The Serotonin Syndrome

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Objective and Method: A review of the literature on the serotonin syndrome in animals and human beings was conducted, and 12 reports of 38 cases in human patients were then analyzed to determine the most frequently reported clinical features and drug interactions, as well as the incidence, treatment, and outcome of this syndrome. Findings: The serotonin syndrome is most commonly the result of the interaction between serotonergic agents and monoamine oxidase inhibitors. The most frequent clinical features are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor. The presumed pathophysiological mechanism involves brainstem and spinal cord activation of the 1A form of serotonin (5-hydroxytryptamine, or 5-HT) receptor. The incidence of the syndrome is not known. Both sexes have been affected, and patients' ages have ranged from 20 to 68 years. Discontinuation of the suspected serotonergic agent and institution of supportive measures are the primary treatment, although 5-HT receptor antagonists may also play a role. Once treatment is instituted, the syndrome typically resolves within 24 hours, but confusion can last for days, and death has been reported. Conclusions: The serotonin syndrome is a toxic condition requiring heightened clinical awareness for prevention, recognition, and prompt treatment. Further work is needed to establish the diagnostic criteria, incidence, and predisposing factors, to identify the role of 5-HT antagonists in treatment, and to differentiate the syndrome from neuroleptic malignant syndrome.

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Serotonin (5-hydroxytryptamine, or 5-HT), discovered by Rapport et al. (1) in 1948, has been shown to have a major role in multiple psychiatric and nonpsychiatric states (anxiety, depression, aggression, pain, sleep, appetite, migraine, and emesis) (2). Two serotonergic agents, fluoxetine and clomipramine, have been on the market in the United States since 1988, and it is expected that others (sertraline, fluvoxamine) will follow in this decade.

Increasingly since the 1960s, a condition of serotonergic hyperstimulation called the "serotonin syndrome" has been described in animals and human beings. This article reviews the history, clinical manifestations, proposed pathophysiology, incidence, precipitating factors, treatment, and outcome of this syndrome with the purpose of helping clinicians to prevent, recognize, and treat the syndrome in their practice.

HISTORY

CNS effects of the 5-HT precursor L-tryptophan (L-Trp) in human beings were reported by Smith and Prockop (3) in the early 1960s. These investigators studied L-Trp in seven normal subjects and found euphoria, drowsiness, and sustained nystagmus in all of the subjects at the two highest doses, 70 and 90 mg/kg. Other signs included hyperreflexia, unsustained ankle clonus, and clumsiness with tandem walking. Neurological disturbances associated with high L-Trp intake were similarly reported in rhesus monkeys (4). Oates and Sjoerdsma (5) administered single doses of L-Trp, 20–50 mg/kg, to seven hypertensive patients being treated with the monoamine oxidase inhibitor (MAOI) β-phenylisopropylhydrazine. The symptoms and signs they noted included feeling drunk and dizzy, as well as clonus, restlessness, hyperactive reflexes, and diaphoresis in the absence of any significant change in blood pressure or heart rate, with symptoms abating within 24 hours. Since it had been shown in animals (6, 7) that administration of L-Trp increased brain levels of tryptamine and 5-HT, Oates and Sjoerdsma concluded that the signs and symptoms they had noted were due to elevated concentrations of tryptamine and 5-HT in their subjects. In a follow-up study, Hodge et al. (8) gave five hypertensive subjects a decarboxylase inhibitor before treating them with pargyline or isocarboxazid, preventing the formation of tryptamine and 5-HT and thus blocking the nystagmus, jaw tremor, hyperreflexia, clonus, sweating, and intoxication that L-Trp produces.

