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REVIEW

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Serotonin syndrome and drug combinations: focus on MAOI and RIMA

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Abstract Serotonin syndrome is a potentially life-threatening complication of psychopharmacological drug therapy. The syndrome is produced most often by the concurrent use of two or more drugs that increase brainstem serotonin activity and is often unrecognized because of the varied and nonspecific nature of its symptomatology. Serotonin syndrome is characterized by alterations in cognition, behavior, autonomic nervous system function and neuromuscular activity. The purpose of this study was to investigate the possibility that any serotomimetic substance alone or in combination may give rise to serotonin syndrome, that this condition is not confined to the use of newly introduced substances, and that the newer reversible inhibitors of monoamine oxidase type A (RIMAs) are at decreased risk for this phenomenon than older, classical (irreversible) monoamine oxidase inhibitors (MAOI). This is a hypothesis-generating study based on a review of all published cases of adverse effects arising in patients receiving serotomimetic substances or combinations. A wide range of substances were involved in 226 cases published worldwide since 1950 where there was any use of single or combined serotomimetic treatments. Of the 226 cases, 105 fulfilled the Sternbach criteria for serotonin syndrome. Some classes of drugs and individual substances were more commonly represented. This may arise from product utilization patterns or from the specific properties of the individual products. However, moclobemide, a RIMA, was represented in only 9 of the 226 published cases and 3 of the 105 defined serotonin syndromes, either in multi-drug combinations and/or in mixed drug overdose. One explanation for the small number of cases involving RIMAs could be the reversibility of these new products. In addition the small number of reports on moclobemide could be an effect of its short availability in routine use during the period of the literature review. We conclude that a spectrum of serotonergic hyperactivity, through to a defined serotonin syndrome, may arise from the use or combination of any serotomimetic substance, as this is a consequence of the mechanism involved, rather than the use of any specific product such as the new antidepressants. We further conclude that this condition is not confined to the use of newly introduced substances and that the newer reversible inhibitors of monoamine oxidase type A (RIMAs) may be at decreased risk for this phenomenon than older, classical (irreversible) (MAOI). Given that a spectrum of serotonergic hyperactivity was observed, this analysis prompts redefinition of the currently accepted criteria for serotonin syndrome.

Key words Serotonin syndrome · Antidepressants · Safety · RIMA · Moclobemide

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Introduction

Serotonin seems to be involved in many psychiatric disorders, including depression, anxiety, social phobia, and obsessive – compulsive disorder [20, 27]. Antidepressants appear to affect central serotonin levels, regardless of their mode of action, i.e., whether they are tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) or amine derivatives. Lithium, mostly administered for prophylactic purposes, but under special conditions also given for the treatment of a depressive episode, also has a serotoninergic mode of action.

Treatment strategies for patients with therapy-resistant disorders may involve combination treatment with more than one antidepressant. This may result in patients commonly receiving at least two, and often many, serotomimetic compounds concomitantly. Consideration of possible interactions between these compounds is therefore important.

Serotonin syndrome is a potentially life-threatening complication of psychopharmacological drug therapy. The syndrome is produced most often by the concurrent

use of two or more drugs that increase brainstem serotonin activity and is often unrecognized because of the varied and nonspecific nature of its symptomatology. Serotonin syndrome is characterized by alterations in cognition, behavior, autonomic nervous system function and neuromuscular activity, both in animals [6, 12, 16, 29, 36, 41] and in humans [44, 45].

A necessary, but not the only, prerequisite for its development is virtually complete inhibition of the degradation and elimination of serotonin from the synaptic cleft (> 85% blockade of both MAO-A and MAO-B and inhibition of serotonin reuptake) [15, 30, 37]. Contributing factors are increased and/or decreased functioning of other systems, particularly of the dopaminergic and cholinergic systems [14, 39]. Both the central and peripheral serotonergic systems and several serotonin receptor types are involved in the symptomatology of serotonin syndrome. The pathogenesis of serotonin syndrome may be due to endogenous as well as iatrogenic deficits in peripheral serotonin metabolism, a stimulus for release of serotonin, and interactions with other neurotransmitter systems [5].

The incidence of serotonin syndrome in humans is unknown. Heightened awareness of this syndrome followed the increase in use of new, serotomimetic antidepressants, leading to the impression that this is a new phenomenon [40].

The development of new, selective antidepressants, such as the reversible inhibitors of monoamine oxidase A (RIMAs, including brofaromine, moclobemide, toloxatone) and selective serotonin reuptake inhibitors (SSRI, including fluoxetine, citalopram, sertraline), has prompted questions on the interaction potential of these two therapeutic groups specifically with respect to serotonergic interactions. Furthermore, certain serotoninergic drugs or drug combinations have been reported to have a higher risk for this syndrome or a higher risk for a fatal outcome of this syndrome than others. In this context the combination of classical (not reversible) MAOI with the long-acting SSRI fluoxetine should be noted [33].

