Serotonin syndrome

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Aims and method To define serotonin syndrome and its symptoms and to discover which drugs or drug combinations are likely to cause it. A review of literature (including case reports) relating to serotonin syndrome collated from searches of MedLine and Micromedex covering the period January 1991 to July 1998.

Results Most of the data found were either individual case reports or reviews of case reports. Reports of serotonin syndrome seem to be growing, certainly since the introduction of selective serotonin reuptake inhibitors. Particular combinations seem most likely to induce serotonin syndrome. Awareness of this syndrome as a distinct clinical entity seems to be growing.

Clinical implications Serotonin syndrome is more likely to occur with drug combinations, especially those involving monoamine oxidase inhibitors. It can also occur when swapping antidepressant therapy, especially if changing from a long acting antidepressant such as fluoxetine. Caution is needed when changing antidepressants and particularly when they are used in combination.

Serotonin syndrome appears to be a new phenomenon. Certainly, awareness of this syndrome seems to have increased in the last decade. Early reports date back to the 1950s and often describe adverse effects of serotonergic agents rather than defining a particular syndrome (Gillman, 1999). Sternbach (1991) was the first to collate and review these case reports. In this review, Sternbach suggested certain criteria for the diagnosis of 'serotonin syndrome' (see Appendix), thus helping clinicians to recognise its symptoms and so ultimately furthering knowledge about it.

The incidence of serotonin syndrome is unknown; one possible reason for this is that symptoms still go unrecognised, particularly the milder symptoms, and it is therefore likely to be under-reported.

True symptoms of serotonin syndrome include mental state changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination and fever. These are sometimes mild and usually occur within a few hours of a dose or drug change. In some, however, symptoms can be more severe and in a very few the syndrome can be fatal. Symptoms of serotonin syndrome are often confused with those of neuroleptic malignant syndrome (Lane & Baldwin, 1997): the two syndromes share some features and may be difficult to distinguish. Gillman (1999) has helpfully observed that hyperkinesia is common to serotonin syndrome, but that bradykinesia often characterises neuroleptic malignant syndrome.

Causes of serotonin syndrome

Theoretically, any drug or combination of drugs that result in a net increase in central serotonergic neurotransmission have the potential to induce serotonin syndrome.

In Sternbach's (1991) review of 38 reports of serotonin syndrome, 35 were a result of combination therapy. The most commonly reported drug combination to be associated with serotonin syndrome was that of L-tryptophan and a monoamine oxidase inhibitor (MAOI), with or without lithium. This was followed in frequency by a combination of fluoxetine and MAOIs or L-tryptophan (note that this review essentially predates widespread use of selective serotonin reuptake inhibitors (SSRIs)).

In a later review, Lane & Baldwin (1997) found the most profound serotonin syndrome reactions had been reported with a combination of MAOIs and SSRIs. Their review focused on SSRI-induced serotonin syndrome, the findings of which are summarised and updated in Table 1. Gillman's still later review (1999) notes the occurrence of serotonin syndrome even with short-acting MAOIs such as moclobemide in combination with fairly weak serotonin reuptake inhibitors such as pethidine and imipramine. Thus, it seems virtually any combination of serotonergic drugs can cause serotonin syndrome.

Serotonin syndrome has also been described with other drug combinations. For example, with sertraline and amitriptyline (Alderman & Lee, 1996), phenelzine and dextromethorphan (Nierenberg & Semprebon, 1993), a combination of SSRIs (Lane & Baldwin, 1997) and nefazodone with sodium valproate (Brazelton *et al*, 1997). Also, since its recent introduction, there have been a number of reports of serotonin syndrome with venlafaxine in combination with tranylcypromine (Brubacher *et al*, 1996; Hodgman *et al*, 1997), phenelzine (Weiner *et al*, 1998) and fluoxetine

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Table 1. Selective serotonin reuptake inhibitor (SSRI) induced serotonin syndrome adapted from Lane & Baldwin (1997)

