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Serotonin Syndrome and Other Serotonergic Disorders

Rasih Atilla Ener, MD, Sharon B. Meglathery, MD, William A. Van Decker, MD, and Rollin M. Gallagher, MD, MPH†

MCP Hahnemann University Hospitals and † Drexel University College of Medicine, Philadelphia, Pennsylvania

ABSTRACT

Serotonin syndrome is an iatrogenic disorder induced by pharmacologic treatment with serotonergic agents that increases serotonin activity. In addition, there is a wide variety of clinical disorders associated with serotonin excess. The frequent concurrent use of serotonergic and neuroleptic drugs and similarities between serotonin syndrome and neuroleptic malignant syndrome can present the clinician with a diagnostic challenge. In this article, we review the pathophysiology, diagnosis, and treatment of serotonin syndrome as well as other serotonergic disorders.

Key Words. Serotonin Syndrome; Neuroleptic Malignant Syndrome (NMS); Akathisia; Tardive Dyskinesia; Parkinson's Disease; Selective Serotonin Reuptake Inhibitors (SSRI); Neuroleptics

Introduction

Over the past 10 years, a myriad of drugs has been developed to manipulate the serotonin system with the goal of treating a variety of disorders of mood, anxiety states, aggression, pain, sleep, and appetite as well as to treat migraine headaches and chemotherapy-induced emesis. Physicians treating patients with chronic pain diseases and disorders use serotonergically active drugs routinely for the treatment of pain as well as for commonly occurring comorbid conditions, such as depression and anxiety. In medical practices where the diagnosis and management of pain is a particular focus of treatment (e.g., rheumatology, pain medicine, neurology, spine), the comorbidity of pain and depression approaches 50% [1]. This high comorbidity increases the likelihood that patients will be treated for both pain and depression with combinations of medications that interact with the serotonin system, potentially creating serotonin excess and problematic symptoms, even central nervous system (CNS) damage, as outlined below. Consider two of the most common syndromes encountered in general medical practice, migraine and neuropathic pain (e.g., diabetic neuropathy, radiculopathy), in which, frequently, two or more serotonergically active drugs might be used in conjunction with the treatment of depression by a selective serotonin reuptake inhibitor (SSRI): Migraine headache (tramadol, sumatriptan, tricyclic antidepressants); neuropathic pain (tricyclic antidepressants, venlafaxine, meperidine, tramadol, trazodone [for sleep]). The addition of over-the-counter medications that are normally innocuous, such as dextromethorphan, a cough suppressant in commonly used cold medicines, adds to the risk for serotonin excess, as the case below illustrates.

Case

A 60-year-old successful executive with arachnoiditis following several low back surgeries, after many controlled trials on other medications, finally functions well on a combination of HS (at bed time) long-acting oxycodone 10 mg, nefazodone 600 mg, and citalopram 30 mg in conjunction with a well-choreographed routine of physical exercises and careful attention to ergonomics and pacing skills. In response to seasonal allergies causing postnasal drip and irritating cough, he begins using a common cough syrup with dextromethorphan around the clock for cough sup-

Reprint requests to: Rasih Atilla Ener, MD, MCP Hahnemann University–Hahnemann University Hospital, Mail Stop 119, Broad And Vine Streets, Philadelphia, PA 19102. Tel: (215)-762-7000; E-mail: rae22@drexel.edu.

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pression. Within a day, he begins to experience fatigue, lethargy, jitteriness, and headache. His vital signs and neurological exam are normal, and there are no new physical findings. These symptoms gradually remit within several hours after stopping dextromethorphan. He holds citalopram for 2 days and lowers nefazodone doses. Full treatment is resumed with no adverse effects.

The SSRI antidepressants top out the market in the pharmaceutical industry, with millions of people all around the world taking one of these medications daily. The incidence of mild serotonin excess, such as in Case 1, may be more common than is known. However, with the increase in the use of serotonergic medications, full-blown serotonin syndrome, a more serious, and sometimes fatal, condition, triggered by serotonin excess within both the brain and the spinal cord, has emerged and may be gaining prevalence. This condition is characterized by autonomic instability, neuromuscular excitability, and mental status changes and appears to be a dose-related phenomenon with predisposing factors that affect both the likelihood of developing it as well as the severity of clinical presentation. It may even be that common side effects of serotonergic medications actually represent a milder form of acute serotonin syndrome. In addition to the acute severe syndrome of serotonin excess, there are motor side effects of the SSRIs very similar to the extrapyramidal side effects (EPS) associated with neuroleptics, including lasting dyskinesias and perhaps even tardive dyskinesia. The existence of SSRI-induced EPS and the clinical similarity between serotonin syndrome and neuroleptic malignant syndrome (NMS), associated with acute dopaminergic blockade, suggests that the balance between serotonergic and dopaminergic systems in the brain may be more important than an excess or deficiency of one of the neurotransmitters in the pathophysiology of these disorders. Finally, there is a concern that the long-term suppression of the CYP2D6 system may increase the risk for developing Parkinson's disease and tardive dyskinesia by blocking the metabolism of certain neurotoxins that destroy the dopaminergic nigrostriatal tract.

