; no laboratory tests are currently available. As the spectrum of clinical manifestations of Serotonin syndrome is fairly broad, key steps in the diagnostic work-up include taking a thorough patient´s history including current medication, physical examination, and exclusion of other potential causes such as neurological disease (meningoencephalitis), septic conditions, delirium tremens, heat stroke, neuroleptic malignant syndrome, and toxic effects of sympatomimetics and anticholinergics. Syndrome-related diagnosis should not be established without identifying the underlying cause. Given the broad spectrum of clinical manifestations on the one hand and absence of laboratory-based diagnostic tools on the other, there have been several attempts to aid Serotonin syndrome diagnosis by developing diagnostic criteria with varied sensitivity and specificity. The first criteria were introduced by Harvey Sternbach, a US professor in psychiatry, in 1991 (Table 2). His criteria have been used to date (Butterfield *et al.* 2012) and were the most frequently used diagnostic tool as late as 2007. Radomski *et al.* (2000) should be credited for criteria distinguishing Serotonin syndrome forms by their intensity into mild, full-blown, and toxic, with symptoms categorized by their relevance into major and minor ones (Table 3).

The currently most often used criteria are those developed by Hunter (2003) and reported to have a sensitivity of 84% and specificity of 97% (Table 4). As compared with the Sternbach criteria, those developed by Hunter are believed to be more accurate and less prone to miss early, mild or subacute forms of Serotonin syndrome.

Laboratory investigations in Serotonin syndrome may reveal elevated creatine kinase and myoglobin levels with the more severe forms; other findings are either non-specific (leukocytosis, hyperazotemia) or

are due to complications. A standard approach includes determination of minerals (sodium, potassium, magnesium, and calcium) because of inadequate hydration and toxicological tests to rule out another source of intoxication when in doubt. Determination of serum serotonin levels has proved to be of no use.

DIFFERENTIAL DIAGNOSIS

The purpose of differential diagnosis is to primarily distinguish three types of disease entities: 1) neuroleptic malignant syndrome (NMS), 2) anticholinergic toxicity and, 3) agitated delirium following alcohol or benzodiazepine withdrawal. Although Serotonin syndrome presentations may be similar to those of NMS (delirium, hyperthermia, rhabdomyolysis, tachycardia, sweating, rigidity, and hypertension), some major differences may serve as a guide in the differential diagnosis (Perry *et al.* 2012). First and foremost, it is the rate of onset of clinical manifestations after drug administration. With Serotonin syndrome, the onset of symptoms occurs within several minutes to hours. Symptoms of Serotonin syndrome occurred within 2 hours of use of medication in 50% of patients and within 24 hours in 75% of patients (Iqbal *et al.* 2012; Ener *et al.* 2003). Mild cases with low levels of manifestations may take a chronic form. In contrast, NMS will develop within several days to weeks of medication use. Differences also exist in clinical symptomatology. Whereas characteristic features of Serotonin syndrome include myoclonus and hyperreflexia, these are rigidity and bradyreflexia with NMS. By contrast, myoclonus and hyperreflexia are a rare occurrence with NMS. Clinical manifestations of Serotonin syndrome resolve quickly after drug withdrawal (within 24 hours), they may take several days to disappear with NMS (mean, 9 days).

Anticholinergic-related intoxication may manifest itself by impaired mental function, hyperthermia, tachycardia, mydriasis, and urine retention. Unlike those with Serotonin syndrome, these patients have dry skin and mucosal membranes while intestinal gurgling is minimal. The most frequent disease entity potentially mimicking Serotonin syndrome develops upon withdrawal of alcohol or benzodiazepines. Clinical manifestations may take the form of hallucinations, tremor, hyperreflexia, clonus, tachycardia, hypertension, and spasms. In these cases, data about current medication, alcohol, withdrawal therapy, and onset of symptoms are of crucial importance.

Differential diagnosis is also used to exclude meningitis and encephalitis. Malignant hyperthermia occurs rarely in predisposed individuals given halogen anesthetics or myorelaxants (succinylcholine).