After the late 1950s, there were reports on the use of

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TABLE 1. Summary of 12 Clinical Reports of the Serotonin Syndrome in 38 Patients

Authors	Diagnosis	Age (years)	Sex	Medications[a]	Time to Onset
Baloh et al. (17)	Bipolar disorder, depressed	26	F	Tranylcypromine, 20 mg; L-Trp, 2 g	1 hour
Insel et al. (18)	Obsessive-compulsive disorder	35	F	Clomipramine, 100 mg, 4 weeks after clorgyline was stopped	30 minutes
	Obsessive-compulsive disorder	30	M	Same as above	"Immediately"
Thomas & Rubin (19)	Depression	21	M	Phenelzine, 90 mg; L-Trp, 6 g	2 hours
Pope et al. (20)	Depression alone (N=1) or with eating disorder (N=8)	20–42	All F	Tranylcypromine, 40–130 mg, and L-Trp, 1–6 g (N=8); phenelzine, 75 mg; L-Trp, 13 g; lithium; benzodiazepine	2 days to 4 weeks from first dose of L-Trp
Levy et al. (21)	Depression	57	M	Phenelzine, 60 mg; L-Trp, 2 g	3 hours
	Bipolar disorder, depressed	28	M	Phenelzine, 105 mg; lithium (0.9 meq/liter); L-Trp, 2 g	2 hours
	Depression	31	F	Phenelzine, 90 mg; L-Trp, 2 g	2 hours
Guze & Baxter (22)	Bipolar disorder, depressed	30	F	Lithium, 1500 mg; isocarboxazid, 50 mg; alprazolam, 6 mg; levothyroxine, 0.15 mg; L-Trp, 8 g; carbidopa, 75 mg	2 days
Price et al. (23)	Depression	63	M	Tranylcypromine, 30 mg; lithium, 900 mg; L-Trp, 2 g	1 week
Steiner & Fontaine (24)	Obsessive-compulsive disorder (N=5)	34–58	3 M, 2 F	Fluoxetine, 50–100 mg; L-Trp, 1–4 g/day for 7–22 days	"Rapidly" to a few days
Sandyk (25)	Parkinson's disease	68	M	Bromocriptine, 20 mg; L-dopa/carbidopa, 25/250 mg t.i.d.	7 days
Sternbach (26)	Depression	31	F	Tranylcypromine, 20 mg, 6 days after fluoxetine, 20 mg, was stopped	2–3 hours
Kline et al. (27)	Depression	45	F	Fluoxetine, 40 mg; levothyroxine; propranolol; quinidine; hydroxyzine; followed by thioridazine, 50 mg; L-Trp, 500 mg; tranylcypromine, 50 mg	2½ hours after L-Trp and thioridazine were added
Feighner et al. (28)	Unipolar (N=9) and bipolar (N=3) depression	22–50	10 F, 2 M	Fluoxetine, 10–100 mg; phenelzine, 30–60 mg (N=9), or tranylcypromine, 10–140 mg (N=4). All but one took other psychotropics, including L-Trp (N=2), benzodiazepines (N=10), neuroleptics (N=6), lithium (N=1), anticonvulsants (N=2), stimulants (N=2), antidepressants (N=5)	Not specified

[a] L-Trp=L-tryptophan.

L-Trp to potentiate the effects of MAOIs in depression (9–13). In one such study (13), patients were given 12–18 g/day of L-Trp with 60 mg of phenelzine; no hypertensive reactions were noted, although one patient who ingested 18–20 g all at once was found to have increased deep tendon reflexes, muscle twitching, and clonus of the masseter, all of which subsided within 12 hours. Further, tricyclic antidepressants were also combined with MAOIs, and Beaumont (14) reported on interactions between these two classes of drugs that were manifested by sweating, restlessness, muscular twitching, rigidity, hyperpyrexia, and loss of consciousness and that led to death in several patients. In all instances, the patients were already taking MAOIs (mebanazine, tranylcypromine) when the tricyclic was added. Subsequently, White and Simpson (15) reviewed the literature on combined MAOI-tricyclic treatment, noting that the adverse reactions to most MAOI-tricyclic combinations in cases in which there was not an overdose differed from typical hypertensive crises, as there was rarely marked elevation of blood pressure, headache, or a cerebrovascular accident. The more typical picture was that of an agitated delirium with generalized hypertonicity, seizures, hyperpyrexia, and variable elevations of heart and respiratory rate, which often progressed to coma, a pattern considered to be "nonspecific."