Clearly, given the potentially life-threatening nature of serotonin syndrome and the possibility of long-term complications from treatment with drugs that manipulate the serotonergic system, it is imperative to take a cautious approach to prescribing these drugs, for example, having clear target symptoms in mind before prescribing, ensuring adequate washout periods between drugs, and carefully monitoring motor side effects in the same way as one does with the neuroleptics (e.g., with the Abnormal Involuntary Movement Scale—AIMS).

Overview of Serotonin System

In order to understand the symptoms, pathophysiology, and triggers for serotonin syndrome and SSRI-induced EPS, it is necessary to understand the anatomy and physiology of the serotonin system. Briefly, activities of serotonin in the peripheral nervous system include vasoconstriction via smooth muscle stimulation, platelet aggregation, uterine contraction, intestinal peristalsis, and bronchoconstriction. Serotonin in the central nervous system has effects on controlled behavior, attention, affect, cardiorespiratory function, pain perception, aggression, motor control, temperature, sleep, appetite, and sexual function. As serotonin is unable to cross the blood–brain barrier, it must be produced both centrally and peripherally. Platelets utilize an uptake pump to scavenge serotonin produced by the intestinal enterochromaffin cells, the only peripheral source of serotonin. The brainstem raphe nuclei consist of nine nuclei that produce serotonin, forming an inferior caudal group, which sends excitatory axons to the spinal cord and medulla (descending pathways), and a superior rostral group, from which ascending projections (ascending pathways) inhibit thalamic and cortical regions [2]. It has been postulated that ascending pathways are associated with sleep and synchronization of cortical neurons, whereas descending antinociceptive-type pathways, when stimulated, result in inhibition of neurons in the spinothalamic tract and cause analgesia.

It is estimated that, in human body, there is about 10 mg of serotonin present, most of which (4–8 mg) is found in enterochromaffin cells located in gastric and intestinal mucosa. The rest is in platelets (serotonin is not synthesized in platelets although it is taken up from plasma and stored in platelets) and in the CNS. Serotonin is generally found to be complexed with ATP and divalent cations in serotonin-containing cells.

The synthesis of serotonin begins when ingested tryptophan crosses the blood–brain barrier via a nonspecific amino acid transporter and enters neurons to be hydrolyzed (the rate-limiting step) and subsequently decarboxylized to serotonin, resulting in placement into storage vesicles ready

for release into the synaptic cleft with depolarization of the presynaptic neuron [3]. There are presynaptic and postsynaptic receptors, the stimulation of the former turning off the further release of serotonin and the latter, with summation at the hillock, affecting depolarization of the axons that run to terminal fields in the cortex, thalamus, medulla, and spinal cord. Serotonin is removed from the cleft via reuptake pumps and is either repackaged into storage vesicles or degraded by monoamine oxidase (MAO), which is present on the mitochondrial membrane, into 5-hydroxy indole acetic acid (5-HIAA). There are two isoforms of MAO: MAO-A preferentially metabolizes serotonin and MAO-B metabolizes catecholamines and is more prevalent in the brain and even in serotonin neurons than MAO-A. The MAO-B in serotonin neurons is postulated to "clean up" catecholamines, which have the ability to "contaminate" the vesicles containing serotonin.

The serotonin system has the largest number of receptors and subtypes of any of the neurotransmitter systems. Currently well-studied serotonin receptors include 5-HT1 (subtypes A, B, C, D, E, F), 5-HT2 (subtypes A, B, C), 5-HT3, and 5-HT4, although there are many other types currently being investigated (5-HT5, 5-HT6, 5-HT7) [4]. 5-HT1B and 5-HT1D are recognized as species homologs of the same receptor subtype. In addition, 5-HT1C is noted to be the same as 5-HT2C, and therefore, also designated as 5-HT2/1C. 5-HT1A receptors seem to play a central role in the pathophysiology of depression (hyperactivity of these receptors) and anxiety (hypoactivity of these receptors). 5-HT1D receptors are found primarily in the cephalic blood vessels and play an important role in the pathophysiology of migraine headaches. 5-HT2 receptors are located in the brain as well as peripherally in the large arteries and veins, mediating vasomotor tone. Of these subtypes of 5-HT2, 5-HT2A and 5-HT2C (these mediate serotonin's excitatory effects) are found in the brain, whereas 5-HT2B exists in gastrointestinal (GI) system, uterus, and vascular endothelium/smooth muscle. 5-HT3 receptors, located in proximity to the emesis center, are believed to be involved in emesis and are targeted by the antiemetics, including ondansetron and metoclopramide. Finally, the GI tract is rich in 5-HT4 receptors, which modify peristalsis.

Whether it is direct or indirect, excess stimulation of postsynaptic, especially 5-HT1A and 5-HT2, receptors appears necessary to produce serotonin syndrome. Therefore, the key point in the management of serotonin syndrome is the identification and discontinuation of the causative agents.