Tab. 5. Reported drug combinations causing serotonin syndrome. Adapted from Volpi-Abadie *et al.* (Volpi-Abadie 2013)

Drug	Drug combinations
SSRIs	SSRI alone
	SSRIs with MAOIs or SNRIs or TCAs or opiates or triptans
MAOIs	MAOI alone
	MAOIs with SSRIs or SNRIs or TCAs or opiates
SNRIs	Venlafaxine alone
	SNRIs with MAOIs or TCAs or opiates or triptans
	Venlafaxine with lithium or calcineurin inhibitors
Other antidepressants	Mirtazapine alone*
	Mirtazapine with SSRIs
	Buspirone with SSRIs
	Trazodone with amitriptyline and lithium
Opiates	Tramadol alone
	Tramadol with mirtazapine and olanzapine
	Opiates with MAOIs or SSRIs or SNRIs or triptans
Over-the-counter cold remedies	Dextromethorphan with SSRIs or amitriptyline or chlorpheniramine
	Dextromethorphan with risperidone and amitriptyline
Atypical antipsychotics	Olanzapine with lithium and citalopram
	Risperidone with fluoxetine or paroxetine
Antibiotics	Ciprofloxacin with venlafaxine and methadone
	Fluconazole with citalopram
	Linezolid with SSRIs or tapentadol
Other	L-tryptophan with SSRIs

MAOI – monoamine oxidase inhibitor; SSRI – selective serotonin reuptake inhibitor; SNRI – serotonin-norepinephrine reuptake inhibitor; TCA- tricyclic antidepressant. *Mirtazapine toxicity is currently being reassessed (Berling & Isbister 2014).

CAUSE

The spectrum of drugs potentially inducing Serotonin syndrome is fairly wide; the most often used ones are listed in Table 5 (Volpi-Abadie *et al.* 2013; Berling *et al.* 2014). The risk of developing Serotonin syndrome is increased in with drugs inhibiting central breakdown of serotonin (e.g., MAO inhibitors). Likewise, the risk is increased in patients taking drugs in combinations shown in the table. The risk will also dramatically rise in cases where the patient uses MAO inhibitors in combination with an SSRI. Up to 50% of patients using this combination at excess doses will usually develop a severe form of Serotonin syndrome (Gillman 1999). Four percent of patients initially taking an SSRI or venlafaxine at doses within the therapeutic range, who later started to take linezolid (with weak MAOI properties), developed Serotonin syndrome (Taylor *et al.* 2006). The risk of developing Serotonin syndrome is variable for each individual patient, and depends

on their ability to metabolize the drug in question, that is, mainly on their liver and kidney function. An important role in the metabolism of antidepressants, neuroleptics, opiates, antiarrhythmics, beta-blockers, and other drug classes is played by the CYP2D6 system. The system metabolizes tricyclic antidepressants and most SSRIs (fluoxetine, fluvoxamine, paroxetine, and desmethylcitalopram, but not citalopram). Other drugs are metabolized by CYP 3A4 (sertraline and norfluoxetine), CYP 1A2 (fluvoxamine), or CYP 3A4, 2C19, and CYP2D6 (citalopram). Up to 7–10% of the European population belong to slow CYP 2D6 metabolizers (Cascorbi 2003). To date, over 80 variant alleles for CYP 2D6 have been identified. Carriers of CYP 2D6 gene polymorphisms are at increased risk for developing Serotonin syndrome when treated with an SSRI. Therefore, the US Food and Drug Administration (FDA) recommends – not requires – genetic testing prior to initiation of therapy with an SSRI (US Food and Drug Administration 2013). Other major factors include age, individual tolerance, and hydration. A specific issue are drug interactions whose importance increases with increasing numbers of polymorbid patients using several medications, or combinations thereof (Montastruc *et al.* 2012; Poeschla *et al.* 2011; Evans *et al.* 2010). A patient treated with paroxetine or venlafaxine who starts to use an inhibitor of CYP 2D6 metabolizing the former two may develop Serotonin syndrome. Many antidepressants such as fluoxetine, paroxetine, and buproprione inhibit the CYP 2D6 pathway and may increase the levels of other drugs, e.g., tricyclic antidepressants. Yet another cytochrome monooxygenase system whose use may potentially result in the development of SS is CYP 3A4. Individuals with genetic CYP 3A4 variants will develop excessive levels of even at normal therapeutic doses.