During the same period of time, there were separate reports in the literature on animals about a behavioral syndrome seen when serotonergic stimulation was induced by the combined use of L-Trp or 5-HT reuptake inhibitors and MAOIs or by stimulation of 5-HT receptors with 5-HT agonists such as 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) or 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT). In 1980 Gerson and Baldessarini (16) reviewed this serotonin syndrome

TABLE 1 (continued)

Clinical Features	Treatment	Time to Resolution
Myoclonus, drowsiness, ocular oscillations, ataxia	Not specified	24 hours
Restlessness, leg contractions, diaphoresis, myoclonus, hyperreflexia, clonus, blood pressure 170/90 mm Hg, temperature 37.4 °C	Clomipramine discontinued	24 hours
"Upper motor neuron" symptoms, myoclonus, "cardiac irritability"	Same as above	6 hours
Shivering, diaphoresis, jocularity, fearfulness, ocular oscillations, hyperreflexia, dysmetria, ataxia	Both drugs stopped	24 hours
Confusion, disorientation, myoclonus, agitation, hypomania	L-Trp and MAOI stopped	12 hours to 4 days
Myoclonus, ataxia, tremor, diaphoresis, hyperreflexia, feeling drunk	L-Trp stopped	12 hours
Myoclonus, hyperreflexia, diaphoresis, teeth chattering, jaw quivering	L-Trp and phenelzine stopped	12 hours
Restlessness, hyperreflexia, diaphoresis, teeth chattering	L-Trp stopped	8 hours
Tremors, myoclonus, hyperreflexia, ataxia, nystagmus	Propranolol, 20 mg every 8 hours	Not specified
Diaphoresis, hyperventilation, shivering, hyperreflexia, increased muscle tone, temperature 38.5 °C	L-Trp stopped	Not specified
Agitation, nausea, diarrhea, paresthesia, chills, headache, cramps, incoordination, aggressive behavior, worsening obsessive-compulsive disorder, poor concentration	L-Trp stopped	"A few weeks"
Shivering, myoclonus, tremor, hyperreflexia, clonus, diaphoresis, diarrhea, temperature 37.9 °C, blood pressure 180/100 mm Hg	Methysergide, 2 mg b.i.d.	12 hours after third dose
Shivering, double vision, nausea, confusion, anxiety, teeth chattering	Tranylcypromine stopped	24 hours
Headache, insomnia, muscle contractions, ataxia, restlessness, neck pain, diaphoresis, flushing, tremor, rigidity, hyperreflexia, seizures, hypotension, disseminated intravascular coagulation	All drugs stopped; dantrolene, dopamine, *l*-ephedrine, lidocaine	44 hours (death)
Tremor, agitation, confusion, hypomania, myoclonus, diarrhea, diastolic pressure 90–120 mm Hg	Not specified	Not specified

in animals and noted that the characteristic features were tremor, rigidity, hypertonicity, hind-limb abduction, Straub (rigidly arched) tail, lateral head shaking, treading movements of the forelimbs, hyperreactivity to auditory stimuli, myoclonus, generalized seizures, and variable autonomic responses including salivation, penile erection and ejaculation. Since 1982 there have been 12 reports (17–28) in the literature on human beings about 38 patients who were given various combinations of serotonergic agents that resulted in the serotonin syndrome (table 1), with the notable exception of the case reported by Sandyk (25), in which the presumed cause of the serotonin syndrome was a combination of bromocriptine with L-dopa/carbidopa (further discussed in the section Drug Interactions).

A review of the signs and symptoms in all 38 reported cases (table 2) reveals mental status changes (confusion, hypomania) as the most frequent, followed by restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination. The frequencies reported, however, are likely to be artifactually low, as some authors did not report or assess all possible signs and symptoms. It is probable, in retrospect, that the toxic interactions reported by Beaumont (14) and White and Simpson (15) also reflected the serotonin syndrome.