Drug combined with serotonin reuptake inhibitor	Comments
Lithium	In practice, generally well tolerated. However, there are reports of serotonin syndrome with the following combinations: fluoxetine and lithium (Muly *et al*, 1993); trazodone, lithium and amitriptyline (Nisijima *et al*, 1996), lithium and paroxetine (Sobanski *et al*, 1997) and lithium and venlafaxine (Mekler & Woggon, 1997).
L-tryptophan	Many reports of serotonin syndrome (see Sternbach, 1991).
Buspirone	May be used to augment SSRI therapy and treat antidepressant-induced sexual dysfunction. There have been two reports of serotonin syndrome, but combination generally well tolerated.
Trazodone Nefazodone	Serotonin syndrome has been reported, this combination should be avoided.
Selegiline (selecive MAO-B inhibitor)	Appears to be well tolerated as MAO-A shows a preference for the metabolism of serotonin. Manufacturers warn against the use of SSRIs with selegiline.
Moclobemide	Serotonin syndrome has been reported, combination is potentially toxic, although Hilton *et al* (1997) found moclobemide safer than older MAOIs. This was later supported by Dingemanse *et al* (1998) who found moclobemide and fluoxetine to be a safe combination in 18 subjects.
Opiates	Serotonin syndrome has been reported with a combination of an SSRI and pentazocine, morphine, tramadol and dextromethorphan (found in some cough mixtures). Case reports of serotonin syndrome have been described for tramadol and paroxetine (Egberts *et al*, 1997) and tramadol and sertraline (Mason & Blackburn, 1997).
Sumatriptan (5-HT_1 agonist)	Although serotonin syndrome has been reported, sumatriptan has been shown to be well tolerated with SSRIs and moclobemide, lithium and buspirone. However, the risk is unclear as sumatriptan can give rise to similar symptoms as serotonin syndrome when given alone. See Gardner & Lynd (1998) for a review of use of sumatriptan with SSRIs, lithium and MAOIs.
Dihydroergotamine (5-HT_{1A} agonist)	Serotonin syndrome has been reported. Crosses the blood-brain barrier more readily than sumatriptan.

MAO-A, monoamine oxidase-A; MAO-B, monoamine oxidase-B; MAOI, Monoamine oxidase inhibitor.

(Bhatara *et al*, 1998). In general, with all drugs the more severe cases involve the use of MAOIs.

Serotonin syndrome can also result from changing drug therapy. Table 2 provides some illustrative examples of switching-induced serotonin syndrome.

It is worthy of note that not all the cases of serotonin syndrome listed above involved changing to or from an MAOI. Indeed, a straight swap (generally from fluoxetine) to another SSRI can clearly induce serotonin syndrome.

Apart from combination therapy and changing drug therapy, serotonin syndrome has also been reported, albeit rarely, with single drug use, for example, with L-tryptophan and with fluvoxamine (Lejoyeux *et al*, 1994) and more recently with clomipramine (Rosebush & Margetts, 1999). Serotonin syndrome has also been reported as occurring following use of 3,4-methylenedioxymetamphetamine (MDMA or Ecstasy) (Demirkiran *et al*, 1996; Mueller & Korey, 1998). Serotonin syndrome is thus likely to present in casualty departments as well as in psychiatric practice.

Reports of serotonin syndrome with drug overdoses are rare, but in many cases, fatal. Neuvonen *et al* (1993) reported five fatal cases of serotonin syndrome with the combination of

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Table 2. Reports of serotonin syndrome as a result of changing drug therapy

Drug → drug	Comments
Clorgiline (MAO-A inhibitor) → clomipramine (Sternbach, 1991)	Clomipramine started four weeks after clorgiline was discontinued → serotonin syndrome
Fluoxetine → MAOIs (Lejoyeux *et al*, 1994)	Serotonin syndrome has been demonstrated when MAOIs have been given less than five weeks after discontinuation of fluoxetine
Clomipramine → moclobemide (Spigset & Mjorn-Dal, 1993)	Clomipramine stopped, moclobemide started, next day → serotonin syndrome
Fluoxetine → moclobemide (Benazzi, 1996)	Fluoxetine 20 mg stopped and moclobemide 150 mg started the next day → serotonin syndrome
Trazodone → nortriptyline (Fink, 1996)	Trazodone 150 mg twice daily stopped and three days later nortriptyline started → serotonin syndrome
Fluoxetine → sertraline (Bhatara & Bandettini, 1993)	Fluoxetine stopped and sertraline started after a 24-hour washout → serotonin syndrome
Fluoxetine → paroxetine (Mills, 1995)	Fluoxetine stopped and two days later paroxetine started → serotonin syndrome
Fluoxetine → venlafaxine (Bhatara, 1994)	Fluoxetine 30 mg stopped abruptly and venlafaxine 37.5 mg twice daily started, 24 hours later → serotonin syndrome
Moclobemide → clomipramine (Gillman, 1997)	Moclobemide 750 mg daily stopped and clomipramine 50 mg daily started 12 hours later → serotonin syndrome
Selegiline → venlafaxine (Gitlin, 1997)	Sodium valproate, selegiline and nortriptyline stopped and 16 days later venlafaxine 37.5 mg daily started → serotonin syndrome within six hours
Nefazodone → paroxetine (John *et al*, 1997)	Nefazodone withdrawn gradually and paroxetine started one day after the last dose of nefazodone
Phenelzine → venlafaxine (Diamond *et al*, 1998)	Four reports of serotonin syndrome when patients were swapped from phenelzine to venlafaxine

moclobemide and citalopram or moclobemide and clomipramine. Also, Singer & Jones (1997) describe one case of fatal serotonin syndrome from an overdose of moclobemide and paroxetine. Overall, there have been 23 deaths reported to be linked to serotonin syndrome in the last 10 years (Gillman, 1999). This probably represents an underestimate of the total number, since many cases may not have been reported because of medico-legal reasons.