TREATMENT

On establishing the diagnosis of Serotonin syndrome, all serotonergic therapy should be discontinued and symptomatic management started. The intensity of treatment depends on the severity of intoxication. With mild forms, symptoms will often resolve within 24 hours of therapy discontinuation. In patients receiving drugs with active metabolites featuring a long half-life, symptoms may persist for several days. Similarly, fluoxetine (a drug of the SSRI class), when used over a prolonged period of time, has a half-life of 1–4 days, and its metabolite norfluoxetine, 7–15 days (Hiemke *et al.* 2000).

A pivotal role is believed to be played by supportive therapy. It includes of wide spectrum of procedures depending on the clinical status including monitoring of vital functions and modulation thereof, oxygen therapy, maintenance of adequate hydration, blood pressure, and temperature. Special emphasis is placed on rehydration using adequate amounts of crystalloid solutions to achieve high urinary excretion rates, with recommended diuresis in the range of 1–2 ml/kg/hr. Factors contributing to fluid loss may include, in addition to elevated temperature and profuse sweating, vomiting and diarrhea. Another reason for fluid administration is an attempt to prevent renal injury due to myoglobinuria. Dehydration and metabolic acidosis enhance myoglobin precipitation in the kidney thus boosting its nephrotoxic effect. Severe intoxication requires alkalization of the urine to achieve a urinary pH ≥6.5 (Walter *et al.* 2008). As alkalization may result in hypocalcemia and hypokalemia, it is critical to monitor the levels of minerals and urinary pH. Patients with severe hypertension should be given short-acting drugs such as esmolol or nitroprusside (Boyer *et al.* 2005). Hypotensive patients using MAO inhibitors should be treated with sympathomimetic amines, e.g., phenylpherine, epinephrine or norepinephrine, while dopamine should be avoided (Boyer 2013; Boyer *et al.* 2005). Patients with hyperthermia are usually managed by external cooling whereas those with body temperature in excess of 41.1 °C require immediate endotracheal intubation, sedation, and complete neuromuscular blockade. The agents used to induce paralysis include etomidate, succinylcholine, or the longer-acting drug vecuronium. Currently, no pharmacological antipyretic is available as the temperature is the result of muscular activity.

Pharmacotherapy often includes benzodiazepines, particularly in agitated patients, with the most frequently used benzodiazepines being lorazepam and midazolam. This class of drugs is employed, in addition to controlling agitation, to manage mildly increased blood pressure as well as spasms in cases of severe intoxication. Diazepam has been shown to extend life in experimental animals with Serotonin syndrome, but there is no evidence of such an effect in man.

In cases where supportive therapy has failed, an antidote is administered, preferably cyproheptadine, an antagonist of the histamine-1 receptor, with non-specific antagonist properties for the 5HT-1 and 5HT-2 receptors. As it is available only as tablets or syrup, it must be administered by nasogastric tube. The starting dose is 12 mg to be followed by a 2-mg dose every 2 hours until obtaining a clinical effect. Another dosing scheme is 4–8 mg every 6 hours until the clinical symptoms have resolved (Iqbal *et al.* 2012). An antagonist effect on the 5HTA2 receptor has also been shown with chlorpromazine and olanzapine However, some authors discourage their use because of their not yet documented efficacy and adverse effects (Boyer 2013; Boyer *et al.* 2005). No drugs potentially increasing serotogenic activity – in particular opiates (fentanyl, tramadol, methadone, meperidine) – should be given, with linezolid to be avoided in the treatment of any infectious complications.