PATHOPHYSIOLOGY

The preponderance of evidence that the constellation of signs and symptoms labeled as the serotonin syndrome is, in fact, due to 5-HT comes from animal models. The literature on human beings in which 5-HT is implicated in the serotonin syndrome is primarily

TABLE 2. The Most Common Clinical Features of the Serotonin Syndrome in 38 Patients in 12 Reports

Clinical Feature	N	%
Mental status changes		
Confusion	16	42
Hypomania	8	21
Restlessness	17	45
Myoclonus	13	34
Hyperreflexia	11	29
Diaphoresis	10	26
Shivering	10	26
Tremor	10	26
Diarrhea	6	16
Incoordination	5	13

anecdotal, with the exception of the reports by Oates and Sjoerdsma (5) and Hodge et al. (8).

Gerson and Baldessarini (16), in their review of the serotonin syndrome in animals, noted that treatments inducing this syndrome include L-Trp or 5-HT reuptake inhibitors given with MAOIs and stimulation of 5-HT receptors with agonists such as 5-MeODMT or 8-OH-DPAT. The serotonin syndrome can be blocked by pretreatment with *p*-chlorophenylalanine, an inhibitor of 5-HT synthesis, and by 5-HT receptor antagonists such as methysergide. There has been debate about the role of catecholamines in the serotonin syndrome, since L-dopa and MAOIs in combination produced a behavioral syndrome similar to that seen with L-Trp and MAOIs (29), which was nevertheless blocked by methysergide (30).

The identification of different types of 5-HT receptors (31–33) in the past decade has led to speculation that the 5-HT_{1A} receptor is involved in the serotonin syndrome. Lucki et al. (34) compared the ability of the 5-HT_2 receptor antagonists ketanserin and pipamperone to block the serotonin syndrome in rats with that of two nonselective 5-HT antagonists, methysergide and metergoline. They noted that only the nonselective antagonists were able to block the serotonin syndrome, while the 5-HT_2 antagonists blocked only the head-shake response. Further, Goodwin et al. (35) reported that the serotonin syndrome in rats is mediated by the postsynaptic 5-HT_{1A} receptor, a finding confirmed in mice by Yamada et al. (36). There are, however, some discrepancies in the literature about the ability of 5-HT_2 receptor antagonists to block the serotonin syndrome, and, as noted by Smith and Peroutka (37), some of these discrepancies are probably due to the different methods used for rating the syndrome and the different drugs administered to induce it, as well as the choice of specific behavioral signs to be rated. The literature nevertheless indicates that 5-HT_{1A} receptor activation is responsible, in large part, for the serotonin syndrome (35–38).

Anatomically, serotonergic cell bodies are primarily found in brainstem nuclei, particularly the dorsal and median raphe (39), which give rise to most of the ascending serotonergic projections. The more caudal brainstem raphe nuclei give rise to intrinsic brainstem connections and some projections to the spinal cord. As discussed by Lucki et al. (34), the 5-HT receptors responsible for producing the serotonin syndrome are located in the lower brainstem or spinal cord and are most likely 5-HT_1 receptors.

Graham and Ilett (40) discussed the importance of both 5-HT and dopamine in the development of the serotonin syndrome when MAOIs are combined with non-MAOIs. In particular, they suggested that the ratio of the concentration of the non-MAOI antidepressant required to halve 5-HT uptake in synaptosomal preparations (IC_{50}) to the IC_{50} for dopamine uptake could be related to the incidence of side effects in combined therapy. Agents with low ratios, clomipramine and fluoxetine, were highly likely to cause serious reactions. Amitriptyline and imipramine were intermediate, and trimipramine had a very low potential for producing a serotonin syndrome.

Blier et al. (41) reviewed the effects of tricyclics, MAOIs, 5-HT reuptake inhibitor antidepressants, ECT, and 5-HT_{1A} receptor agonists on 5-HT_{1A} receptors, both presynaptically and postsynaptically, as well as on overall 5-HT neurotransmission. All of these treatments, and lithium as well, have in common the enhancement of 5-HT neurotransmission, albeit through different modifications of the 5-HT_{1A} autoreceptors and postsynaptic receptors. Given these findings, one means of assessing the role of 5-HT in the serotonin syndrome would be to measure directly the concentration of brain 5-HT. Using intracranial dialysis as a means of measuring extracellular levels of 5-HT in vivo, Sleight et al. (42) assessed the relation between extracellular 5-HT and behavior following administration of selective and nonselective MAOIs and L-Trp. Although they were able to raise extracellular 5-HT levels with clorgyline, for example, they were not able to induce the serotonin syndrome. Inhibition of both MAO-A and MAO-B was considered to be essential for the development of the serotonin syndrome, but increased extracellular 5-HT appears not necessarily to result in the syndrome. Sleight et al. postulated that the syndrome may also be the result of a change in the extracellular level of some other, not defined, compound.

