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Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions

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ABSTRACT: Serotonin syndrome (SS) (also referred to as serotonin toxicity) is a potentially life-threatening drug-induced toxidrome associated with increased serotonergic activity in both the peripheral (PNS) and central nervous systems (CNS). It is characterised by a dose-relevant spectrum of clinical findings related to the level of free serotonin (5-hydroxytryptamine [5-HT]), or 5-HT receptor activation (predominantly the 5-HT_{1A} and 5-HT_{2A} subtypes), which include neuromuscular abnormalities, autonomic hyperactivity, and mental state changes. Severe SS is only usually precipitated by the simultaneous initiation of 2 or more serotonergic drugs, but the syndrome can also occur after the initiation of a single serotonergic drug in a susceptible individual, the addition of a second or third agent to long-standing doses of a maintenance serotonergic drug, or after an overdose. The combination of a monoamine oxidase inhibitor (MAOI), in particular MAO-A inhibitors that preferentially inhibit the metabolism of 5-HT, with serotonergic drugs is especially dangerous, and may lead to the most severe form of the syndrome, and occasionally death. This review describes our current understanding of the pathophysiology, clinical presentation and management of SS, and summarises some of the drugs and interactions that may precipitate the condition. We also discuss the newer novel psychoactive substances (NPSs), a growing public health concern due to their increased availability and use, and their potential risk to evoke the syndrome. Finally, we discuss whether the inhibition of tryptophan hydroxylase (TPH), in particular the neuronal isoform (TPH2), may provide an opportunity to pharmacologically target central 5-HT synthesis, and so develop new treatments for severe, life-threatening SS.

KEYWORDS: Serotonin syndrome, serotonin toxicity, novel psychoactive substances, neuroleptic malignant syndrome, toxidromes, tryptophan hydroxylase inhibitors

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Introduction

Epidemics of ‘convulsive ergotism’ were widespread and well described east of the Rhine river from 1085 to 1927.¹ Given that ergot alkaloids, a known contaminant of human cultivated grains, are now recognised to induce serotonin syndrome (SS), this suggests that the syndrome may have been a public health problem long before its more recent ‘discovery’ as a complication of modern pharmacology.¹

5-Hydroxytryptamine (5-HT), a monoamine neurotransmitter, first recognised in 1948,² has a wide range of functions in the central nervous system (CNS), including modulation of attention, cognition, behaviour, memory, and thermoregulation, as well as in the peripheral nervous system (PNS), where it regulates, for example, gastrointestinal (GI) motility, uterine contraction, vasoconstriction, and bronchoconstriction.³ The first report of a clinical picture consistent with what nowadays is termed SS was in 1960,⁴ which described the coadministration of L-tryptophan (the substrate of the rate-limiting enzyme, tryptophan hydroxylase [TPH], in the biochemical synthesis of serotonin) with a monoamine oxidase inhibitor (MAOI) inducing delirium. The first use of the term SS came 20 years later, describing the characteristic features in rats of tremor, rigidity, hypertonicity, hind-limb abduction, Straub tail, lateral head shaking, hyperactivity to

auditory stimuli, myoclonus, generalised seizures, and various autonomic responses such as salivation, penile erection, and ejaculation.⁵ Two years later, the first contemporaneous case in humans was reported by Insel et al,⁶ followed by numerous case reports and reviews.^{7–11}

The aim of this review is to summarise the pathophysiology of SS in relation to the 5-HT signalling pathway in the CNS, clinical features, diagnosis, management, and prognosis.

Epidemiology

Serotonin syndrome is observed across the full range of age groups, from neonates all the way through to the elderly, with an increasing incidence likely to represent the increasing use of serotonergic drugs in clinical practice.^{7,12,13} The percentage of adults taking antidepressants in the United States nearly doubled between 1999 and 2010, increasing from 6% to 10.4%.¹⁴ In 2016, the Toxic Exposure Surveillance System, which receives case descriptions from emergency departments, inpatient settings, and office-based practices, reported 54 410 incidences of exposures to selective serotonin reuptake inhibitors (SSRIs; 43% of which were single exposures), with 102 deaths (the ninth most common cause of fatality in drug overdoses in the United States in this period). This represented an 18% increase in cases between 2002 and 2016 and



an 8% increase in the number of deaths.¹⁵⁻¹⁷ Large case series suggest that moderate SS occurs in approximately 15% of poisonings with SSRIs.¹⁸ A recent study found that close to half of U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) SS reports involved a single drug (depending on the diagnostic criteria used), which is, perhaps, a little surprising, given the common perception of a multidrug aetiology.¹⁹

The true incidence of SS, however, is unknown, as is the number of cases that are mild, moderate, or severe. There are a number of reasons for this: it is a relatively uncommon condition that cannot be easily picked up in randomised clinical control trials,²⁰ and the condition is under-recognised and under-reported by physicians (85% of general physicians [GPs] were not familiar with the condition in one survey,²¹ and mild cases are often dismissed or self-limiting).²⁰

Pathophysiology and Molecular Mechanisms

The serotonin signalling pathway

The cells of the raphe nuclei located in the midline of brainstem (from the midbrain to the medulla) are the source of neuronal 5-HT in the CNS.²² The 9 raphe nuclei (B1-B9) are centred in the reticular formation, and axons from the serotonergic neurons in this region form a neurotransmitter system that functionally affects most parts of the CNS. The rostral group of nuclei project into multiple cortical and sub-cortical structures contributing to the regulation of wakefulness, attention, affective behaviour (depression and anxiety), sexual behaviour, appetite, thermoregulation, and migraine.²² The caudal group project into the spinal regions and are involved in motor tone as well as nociception.²² In the periphery 5-HT, produced in the enterochromaffin (EC) cells of the GI tract, is involved in the regulation of GI motility as well as a number of roles in vascular biology.²² These include control of blood pressure through vasoconstriction or vasodilation depending on the expressed receptor type in the vessel wall, as well as control of haemostasis and platelet function. Serotonin is secreted during platelet activation, playing an important role in their aggregation and concomitant vasoconstriction of the surrounding blood vessels during haemostasis. Platelets lack enzymes to synthesise serotonin,²³ and are therefore reliant on taking up serotonin from the plasma via the serotonin transporter. Selective serotonin reuptake inhibitors can inhibit the uptake of serotonin by platelets leading to decreased aggregation responses and thereby increasing bleeding time.²⁴ For this reason, SSRIs should be used in caution in those patients on anticoagulants or at higher risk of bleeding. Intriguingly, there is emerging evidence that SSRI treatment may lower myocardial infarction risk though their inhibition of platelet aggregation.^{25,26} The occurrence of disseminated intravascular coagulation in severe SS²⁷ may be due to an exaggerated platelet aggregation response driven by excess peripheral serotonin.

