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REVIEW

The serotonin syndrome

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ABSTRACT

The serotonin syndrome is a complex of symptoms that are thought to be largely attributable to changes in sensitivity in the serotonin receptor systems in the brainstem and the spinal cord due to drugs. Severe cases are almost always caused by a combination of two or more 'serotonergic' drugs, of which at least one is a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor. Usually, the syndrome heals spontaneously after withdrawal of the medication. Cessation of 'serotonergic' medication is the preferred treatment as well as supportive care.

INTRODUCTION

Case report[1]

A 50-year-old man was admitted to hospital with hyperhydrosis (diaphoresis), nausea, vomiting and diarrhoea. He was on fluoxetine (120 mg/day) for major depression, meprobamate (400 mg/day) for comorbid anxiety disorder and prometazine (13.55 mg/day) for insomnia ('off-label' use). The dose of fluoxetine had just been increased because it was insufficiently effective. The patient was agitated and confused and had insomnia. Hyperreflexia was present, but there were no focal neurological findings. His blood pressure was 155/80 mm Hg, heart rate 96 beats/min and regular, respiratory rate 20 breaths/min and temperature 37.2 °C. The findings of the complete blood count, blood potassium, blood glucose, liver and kidney function tests, and erythrocyte sedimentation rate were normal. A blood alcohol test was negative. ECG, chest radiograph, arterial blood gas measurements and a brain CT scan showed no anomalies.

A diagnosis of serotonin syndrome was made. The patient's medication was discontinued. Electrolyte solution and metoclopramide (10 mg every 8 hours) were administered intravenously. Clorazepate (20 mg orally every 12 hours) was also given. Nausea, vomiting, diaphoresis and diarrhoea disappeared within 72 hours. The patient's anxiety gradually subsided, and he was discharged five days later.

The treatment of depression has evolved greatly over the last two decades. The use of tricyclic antidepressants (TCAs) is decreasing, while the use of selective serotonin reuptake inhibitors (SSRIs) is increasing.[2] In 2001, prescriptions for SSRIs in Australia outnumbered those for tricyclics by two to one.[3] These figures in general compare with data from the Netherlands in the period 1999 and 2000.[2,4] Other new antidepressants with serotonergic properties are also being introduced. Although SSRIs and the other 'atypical' antidepressants (trazodone, venlafaxine and nefazodone, which was recently withdrawn from the market) are generally regarded as having lower toxicity than tricyclics, minor toxic effects are common, and serious toxicity can occur. Furthermore, it was recently concluded that the clinical relevance of differences in side-effect profile between TCAs and SSRIs is not great.[5] Apart from that, the efficacy of TCAs in general is somewhat greater than that of SSRIs.

Serotonin syndrome refers to a drug-induced syndrome that is characterised by mental, autonomic and neuromuscular changes.[6] It is not an idiosyncratic adverse reaction, but a complex of symptoms that are largely attributable to a changed serotonin sensitivity in the brainstem and spinal

cord. Serotonin syndrome was first described in 1955, but during the 1990s reports became increasingly common, as the signs, symptoms, and precipitants became more widely recognised and antidepressants were prescribed more often.[7-9] In the Netherlands up until now, a dozen adverse reactions have been reported to the Netherlands Pharmacovigilance Foundation (Lareb). Although severe cases have been reported with an overdose of a single drug, they usually only occur with a combination of two or more 'serotonergic' drugs, even when each is given at a therapeutic dose.

This article focuses on the pathophysiology, clinical features and diagnosis, incidence and the offending drugs, and treatment. Finally, a conclusion is drawn.