Serotonin Syndrome

Clinical Characteristics and Diagnosis

Serotonin syndrome, the most acute manifestation of excess serotonin at the synapse, usually consists of a triad of symptoms including cognitive-behavioral changes, neuromuscular excitability, and autonomic instability, although only one category of symptoms may predominate. The diagnosis is made on clinical grounds alone, and there is a broad range in both the severity of presentation and the constellation of symptoms observed, and hence mild, atypical cases are very likely to be missed or mistaken for worsening psychiatric or neurological illnesses. The most current diagnostic criteria require three of the following: Agitation, mental status changes (confusion, hypomania), myoclonus, shivering, tremor, hyperreflexia, ataxia, diarrhea or fever [5]. In addition, a recent increase in dosage or addition of known serotonergic agents to an established medication regimen, with no recent change in dosage or addition of a dopaminergic agent, must be present, and of course, other possible etiologies, for example, infection, metabolic disorder, or substance intoxication or withdrawal, need to be ruled out before a diagnosis of serotonergic syndrome can be made. Other symptoms, although not required for diagnosis, can include: Diaphoresis, trismus, parasthesias, incoordination, and head twitching. Typically, the onset of symptoms is rapid, 50% within 2 hours of the medication change and 75% within 24 hours. Neuromuscular excitability, including myoclonus, rigidity, and/or tremor, is present 50% of the time [6], lower extremity hyperreflexia and ataxia are frequently found, and less commonly noted are dilated, unresponsive pupils, nystagmus, bilaterally positive Babinski sign, and bilateral clonus. Mental status changes are present 40% of the time [6], usually characterized by excitation, but coma does occur. Autonomic instability involving diaphoresis, mild elevations in temperature, hypertension, and tachycardia is commonly seen. Less often, hypotension can occur. Although patients often hyperventilate and appear flushed on presentation, in severe cases, muscular rigidity can lead to progressive hypoventilation with ensuing cyanosis.

Life-threatening complications can include disseminated intravascular coagulation, leukopenia,

thrombocytopenia, tonic-clonic seizures, multiorgan failure, rhabdomyolysis with resultant hyperkalemia, renal failure and acidosis, and finally, respiratory failure and/or aspiration pneumonia due to rigid thoracic muscles. Lab tests are not useful for the diagnosis of serotonin syndrome. Urinary 5-HIAA has too long of a laboratory turnover time, and drug levels are often within the therapeutic range. Additionally, cerebrospinal fluid studies, computerized tomography scans, electrolytes, and liver enzymes are unremarkable. Occasionally, abnormal lab findings can include mildly elevated muscle creatine kinase levels in correlation with the degree of muscle rigidity, a mild elevation in liver enzymes with associated hyperammonemia, abnormally low or high white blood cell counts, and EEG findings of diffuse slowing consistent with a diffuse metabolic encephalopathy.

The differential diagnosis usually includes neuromuscular malignant syndrome (NMS), sepsis with meningitis, delirium tremens, anticholinergic toxicity, heat stroke, and sympathomimetic overdose. Historical and lab data are crucial to rule out these other disorders.

Treatment of Serotonin Syndrome

The treatment of serotonin syndrome is primarily supportive, consisting of external cooling with blankets, charcoal lavage, and dialysis in the case of lithium overdose. Usually the syndrome resolves with discontinuation of the serotonergic medications alone, with 70% of patients recovering within 24 hours, 40% requiring ICU admission, and 25% requiring intubation [6]. Treatment recommendations for more severe cases are based on case reports only. Accordingly, benzodiazepines are first-line treatments to decrease myoclonus and the muscle rigidity that can lead to respiratory compromise and rhabdomyolysis, and are particularly indicated if severe agitation is present or if seizures appear to be imminent. Failure of benzodiazepines to decrease muscular rigidity calls for immediate use of nondepolarizing paralytic agents and prophylactic intubation. Beta blockers with 5-HT1A-receptor blocking properties, that is, propranolol and pindolol, show some promise in reversing some of the neuromuscular and autonomic complications and are especially useful if tachycardia and/or hypertension are present.

Additionally, nonspecific 5-HT2 blockers, including methysergide and cyproheptadine, have been used with varying success, and there may be some role for phenothiazines. The efficacy of the phenothiazines is puzzling, given the theory that a disturbance in the balance between dopaminergic and serotonergic systems leads to serotonin syndrome. However, in addition to dopaminergic blockade, phenothiazines also block 5-HT2 receptors and likely improve the symptoms of serotonin syndrome via this mechanism. A meta-analysis by Gillman, looking at the treatment of serotonin syndrome with chlorpromazine versus cyproheptadine, demonstrated superior efficacy (i.e., less morbidity and mortality) with chlorpromazine [7]. His recommendations include 50 mg intramuscular (IM) chlorpromazine in mild cases and 100 mg IM in severe cases with the addition of high doses of cyproheptadine (30 mg is needed to block 85–95% of brain 5HT2A receptors [8]. Gillman does point out, however, that some of his conclusions from the meta-analysis may be flawed given that the natural course of serotonin syndrome is unknown and the studies were case studies, not controlled for severity of features or inciting agents. One feared complication of using the dopaminergic agents is the potential to decrease the seizure threshold or increase dystonia, neither of which was borne out in the studies analyzed by Gillman.