In summary, evidence points to the importance of 5-HT_{1A} activation or modification in brainstem and spinal cord neurons, with enhancement of overall 5-HT neurotransmission, as a necessary but possibly not sufficient cause of the serotonin syndrome. Since this hypothesis is based on the literature on animals, however, caution must be used when extrapolating these findings to human beings, as has previously been discussed (15).

INCIDENCE

The incidence of the serotonin syndrome in human beings is unknown. Prospective studies have not been conducted, and the syndrome is likely to be underre-

ported because it is not recognized, it is confused with neuroleptic malignant syndrome, or it appears in different gradations (mild, moderate, or severe). The cases reviewed by Beaumont (14) and White and Simpson (15), for example, probably represented the serotonin syndrome, as did reports of interactions between meperidine and isoniazid or iproniazid (43, 44). Further, there have been reports of cases in which the serotonin syndrome was thought to be neuroleptic malignant syndrome (27, 45), since there is much overlap between the signs and symptoms of the two. Rosebush and Stewart (46), for example, noted in their prospective study of neuroleptic malignant syndrome that the most frequent clinical features were fever, tachycardia, delirium, diaphoresis, rigidity, muteness, tremulousness, and movement disorder. Thus, Kline et al. (27) initially believed that their patient had neuroleptic malignant syndrome but later changed the diagnosis to serotonin syndrome; Brennan et al. (45) reported that a patient had neuroleptic malignant syndrome "without neuroleptics" while taking a combination of phenelzine, lithium, L-Trp, diazepam, and triazolam.

The incidence of the serotonin syndrome secondary to L-Trp will decline now that all products which contain L-Trp have been removed from the U.S. market because of the association of L-Trp with the eosinophilia-myalgia syndrome (47). However, L-Trp could be put back on the market if it is determined that contaminants were responsible for the cases of eosinophilia-myalgia syndrome, and clinicians should remain alert to this possibility.

The serotonin syndrome has been reported in patients with unipolar and bipolar depression, obsessive-compulsive disorder, eating disorders with depression, and Parkinson's disease. Except for the last disorder, the concentration of cases in these diagnostic groups is probably an artifact of prescribing these types of agents for patients with these conditions. The early literature on the same interactions in patients with tuberculosis given meperidine with isoniazid or iproniazid (43, 44) suggests, however, that anyone could develop this syndrome when given the "wrong" combination of serotonergic agents. Further, there are not, at present, adequate data to suggest that sex or age plays an important role in the incidence of or predisposition to this syndrome. A prospective study is needed to assess accurately the incidence of the serotonin syndrome. Additionally, to facilitate recognition and reporting, consensus is needed to establish formal diagnostic criteria, possibly including different gradations such as mild (tremor, confusion, incoordination), moderate (agitation, hyperreflexia, diaphoresis, shivering), and severe (fever, myoclonus, diarrhea). Suggested diagnostic criteria are listed in appendix 1.

DRUG INTERACTIONS

The drug interactions most commonly reported in connection with the serotonin syndrome are those between L-Trp and MAOIs, with or without concomitant lithium (table 3). In the cases in which lithium was also prescribed and its levels were reported (21–23), the levels were within normal limits. Further, it has been shown that in animals lithium enhances the serotonin syndrome produced by either 5-MeODMT (48) or 8-OH-DPAT (49), suggesting that lithium may also enhance this syndrome in human beings when it is administered with serotonergic agents.