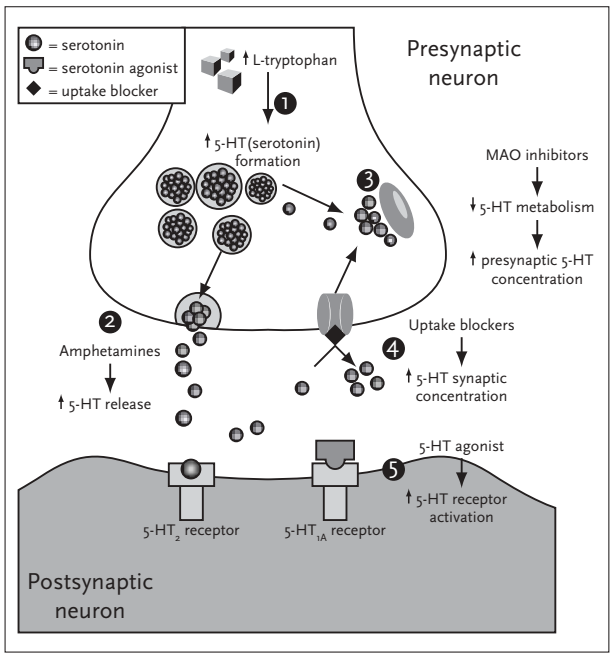

Figure 1

Mechanisms of serotonin syndrome

(1) Increased doses of L-tryptophan will proportionally increase 5-hydroxytryptamine (5-HT or serotonin) formation. (2) Amphetamines and other drugs increase the release of stored serotonin. (3) Inhibition of serotonin metabolism by monoamine oxidase (MAO) inhibitors will increase presynaptic 5-HT concentration. (4) Impairment of 5-HT transport into the presynaptic neuron by uptake blockers (e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants) increases synaptic 5-HT concentration. (5) Direct serotonin agonists can stimulate postsynaptic 5-HT receptors.

PATHOPHYSIOLOGY

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is synthesised from the amino acid tryptophan (*figure 1*). It has central and peripheral effects and there are at least seven different types of serotonin receptors.[10,11] Centrally, serotonin acts as a neurotransmitter with influences on mood, sleep, vomiting and pain perception. Depression is often associated with low concentrations of serotonin, but the functional meaning of this in the individual is not known. Peripherally, the primary effect of serotonin is on muscles and nerves. The majority of serotonin is synthesised and stored in the enterochromaffin cells of the gut where it causes contraction of gastrointestinal smooth muscle. Serotonin is also stored in platelets and promotes platelet aggregation. It also acts as an inflammatory mediator.

Serotonin syndrome

The pathophysiology of the serotonin syndrome remains poorly understood. It is thought to result from stimulation of the 5-HT_{1a} and 5-HT_2 receptors, and the drug classes implicated in serotonin syndrome reflect this theory. These include serotonin precursors, serotonin agonists, serotonin releasers, serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs), lithium and some herbal medicines (*table 1*).

Table 1

Mechanisms of serotonergic drugs implicated in serotonin syndrome[*12,13]*

Increase in serotonin production	L-tryptophan
Inhibition of metabolism of serotonin	MAO inhibitors, such as tranylcypromine MAO-A inhibitors, such as moclobemide MAO-B inhibitors, such as selegiline
Increase of serotonin release	Amphetamines, mirtazapine, anorectics
Serotonin reuptake inhibition	SSRIs: citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine in low dosage Nonspecific serotonin reuptake inhibitors: venlafaxine in high dosage, trazodone Tramadol Sibutramine TCAs: amitriptyline, clomipramine, doxepin, imipramine
Stimulation of serotonin receptors	Buspirone, pethidine, LSD, lithium

**Note: Interactions are more severe between drugs with different mechanisms of increasing serotonin. MAO = monoamine oxidase, TCA = tricyclic antidepressants.*

CLINICAL FEATURES AND DIAGNOSIS

General

The diagnosis of serotonin syndrome is purely clinical. It is based upon the recognition of a varied combination of signs and symptoms in the presence of selected 'serotonergic' medications. The diagnosis should not be made without identifying a cause. Serotonin syndrome most commonly occurs after a dose increase (or overdose) of a potent serotonergic drug or shortly after a second drug is added. Some of the drugs involved have very long half-lives (e.g. fluoxetine) and may have been stopped weeks before. There may be a history of recent overdose or use of illicit drugs, particularly ecstasy, amphetamines or cocaine. Herbal medicines may be implicated (St John's wort, ginseng, extracts from soya, or the food supplement S-adenosylmethionine).