The initial and rate-limiting step in the biosynthesis of 5-HT, the decarboxylation and hydroxylation of the essential amino acid tryptophan, is catalysed by TPH.²⁸ There are 2 isoforms of this enzyme, TPH1 and TPH2, which are highly homologous but differ in their kinetic properties and their tissue distribution.^{29,30} Tryptophan hydroxylase 1, the source of most peripheral 5-HT, is predominantly expressed in the EC cells of the gut and other peripheral tissues, such as the pancreas, lung, and adipose tissue, though is also expressed in the pineal gland where 5-HT serves as the precursor molecule for melatonin biosynthesis.^{29,31,32} Tryptophan hydroxylase 2, the source of the central neurotransmitter pool of 5-HT, is predominantly expressed in the raphe projection neurons of the brainstem,^{29,33} though is also found in the myenteric neurons of the gut.^{32,34} Work with knockout animals suggests that TPH1 expression in the pineal gland does not significantly contribute to the central 5-HT pool,³⁵ and similarly, TPH2 expression in the myenteric plexus does not significantly contribute to the peripheral 5-HT pool.³⁶ Once synthesised from tryptophan, 5-HT is then stored in presynaptic vesicles until it is required for neurotransmission and released into the synaptic cleft. Serotonergic signalling is a tightly regulated process characterised by a combination of feedback loops, multiple reuptake mechanisms, and metabolising enzymes (Figure 1). Depolarisation of the presynaptic axon leads to the release of serotonin into the synaptic cleft, which leads to multiple downstream effects; activation of presynaptic serotonin autoreceptors inhibits exocytosis of further vesicles, while binding to postsynaptic 5-HT receptors effects neurotransmission. Serotonergic signalling is terminated primarily by the uptake of 5-HT from the synaptic cleft back into the presynaptic neuron. This is accomplished predominantly by the serotonin reuptake transporter protein (SERT) on the presynaptic membrane, though there is evidence that the plasma membrane monoamine transporter (PMAT) may also contribute.³⁷ 5-Hydroxytryptamine is then metabolised into 5-hydroxyindoleacetic acid (5-HIAA) primarily by monoamine oxidase A (MAO-A).

There are at least 7 families of 5-HT receptors (5-HT₁ to 5-HT₇), some of which have multiple subtypes, resulting in a total of 14 structurally and pharmacologically distinct receptors.³⁸

The 5-HT₁ receptor family consist of 5 subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1e}, and 5-HT_{1F} receptors are G-protein-coupled receptors (GPCRs) that signal via the inhibition of adenylate cyclase or G-protein-sensitive K⁺ channels (note that the 5-HT_{1e} receptor is still just recognised as a gene product, since no function has been attributed to this receptor in native tissue). While a number of clinically used drugs affect these receptors, the 5-HT_{1A} receptor provides a pharmacological target for the anxiolytic agent, buspirone, which lacks potential for dependency. However, 5-HT_{1B/1D} (and possibly 5-HT_{1F}) receptors are targeted by the antimigraine 'triptans',

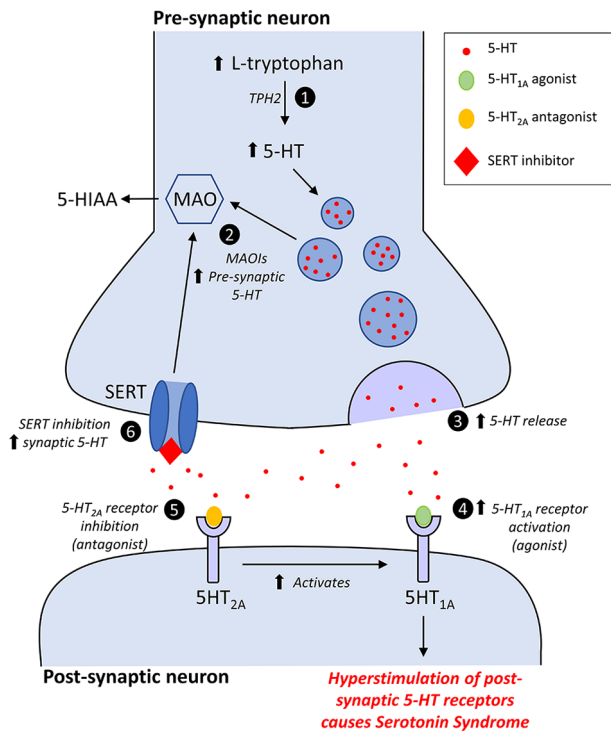


Figure 1. Mechanisms of serotonin syndrome: (1) Increased levels of L-tryptophan will lead to increased levels of endogenous 5-HT; a step catalysed by the enzyme tryptophan hydroxylase 2 (TPH2). (2) Increased presynaptic concentrations of 5-HT due to inhibition of serotonin metabolism by MAOIs. (3) Increased 5-HT release by drugs including amphetamines and their derivatives, cocaine, MDMA, and levodopa. (4) Direct or indirect activation of postsynaptic 5-HT_{1A} receptors. (5) Direct or indirect antagonism of postsynaptic 5-HT_{2A} receptors is thought to enhance the effect of 5-HT_{1A} agonists. (6) Increased synaptic levels of 5-HT due to inhibition of the SERT by reuptake inhibitors such as SSRIs, and TCAs. MAOIs indicate monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; SERT, serotonin reuptake transporter protein; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressant.

examples of which include sumatriptan and zolmitriptan (which are also used for cluster headaches).

The 5-HT₂ receptor family consists of 3 members: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors that are excitatory GPCRs signalling via Gq to activate, for example, phospholipase C to generate Inositol 1,4,5-triphosphate (IP3) and diacyl glycerol. Many antipsychotic drugs at relevant clinical concentrations interact with 5-HT₂ receptors, with antagonism of the 5-HT_{2A} receptor likely to contribute to therapeutic effects (eg, risperidone). More recently (2012), the 5-HT_{2C} receptor has been targeted selectively with the agonist, lorcaserin, to treat obesity by reducing food intake (although not yet approved in Europe).

The 5-HT₃ receptor is a ligand-gated ion channel of the cys-cys loop class that conducts Na⁺/K⁺/Ca²⁺; this excitatory receptor is expressed predominantly by neurons and is responsible for initiating emesis following aggressive anticancer therapy (that releases copious quantities of 5-HT from the EC GI

tract) such that antagonists such as ondansetron offer effective antiemetic treatment. The 5-HT₃ receptor also mediates prokinetic activity of the GI tract – as occurs in irritable bowel syndrome (IBS) or carcinoid patients; for both patient cohorts, 5-HT₃ receptor antagonists are beneficial to reduce diarrhoea, although currently, they are only indicated for IBS (and only in some territories like the United States and Japan).

The 5-HT₄ receptor is a GPCR that promotes adenylate cyclase activity via Gs. The receptor increases gastric motility by increasing the activity of, for example, cholinergic neurons in the GI tract and is activated by some drugs used to reverse constipation (eg, prucalopride).

The 5-HT₅ receptors are GPCRs and the family has 2 members: 5-HT_{5A} and 5-HT_{5B} receptors. The latter receptor is not functional in humans due to the insertion of a stop codon into the gene that results in a truncated protein. Little is known about the 5-HT_{5A} receptor, and it is not actively targeted for therapeutic benefit.

The 5-HT₆ and 5-HT₇ receptors are both GPCRs that couple via Gs to promote cAMP synthesis via adenylate cyclase. There has been much interest in these as potential clinical targets, largely due to the known interaction of a wide range of antipsychotic and antidepressant drugs that antagonise these receptors. However, to date, no clinically used drug selectively targets either receptor.