Pathophysiology of Serotonin Syndrome

The classic triad of symptoms that characterizes serotonin syndrome seems to be mediated primarily by the postsynaptic 5-HT1A receptors and secondarily by the 5-HT2A receptors. The majority of 5-HT1A receptors are found in the raphe nuclei and are associated with tracts descending to innervate the medulla and brainstem. Without stimulation of these tracts, serotonin syndrome cannot occur [9]. 5-HT1A activation typically results in repetitive behaviors like chewing and licking, myoclonus, hyperreflexia, a centrally mediated increase in respiratory rate, and changes in peripheral vasomotor tone, which may contribute to the mental status changes observed in serotonin syndrome [10]. 5-HT2-receptor stimulation is not as vital to the expression of serotonin syndrome, but via the presence of these receptors on platelets, smooth muscle, and in the frontal cortex, it contributes to platelet aggregation, vasoconstriction with resultant increases in blood pressure and heart rate, and neural stimulation of the frontal cortex, resulting in both behavioral and cognitive changes. Additionally, 5-HT2 receptors may be involved in the less commonly seen symptoms of bronchospasm and incoordination, secondary to their presence in the lungs and

cerebellum, respectively. Finally, excessive 5-HT3-receptor activation has the potential to cause diarrhea, nausea, and abdominal pain [11].

Pharmacological Triggers of Serotonin Syndrome

In theory, any dramatic increase in serotonergic transmission can cause serotonin syndrome. Pharmacologically, serotonin syndrome can occur by seven mechanisms: 1) Increased substrate supply; 2) Increased serotonin release; 3) Blockade of reuptake transporter; 4) Inhibition of the metabolism of serotonin in the cleft (decreased levels or inactivity of MAO); 5) Direct stimulation of 5-HT1A and 5-HT2 receptors; 6) Hypersensitivity of the postsynaptic receptors; and possibly 7) Decreased dopaminergic activity with only a modest increase in serotonin activity by any of the above mechanisms. Table 1 shows the mechanisms of common drugs that influence serotonin syndrome.

Increased Substrate Supply

Briefly, increased serotonin synthesis can occur with ingestion of excessive amounts of tryptophan, and in fact, the earliest cases of serotonin syndrome involved combinations of tryptophan, prescribed as a hypnotic agent, with MAO inhibitors (MAOIs) or fluoxetine. Tryptophan, in pill form is no longer available as a result of the eosinophilia-myalgia syndrome that occurred with several formulations of dietary supplements.

Increased Serotonin Release

Drugs that increase the release of serotonin into the synaptic cleft include amphetamine and amphetamine derivatives, that is, drugs previously marketed as diet pills and recreational drugs like methylenedioxymetamphetamine (MDMA, i.e., ecstasy), which, in higher doses, stimulate dopamine and noradrenaline release as well.

Blockade of Reuptake Transporter

Reuptake blockers include the SSRI antidepressants, trazadone, nafazadone, venlafaxine, tricyclic antidepressants (especially amitriptyline, imipramine, clomipramine, doxepin, and desipramine), and opiates (including meperidine, dextromethorphan, and tramadol).

Inhibition of Metabolism

MAOIs inhibit the metabolism of serotonin in the cleft and are, thus, very potent serotonergic agents. Even though MAO-B preferentially degrades catecholamines rather than serotonin, inhibition of either isoform has the potential to increase serotonin due to a loss of specificity at higher doses. In fact, the MAO-B inhibitor selegiline, which is used to treat Parkinson's disease, may be safe with SSRIs in general [13], but at greater than 10 mg per day, it loses its specificity and has been associated with a bad reaction with fluoxetine

Table 1 Mechanisms of common drugs that influence serotonin syndrome

5-HT Synthesis	5-HT Release	Inhibit 5-HT Uptake	Inhibit 5-HT Metabolism	Postsynaptic Receptor Stimulation
L-tryptophan	Amphetamines	SSRIs	MAOIs	Buspirone
5-hydroxytryptophan	and derivatives	fluoxetine	phenelzine	5HT1 agonists
	dextramphetamine	paroxetine	tranylcypromine	sumatriptan
	metamphetamine	sertraline	isocarboxazide	zolmitriptan
	fenfluramine	fluvoxamine	selegiline	naratriptan
	dexfenfluramine	citalopram	meclobemide	rizatriptan
	phenteramine	Trazadone	St. John's wort	Lithium
	MDMA (ecstasy)	Nefazadone		Carbamazepine
	Cocaine	Venlafaxine		
	Reserpine	TCAs		
	Tetrabenazine	amitriptylline		
	Levodopa	imipramine		
	MAOIs	clomipramine		
	phenelzine	doxepin		
	tranylcypromine	desipramine		
	isocarboxazide	Bupropion		
	selegiline	Dextromethorphan		
	meclobemide	Tramadol		
		Meperidine		
		Sibutramine		
		Cocaine		
		St. John's wort		
		Amphetamine and derivatives		

[14,15]. Of note, most MAOIs inhibit MAO irreversibly and, thus, require time for more MAO to be synthesized before their effects diminish; it takes 2 weeks to regenerate 50% of MAO activity after an MAOI has been administered. Meclobemide, the exception, is a reversible inhibitor.