TABLE 3. The Most Common Drug Interactions Associated With the Serotonin Syndrome in 38 Patients in 12 Reports

Drug Combination[a]	Number of Patients	Reference Numbers for Reports
L-Trp and an MAOI (with lithium)	16	17, 19, 20–23, 27
Fluoxetine and an MAOI	14	26–28
Fluoxetine and L-Trp	5	24
Clomipramine and clorgyline	2	18
Bromocriptine and L-dopa/carbidopa	1	25

[a]L-Trp=L-tryptophan; MAOI=monoamine oxidase inhibitor.

Fluoxetine in conjunction with MAOIs (26–28) or L-Trp (24) is the second most frequent drug combination associated with the serotonin syndrome. Marley and Wozniak (50) reported that in rats the most intense serotonin syndromes with MAOIs have been those seen with the 5-HT reuptake inhibitors, and they cautioned against the sequential use of these agents (fluoxetine, clomipramine, citalopram, paroxetine) with MAOIs. Additionally, since the serotonin syndrome has been reported when MAOIs were used after fluoxetine had been discontinued (26–28), the manufacturers of fluoxetine notified physicians on June 28, 1988, of three fatalities possibly secondary to use of tranylcypromine after withdrawal of fluoxetine. They recommended that at least 5 weeks elapse between discontinuation of fluoxetine and initiation of an MAOI.

Combinations of MAOIs with tricyclic antidepressants were not formally connected with the serotonin syndrome until the report of Insel et al. (18). In both of their patients, the syndrome developed when clomipramine was started 4 weeks after discontinuation of the MAO-A inhibitor clorgyline. As noted by Insel et al. (18), MAO-A may have a delayed recovery time following irreversible inhibition, with approximately 20% reduction in enzyme activity remaining at 4 weeks, and "adaptive changes" that could contribute to a drug interaction may also persist. Further, in a comparison of tranylcypromine with the reversible MAO-A inhibitor brofaromine, Bieck and Antonin (51) reported that 30 days were needed for complete normalization of the pressor response to tyramine after discontinuation of tranylcypromine, suggesting that tyramine could still interact adversely with the irreversible MAOIs at 4 weeks, which is consistent with the report of Insel et al. (18). Both reports suggest, therefore, that caution must also be used when sero-

tonergic agents are started within 2–4 weeks of discontinuing an MAOI.

Sandyk (25) reported a case of serotonin syndrome in a patient with Parkinson's disease who had been hospitalized for reevaluation of his antiparkinsonian treatment. He had been taking bromocriptine, 60 mg/day, for nearly 3 years. Bromocriptine was reduced to 20 mg/day, and L-dopa/carbidopa was started, with the dose raised during 1 week from one to three 25/250-mg tablets a day. On the seventh day of this regimen, a "toxic encephalopathic syndrome" developed, which was manifested by shivering, myoclonus, hyperreflexia, clonus, tremor, diaphoresis, anxiety, diarrhea, a temperature of 37.9 °C, blood pressure of 180/100 mm Hg, and tachycardia. Sandyk reviewed evidence that L-dopa becomes decarboxylated to dopamine in serotonergic neurons, which could then cause displacement of intraneuronal 5-HT stores into the synaptic cleft and onto 5-HT receptor sites. Dickinson and Curzon (52) reported, however, that the dopamine agonist apomorphine inhibited the serotonin syndrome. Because Sandyk's patient (25) responded to treatment with the 5-HT antagonist methysergide, an agent reported to induce akathisia (53), it is likely that his patient did have a serotonin syndrome and not a misidentified neuroleptic malignant syndrome secondary to reduction of a dopamine agonist (bromocriptine), a condition which would probably have worsened with a dopamine antagonist.

Buspirone, a 5-HT_{1A} partial agonist with weak dopaminergic activity (54), has not been reported to produce the serotonin syndrome in human beings, although when Neppe (55) used high doses of buspirone (up to 160 mg/day) to treat tardive dyskinesia in a woman with bipolar disorder who was taking lithium, she developed diarrhea at doses above 60 mg/day. The literature on animals, however, has been variable on this subject. Two reports showed full (56) or partial (37) serotonin syndromes secondary to buspirone, while another (57) did not. Gepirone, a related compound, was shown to induce the serotonin syndrome in rats (57).