Further structural and functional diversity occurs in 5-HT receptors through allelic polymorphisms, splice variants, and the formation of receptor heterodimers.^{34,39}

Pharmacology of serotonin and cellular toxicity

Serotonin syndrome can result from agonism (either from increased concentrations of 5-HT or medications that act directly as receptor agonists), and/or antagonism, of varying combinations of the 5-HT receptor subtypes. Stimulation of the postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors has been implicated in SS, but no single receptor is likely to be solely responsible. The classical view, mainly supported by evidence from animal studies (with few studies in humans), is that the life-threatening effects of SS, in particular, severe hypertonicity and hyperthermia, are primarily mediated by the activation of 5-HT_{2A} receptors at higher serotonin concentrations.¹⁸ The 5-HT_{1A} receptors, which have a higher affinity for 5-HT and are therefore likely to be nearly fully occupied at much lower extracellular 5-HT concentrations, possibly contribute to some of the milder symptoms including anxiety and hyperactivity.⁴⁰ This may provide a pharmacological explanation for why severe SS is usually only seen with particular combinations of drug classes, in particular MAOIs (that increase 5-HT concentration in the synapse) and SSRIs (that modulate 5-HT receptor signalling at the postsynaptic membrane in addition to inhibiting serotonin reuptake via the SERT).^{18,41,42}

Recently, a bioinformatics approach has demonstrated an association between second-generation antipsychotics (SGAs)

and SS.⁴³ Counter to the classical view that 5-HT_{2A} agonism is a significant contributor to severe SS, the authors have suggested a potential role for 5-HT_{2A} antagonism in concert with 5-HT_{1A} agonism as a common mechanism that may explain the SGA-SS association. It is this effect on the serotonergic system that distinguishes the SGAs ('atypical' antipsychotics) from the older 'typical' antipsychotics (butyrophenones, diphenylbutylpiperidines, and phenothiazines) that predominantly antagonise D2 dopaminergic receptors and are not associated with SS. They postulate that in the presence of SERT inhibition, 5-HT levels are increased throughout serotonergic synapses, and 5-HT_{2A} antagonism then shunts elevated levels of 5-HT to the co-localised 5-HT_{1A} receptor.^{44,45} This selective activation of the 5-HT_{2A} receptor not only appears to increase its sensitivity to 5-HT⁴⁶⁻⁴⁸ but may also enhance the effects of 5-HT_{1A} agonists.^{49,50} In addition, there is evidence that 5-HT_{2A} receptor antagonists may elevate 5-HT neurotransmission via a disinhibitory feedback loop, through inhibition of local gamma-aminobutyric acid (GABA) interneurons in the dorsal raphe nucleus.⁵¹ This association (and potential mechanistic explanation) is reinforced by a recent meta-analysis of SS cases, in which 3% (10/299) of cases were associated with SGAs as the decisive triggering factor. Eight of these cases occurred in combination with antidepressants and 2 in the context of an SGA swap. Interestingly, in this study, 45.4% of the SS cases had rigidity/hypertonicity, and 14.0% of cases had rhabdomyolysis and symptoms also commonly associated with neuroleptic malignant syndrome (NMS).²⁰ Whether 5-HT_{2A} receptor antagonism in concert with 5-HT_{1A} agonism plays a role in all cases of SS or is the exception in the case of SGAs remains to be determined.

An additional question is whether other neurotransmitters play a role, particularly in the development of severe SS. A full review of the large body of evidence in this area is beyond the scope of this review, though it is important to emphasise that active research is ongoing, and many questions remain to be definitively answered. In animal models, it has been shown that 5-HT can cause the release of noradrenaline from the anterior hypothalamus, a neurotransmitter known to cause CNS hyperexcitability, which may correlate with the clinical outcome.⁵²⁻⁵⁴ Gamma-aminobutyric acid, N-methyl-D-aspartate (NMDA), and dopamine may also play a role through their recruitment, in addition to direct serotonin stimulation, in severe SS.^{52,55} A recent study using a systematic bioinformatics approach to analyse off-target effects of the drugs most commonly involved in SS supports the hypothesis that multiple neurotransmitter pathways may be recruited in addition to direct serotonin stimulation in severe SS.¹⁹ As well as highlighting the importance of SERT inhibition (46/71 serotonergic drugs interacted with this protein), there was a higher than expected association of SS cases in the triple receptor drug cohort (drugs that interact at SERT, norepinephrine transporter [NET], and muscarinic receptors).¹⁹ Off target receptor activity may help to explain the differences in the severity of the syndrome as well as the

spectrum of clinical features. These findings raise the possibility that when the offending drug (or combination of drug classes) has (have) both antidopaminergic and serotonergic activity,²⁰ the resulting toxidrome may share features of both SS and NMS.

Drugs commonly associated with SS

A wide range of drug types and combinations have been implicated in SS, with the final common pathway thought to involve a net increase in serotonergic neurotransmission. The main drug classes classically implicated in SS can be divided into serotonin precursors, inhibitors of serotonin reuptake from the synaptic cleft, inhibitors of serotonin metabolism, direct serotonin receptor agonists, and drugs that sensitise serotonin receptors (Table 1). As discussed in the previous paragraph, there is evidence that serotonin antagonism (in particular 5-HT_{2A} antagonism) may also play a role, based on the observed association between SGAs and SS.⁴³

Pharmacokinetic drug interactions are also implicated through the inhibition of the cytochrome P450 pathway, a pathway that SSRIs themselves inhibit (in particular CYP2D6 and CYP3A4).^{56,57} At least 25 serotonergic drugs are metabolised by the cytochrome P450 pathway,¹⁹ and a recent study has shown that 50% of the top 20 drugs associated with SS have known pharmacokinetic interactions in which coadministration of cytochrome P-450 inhibitors may elevate drug concentrations to toxic levels. These drugs collectively were shown to participate in >70% of all the reported SS reports in their study.¹⁹ Examples include the concomitant use of SSRIs and tramadol,^{12,58} SSRIs and ciprofloxacin,⁵⁹ as well as of citalopram and fluconazole.⁶⁰

Although SS has been described after overdose of a single drug,⁶¹ and occasionally from increasing therapeutic doses in susceptible individuals, this only usually results in mild to moderate SS.^{4,13,62} Severe SS usually only occurs with the concomitant administration of 2 or more serotonergic drugs (even at therapeutic doses) (Table 2), with the combination of serotonergic drugs with MAOIs being especially dangerous, causing serious adverse outcome including death.^{8,41,42}

Taken together, these observations are consistent with the hypothesis that SS is a dose-dependent spectrum of adverse effects mediated by a combination of elevation of endogenous intrasynaptic or extrasynaptic serotonin and direct or indirect activation of 5-HT receptors.⁶³ However, the fact that different patients present with SS at differing drug dosages and/or combinations suggests that there may also be underlying genetic and pharmacodynamic factors that modulate susceptibility.¹¹ Genetic factors could include polymorphisms in the CYP450 pathway,⁶⁴ the SERT gene,⁶⁵ as well as the 5-HT₂ receptor.^{18,13,66}

The role of novel psychoactive substances in SS

Novel psychoactive substances (NPSs), commonly described as novel, designer, or synthetic drugs,⁶⁷ are a growing public health concern due their increasing availability and use. They

Table 1. Drugs associated with serotonin syndrome.