Stimulation of Serotonin Receptors

Serotonin-receptor agonists include buspirone, an anxiolytic that directly binds 5-HT1A somatodendritic autoreceptors, sumatriptan, an anti-migraine agent that binds 5-HT1D receptors, and LSD and psilocybin, which stimulate 5-HT1A brainstem receptors. Both nefazodone and trazodone are metabolized into m-chlorophenylpiperazine (MCPP), a 5-HT2C agonist that also has the effect of potentiating other pharmacological agents through inhibition of CYP2D6.

Hypersensitivity of Postsynaptic Receptors

There is evidence that lithium increases the sensitivity of the postsynaptic receptors.

Decreased Dopaminergic Activity

Finally, it is possible that a blockade of dopamine receptors with a resultant decrease in dopaminergic activity could predispose to serotonin syndrome.

It has been postulated that a balance between the serotonergic and dopaminergic blocking potencies of antidepressants determines the risk for the development of serotonin syndrome [16,17]. Some drugs exert their effects via multiple mechanisms, for example, cocaine and MDMA block reuptake transporters and stimulate the release of serotonin into the cleft. A meta-analysis looking at all cases of serotonin syndrome prior to 1991 revealed that the majority of cases has been associated with combinations of L-tryptophan and MAOIs, with or without the addition of lithium, or with coadministration of fluoxetine and MAOIs [18]. The syndrome has also been associated with combinations of SSRIs with carbamazepine, pentozocine, dextromethorphan, buspirone, tryptophan, lithium, or tramadol; with SSRIs used alone in high doses or with overdose; with MAOIs and meperidine or dextromethorphan; and finally, with clomipramine and trazadone as single therapeutic agents. Even sumatriptan, a serotonin agonist that has a very limited capacity to cross the blood–brain barrier, has been reported to be associated with serotonin syndrome [5,19]. Of note, the symptoms of serotonin syndrome overlap a great deal with commonly seen side effects of serotonergic-enhancing medications and may represent the severe end of a continuum.

Pharmacokinetics

In addition to the above pharmacodynamic causes of serotonin syndrome, pharmacokinetic reactions are important. The long half-life of fluoxetine and the lag time in MAO production after administration of an irreversible MAOI necessitate an adequate washout period after discontinuation of either of these agents before another serotonergic drug is initiated. Additionally, several important interactions can occur with the cytochrome P450 enzyme CYP2D6. Both fluoxetine and paroxetine are potent inhibitors of CYP2D6, increasing their potential to invoke toxic serum levels of dextromethorphan, a known serotonergic agent, which is primarily metabolized through this system. Also, both trazodone and nafazodone have, as a metabolite, MCPP, a strong serotonin agonist, which is metabolized by and inhibits CYP2D6. This is an important consideration given that many cough suppressants frequently contain dextromethorphan, as illustrated in Case 1, and trazadone is often prescribed as a hypnotic agent for patients on antidepressants.

Predisposing Factors in Serotonin Syndrome

There is a great deal of evidence that the symptoms of serotonin syndrome correlate with the amount of serotonergic activity at the synapse in a loosely dose-dependent manner, which increases the likelihood of toxic effects in certain individuals who are unable to metabolize serotonin efficiently. In theory, damage to pulmonary or vascular endothelium in such conditions as hypertension, atherosclerosis, hypercholesterolemia, and connective tissue diseases is all associated with a decrease in MAO-A activity and a decreased capacity to metabolize serotonin [20], perhaps predisposing affected patients to the development of serotonin syndrome. Genetic variations in the activity of MAO isoenzymes have been found [21,22], and there is also significant genetic variability in the metabolism of serotonergic drugs [23], since approximately 7% of the population has been shown to be slow metabolizers of the SSRIs [24]. If this is the case, there is a group of patients that, when given agents that are known to inhibit the CYP2D6 system, may be at a very high risk for untoward reactions to serotonergic agents alone or in combination with other agents, even drugs which are known to have less potent effects on the central serotonergic system, like sumatriptan.

Other Disorders Associated with Serotonin Excess

There are other conditions involving motor dysfunction/rigidity that seem to be associated with serotonin excess as well as dopaminergic deficiency, including EPS, akathisia, and chronic dystonias [25]. The similarity between disorders of increased serotonergic activity and disorders of low dopaminergic activity suggests that they may both result from an imbalance between the serotonergic and dopaminergic systems, which have been shown to have a reciprocal relationship in the CNS; serotonin excess will inhibit dopamine secretion, as evidenced by prolactin levels [26].

Regarding the acute syndromes of serotonin excess and dopaminergic deficiency, the serotonin syndrome and NMS, respectively, it is often very difficult to discriminate between these disorders clinically, especially when both antipsychotics and serotonergic agents have been recently added to a treatment regimen or escalating doses of either have recently been used. Theoretically, the reciprocal balance between the dopaminergic and serotonergic systems may become disrupted by either dopaminergic blockers or serotonergic enhancers, with these two syndromes representing a common end point for two pathophysiological pathways. Generally, however, the two conditions can be differentiated by the fact that NMS often involves greater toxicity, is an idiosyncratic process, is never associated with myoclonus (a common finding in serotonin syndrome), and rarely is associated with diarrhea. This hypothesis of a disruption in the balance between serotonergic and dopaminergic systems may also explain the apparent similarities between EPS induced by SSRIs and those induced by neuroleptics. It also explains why treatment with antidopaminergic agents predisposes patients to serotonin syndrome and SSRI-induced EPS, while treatment with serotonin enhancing agents may predispose patients to NMS.