PROGNOSIS

The prognosis of patients with serotonin syndrome is mostly good, with patients usually completely recovering without any sequels. The majority of deaths occur within 24 hours of intoxication. In 2012, there were 2 576 cases of fatal intoxication in the USA, with SSRIs implicated in 89 (3%) of these cases (Mowry *et al.* 2013).

PREVENTION

In everyday practice, patients with Serotonin syndrome are encountered by physicians both in the outpatient (general practitioners) and hospital setting. In the case of general practitioners, those presenting with Serotonin syndrome include most often patients treated with serotonergic drugs and prescribed opioids to relieve pain (elderly patients with osteoarthrosis, tumors, injuries, etc.). Younger individuals tend to develop Serotonin syndrome secondary to illegal drug abuse, typically ecstasy and its substitutes (Warrick *et al.* 2012). Not infrequently, Serotonin syndrome develops after taking an over-the-counter drug, e.g., herbal remedies (St. John´s Wort) as well as various dextromethorphan-containing cough syrups and antiobesity drugs (sibutramine), or previously fenfluramine (still used today in the treatment of epilepsy in children with Dravet syndrome). Among hospital-based physicians, those most likely to encounter patients include surgeons and anesthesiologists in the perioperative period, again in connection with opioids administered to relieve pain (Rastogi *et al.* 2011).

Based on the above, preventive measures relative to Serotonin syndrome should be defined as follows: 1. To provide every patient prescribed a serotonergic drug, particularly one belonging to the SSRI class, with detailed information about manifestations of serotonin toxicity and drug interactions, including those with over-the-counter drugs, and herbal remedies. 2. To improve the knowledge and awareness of physicians, particularly in the above specialties, in this area. 3. To expand our knowledge in pharmacogenetics allowing us to more reliably identify individuals at increased risk for developing Serotonin syndrome. 4. To perform thorough post-marketing surveillance in novel serotonergic agents being introduced into clinical practice.

CONCLUSION

Serotonin syndrome can be a life-threatening adverse effect of some drugs. Its early diagnosis may help prevent the development of its severe forms and potential subsequent complications. Therefore, it is critical for the physician to be adequately informed about serotonin syndrome and the patient advised about the potential side effects of drugs. It is particularly the elderly who are at increased risk for developing Serotonin syndrome. Serotonin syndrome should be considered in the differential diagnosis in elderly individuals presenting with altered mental status.

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REFERENCES

1 Ables AZ, Nagubilli R (2010). Prevention, diagnosis, and management of serotonin syndrome. Am Fam Physician **81**: 1139–1142.
2 Amireault P, Sibon D, Coté F (2013). Life without peripheral serotonin: Insight from tryptophan hydroxylase 1 knockout mice reveal the existence of paracrine/autocrine serotonergic networks. ACS Chem Neurosci **4**: 64–71.
3 Beikmann BS, Tomlinson ID, Rosenthal SJ, Andrews AM (2013). Serotonin uptake is largely mediated by platelets versus lymphocytes in peripheral blood cells. ACS Chem Neurosci **16**: 161–70.
4 Berling I, Isbister GK (2014). Mirtazapine overdose is unlikely to cause major toxicity. Clin Toxicol (Phila) **52**: 20–24.
5 Bogdanski DF, Weissbach H, Udenfriend S (1958). Pharmacological studies with the serotonin precursor 5-hydroxytryptophan. J Pharmacol Exp Ther **122**: 182–194.
6 Boyer EW, Shannon M (2005). The serotonin syndrome. N Engl J Med **352**: 1112–20.
7 Boyer EW (2013). Serotonin syndrome. Up To Date. http://www.uptodate.com/contents/serotonin-syndrome?topicKey=EM%2F301
8 Buckley N, Dawson AH, Isbister GK (2014). Serotonin syndrome. BMJ **348**: g1226.
9 Butterfield JM, Lawrence KR, Reisman A, Huang DB, Thompson CA, Lodise TP (2012). Comparison of serotonin toxicity with concomitant use of either linezolid or comparators and serotonergic agents: an analysis of phase III and IV randomized clinical trial data. J Antimicrob Chemother **67**: 494–502.
10 Cascorbi I (2003). Pharmacogenetics of cytochrome P450D6: genetic background and clinical implication. Europ J Clin Invest **33**(suppl 2): 17–22.
11 Diaz SL, Maroteaux L (2011). Implication of the 2-HT(2B) receptors in the serotonin syndrome. Neuropharmacology **61**: 495–502.
12 Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (2003). The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. Q J Med **96**: 635–642.
13 Ener RA, Meglathery SB, Van Decker WA, Gallagher RM (2003). Serotonin syndrome and other serotonergic disorders. Pain Med **4**: 63–74.
14 Erspamer V, Asero B (1952). Identification of enteroamine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. Nature **169**: 800–802.
15 Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE (2010). The FDA alert on serotonin syndrome with use of tryptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. Headache **50**: 1089–1099.
16 Frank C (2008). Recognition and treatment of serotonin syndrome. Can Fam Phys **54**: 988–992.
17 Frazer A, Hensler JG (1999). Serotonin Receptors. In: Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD, editors. Basic Neurochemistry: Molecular,Cellular, and Medical Aspects. Philadelphia, Lippincot-Raven, 263–292.
18 Gaddum JH,Picarelli ZP (1957). Two kinds of tryptamine receptor. Br J Pharmacol **12**: 323–328.
19 Gerson SC, Baldessarini RJ (1980). Motor effects of serotonin in the central nervous system. Life Sci **27**: 1435–51.