MECHANISM	DRUGS ASSOCIATED WITH SS
Increased 5-HT synthesis	Dietary supplements: Tryptophan
Inhibition of 5-HT metabolism	MAOIs: include safinamide, selegiline, rasagiline, phenelzine, tranylcypromine, isocarboxazid, moclobemide, linezolid, tedizolid, methylene blue, procarbazine, and Syrian rue [<i>Peganum harmala</i> and harmine]
	Herbal supplements: St. John's wort [<i>Hypericum perforatum</i>]
	DNRIs: include buspirone
Increased release of 5-HT	Drugs of abuse: cocaine, MDMA ('Ecstasy')
	Amphetamine and derivatives: include phentermine, fenfluramine, and dexfenfluramine
	Cold remedies: dextromorphan
Activation of 5-HT ₁ receptors	DNRIs: buspirone
	Triptans: include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan
	Ergot derivatives: include ergotamine and methylergonovine
	Opiates: fentanyl and meperidine
	Drugs of abuse: LSD
	Antidepressants/mood stabilisers: mirtazapine, trazodone, and lithium
Antagonism of 5-HT _{2A} receptors	Second-generation antipsychotics: include quetiapine, risperidone, olanzapine, clozapine, and aripiprazole ^{20,43}
Inhibition of 5-HT uptake from synaptic cleft	Amphetamine and derivatives: include phentermine, fenfluramine, and dexfenfluramine
	Drugs of abuse: cocaine and MDMA ('Ecstasy')
	SSRIs: include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
	SNRIs: include venlafaxine, duloxetine, milnacipran, and desvenlafaxine
	TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine
	DNRIs: include buspirone
	Opioids: include levomethorphan, levorphanol, meperidine, methadone, pentazocine, pethidine, tapentadol, and tramadol
	5-HT ₃ receptor antagonists: ondansetron, and granisetron
	Antihistamines: chlorphenamine
	Herbal supplements: St. John's wort [<i>Hypericum perforatum</i>]
Cold remedies: dextromorphan	

Abbreviations: 5-HT, 5-hydroxytryptamine; SS, Serotonin syndrome; MAOI, monoamine oxidase inhibitor; DNRI, dopamine-norepinephrine uptake inhibitor; MDMA, 3,4-methylenedioxy-methamphetamine; LSD, lysergic acid diethylamide; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

are often synthetic derivatives and analogues of known compounds currently prohibited under current drug laws, such as amphetamines and cannabis.⁶⁸ The ease of synthesising and speed of technological innovation has led to an explosion in the number of newly identified NPS, creating significant challenges to the regulatory authorities as well as to the research community investigating the pharmacology of these agents.⁶⁹⁻⁷²

In 2014, 101 newly identified NPSs were reported to the European Union early warning system,⁷¹ and by 2017, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring more than 620 NPSs,⁷³ with 1 new NPS being identified each week. There is currently limited population-based data detailing NPS use, and a wide range of estimates based on the data that does exist. A 2014/15

Table 2. Reported drug combinations causing moderate to severe serotonin syndrome.^{78,11}

DRUG CLASS	DRUG COMBINATIONS
MAOIs	MAOIs + SSRIs or SNRIs or TCAs or opiates Imipramine + tranylcypromine Phenelzine + meperidine Methylene blue + clomipramine or paroxetine
SSRIs	SSRIs + MAOIs or TCAs or SNRIs or opiates or triptans Fluoxetine + carbamazepine or phentermine or fentanyl
SNRIs	SNRIs + TCAs or MAOIs or opiates or triptans Venlafaxine + lithium or calcineurin inhibitors or mirtazapine or tranylcypromine
Other antidepressants	Mirtazapine + SSRIs Trazadone + amitriptyline + lithium
Opiates	Opiates + MAOIs or SSRIs or SNRIs or triptans
Cold remedies	Dextromorphan + SSRIs or TCAs or atypical antipsychotics
Atypical antipsychotics	Olanzapine + citalopram and lithium Risperidone + paroxetine or fluoxetine
Antibiotics/antifungals	Linezolid + SSRIs or tapentadol Fluconazole + citalopram Ciprofloxacin + methadone + venlafaxine

Abbreviations: MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

Crime Survey for England and Wales estimated that 0.9% of 16 to 59 year olds are users, with this figure rising to 2.8% in the 16- to 24-year-old age group.⁷⁴ This compared to 6.7% for cannabis, 2.4% for cocaine, 1.7% for 3,4-methylenedioxy-methamphetamine (MDMA), and 0.6% amphetamines.⁷⁴ Another annual survey reported that 10% of United Kingdom and 22% of Irish 15 to 24 year olds had experimented with NPS.⁷⁵ A recent review of the presence of NPS in HM Coroners or Police Forces cases in the United Kingdom, showed that over a 2-year period, NPSs were detected in 203 cases; the presence of multiple NPSs and/or other stimulants was a particular feature in some cases, and of the drug deaths (58% of total cases), 7% were solely due to an NPS.⁷⁶

Classification of these compounds can be based either on their psychotropic effects (stimulant, empathogen/enactogen, hallucinogen, and dissociative)^{68,77} or based on their chemical family (phenethylamines, amphetamines, cathinones, piperazines, pipradrols/piperidines, aminoindanes, benzofurans, and tryptamines).⁷⁸ Most of these drugs interact with the monoamine neurotransmitter transporters (dopamine transporter [DAT], SERT, NET), in the CNS to varying degrees altering levels of dopamine, serotonin, and noradrenaline, and therefore, in overdose can produce a range of overlapping toxidromes (serotonergic, sympathomimetic, and so on) depending on their particular receptor specificities. The relative dopaminergic to serotonergic properties in vitro (dopamine/serotonin transporter inhibition ratio) of an NPS have been postulated as a useful marker for its potential clinical psychotropic and acute toxic effects;⁷⁹ MDMA-like agents

are associated with a high serotonin:dopamine transporter-inhibition ratio, whereas more pure amphetamine-like agents have a higher dopamine:serotonin transporter-inhibition ratio.⁶⁸ This ratio, however, does not capture the full complexity of action of these NPSs, not least because it does not account for the noradrenergic effects that can be a predominant feature in particular with the amphetamine, cathinone, and aminoindane drug classes.

The empathogenic NPSs are of particular interest in relation to SS, given that the effects of MDMA, the prototypic empathogen, are generally considered to depend on its serotonergic effects (driving increased 5-HT efflux into the synaptic cleft).^{68,80} 3,4-Methylenedioxy-methamphetamine has been consistently associated with serotonergic toxicity and SS.⁸¹⁻⁸³ In addition, MDMA and other amphetamine-like drugs such as fenfluramine, are direct agonists of the 5-HT_{2B} receptor and may cause fibrosis in the periphery (eg, cardiac valvulopathy). Therefore, NPS drug classes (cathinones, aminoindanes, piperazines, and phenylethylamines) that have similar empathogenic effects to MDMA are likely to similarly lead to increased levels of serotonin, and a similar risk of SS at higher doses. In support of this, there are numerous case reports, as well as toxicity studies in animal models, documenting the development of SS with abuse of those drug classes with a high serotonin:dopamine transporter-inhibition ratio (cathinones,^{84,85} phenylethylamines,^{67,86-90} aminoindanes,⁹¹⁻⁹³ as well as mixed serotonergic/sympathomimetic toxidromes in those where the dopamine:serotonin transporter-inhibition ratio is higher).^{77,86,94}