SSRI-Induced EPS

It has clearly been demonstrated that SSRIs can and do elicit some of the same motor side effects and long-term complications as the neuroleptics, including EPS, akathisia, and chronic dyskinesias, which may eventually prove to be a form of tardive dyskinesia. A review by Lane provides a table listing all forms of EPS associated with SSRI administration prior to 1988, and they have included primarily bruxism, akathisia, dyskinesias, and dystonias, many of which appeared in patients not on any potentially confounding medications and some of which occurred during withdrawal from SSRIs [27]. He concluded that these reactions are dose related, can affect all patients to some degree, and do not represent idiosyncratic reactions, but chronic dyskinesias that develop weeks to months after the initiation of an SSRI are not dose related and continue even after the SSRI is withdrawn [28].

Lane suggested that clinical similarities among the physical and emotional discomfort experienced by many patients when starting SSRIs, psychomotor agitation as part of serotonin syndrome, and SSRI-induced akathisia can be explained by the same underlying process, which is an atypical, mild presentation of serotonin syndrome in patients with a set of predisposing characteristics for the neuromuscular or psychomotor aspects of the syndrome.

In his examination of these case reports, Lane examined potential predisposing conditions for SSRI-induced EPS and determined that possible predisposing conditions include: Previous brain damage (e.g., stroke), basal ganglia disease, (e.g., Parkinson's disease), and concomitant treatment with other serotonergic agents (e.g., lithium) or dopaminergic agents (including neuroleptics or motility agents like metoclopramide, especially if initiated recently). Risk factors for akathisia are similar but also include MAOI discontinuation in the previous 4 weeks, a high dose of SSRI, and an agitated or restless depression at baseline.

There are several pathophysiological explanations for the motor side effects of SSRIs. First, serotonin neurons are known to directly innervate the basal ganglia and primary motor areas, including the axial skeleton, the jaw, the face, and the neck [29], and it may be that simple direct stimulation of these areas results in EPS, including bruxism, dyskinesias, and dystonias. Another simple explanation for these symptoms in neuroleptic-maintained patients is that SSRIs may interfere pharmacokinetically with the metabolism of dopaminergic agents. It has been demonstrated, for example, that fluvoxamine inhibits CYP1A2, doubling the concentration of haldol in the blood [30]. It may also be that serotonin inhibition of dopaminergic transmission in the nigrostriatal pathway results in parkinsonism [31,32], and 5-HT2 receptors may mediate this effect [33]. In the cases where patients have developed dyskinesias that persist after withdrawal from an SSRI, it is possible that a chronic decrease in dopaminergic transmission resulting from serotonergic stimula-

tion induces hypersensitivity in postsynaptic dopamine receptors, the same mechanism believed to underlie neuroleptic-induced tardive dyskinesia [34]. In support of this theory, fluoxetine has been shown to upregulate both D1 and D2 receptors in the mesolimbic terminals [35].

SSRI-Induced Akathisia and Dyskinesia

Akathisia is postulated to be the result of serotonergic or noradrenergic inhibition of the dopaminergic mesocorticolimbic system [36]. It has been demonstrated that a low-dose of 5-HT2-receptor antagonists will increase firing rates in the mesocorticolimbic system without affecting the nigrostriatal system until higher doses are employed [37]. Conversely, it may be that SSRIs in low doses will affect the mesocorticolimbic system resulting in akathisia, and at higher doses, will cause both EPS and psychomotor symptoms via stimulation of both the mesocorticolimbic and nigrostriatal tracts. Clinically, anxiety and psychomotor agitation are common and almost universal side effects seen in patients starting treatment with an SSRI, akathisia is usually seen without EPS present, and EPS, a rare finding, tends to occur in patients with predisposing characteristics, such as brain injury, basal ganglia disease, or previous treatment with neuroleptics [38].

Treatment of SSRI-Induced EPS, Akathisia, and Dyskinesia

Treatment of SSRI-induced EPS usually only requires the removal or reduction of the offending agent. Additionally, these symptoms do respond to the addition of anticholinergics (benztropine, biperiden), and perhaps, buspirone [27]. Bromocriptine has demonstrated some benefit in treating these conditions but seems to trigger increased dyskinesis. In the case of the dyskinesias that continue after drug withdrawal, it may be that, like neuroleptic-induced tardive dyskinesia, there is no clearly effective treatment. Regarding akathisia, it is best to avoid it in the first place with slow titration of the medication, by avoiding concurrent use of other serotonin drugs, and by invoking a 2-week washout time before administering an SSRI after the discontinuation of an MAOI or fluoxetine. If akathisia should occur, the SSRI dose should be decreased/tapered off completely and propranolol, a benzodiazipine, or a 5-HT2C-receptor antagonist, like cyproheptadine, can be added. It seems that some SSRIs have a greater ability to evoke akathisia, and it may be prudent to avoid these agents in patients with an agitated depression or a past history of SSRI-induced akathisia. Similarly, some agents, including fluoxetine, trazodone, and nefazodone, have the potential to increase the risk of motor side effects.