20 Gillman PK (2006). A review of serotonin toxicity data: Implications for the mechanisms of antidepressant drug action. Biol Psychyatry **59**: 1046–1051.
21 Gillman PK (2005). Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth **95**: 434–441.
22 Gillman PK (1998). Serotonin syndrome: history and risk. Fundam Clin Pharmacol **12**: 482–491.
23 Gillman PK (2013). Serotonin toxicity, serotonin syndrome. http: //www.psychotropical.com/index.php/introduction?tmpl=component
24 Gillmann PK (1999). The serotonin syndrome and its treatment. J Psychopharmacology **13**: 100–109.
25 Grahame-Smith DG (1971). Inhibitory effect of chlorpromazine on the syndrome of hyperactivity produced by L-tryptophan or 5-methoxy-N,N-dimethyltryptamine in rats treated with monoamineoxidase inhibitor. Br J Pharmacol **43**: 856–64.
26 Grahame-Smith DG (1971). Studies in vivo on the relationship between brain tryptophan brain 5-HT synthesis and hyperactivity in rats treated with monoamine oxidase inhibitor and L-tryptophan. J Neurochem **18**: 1053–1066.
27 Haberzettl R, Bert B, Fink H, Fox MA (2013). Animal models of the serotonin syndrome: A systematic review. Behav Brain Res **256**: 328–345.
28 Hall RCW, Hall R, Chapman MJ (2007). Central serotonin syndrome: Part II-Pathophysiology,drug interactions, and treatment. Clin Geriatrics **16**: 24–28.
29 Hall RCW, Hall RCW, Chapman MJ (2007). Central serotonin syndrome: Part I – Causative agents, presentation, and differential diagnossis. Clin Geriatrics **15**: 18–25.
30 Hiemke C, Härtter S (2000). Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Therapeut **85**: 11–28.
31 Hoyer D, Hannon JP, Martin GR (2002). Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav **71**: 533–554.
32 Insel TR, Roy BF, Cohen RM, Murphy DL (1982). Possible development of the serotonin syndrome in man. Am J Psychiatry **139**: 954–955.
33 Iqbal MM, Basil MJ, Iqbal T (2012). Overwiew of serotonin syndrome. Ann Clin Psychiatry **24**: 310–318.
34 Isbister GK, Bowe SJ, Dawson A, Whyte IM (2004). Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. J Toxicol Clin Toxicol **42**: 277–85.
35 Isbister GK, Buckley NA, Whyte IM (2007). Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust **187**: 361–365.
36 Isbister GK, Buckley NA (2005). The pathophysiology of serotonin toxicity in animals and humans: Implications for diagnosis and treatment. Clin Neuropharmacol **28**: 205–2014.
37 Izumi T, Iwamoto N, Kitaichi Y *et al.* (2006). Effect of co-administration of a selective serotonin reuptake inhibitor and monoamine oxidase inhibitors on 5-HT-related behavior in rats. Eur J Pharmacol **532**: 258–264.
38 Jacobs BL, Klemfus H (1975). Brain steam and spinal cord mediation of a serotonergic behavioral syndrome. Brain Research **100**: 450–457.
39 Jacobs BL (1976). An animal behavioral model for studying central serotonergic synapses. Life Sci **19**: 777–785.
40 Jedlitschki G, Greinacher A, Kroemer K (2012). Transporters in human platelets: physiologic function and impact for pharmacotherapy. Blood **119**: 3394–3402.
41 Keck PE jr., Arnold LM (2000). Serotonin syndrome. Psychiatr Ann **30**: 333–343.
42 Lawrence L (2013). Be prepared: The ins and outs of serotonin syndrome. APC Hospitalist. http: www.acphospitalist.org/archives/2013/04/serotonin.htm
43 Mackay FJ, Dunn NR, Mann RD (1999). Antidepressant and the serotonin syndrome in general practice. Br J Gen Pract **49**: 871–874.
44 Mitchell R (1955). Fatal toxic encephalitis occuring during iproniazid therapy in pulmonary tuberculosis. Ann Intern Med **42**: 417–424.