The RIMA antidepressants have properties which suggest that they might be at decreased risk of such phenomena when administered alone or in combination with other drug combinations. This is because they affect the brain monoaminergic neurotransmitter system through selective and reversible inhibition of MAO preferentially of type A [7, 9, 17, 19, 25, 48].

The authors set out to investigate this issue by detailed retrospective review and analysis of the literature published over the past 45 years.

Aim

The purpose of this study was to investigate the possibility that any serotomimetic substance alone or in combination may give rise to serotonin syndrome, that this condition is not confined to the use of newly introduced substances, and that the newer reversible inhibitors of monoamine oxidase type A (RIMAs) are at decreased risk for this phenomenon than older, classical (irreversible) MAOI.

Method

This is a hypothesis generating study based on all published cases of any adverse effects arising in patients receiving serotomimetic substances or combinations. Publications covering the period 1950 to the end of June 1996 were retrieved from a comprehensive search of the Medline database system. Additional literature was obtained from reference lists of articles identified through the search. All publications were reviewed and classified by the authors. The pattern and incidence of symptoms in each case were systematically studied. Employing the diagnostic criteria suggested by Sternbach (see below) we examined each published case and systematically recorded demographic data, diagnosis, all drugs involved and doses where stated, all Sternbach inclusion and exclusion criteria for serotonin syndrome, all additional symptoms and signs, and the eventual outcome.

Results

A wide range of substances were involved in 226 cases published worldwide since 1950 where there was any use of single or combined serotomimetic treatments. Of the 226 cases, 105 fulfilled the Sternbach criteria for serotonin syndrome.

Patients

In 226 published cases there were 83 males, 108 females and 35 patients of unspecified gender, together of stated age 9–76 years (mean 40.8 years, SD 17 years, median 38.5 years). The distribution of treatment indications in these 226 cases is shown in Table 1.

Table 1 Indications for treatment among the 226 cases

Indication	No. of cases	% total cases
Overdose, abuse	20	9
Bipolar depression	14	6
Unipolar depression	10	4
Depression	46	20
Major depression	32	14
Mania	10	4
Depression/parkinsonism	5	2
Depression/psychosis	2	1
Depression/convulsions	1	< 1
Epilepsy	1	< 1
Huntington's chorea	1	< 1
Major depression/bulimia	4	2
Obsessive-compulsive disorder	13	6
Parkinson's disease	22	10
Schizophrenia	3	1
Not stated	42	19

A total of 53% of the cases had been given the drugs involved for an affective disorder. Of the cases, 9% had taken an accidental or deliberate overdose, 12% had a movement disorder, 6% had an anxiety disorder and 1% had a schizophrenic disorder. In 19% of the cases the reason for treatment was not stated.

In 24 of the 226 cases there had been drug abuse. In 2 cases the adverse events occurred following withdrawal of one or more of the drugs involved. Twenty cases were, at the time of first publication, diagnosed as having neuroleptic malignant syndrome. When currently reviewed, not all of these cases fulfilled the currently recognized criteria for this disorder. Indeed, some of these cases instead fulfilled the criteria for serotonin syndrome. Thirty-five of the 226 patients died.

Drugs

In all, 565 compounds were mentioned in the 226 published cases, with some patients ingesting up to eight different substances. The distribution of cases by number of drugs ingested is shown in Table 2. The distribution of drug classes represented in the drug combinations reviewed is shown in Table 3.

Monoamine oxidase inhibitors were the most commonly implicated drugs, most often in combination with selective serotonin reuptake inhibitors or with tricyclic antidepressants. Monoamine oxidase inhibitors in combination with lithium, meperidine, dextromethorphan and L-tryptophan have also been reported. Selective serotonin reuptake inhibitors in combination with lithium, meperidine, dextromethorphan, and L-tryptophan were observed, as were isolated cases including carbamazepine, fentanyl, pentazocine and bromocriptine. There were reports implicating the "street" drug methylenedioxymethamphetamine (MDMA) [13].

Some classes of drugs and individual substances were more commonly represented. This may arise from product utilization patterns or from the specific properties of the individual products. However, the RIMA moclobemide was represented in only 9 of the 226 published cases and 3 of the 105 defined serotonin syndromes. All cases involving moclobemide were mixed drug overdose, where the other drugs concurrently ingested included alprazolam, clonazepam, chlordiazepoxide, carbamazepine, alcohol, diazepam, cannabis, amphetamine, maprotiline and/or temazepam or multi-drug combinations. No cases involving brofaromine were reported [48]. Only one published case involved clorgyline. It is not known whether this arises from low prescribing rate, low product utilization patterns, or from the specific properties of the product.