Fenfluramine acts as both a 5-HT releasing agent (58) and a 5-HT reuptake inhibitor (59) and has been shown to induce the serotonin syndrome in rats (58, 60). Hollander et al. (61) reported on the adjunctive use of fenfluramine with either fluoxetine, fluvoxamine, or clomipramine for the treatment of obsessive-compulsive disorder, although no evidence of the serotonin syndrome was apparent in patients taking these combinations.

Two reviews in journals of anesthesia (43, 44) noted that the MAOI-meperidine (pethidine) interaction is one of central serotonergic overactivity. These reviews discussed patients experiencing muscle twitching, fever, hyperreflexia, diaphoresis, hypotension, hypertension, coma, and death. Meperidine has been reported (62) to block the neuronal reuptake of 5-HT and, in conjunction with an MAOI, to cause an increase in the 5-HT content of the CNS. Similarly, dextromethorphan blocks neuronal uptake of 5-HT and has been implicated in the serotonin syndrome (63) when used with an MAOI. Further, Hansen et al. (64) recently reported an interaction in a patient who was given 100 mg of pentazocine in conjunction with 40 mg of fluoxetine. Within 30 minutes of taking this combination, the patient complained of lightheadedness, anxiety, nausea, and upper extremity paresthesias, in addition to which he was diaphoretic, flushed, ataxic, tremulous, and hypertensive. Hansen et al. speculated that their patient's reaction was secondary to serotonergic excitation.

TREATMENT

No prospective studies evaluating the treatment of the serotonin syndrome in human beings have been conducted. Treatment strategies, therefore, are based on case reports of human patients and the literature on animal models of the syndrome.

The published reports since 1982 indicate that in human patients, if the added offending agent (e.g., L-Trp) is discontinued, the syndrome will often resolve on its own within 24 hours. Supportive measures can be used, however. These include cooling blankets for hyperthermia, intramuscular chlorpromazine as an antipyretic and sedative agent, artificial ventilation for respiratory insufficiency, anticonvulsants for seizures, clonazepam for myoclonus, and nifedipine for hypertension (15, 28, 43, 44).

Animal models have suggested that pretreatment with agents that deplete 5-HT or block 5-HT receptors will prevent the serotonin syndrome (16, 34, 36, 50, 65). More specifically, however, the blockade of 5-HT_1 receptors is crucial, since 5-HT_2 antagonists did not block the syndrome (34). Sandyk (25) successfully treated the serotonin syndrome by using the nonspecific 5-HT antagonist methysergide. Cyproheptadine, another nonspecific 5-HT receptor antagonist, has also blocked the syndrome in animal models (16), although there are no reports in the literature on its use in this syndrome in human beings.

It has been reported that β blockers block 5-HT receptors (30, 66) and inhibit the serotonin syndrome induced by L-Trp and tranylcypromine (30). Further, it has been noted that propranolol is a 5-HT_{1A} receptor antagonist (54, 67). Guze and Baxter (22) were able to use propranolol to block the serotonin syndrome in a patient taking isocarboxazid, L-Trp, and lithium. It should be noted, however, that in the one report of a fatality (27), the patient appeared to have already been taking propranolol as part of an ongoing medication regimen and still developed the serotonin syndrome.

The literature suggests that the optimal treatment approach is to discontinue the suspected medication, provide supportive measures when necessary, and wait for the syndrome to resolve. In cases in which these measures are not effective, however, methysergide and propranolol can be considered as adjuncts to treat-

ment. Further research is needed, however, to delineate the role of these agents in the treatment of the serotonin syndrome in human beings.

OUTCOME

The measurement of outcome prior to the first published report that recognized the serotonin syndrome in human beings (17) is fraught with difficulty because of cases of overdose with MAOIs and tricyclics. In the 12 reports since 1982 on the 38 patients with the serotonin syndrome (17–28), one fatality was recorded (27); the syndrome resolved in all of the other cases once the offending agent that had been added was discontinued. Further, resolution typically occurred within 24 hours, although when delirium was present, it took up to 4 days to abate. There were only two reports (22, 25) that specific treatment, propranolol or methysergide, was instituted and found to be effective.