45 Montastruc F, Sommet A, Bondon-Guitton E, Durrieu G, Bui E, Bagheri H, Lapeyre-Mestre M, Schmitt L, Montastruc JL (2012). The importance of drug-drug interactions as a cause of adverse drug reactions: a pharmacovigilance study of serotoninergic reuptake inhibitors in France. Eur J Clin Pharmacol **68**: 767–75.
46 Mowry JB, Spyker DA, Cantilena LR jr, Bailey JE,Ford M (2013). Annual report of the American Association of Poison Control Centers´National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol (Phila) **51**: 949–1229.
47 Nisijima K, Shioda K, Yoshino T, Takano K, Kato S (2003). Diazepam and chlormethiazole attenuate the development of hyperthermia in an animal model of the serotonin syndrome. Neurochem Int **43**: 155–164.
48 Nisijima K, Shioda K, Yoshino T, Takano K, Kato S (2004). Nemantine, an NMDA antagonist, prevents the development of hyperthermia in an animal model for serotonin syndrome. Pharmacopsychiatry **37**: 57–62.
49 Nisijima K, Yoshino T, Ishiguro T (2000). Risperidone counteracts lethality in an animal model of the serotonin syndrome. Psychopharmacology (Berl) **150**: 9–14.
50 Nisijima K, Yoshino T, Yui K, Katoh S (2001). Potent serotonin (5-HT) (2A) receptor antagonist completely prevents the development of hyperthermia in an animal model of the 5-HT syndrome. Brain Res **26**: 890: 23–31.
51 Oates JA, Sjostrand U (1960). Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor. Neurology **10**: 1076–78.
52 Peroutka S, Snyder SH (1979). Multiple serotonin receptors. Differential bindings of 3H-5-hydroxytryptamine, 3H-lysergic acid diethylamine and 3H-spiroperidol. Mol Pharmacol **16**: 687.
53 Peroutka SJ, Snyder SH (1981). Two distinct serotonin receptors: regional variations in receptor binding in mammalian brain. Brain Res **208**: 339–347.
54 Perry PJ, Wilborn CA (2012). Serotonin syndrome vs neuroleptic malignant syndrome: A contrast of causes, diagnoses, and management. Ann Clin Psychiat **24**: 155–162.
55 Poeschla BD, Bartle B, Hansen KP (2011). Serotonin syndrome associated with polypharmacy in the elderly. Gen Hosp Psychiatry **33**: 301.e9–e11.
56 Pytliak M, Vargová A, Mechírová V, Felšöci M (2011). Serotonin receptors-from moleculqar biology to clinical applications. Physiol Res **60**: 15–25.
57 Radomski JW, Dursun SM, Reveley MA, Kutcher SP (2000). An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. Med Hypotheses **55**: 218–224.
58 Rapport MM, Green AA, Page I (1948). Serum vasoconstrictor (serotonin). IV. Isolation and characterization). J Biol Chem **176**: 1243–51.
59 Rastogi R, Swarm RA, Patel TA (2011). Case scenario: Opioid association with serotonin syndrome. Anesthesiology **115**: 1291–1298.
60 Sternbach H (1991). The serotonin syndrome. Am J Psychiatry **148**: 705–713.
61 Taylor JJ, Wilson JW, Estes LL (2006). Linezolid and serotonergic drug interactions: A retrospective survey. Clin Infect Dis **43**: 180–187.
62 Tseng YL, Chiang ML, Lane HY, Su KP, Lai YC (2013). Selective serotonin reuptake inhibitors reduce P2Y12 receptor-mediated amplification of platelet aggregation. Thromb Res **131**(4): 325–32.
63 US Food and Drug Administration (2013). FDA Table of Pharmacogenomic Biomarkers in Drug Labels. http: //www.fda.gov/Drugs/Science Research/ResearchAreas/Pharmacogenetics/ucm083378.htm
64 Vialli M, Erspamer V (1937). Ricerche sul secreto delle cellule enterochmaffini.IX. Intorno alla natura chimica della kostanza specifica. Boll Soc Med –chir Pavia **51**: 1111–1116.
65 Volpi-Abadie J, Kaye AM, Kaye AD (2013). Serotonin syndrome. Ochsner J **13**: 533–540.
66 Wacker D, Wang C, Katritch V, Han GW, Huang X,Vardy E, McCorvy JD, *et al.* (2013). Structural features for functional selectivity at serotonin receptors. Science **340**: 615–619.