Table 2 Number of drugs ingested among the 226 cases

No. of drugs ingested	No. of patients
1	49
2	100
3	35
4	15
5	19
6	5
7+	3

Table 3 Distribution of drug classes represented in the drug combinations. *MAOI* monoamine oxidase inhibitors; *RIMA* monoamine oxidase type A

Drugs	No. of patients (n = 226)	No. of patients with more than one drug in that category	No. of SS cases (n = 105)
Antidepressants			
AD MAOI	94		52
AD RIMA	10		3
AD SSRI	72		38
AD tricyclic antidepressants	62		37
AD amino acid derivatives	59	3	33
Lithium	27	5	13
AD methionine derivatives	1		1
Sedatives			
Active benzodiazepines	22		6
Other sedatives	19	2	4
Weak benzodiazepines	19	2	7
Non-benzodiazepines	6		2
Antipsychotics			
AP neuroleptic	29		5
AP dopaminergic	1		0
Antiparkinson	27		2
Anticonvulsant	13	10	1
Stimulant–anorectic	10		5
Narcotic analgesic	9		6

Table 4 Symptoms among the 226 cases, classified according to the criteria of Sternbach

Symptom	No. of patients with that symptom	%
Mental status changes	154	68
Agitation	67	30
Myoclonus	101	45
Hyperreflexia	65	29
Diaphoresis	50	22
Shivering	34	15
Tremor	93	41
Diarrhea	20	9
Incoordination	68	30
Fever	80	35

NOTE: Each patient had more than one symptom. Each patient was counted once for each symptom or sign they experienced

Table 5 Other commonly reported symptoms in the published series. *CPK* creatine phosphokinase

Symptom	No. of patients with that symptom	%
Dizziness/disorientation	10	4
Hypertonia	66	29
Increased CPK	15	7
Visual disturbances	24	11
Cardiovascular instability	47	21
Dyskinesia	16	7
Chattering teeth	7	3

NOTE: Each patient had more than one symptom. Each patient was counted once for each symptom or sign they experienced

Symptoms

Sternbach proposed that coincident with the addition of, or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features should be present: changes in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, mental incoordination, and fever [45]. Other etiologies (infectious, metabolic, substance abuse, or withdrawal) should have been excluded and a neuroleptic should not have been started or increased in dosage prior to the development of the symptomatology.

There was a range of symptoms and signs, ranging from mild symptoms resolving within 24 h, to severe symptomatology requiring intensive care. Of the 226 patients, 35 died. The distribution of symptoms among the 226 cases, classified according to the criteria of Sternbach, and showing other commonly reported symptoms in the cases, are shown in Tables 4 and 5.

Cases fulfilling the Sternbach criteria for serotonin syndrome

A total of 30 patients were excluded from the diagnosis as other etiologies for the symptoms were noted. An additional 24 patients were excluded as they had received a neuroleptic, as were 67 patients fulfilling less than three Sternbach criteria. The symptoms in the remaining 105 patients are shown in Table 6. This symptom profile contrasts with that of the original series of 38 patients described by Sternbach, the key symptoms of which are shown in Table 7.

Table 6 Symptoms among the 105 cases fulfilling the Sternbach criteria for serotonin syndrome

Symptom	No. of patients with that symptom	%
Mental status changes	81	77
Agitation	44	42
Myoclonus	66	63
Hyperreflexia	46	44
Diaphoresis	41	39
Shivering	31	30
Tremor	64	61
Diarrhea	18	17
Incoordination	42	40
Fever	36	34

NOTE: Each patient had more than one symptom. Each patient was counted once for each symptom or sign they experienced

Table 7 Key symptoms among the 38 cases originally described by Sternbach

Symptom	No. of patients with that symptom	%
Mental status changes	24	63
Agitation	17	45
Myoclonus	13	34
Hyperreflexia	11	29
Diaphoresis	10	26
Shivering	10	26
Tremor	10	26
Diarrhea	6	16
Incoordination	5	13
Fever	Not stated	–

NOTE: Each patient had more than one symptom. Each patient was counted once for each symptom or sign they experienced

Spectrum of clinical features in the sample

We were interested that in the 226 published cases, a spectrum of serotonergic hyperactivity, through to a defined serotonin syndrome, was observed. This was shown by the number of patients who had one or more of the key clinical features as proposed by Sternbach, but who did not fulfill the criteria set by him for the full serotonin syndrome. This spread of severity is shown in Table 8.

Of note is that 73 patients fulfilled only one or two of the Sternbach criteria and yet clearly had serotonergic overactivity which could not be explained by the pharmacological properties of the ingested substances alone.