Clinical features

The clinical features of serotonin syndrome are highly variable, reflecting the spectrum of toxicity (*table 2*). A distinction is usually made between major and minor symptoms. Diagnosis is made in the presence of three major symptoms and two minor symptoms.
The onset can be dramatic or insidious. The most useful features in the diagnosis of serotonin syndrome are hypereflexia and clonus (inducible/spontaneous/ocular). However, many patients taking SSRIs may display one or more of the clinical features without gross toxicity. Investigations are generally unhelpful in the diagnosis of serotonin syndrome, but may assist in treatment and in ruling out a differential diagnosis. The white cell count is often mildly raised and elevations in creatine kinase levels may occur, but both are nonspecific signs.

Table 2
Clinical features of serotonin syndrome[14-16]

DOMAIN	MAJOR SYMPTOMS	MINOR SYMPTOMS
Psychic (cognitive and behavioural)	Confusion (semi)coma	Hyperactivity Agitation Insomnia Restlessness
Autonomic	Fever or hyperthermia Hypertranspiration (diaphoresis)	Tachycardia Tachypnoea Dyspnoea Hypotension or hypertension Flushing Diarrhoea
Neuromuscular	(Myo)clonus* (spontaneous /inducible/ocular) Hypertonia* Tremor Shivering Hyperreflexia	Incoordination Mydriasis Acathisia Ataxia

** Hypertonia and clonus are always symmetrical and are often much more dramatic in the lower limbs.*

Differential diagnosis

The differential diagnosis includes neuroleptic malignant syndrome, carcinoid syndrome, dystonic reactions, encephalitis, tetanus, thyroid storm and sepsis, as well as poisoning by anticholinergic drugs, cocaine, ecstasy, lithium, MAOIs, salicylates and strychnine. The serotonin syndrome and the other agitated deliriums share many clinical features, but clonus, hyperreflexia and flushing are the most specific signs. *Table 3* shows the characteristics of the other two most important conditions that should be involved in the differential diagnosis. Serotonin syndrome can also be confused with withdrawal of antidepressant treatment.[17] Stopping SSRIs can give rise to symptoms as fear, dizziness, lethargy, paraesthesiae nausea, vivid dreams, insomnia, being irritated quickly and depression.[18,19] These symptoms almost always appear, even if the dosage is reduced slowly. They especially occur with drugs that have a short half-life, such as paroxetine.[18,19] Of all the SSRIs, more than one case of withdrawal symptoms has been published.[19,20]

Table 3
*Differential diagnostic characteristics of the serotonin syndrome**

	DELIRIUM	NEUROLEPTIC MALIGNANT SYNDROME	SEROTONIN SYNDROME
Change in consciousness	+	+	+
Tremors	+	+	+
Tachycardia	+	+	+
Hypertension	+	+	+
Profuse transpiration	+	+	+
Repetitive movements	+	-	-
Disorders of perception and thinking	+	-	-
Acute onset	+	-	-
Fluctuating time course	+	-	-
Changes in sleep-wakefulness cycle	+	-	-
Good reaction on antipsychotics	+	-	-
Muscle rigidity	-	+	+
Hyperthermia	-	+	+
Nonspecific blood changes	-	+	+
Confusion	+	-	+
Restlessness and agitation	+	-	+
Disorders of coordination	+	-	+
Hyperreflexia	-	-	+
Myoclonus	-	-	+
Shivering	-	-	+

** Adapted with permission from Verhoeven WMA, et al. Het serotoninesyndroom; een miskende complicatie van antidepressiva. Ned Tijdschr Geneeskd 1995;139:2073-5.*[7]