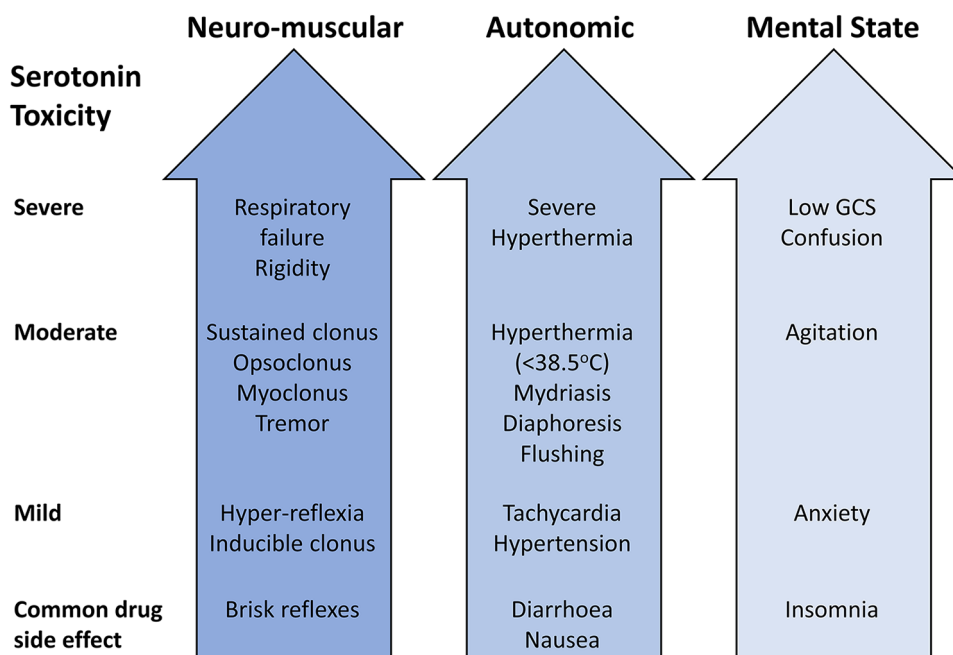


Figure 2. The spectrum of clinical features in serotonin syndrome. GCS indicates Glasgow Coma Scale. Source: Buckley et al.⁸

The difficulty in identifying the true levels of usage of these NPSs, as well the associated clinical presentation in acute toxicity, is highlighted in a recent study that reviewed what data are currently being collected in Europe on emergency department presentations with acute toxicity related to NPSs and classical drugs of abuse.⁹⁵ This revealed that of the 27 countries included, more than half (52%) did not perform any registration of such data, while only 37% collected systematic clinical data on NPS at a national level. The lack of knowledge about these NPSs is reflected in the lack of confidence among the health care team in managing acute NPS toxicity in the emergency setting.⁹⁶ Current research into the effects of these NPSs, however, suggests that toxicity associated with these agents broadly falls into 3 broad groups similar to that seen with classical drugs (stimulant, hallucinogenic, and depressant). Future training should therefore focus on recognising and managing the particular toxidrome(s) that an individual presents with, rather than the particular agent (which is often never identified) that the patient has taken.^{94,97} The reader is directed to the recent review on the practical management of toxicity associated with NPS.⁹⁴

Clinical Features

Given that the diagnosis of SS is made solely on clinical grounds, a detailed history and comprehensive physical and neurological examinations are essential. The presentation is highly variable ranging from mild symptoms to a severe life-threatening syndrome, a spectrum that likely reflects a combination of the degree of excess serotonergic activity in the CNS, or the particular 5-HT receptor subtype(s) that is (are) activated (directly or indirectly). Given the difficulty in determining the exact point at which serotonergic signs associated with

therapeutic drug administration meet the criteria for SS, has led some experts in the field to prefer the use of the term serotonin toxicity, as they feel this more accurately represents the wide range of clinical features of varying severity.^{18,41} Traditionally, it is said that, in contrast to the onset of NMS, symptoms in SS usually begin within 24 hours of ingestion of the causative agent(s) and that most patients seek medical advice within 6 hours.¹¹ However, these claims appear to be based on one review of 41 cases of SS from 1995 to 1999,¹² and in a more recent meta-analysis, just more than 60% presented within 6 hours of ingestion (usually where pro-serotonergic drugs were administered quickly or in large doses including overdose), while around one quarter of patients presented later than 24 hours (usually when medication were more gradually titrated and/or cross-tapered).²⁰ This temporal disparity may depend on the context in which the syndrome occurs, as well as pharmacokinetic and dynamic factors; an example would be the delayed onset of linezolid-associated SS in the elderly.⁹⁸

The classic triad of clinical features (Figure 2) are altered mental status (including anxiety, agitation, and confusion), autonomic nervous system overactivity (including diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhoea), and neuromuscular hyperactivity (muscle rigidity, hyperkinesia including myoclonus and tremor, hyperreflexia, and bilateral Babinski sign).¹² The acute onset of these features should alert the physician to the potential diagnosis, and trigger a search for a toxic cause, while also excluding other mimics such as encephalitis (infectious or autoimmune), alcohol and/or drug withdrawal, epileptic, and nonepileptic seizures.⁸ In milder cases, the patients are usually normothermic, with mild autonomic symptoms and neuromuscular signs. In moderate SS, in addition to hyperthermia (>40°C), patients usually

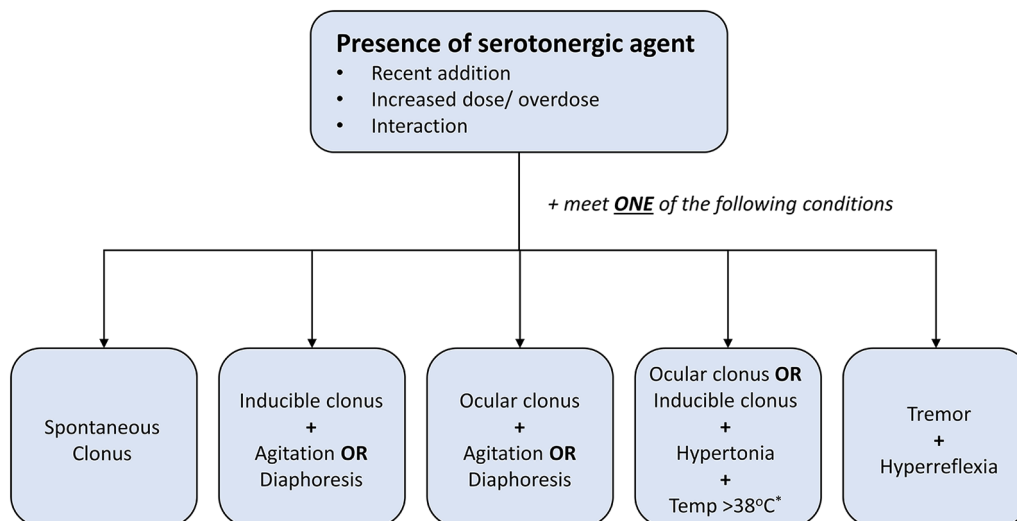


Figure 3. The Hunter Serotonin Toxicity Criteria: for diagnosing serotonin syndrome. Note that the requirement for the presence of some form of neuromuscular excitation, the sine qua non for a diagnosis of serotonin syndrome. *The presence of temperature $\geq 38.5^{\circ}\text{C}$ and/or marked hypertonia or rigidity (especially truncal) indicates severe SS with a risk of progression with respiratory compromise.

develop eye movement abnormalities, agitation, pressured speech, and hypervigilance. Patients may also startle easily or develop an unusual movement disorder characterised by repetitive head rotation with the neck held in moderate extension.⁷ In severe cases, as well as the above features, patients usually have a temperature greater than 41.1°C , haemodynamic/autonomic instability, hyperactive bowel sounds, delirium, and muscle rigidity. Complications in severe cases include seizures, renal failure, metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation, acute respiratory distress syndrome, respiratory failure, and even death.⁷ Interestingly, the hyperreflexia and clonus are usually more prominent in the lower limbs,⁷ and this gives a clue as to the underlying diagnosis.