Table 8 Number of cases having the key clinical features originally described by Sternbach (n = 226)

No. of Criteria	No. of patients	%
1	37	16
2	36	16
3	37	16
4	57	25
5	22	10
6	9	4
7+	16	7
None	12	5

Discussion

Review of published case reports are valuable for raising hypotheses. However, these hypotheses then need to be tested with more rigorous study designs. In our review of published case reports, we cannot distinguish whether these published cases are typical of the exposed population or typical of those who develop serotonin syndrome. In addition, in a setting of multiple drug exposure, it is difficult to identify causation. We have no information about the size of the exposed population to either single or combination therapies and no control group to estimate the size of the risk.

Serotonin syndrome is increasingly recognized and reported in the literature. However, the present analysis shows that this is not a new phenomenon and cases fulfilling the criteria for this syndrome suggested by Sternbach have, in fact, been reported as early as 1955 [32] and 1958 [38] in patients receiving iproniazid and pethidine in combination. It is clear from review of the published cases that a syndrome similar to that described by Sternbach has been described following the use of a large number of serotomimetic agents (serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, tryptophan, 3,4-methylenedioxy methamphetamine, dextromethorphan, meperidine, S-adenosylmethionine), either alone or in combination with MAOI. At present, there are insufficient data to be certain whether isoniazid has the same potential for drug interactions with antidepressants, particularly the serotonin reuptake inhibitors [24].

Based on the published cases, it appears that serotonin syndrome is not an all-or-nothing phenomenon. Indeed, a spectrum of serotonergic hyperactivity, through to a defined serotonin syndrome, was observed in the sample of reviewed cases. There have been various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, low-grade fever, nausea, diarrhea, diaphoresis, flushing, and, rarely, rhabdomyolysis and death.

Patients with serotonin syndrome usually respond to discontinuation of drug therapy and supportive care alone, but as in the sample reviewed, some require treatment with a specific antiserotonergic drug such as cyproheptadine, methysergide, and/or propranolol [31]. Lorazepam and nitroglycerin have also been used successfully to treat serotonin syndrome [5].

Certain serotoninergic drugs or drug combinations do appear to have a higher risk for this syndrome or a higher risk for a fatal outcome of this syndrome than others. Indeed, a prospective study of patients receiving clomipramine showed that 42% of patients developed at least one serotonergic symptom [28]. Irreversible MAOI were the most commonly implicated drugs in the sample, most often in combination with SSRI. In this context the combination of classical (not reversible) MAO inhibitors with the long-acting SSRI fluoxetine should be noted [2, 33]. The long-acting metabolite of fluoxetine is important in this regard [8]. However, other factors, such as product utilization patterns and adverse drug reaction reporting rates, should be considered in the overall risk–benefit evaluation of such combinations.

Irreversible MAOI were also implicated in combination with or with tricyclic antidepressants. Indeed, seizures have been associated with this combination of drug classes [3, 4, 42].

Unlike the selective reversible inhibitors of MAO-A (RIMAs), the selective MAO-B inhibitor selegiline has been implicated at therapeutic doses in reported cases of serotonin syndrome in combination with SSRI [22, 46, 47]. One explanation for these cases may be that selectivity for MAO-B is lost with higher doses of selegiline. One explanation for the small number of cases involving RIMAs could be the reversibility of these new products, although the small number of reports on moclobemide could be an effect of its short availability in routine use during the period of the literature review.

No case of serotonin syndrome has been reported following ingestion of moclobemide alone. Indeed, overdoses of moclobemide alone induce generally mild and reversible signs of central nervous system (CNS) and gastrointestinal irritation which do not need particular intervention [18, 21, 34], although as with other antidepressants, mixed overdoses with moclobemide and other CNS-acting drugs could be life-threatening [26, 35, 40].

Studies of combined moclobemide–SSRI therapy have shown this combination to be safe and well tolerated [1, 10, 11, 23, 49], although this treatment strategy should be approached with caution. However, these studies were performed on selected populations and sample sizes were small. Moclobemide has been implicated in fatal cases of serotonin syndrome in mixed drug overdose [35] and in combination with fluoxetine and clomipramine [43], a combination at high risk of developing the syndrome.

Conclusions

We conclude that a spectrum of serotonergic hyperactivity, through to a defined serotonin syndrome, may arise from the use or combination of any serotomimetic substance, as this is a consequence of the mechanism involved, rather than the use of any specific product such as the new antidepressants. We further conclude that this condition is not confined to the use of newly introduced substances and that the newer reversible inhibitors of

MAO-A, RIMAs, may be at decreased risk for this phenomenon than older, classical (irreversible) MAOI. Given that a spectrum of serotonergic hyperactivity was observed, this analysis prompts redefinition of the currently accepted criteria for serotonin syndrome.

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