INCIDENCE, OFFENDING DRUGS AND TIME COURSE

Incidence

Almost all data on the incidence of serotonin syndrome consist of case reports or small series of patients. In the UK, GPs of patients who were taking nefazodone were sent a questionnaire in which, among other things, information was requested on symptoms that were regarded as characteristic for the serotonin syndrome.[21] The diagnosis was made retrospectively when there were three or more major symptoms. The results showed that in 53 of 11,834 users, two or more major symptoms had occurred. In 19 patients a serotonin syndrome had occurred which equals to an incidence of 0.4 per 1000 patient-months of treatment with nefazodone. Eight patients suffered symptoms while not taking comedication. In users of other antidepressants (fluoxetine, moclobemide, paroxetine, sertraline, venlafaxine) serotonergic symptoms arose in equal amounts. Of the GPs who were interviewed, 85% were not familiar with the serotonin syndrome.

Offending drugs

In *table 4* drugs and drug groups are listed in which a severe serotonin syndrome has been described in the literature.

Most cases will involve either an SSRI or an MAO inhibitor and at least one other medication. Generally, drugs with two different mechanisms of action on serotonin must be present for a severe serotonin syndrome to develop. Yet, serotonin syndrome has also been described in patients taking only one drug, such as clomipramine or paroxetine.[8,21] Serotonin syndrome has also been described in patients using the popular hard drug ecstacy.[26]

Table 4
Combinations of drugs and individual drugs implicated in severe serotonin syndrome[8,12,22-25]

COMBINATIONS OF DRUGS	INDIVIDUAL DRUGS
Trazodone and buspirone	Almotriptan
Fluoxetine and sertraline	Eletriptan
Fluoxetine and tramadol	Naratriptan
Clomipramine and MAO inhibitor as	Rizatriptan
tranylcypromine, fenelzine and benzatropine	Sumatriptan
Clomipramine and trazodone	Zolmitriptan
Clomipramine and moclobemide	Dihydroergotamine
All SSRIs in combination with each other	Clomipramine
Venlafaxine and lithium,	Paroxetine
Venlafaxine and moclobemide	Ecstasy
Dextromethorphan and paroxetine	
Dextromethorphan and moclobemide	
Venlafaxine and fluoxetine	
Venlafaxine and mirtazapine	
Bromocriptine and levodopa and carbidopa	

Time course

In most cases, serotonin syndrome is a self-limiting condition and will improve on cessation of the offending drugs. Mild to moderate cases usually resolve in 24 to 72 hours. In severe cases patients require intensive care as the syndrome may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and/or adult respiratory distress syndrome.

TREATMENT AND PREVENTION

Patients with moderate to severe serotonergic symptoms should be admitted to hospital. Those with hyperthermia should be admitted to an intensive care unit. All serotonergic medications should be ceased, and care taken that other precipitants are not inadvertently administered. Benzodiazepines may be used to control seizures and muscle hyperactivity. Specific treatment of hypertension is usually not required.

No randomised clinical studies have been published on the treatment of serotonin syndrome. Serotonin antagonists have been used in the management of moderate to severe serotonin syndrome. Some experience has been gained with cyproheptadine.[27] The initial dose is 4 to 8 mg orally. This may be repeated in two hours. If no response is seen after 16 mg it should be discontinued. If there is a response, then it may be continued in divided doses up to 32 mg/day (e.g. up to 8 mg four times daily).

Furthermore, case reports have been published regarding treatment of serotonin syndrome with mirtazapine.[28] Other drugs that have been suggested include chlorpromazine and propranolol, but these have more contraindications and adverse effects that limit their use.

After the patient has recovered, the ongoing treatment of the condition for which the serotonergic drug was prescribed should be reconsidered.

The prevention of serotonin syndrome involves awareness of the toxic potential of serotonergic drugs. The manufacturer's advice about washout periods should be carefully considered when switching antidepressants and patients should also be educated about possible drug interactions.