67 Walsh J (2010). Serotonin syndrome. Anaesthesia Tutorial of the week **166**, 1–5.
68 Walter LA, Catenacci MH (2008). Rhabdomyolysis. Hosp Physician **44**: 25–31.
69 Walther DJ, Peter JU, Bashammakh S, Hortnagl H, Voits M, Fink H, Bader M (2003). Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science **299**: 76.
70 Wang C, Jiang Y, Ma J, Wu H, Wacker D, Katritch V *et al.* (2013). Structural basis for molecular recognition at serotonin receptors. Science **340**: 610–614.
71 Warrick BJ, Wilson J, Hedge M, Freeman S, Leonard K, Aaron C (2012). Lethal serotonin syndrome after methylone and butylone ingestion. J Med Toxicol **8**: 65–68.
72 Watson WA, Litovitz TL, Rodgers GC *et al.* (2005). 2004 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med **23**: 589–666.
73 Watts SW, Morrison SF, Davis RP, Barman SM (2012). Serotonin and blood pressure regulation. Pharmacol Rev **64**: 359–388.
74 Yadav VK, Ryu JH, Suda N, Tanaka K, Gingrich JA, Schütz G, Glorieux FH, Chiang CY, Zajac JD, Insogna KL, Mann JJ, Hen R, Ducy P, Karsenty G (2008). Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum: an entero-bone endocrine axis. Cell **135**: 825–837.
75 Yu B, Becnel J, Zerfaoui M, Rohatgi R, Boulares AH, Nichols CD (2008). Serotonin 5-hydroxytryptamine 2A receptor activation supress tumor necrosis factor-alfa-induced inflammation with extraordinary potency. J Pharmacol Exp Ther **327**: 316–323.
76 Zhang W, Drake MT (2012). Potential role for therapies targeting DKK1, LPR5, and serotonin in the treatment of osteoporosis. Curr Osteoporos Rep **10**: 93–100.