Diagnosis

Serotonin syndrome is a diagnosis of exclusion with no single diagnostic test that confirms the syndrome.^{7,11,99} It is an abstract construct combining various concepts, clinical signs, and symptoms that aims to relate signs of CNS hyperexcitability with purported drug-induced serotonin excess.²⁰ Given the protean ways that CNS hyperexcitability can present, combined with the ability of multiple nonserotonergic pathways to manifest similar symptoms, makes it difficult to establish a gold standard to confirm SS. A plausible diagnosis of SS can therefore only be made when there is a high Bayesian prior probability (high index of clinical suspicion) in the setting of starting, increasing (or overdose) of a relevant serotonergic drug, or shortly after a second serotonergic drug is added.⁸ Linked to this, it is critically important that there is a strict definition for what is classed as a serotonergic drug; namely, it causes a generalised increase in endogenous 5-HT and/or activates 5-HT receptors directly or indirectly, as well as producing clinical signs that are specific for SS.¹⁸

Therefore, a diagnosis of SS is entirely clinical, based on a careful history and examination, with a detailed enquiry about

the use of prescription, over-the-counter, and illicit drugs (stimulants such as cathinones and other synthetic stimulants, ecstasy, amphetamines, or cocaine), as well as any dietary supplements (such as St John's wort, ginseng, tryptophan, and pharmaceutical adulterants in appetite suppressants).^{7,8} The rate of change of symptoms from onset, as well as development of new symptoms should also be reviewed. The presence of certain comorbidities, including long-term pain and depression, should alert to the clinician to the possibility of the use of serotonergic drugs,¹¹ and the presence of renal disease may predispose those on certain SSRIs (such as sertraline) to developing SS.¹⁰⁰ The clinical examination should focus on eliciting any signs of muscle rigidity, increased deep-tendon reflexes, as well as autonomic signs such as the presence of diaphoresis, increased bowel sounds, and mydriasis.⁷ There must be a high index of suspicion for the diagnosis in patients with any combination of the aforementioned classical clinical features and a supporting drug history, so treatment can be rapidly initiated to prevent the morbidity and mortality associated with this condition. Misdiagnosis can be an issue however; in severe cases, SS can be confused with NMS, while the nonspecific symptoms in mild cases can be confused with other causes such as infection. Symptoms such as anxiety and akathisia can be misattributed to the patient's mental state, while hypertension, diarrhoea, or tremor can easily be dismissed as part of a systemic or metabolic disorder unrelated to drug therapy.¹⁰¹

There are 3 diagnostic classification systems available, the Sternbach (SC), Radomski (RC), and Hunter Serotonin Toxicity Criteria (HSTC), all of which try to reflect symptoms and symptom constellations that are felt to be characteristic of serotonin toxicity and therefore SS. The most recent and commonly used criteria are the HSTC, which are set of decision rules that focus on the classic features of generalised clonus (inducible, spontaneous, and ocular), agitation, diaphoresis, tremor, and hyperreflexia⁴¹ (Figure 3). Spontaneous clonus is

Table 3. Differentiating serotonin syndrome from other toxidromes.

TOXIDROME	CAUSATIVE AGENT	ONSET, RESOLUTION	VITAL SIGNS	PUPILS	MENTAL STATE	OTHER CLINICAL FEATURES
Serotonin syndrome	Serotonergic drugs	Sudden <24 h Most resolve with 24 h with treatment (though 25% develop symptoms after >24 h)	Hyperthermia (>41.1°C), tachycardia, hypertension, and tachypnoea	Mydriasis	Delirium, agitation, and coma	Neuromuscular hyperactivity (tremor, myoclonus, hyperreflexia, and clonus), diaphoresis, and hyperactive bowel sounds
Neuroleptic malignant syndrome	Dopamine antagonists and dopamine withdrawal	Slower onset (days to weeks) Up to 10 days to resolve with treatment	Hyperthermia (>41.1°C), tachycardia, hypertension, and tachypnoea	Normal or mydriasis	Delirium, agitation	Neuromuscular hypoactivity ('lead-pipe' rigidity and bradykinesia) Hypoactive bowel sounds
Anticholinergic toxicity	Anticholinergic agents	Sudden <24 h Resolves hours to days with treatment	Hyperthermia (usually <38.8°C), tachycardia, hypertension (mild), and tachypnoea	Mydriasis	Hyper-vigilance, agitation, hallucination, delirium with mumbling speech, and coma	Normal muscle tone and reflexes Dry flushed skin and mucous membranes Hypoactive bowel sounds Urinary retention Hyperkinesia (myoclonus, choreoathetosis, and picking behaviour) Seizures (rare)
Malignant hyperthermia	Inhalational anaesthetics and depolarising muscle relaxants (succinylcholine)	Very sudden (mins to hours) Resolves 24-48 h with treatment	Hyperthermia (can be as high as 46°C), tachycardia, hypertension, and tachypnoea	Normal	Agitation	Rigour-mortis like rigidity Hyporeflexia Hypoactive bowel sounds Rising end-tidal CO ₂ Mottled skin with flushing and cyanosis

characterised by rhythmic, large muscle contractions (which helps to differentiate it from myoclonic jerks), and as is often triggered by minor movement. Ocular clonus refers to abnormal involuntary, fine or coarse, oscillatory eye movements that can either be continuous or triggered by eye movement.⁸ Rarer eye movements seen include periodic alternating gaze deviation (so-called 'ping-pong' gaze).⁸

Compared to the original SC the HSTC are simpler to use, more sensitive (84% vs 75%), and marginally more specific (97% vs 96%).⁴¹ A recent study analysing SS using a systematic bioinformatics approach applied to the FAERS database, found that the number of identified SS cases varied considerably depending on which diagnostic criteria were used.¹⁹ The SC identified an additional 1140 cases suggesting that they may indeed be less specific compared to the HSTC and likely picks up milder cases where off-target neurotransmitter effects contribute to a broader nonspecific toxicity presentation.¹⁹ It should be noted, however, that the purported superiority of the HSTC is based on one study only.²⁰ Other criticisms of the HSTC include their validity/generalisability to nonoverdose cases, given the criteria were derived solely from single SSRI overdoses; that a percentage of the cases in the derivation data set was also present in the test data set in the original study, which could potentially lead to an overestimation of the validity of the criteria²⁰; and finally that they may not perform well in patients with concomitant neurological disease. The cardinal signs of hyperreflexia and clonus may be masked, both in

patients with peripheral neuropathy,¹⁰² as well as those with severe SS who have substantial muscle rigidity.⁷

In addition to truncal rigidity, in severe, life-threatening cases of SS rapidly rising temperatures above 38°C and peripheral hypertonicity are usually key features. Investigations are of little diagnostic value, though are useful to help identify complications of hyperthermia and muscle rigidity (rhabdomyolysis, disseminated intravascular coagulation, and multiorgan failure); abnormalities that are often seen include elevated creatine kinase, liver enzymes, deranged renal function, and low bicarbonate levels.¹¹ It is important to also exclude cardiologic effects of drugs in overdose with an electrocardiogram (ECG), as well as alternative diagnoses such as encephalitis and cerebral vasculitis, where relevant, with magnetic resonance imaging (MRI), electroencephalogram (EEG), and lumbar puncture.¹⁸ In intentional overdoses, a toxicology screen should be sent including for paracetamol and salicylates. There is no role for testing of blood concentrations of serotonin, as there is no correlation with clinical severity.¹²

Differential diagnosis

The differential diagnosis for SS includes other toxidromes such as NMS, malignant hyperthermia, and anticholinergic toxicity (Table 3), as well conditions such as meningitis, encephalitis (in particular autoimmune encephalitis), central hyperthermia, and heatstroke.