CONCLUSION

It is assumed that the serotonin syndrome results from a change in sensitivity in the serotonin receptor systems in the brainstem and spinal cord. Severe cases are almost always caused by a combination of two or more 'serotonergic' drugs, of which at least one is a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor. Yet, there are reports of serotonin syndrome resulting from single drug use.

The incidence of serotonin syndrome is not known. It is often not properly recognised because doctors are not familiar with it.
The syndrome usually heals spontaneously after withdrawal of the medication but the course can be so severe that the patient dies. Cessation of 'serotonergic' medication is the preferred treatment as well as supportive care.

NOTE

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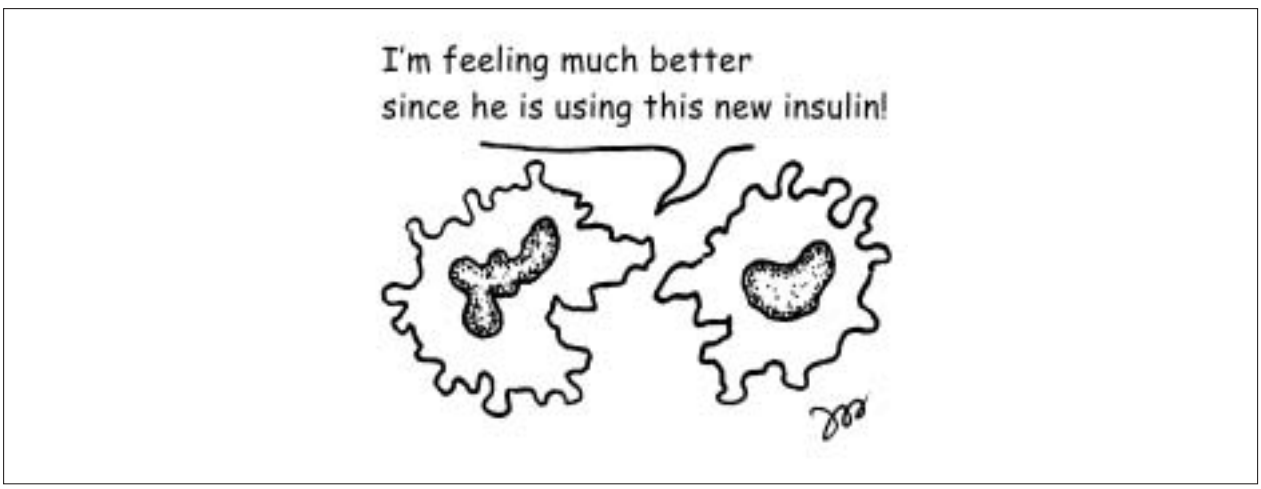

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De Maag Lever Darm Stichting verleent subsidies voor wetenschappelijk onderzoek op het gebied van (aandoeningen aan) de spijsverteringsorganen. Voor het jaar 2005 wordt er wederom een inschrijvingsronde voor subsidieaanvragen op het gebied van medisch wetenschappelijk onderzoek opengesteld. In principe wordt subsidie verleend voor projecten met een looptijd van 2 jaar en voor 4- jarige AIO projecten. Het Bestuur van de Maag Lever Darm Stichting maakt bekend dat:

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- De Maag Lever Darm Stichting stelt als voorwaarde dat per subsidieronde slechts één projectvoorstel per onderzoeksafdeling kan worden ingediend.
- Na beoordeling door de Wetenschappelijke Raad, zal de Maag Lever Darm Stichting alleen de aanvragers van goedgekeurde vooraanmeldingen verzoeken een volledig protocol in te dienen.
- Begin december 2005 neemt het bestuur van de Maag Lever Darm Stichting een besluit over de subsidietoekenningen van de projecten.

U dient uw aanvraagformulier uiterlijk 1 maal *per e-mail* en 1 maal per post met handtekeningen vóór *11 februari 2005 12.00 uur* op te sturen naar: peters@mlds.nl en de Maag Lever Darm Stichting, Postbus 430, 3430 AK Nieuwegein.
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