Fluoxetine is a weak agonist of 5-HT2 receptors in addition to being a potent reuptake blocker with a relatively long half-life, and its use is associated with a higher incidence of agitation, aggressive symptoms, and suicidal ideation. Trazodone and nefazodone are metabolized to MCPP, a strong 5-HT2 agonist, and both are noted to cause greater-than-expected increases in anxiety, derealization, agitation, and impaired cognition [39]. Finally, the two SSRIs with the most CYP2D6 inhibition, paroxetine and fluoxetine, are noted to have the most adverse drug reactions reported. According to the United Kingdom Committee on the safety of medications, EPS, especially orofacial dystonias, are most commonly seen in patients treated with paroxetine, and as mentioned above, fluoxetine is associated more with psychomotor disturbance [40,41].

Tardive Dyskinesia and Parkinson's Disease with Long-Term SSRI Suppression of CYP2D6

In addition to the above described motor disturbances associated with SSRI treatment, there are some concerns about the effects of long-term suppression of CYP2D6 in patients taking paroxetine or fluoxetine. It has been found that genetically based decreases in CYP2D6 function are two times as common in patients with Parkinson's disease versus age-matched controls [42–44], and it may be that adequate CYP2D6 function is necessary to detoxify compounds that destroy the nigrostriatal pathway. In support of this theory, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a toxin known to cause Parkinson's disease, is metabolized by CYP2D6. Another concern is that the degree of tardive dyskinesia and the incidence of EPS associated with neuroleptic treatment correlate with the degree of impairment of the CYP2D6 system [45–48]. SSRI-induced movement disorders may be mediated by serotonin's effect on the dopamine system, and CYP2D6 inhibition has the potential for exacerbating these symptoms and perhaps leading to tardive dyskinesia in SSRI-treated patients.

Prevention of Complications from Serotonin Excess

Given the potential for serious complications, the discomfort and embarrassment of EPS, and the

potential for, perhaps, long-term consequences from the use of serotonergic agents, more consideration should be given to the dosing and clinical indications for initiating treatment with these drugs. Clearly, adequate response time should be given when initiating treatment with these agents before an increase in dose is recommended. Clinically, anxiety, worsening agitated depression, and akathisia due to serotonin excess are difficult to distinguish, and if the latter is present, increasing the dose of the SSRI will exacerbate the symptoms, potentially setting up a counterproductive cycle of dose increases and, possibly, increased risk of serotonin syndrome or inadequate pharmacological trials. It should also be recognized that certain patients, including patients with prior head trauma or basal ganglia disease, are at a greater risk for SSRI-induced EPS, and if these symptoms develop or become exacerbated by treatment with an SSRI, it would be prudent to stop treatment and initiate therapy with a more noradrenergically active antidepressant, such as desipramine (Tricyclic antidepressant).

Cardiovascular Effects of Serotonin

The physician should be aware of the cardiovascular effects of serotonin because of the high rates of comorbid cardiovascular disease in older patients being treated for pain syndromes and depression. The effects of serotonin on the cardiovascular system are highly variable, for several reasons. First, serotonin produces both direct and reflex cardiovascular effects; these effects may change with tonus, innervation, and development of tachyphylaxis with repeated doses in experimental studies. Second, there are many types and subtypes of serotonin receptors, of which each may exist in different vessel beds.

Serotonin, by its direct effect, causes vasoconstriction in many vessel beds (except in vessels at skeletal muscles) via 5-HT1 and/or 5-HT2 receptors. Secondarily, it may amplify effects of some of the endogenous vasoconstrictors, such as angiotensin II and catecholamines. When serotonin is given systemically to humans, it vasoconstricts coronary vessels (when it is given intracoronarily, it causes vasodilatation, in small doses, and vasoconstriction, in high doses). It results in a transient constrictive effect in patients with stable angina. Platelets in the vicinity of the thrombotic plaque or in embolized vessel segments (microembolization) induce temporary vasospasms through the release of serotonin and thromboxane A2. In conditions where platelet aggregation takes place in vessel walls, co-release of ADP along with serotonin from dense bodies of platelets may further result in the release of nitric oxide that can contribute its vasodilatory effect. In isolated hearts, serotonin has both positive chronotopic and inotropic effects via 5-HT4 receptors in the myocardium.