The one fatality in this series (27) was a complicated case in which a patient taking multiple medications (fluoxetine, levothyroxine, propranolol, quinidine, and hydroxyzine) was hospitalized for severe depression. Fluoxetine was discontinued, and 10 hours later the patient was started on 20 mg of tranylcypromine, followed the next day by 50 mg of thioridazine (for agitation and depersonalization), 30 mg of tranylcypromine, and 500 mg of L-Trp for insomnia. Within 2½ hours of receiving L-Trp, she experienced muscle contractions and headache, followed by restlessness, neck pain, fever, diaphoresis, tremulousness, rigidity, and hyperreflexia. Since it was presumed, initially, that the patient had neuroleptic malignant syndrome, dantrolene and bromocriptine were administered, but she went on to have a seizure, require intubation, and develop ventricular tachycardia and hypotension. Oral and nasal bleeding were noted, and her temperature rose to 42.2 °C. Laboratory evaluation showed elevated creatine kinase levels, and results of coagulation studies were consistent with disseminated intravascular coagulation. The patient died approximately 49 hours after the onset of symptoms; the autopsy listed the cause of death as neuroleptic malignant syndrome, although the authors opined, in retrospect, that this patient had the serotonin syndrome instead, noting that the rapid onset of symptoms (within 3 hours) after thioridazine, a low-potency neuroleptic, was unusual for neuroleptic malignant syndrome. (This was, apparently, one of the first deaths reported to the manufacturer of fluoxetine as possibly being linked to a fluoxetine-tranylcypromine interaction.)

Brennan et al. (45) reported on a fatal outcome in a 42-year-old woman with depression who had been treated daily with phenelzine, 45 mg; lithium, 800 mg; L-Trp, 1 g; diazepam, 6 mg; and triazolam, 0.25 mg. She came to the emergency room because of restlessness, sweating, and confusion. Within 3 hours she developed coma, with hypertonicity, hyperreflexia, fever (42.5 °C), tachycardia, hypotension, a serum creatine kinase level of 41,355 U/liter (normal range=24–175 U/liter), and progression to disseminated intravascular coagulation after 12 hours. Since she was presumed to have neuroleptic malignant syndrome, dantrolene was administered, and her temperature returned to normal within 14 hours. In spite of supportive care, antibiotics, mechanical ventilation, and peritoneal dialysis for acute renal failure, severe hepatocellular damage ensued, and the patient died on the sixth day. This patient probably had a serotonin syndrome, rather than neuroleptic malignant syndrome, and her course of illness was very similar to that of the patient of Kline et al. (27).

In summary, the serotonin syndrome typically appears to be a self-limited condition that resolves quickly when offending agents are removed, although fatalities can occur, which makes early recognition and treatment vital.

CONCLUSIONS

The serotonin syndrome is a toxic hyperserotonergic state, typically the result of combining serotonergic agents with MAOIs, that results from hyperstimulation of brainstem and spinal cord 5-HT_{1A} receptors. This syndrome usually resolves with discontinuation of the suspected serotonergic agent or agents and conservative supportive measures. In severe cases, 5-HT receptor antagonists may be helpful, although their exact role in treatment has yet to be elucidated. The incidence of the syndrome is not known but could rise because of the introduction of more specific serotonergic agents into clinical practice. Heightened awareness by clinicians will help to minimize prescription of combinations of medications that have a higher probability of inducing the syndrome, and if it develops, this same awareness should lead to prompt institution of measures to resolve it.

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APPENDIX 1. Suggested Diagnostic Criteria for Serotonin Syndrome

A. 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 are present:
   1) mental status changes (confusion, hypomania)
   2) agitation
   3) myoclonus
   4) hyperreflexia
   5) diaphoresis
   6) shivering
   7) tremor
   8) diarrhea
   9) incoordination
   10) fever
B. Other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out.
C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.