Neuroleptic malignant syndrome is a fulminant and life-threatening idiosyncratic drug reaction to therapeutic doses of dopamine antagonists. Although the exact pathophysiology is not completely understood, central dopaminergic blockade is thought to play a pivotal role, with sympathoadrenal dysfunction also potentially involved.¹⁰³ Although NMS is often confused with SS, a detailed history focusing on time course of onset and medication usage, examination findings and clinical course allow differentiation of the 2 conditions. While SS is characterised by neuromuscular hyperactivity (hyperreflexia with clonus, myoclonus, and tremor), in NMS, there is usually decreased neuromuscular activity with extrapyramidal features (hypokinesia and lead-pipe rigidity). Importantly in NMS, hyperreflexia and clonus are rarely feature¹⁰⁴ something reflected in the primacy of clonus in establishing a diagnosis of SS in the HTSC.⁴¹ Established orthodoxy is that NMS develops over days to weeks while SS develops more rapidly (usually within 24h), though this has been challenged recently by a group that have shown that 25% of patients in their study developed SS later than 24 hours after ingestion of the causative agent.²⁰ In those patients where serotonergic medications were gradually titrated and cross-tapered, the percentage presenting after 24 hours increased to more than 60.4%. Hyperthermia, muscle rigidity, altered mental status, rhabdomyolysis, and deranged blood tests (leucocytosis, elevated hepatic transaminases, elevated creatine kinase, and metabolic acidosis) can be seen in severe cases of both syndromes. Care must therefore be taken in weighting the diagnosis too heavily based these findings as well as speed of onset.

In anticholinergic toxicity, muscular tone and reflexes are normal, with hypoactive bowel sounds and dry, erythematous skin; all features that help distinguish it from SS. They classically present in addition with hyperthermia, agitation, altered mental status, dry mucous membranes, and mydriasis.¹⁸

Malignant hyperthermia occurs in genetically susceptible individuals within minutes of exposure to inhalational halogenated anaesthetic agents and depolarising muscle relaxants (such as succinylcholine). The syndrome is characterised by hyperthermia, tachycardia, rigour-mortis-like muscle rigidity, metabolic acidosis, and increasing concentrations of end-tidal carbon dioxide.¹⁰⁵

With regards to the other differential diagnoses, SS can usually be distinguished from them based on increased neuromuscular activity; patients with CNS infections or sympathomimetic toxidromes are less likely to exhibit this increased activity.¹⁰⁶

Management

The 2 main components for optimal management of SS are first good supportive care (especially in severe cases) and second risk assessment and close monitoring of those with mild to moderate SS to avoid progression to severe life-threatening SS.¹⁸ The first step is to identify and stop the offending serotonergic medication(s), with supportive care to stabilise vital

signs (maintenance of oxygen saturations, intravenous fluids, and continuous temperature cardiac monitoring), sedation with benzodiazepines (such as diazepam or midazolam), and in more severe cases, consideration of serotonin antagonists alongside muscle paralysis. When paralysis is indicated, strong consideration should be given to the initiation of continuous EEG, if available, to assess for electrographic seizure activity that cannot be clinically manifest while chemically paralysed. Alongside early recognition, it is essential the clinician recognises the potentially rapid rate of progression of SS and instigates immediate aggressive treatment in those who were previously being treated conservatively that deteriorate.^{7,13,107}

The intensity of treatment depends on the severity of the toxicity (Figure 2). In mild cases, discontinuation of the offending medication, sedation with benzodiazepines and supportive care is often sufficient, whereas in moderate SS, there needs to be more aggressive treatment of haemodynamic/autonomic instability with consideration of adding in a serotonin antagonist (such as cyproheptadine). Severe SS is a medical emergency often complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, and acute respiratory distress syndrome (ARDS), requiring sedation, muscle paralysis, and intubation in the intensive care setting.¹⁰⁶ Most cases of SS usually resolve with 24 to 72 hours, though this may take longer in those on drugs with longer elimination half-lives, active metabolites, or a longer duration of action.⁷ Irreversible MAOIs carry the greatest risk with symptoms lasting for several days, while patients can still be at risk of SS up to several weeks after the discontinuation of SSRIs. Fluoxetine is a particular risk, with a half-life as long as 7 days after long-term admission and its metabolite norfluoxetine up to 2.5 weeks.¹⁰⁸

Agitation

Chemical restraint is preferred to sedating agitated patients, due to the risk of severe lactic acidosis and hyperthermia from physical restraints causing isometric muscle contractions. Of the sedating agents, benzodiazepines are commonly used first line; not only do they control agitation, but they also blunt the hyperadrenergic component, helping to correct mild increases in blood pressure and heart rate.¹⁰⁷ There is evidence in animal models of SS that pretreatment with diazepam and chlormethiazole prolongs survival,⁵⁵ though there is no evidence currently in humans. Clinicians should titrate the benzodiazepine to clinical effect, with the goal of patient sedation and maintenance of normal vital signs.¹⁰⁶

Autonomic instability

In severe SS, patients can often have large and rapid changes in heart rate and blood pressure, making management difficult.⁷ If benzodiazepines are not sufficient to lower blood pressure, then patients should be treated with short-acting agents such

as esmolol or nitroprusside.⁴¹ Longer acting agents such as propranolol, which can cause hypotension and mask tachycardia (a sign which is useful in monitoring patient response and improvement), should be avoided.^{7,41} Hypotension can be a particular problem in those patients who have taken MAOIs, and preferred treatment in this situation is with low doses of direct-acting sympathomimetic amines (such as norepinephrine, epinephrine, or phenylephrine).⁷ Indirect sympathomimetic agents such as dopamine should be avoided, due to theoretical risk of an exaggerated haemodynamic response in the setting of MAOI inhibition.

Hyperthermia

In severe SS, preventing hyperthermia and consequent multi-organ failure is a key goal. Lowering temperature in animal models has also been shown to indirectly downregulate 5-HT_{2A} receptors in the CNS and reduce overall serotonin levels.¹⁰⁹ Given the increase in body temperature in these patients is due to an increase in muscular activity, rather than an increase in the hypothalamic set point (that is seen in pyrexia), antipyretic agents have little effect and are not indicated.^{7,48} Key components of management include sedation (oral diazepam or a midazolam infusion) to reduce muscle activity, active cooling (including fans, water sprays, ice packs, cooled crystalloids, or cooling blankets), and in severe cases muscle paralysis and ventilation on the intensive care unit (ITU). In the severe cases where the temperature is greater than 41.1°C, patients should be immediately paralysed and intubated, with nondepolarizing agents such as vecuronium to maintain paralysis. It is important for clinicians to be aware that in rare cases succinylcholine can worsen rhabdomyolysis and put the patient at risk of hyperkalaemic-induced arrhythmias.⁷ Fentanyl should also be avoided due its serotonergic effect. Adequate sedation with a benzodiazepine while the patient is paralysed should be maintained. The optimum timing for stopping of neuromuscular paralysis is not currently known, but there is evidence from case reports that premature termination can lead to recrudescence of the hyperthermia⁷; as such, the clinician should anticipate this rebound and have a low threshold for restarting muscle paralysis.