From a hematology/cardiology (thrombocardiology) perspective, platelet activation is an important step in the development of catastrophic events in patients with coronary artery disease. Serotonin, as a neuromediator, not only has a role in the neuropathophysiology of depression but also participates in hemostasis by affecting platelet aggregation. Depressed patients, compared with healthy controls, have been reported to exhibit greater than 40% higher platelet activation and enhanced procoagulant properties. In addition, these patients may have additional cardiovascular risk factors, for example, obesity, smoking, etc. Therefore, modulation of platelet activity with SSRI therapy in patients with major depression has been suggested as a potential mechanism responsible for the reduction of cardiovascular mortality. In a recent article by Serebruany et al., 126 patients who were undergoing elective coronary artery stenting were evaluated in terms of their platelet activation in regard to their use of SSRIs [49]. This study showed that antecedent therapy with SSRIs significantly inhibited baseline platelet characteristics, manifested by decreased ADP- and collagen-induced aggregation, and decreased glycoprotein IIb/IIIa, P-selectin, and CD107a expression, in patients with angina pectoris presenting to a cardiac catheterization laboratory for revascularization and, therefore, is beneficial for the survival of patients after ischemic events. Other possible beneficial effects on mortality have also been linked to their antidepressant properties, regulation of sympathetic and parasympathetic balance, and modulation of vascular tone via dopamine and norepinephrine blockade. On the other hand, since SSRIs may produce vasospasm in the presence of coronary artery disease [50], they can cause acute coronary syndromes, that is, anginal symptoms. In summary, based on the available data, until the net effect and different mechanisms of action of SSRIs on cardiovascular system are well understood, they should be used with caution in the clinical practice of cardiovascular medicine.

Prescribing Guidelines for Serotonergic Medications

Some basic prescribing guidelines can be generated from the above available information on syndromes of excess serotonin:

1) It is imperative to wait 2 weeks before starting an MAOI after discontinuing an SSRI, with the exception of fluoxetine, which requires a 5-week wait. Remember that the kinetics of citalopram and paroxetine are nonlinear, so subsequently, serum concentrations may be higher than expected, especially in the elderly, and a longer than 2-week washout time may be necessary.
2) In switching from treatment with an MAOI, a 2-week drug-free period is necessary before starting an SSRI, with meclobemide being the exception, requiring only a 24-hour wait.
3) Keep in mind that while the long half-life of fluoxetine, now available in a once-a-week form, can be an advantage in treating noncompliant patients, it is at the cost of a significantly greater risk for symptoms of serotonin excess.
4) Fluoxetine takes 6–8 weeks to reach steady state and should be used with great caution in combination with TCAs, carbamazepine, and dextromethorphan.
5) Fluoxetine use appears to be associated with a higher incidence of akathisia and is probably not the best first-line treatment for agitated depression.
6) Fluoxetine and paroxetine are potent inhibitors of the CYP2D6 system, and thus, have the potential to increase serotonergic metabolites in combination with trazadone and nafazadone, and should not be used with these agents unless the patient is closely monitored.
7) Paroxetine and fluvoxamine inhibit the liver enzymes for metabolism of both TCAs and neuroleptics and have the potential for increasing the risk for serotonin syndrome and EPS, respectively.
8) The use of MAOIs, including meclobemide, in combination with TCAs, SSRIs, and sumatriptan is contraindicated, and serious consideration should be given to the use of SSRIs, especially fluoxetine, and MAOIs in patients who use sympathomimetic recreational drugs.
9) Pain medicine specialists, psychiatrists, primary care physicians, neurologists, and intensivists should be aware of the potential for some opiates, including meperidine, fentanyl, and pentazocine, certain migraine medications (e.g., sumatriptan), and dextromethorphan to precipitate symptoms of serotonin excess in patients being treated with SSRIs.
10) Conversely, the action of certain SSRIs that directly inhibit P450 enzyme subtypes, including fluoxetine, paroxetine, sertraline, and nefazodone, may increase methadone levels, making standard dosing conversions from other opioids to methadone unreliable in these circumstances [51].
11) Finally, although these medications are generally thought to be safe, with many years in the field with millions of users, the longer term consequences of chronic SSRI use are still unknown and may include dyskinesias and EPS. Whether these risks warrant that future guidelines for long-term use of SSRIs include AIMS testing, in the same way is done for patients on neuroleptics, is yet to be determined.

Conclusions

Although SSRIs are widely considered to be safe with little established toxicity, there appear to be several side effects associated with their use that may be generally unrecognized and therefore under-reported. All clinicians should be aware of the risk for psychiatric, neurological and medical side effects to ensure proper caution in prescribing combinations of drugs affecting serotonin and to ensure early detection and proper management of the conditions associated with serotonergic excess and toxicity. Prompt recognition of the most severe condition, serotonin syndrome, can be life saving. Use of medication combinations that induce serotonin toxicity could potentially result in morbidity and mortality, so physicians should consider the potential for these effects when using such combinations. Further studies should seek prevalence rates of serotonin excess in various illness populations, starting in groups at higher risk for exposure, such as patients with comorbid pain and depression, to identify both prevalence and incidence rates of toxicity. The problem of the variability of drug–drug interactions within the patient population and the prediction of health risk for using polypharmacy in settings such as geriatric or pain clinics calls for the introduction of a predictive pharmacotherapy model. Pharmacogenetics is a promising new field of basic and clinical research that should provide practitioners with useful information about risks in individual

patients and groups of patients [52,53] to reduce the risk of drug interactions and to allow for a more effective and safer polypharmacy.

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