Surprisingly, there have been reports of recoveries after overdose with moclobemide and clomipramine (Francois *et al*, 1997) and moclobemide and venlafaxine (Roxanas & Machado, 1998).

Biochemical mechanism of serotonin syndrome

A number of possible mechanisms underlying serotonin syndrome have been suggested. The mechanism is generally thought to involve brainstem and spinal cord activation of 5-HT_{1A} receptors (Sternbach, 1991), although stimulation of 5-HT_{2A} receptors may also be causative (Gillman, 1999).

The combination of MAOIs and SSRIs appears to be particularly toxic. This is probably a result of simultaneous blockade of serotonin reuptake by SSRIs and the inhibition of serotonin degradation by MAOIs, leaving essentially no mechanism to control serotonin concentration in the synapse.

Managing serotonin syndrome

Serotonin syndrome is often self-limiting and symptoms usually resolve within 24 hours of discontinuing the causal agent. Severe cases may require the use of a serotonin antagonist or supportive care. The management will, therefore, largely depend on the symptoms of

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Table 3. Summary of suggested management of serotonin syndrome

Treatment	Drug	Comments
Sedatives	Lorazepam or diazepam	Has been used as a sedative and is usually hypothermic but may further lower seizure threshold (fairly potent 5-HT_{2A} antagonist).
	Chlorpromazine	
Serotonin antagonists	Cyproheptadine	Non-specific 5-HT receptor antagonist.
	Chlorprothixene	5-HT_{2A} antagonist; not used in UK.
	Propranolol	5-HT_{1A} receptor antagonist.
Anticonvulsants	Benzodiazepines	
Cooling blanket	Hyperthermia is usually a sign of severe serotonin syndrome and so carries higher risk of complications and death, aggressive therapy is needed.	

serotonin syndrome is summarised in Table 3 and reviewed fully by Brown *et al* (1996), Lane & Baldwin (1997) and Gillman (1999). Note that treatments have a largely theoretical basis; none has been robustly, clinically tested.

Avoiding serotonin syndrome

Many of the episodes of serotonin syndrome reviewed in this article could have been avoided. Many recommended drug combinations aim specifically to increase serotonergic function and so predictably increase the risk of serotonin syndrome. Combinations including MAOIs and L-tryptophan should therefore be used with extreme caution.

A combination of two drugs can also occur inadvertently, for example, when changing drug therapy from a drug with a long half-life. In such cases, there may also be the potential for a pharmacokinetic interaction which may increase the risk of serotonin syndrome, for example, if both drugs are serotonergic in action and one inhibits the metabolism of the other. When changing drug therapy, the half-life of the discontinued drug should be taken into consideration as well as potential pharmacodynamic and perhaps, more importantly, pharmacokinetic interactions between the old and new drug. For example, SSRIs are not only potent inhibitors of serotonin reuptake, but some, such as, fluoxetine, paroxetine and fluvoxamine are also potent inhibitors of the cytochrome P450 isoenzyme system and therefore have the potential to increase levels of other serotonergic drugs. Indeed, all SSRIs (except citalopram) have been shown significantly to increase tricyclic plasma levels when given in combination (Taylor, 1995). Therefore, when considering switching from a drug with a long-half, such as fluoxetine, long wash-out periods are often necessary in order to avoid the risk of serotonin syndrome. Shorter wash-out periods may be necessary with other SSRIs.

Discussion

Awareness of serotonin syndrome and its symptoms has rapidly increased and it is now a recognised adverse effect of antidepressant therapy. The symptoms are often mild, but in some can prove fatal.

The risk of serotonin syndrome is difficult to establish, but from the available literature it appears that combinations including an MAOI are likely to be more toxic than others and should therefore probably be avoided, except in specialist centres treating refractory depression. In addition, when changing drug therapy, wash-out periods may be necessary before starting the new drug.

Management of serotonin syndrome in most cases is simple, the first step being to discontinue drug therapy after which in many cases, symptoms resolve within 24 hours. In theory, more severe cases may require a serotonin antagonist such as chlorpromazine, cyproheptadine or propranolol (for which there is largely only a theoretical basis for their use) and where appropriate supportive measures should be provided.

Appendix

Diagnostic criteria for the serotonin syndrome (Sternbach, 1991)

(a) Coincident with the addition of or an increase in dosage of a known serotonergic agent to an established medication regimen. At least three of the following clinical features must be present:

  (a) mental status changes (e.g. confusion, hypomania);
  (b) agitation;
  (c) myoclonus;
  (d) hypereflexia;
  (e) diaphoresis;
  (f) shivering;

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(g) tremor;
(h) diarrhoea;
(i) incoordination;
(j) fever.

(b) Other aetiologies (e.g. infectious, metabolic, substance misuse or withdrawal) have been ruled out.

(c) An antipsychotic drug has not been started or increased in dosage prior to the onset of the symptoms.

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