Antidote(s)

If the use of the aforementioned strategies fails to control the agitation and correct vital signs, then there is some evidence for the use of serotonin antagonists. Animal studies have suggested that 5-HT_{2A} receptor antagonists may reduce hyperthermia and other severe manifestations of SS.^{18,109,110} Both chlorpromazine and cyproheptadine in high doses have been used, though given chlorpromazine can cause severe hypotension, as well as case reports that antipsychotics can themselves precipitate SS, means cyproheptadine is usually favoured first line.¹⁰⁶ There is some evidence from case reports that support its role

in reducing symptoms in mild to moderate SS, though there its role in severe SS is less clear.¹¹¹⁻¹¹⁵ Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, 5-HT₆, and 5-HT₇ receptor antagonistic properties as well as some weak anticholinergic effects.¹¹¹ The purported role of 5-HT_{2A} antagonism in mediating cyproheptadine's beneficial effect is interesting, given that there appears to be an association between 5-HT_{2A} antagonists themselves in the form of SGAs and the risk of SS.⁴³ Given that it antagonises a number of different serotonin receptors in addition to 5-HT_{2A}, it may be that concomitant antagonism of 5-HT_{1A} receptors (as well as others) at higher doses accounts for this apparent contradiction, though evidence for this is currently lacking.

An initial loading dose of 12mg orally or crushed via a nasogastric tube is recommended, followed by 2mg every 2 hours until clinical improvement is seen.¹¹ An alternative dosing regimen involves switching to 8mg every 6 hours once symptoms are controlled.⁷ Cyproheptadine is only available in an oral form, but the tablets may be crushed and given through a nasogastric or orogastric tube. It can cause a decrease in vascular tone with a consequent transient hypotension, though this is usually responsive to intravenous fluids.

Historically, therapeutics targeting the serotonergic system centrally have been focused on 5-HT transporters and receptors, to modulate conditions such as depression, migraine, or psychosis.¹¹⁶⁻¹¹⁸ There is currently a lack of novel therapeutics targeting serotonin synthesis in the CNS, drugs which if developed, might offer a therapeutic option in SS. An interesting avenue of research comes from work in the carcinoid syndrome. Carcinoid syndrome describes a constellation of clinical symptoms including diarrhoea, wheezing, bronchoconstriction, cutaneous flushing, cardiac valve disease, and mesenteric fibrosis.¹¹⁹ It is usually caused by neuroendocrine tumours, a clinically and genetically heterogeneous group of GI, bronchial, and more rarely pancreatic, kidney, or ovarian tumours. These tumours can release a cocktail of vasogenic amines (predominantly 5-HT), as well as prostaglandins, and other polypeptides which induce the clinical syndrome. Gastrointestinal NETs account for up to 80% of cases of carcinoid syndrome usually in the setting of hepatic metastases.¹²⁰ The inability of 5-HT to cross the blood brain barrier opens up the opportunity to pharmacologically target the central and peripheral 5-HT systems independently. Since the functional classification of TPH isoforms in 2003,²⁸ TPH1, the peripheral isoform, has been established as a pharmacological target for the treatment of peripheral 5-HT-associated diseases such as carcinoid. Early inhibitors developed to treat carcinoid syndrome, the low molecular weight phenylalanine analogues p-chlorophenylalanine (fenclonine, PCPA) and p-ethynylphenylalanine (PEPA), showed promise in terms of lowering peripheral 5-HT. However irreversible inhibition of TPH2 centrally, limited their therapeutic use, due to the significant reduction in brain 5-HT concentrations.¹²¹⁻¹²³ This off-target

effect may however offer an opportunity to develop specific, reversible TPH2 inhibitors that could play a role in treatment of SS, through inhibition of synthesis leading to depletion of endogenous CNS serotonin. More recently, reversible TPH inhibitors such as telotristat (Masib) derived from administration of the relatively inactive prodrug telotristat ethyl have been developed. Telotristat is indicated in combination with somatostatin analogues (eg, octreotide) for the treatment of diarrhoea in carcinoid patients. Due to significant active-site structural homology, telotristat inhibits both TPH1 and TPH2 with similar affinity in vitro, yet the inability to penetrate the blood-brain barrier prevents reduction in central serotonin levels.²⁸

Prognosis

As emphasised previously, the SS is a spectrum of dose-dependent clinical features ranging from very mild to life-threatening severe toxicity. Prognosis is generally favourable if the syndrome is recognised early, the causative agent is stopped, and complications are treated. This requires the clinician to have a high clinical suspicion for SS, and even if the diagnosis is unclear, discontinue any serotonergic agents and start supportive care. In severe cases, aggressive management on ITU is required, whereas those with moderate features need admitting for observation and vital system monitoring until symptoms resolve, with a low threshold for escalating management should there be any early signs of deterioration. These patients can usually be monitored for up to 6 hours, and if vital signs and mental state remain normal, with no evidence of neuromuscular hyperexcitability (in particular clonus or hyperreflexia), then they can be discharged home with close follow-up.¹⁰⁶ In most cases of SS, symptoms usually resolve within 24 hours of stopping the drug, though in a minority of cases where the drug has active metabolites or a longer half-life, symptoms can last for longer than this.⁷ In milder cases, it is necessary for the clinician, in close collaboration with the patient, to weigh up risks and the benefits to decide whether the patient should restart the serotonergic agent (preferably at a lower dose).

Prevention

Prevention of SS requires a multitiered approach including education of both physicians and patients regarding potent serotonergic drug interactions, and the clinical signs and symptoms of SS to look out for, modification of prescribing practices to integrate automated e-prescribing algorithms to flag potential drug interactions, and ongoing pharmacogenetic research.

Although there are numerous systematic reviews focused on identifying which drug interactions can precipitate severe SS,^{63,124-128} there has been a proliferation in spurious drug associations, in part driven by the nonspecific clinical features in milder forms of the condition, and a (some might argue too) broad definition of what entails a serotonergic agent.⁸ Currently, clinicians prescribing an SSRI, or patients looking for information online, can be presented with up to 1000

interacting drugs, with a significant number of these warning of the potential for SS. While some of these interactions are potentially lethal and should be avoided (for example, SSRIs and MAOIs),⁸ many are likely to only result in minor effects, and for some drugs (including carbamazepine, triptans,¹²⁷ most tricyclic antidepressants [TCAs], and atypical antidepressants),^{63,129} there is no or little evidence to support precipitating SS with coadministration. For the diagnosis of SS to be clinically meaningful, if the classification of a serotonergic agent is broadened to include any agent that has any modulatory effect on the serotonergic system in the CNS, then the clinical features need to be highly specific for the condition. Conversely, if we accept that the clinical features in the current criteria do not meet this threshold of specificity, then there must be evidence with a particular drug, or combination of drugs, that they directly lead to excessive serotonergic activity¹⁸ rather than simply a poorly defined modulatory action on the serotonergic pathway. Ongoing drug surveillance to identify potent serotonergic effects and integration of the results into physician and patient education is also critical, both to maintain awareness and also to keep these groups abreast of developments in the field.²¹ Patients also need to be aware that over-the-counter medications and herbal remedies, such as St John's wort, can have serotonergic activity and can lead to serious interactions with prescribed serotonergic drugs such as SSRIs and MAOIs.⁸

Author Contributions

WJS, LJH, ACW and NMB drafted, proofed and submitted the final manuscript.

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