Selective Serotonin Reuptake Inhibitor Toxicity And Serotonin Syndrome

Objectives

When the student has finished this module, he/she will be able to

1. Explain the basic mechanism by which the selective serotonin reuptake inhibitors (SSRIs) work.
2. Identify three serious side effects of the SSRIs.
3. Identify three physiological processes that the SSRIs are involved in regulating.
4. Explain the basic mechanism of serotonin syndrome.
5. Disucss one pathological condition that can be confused with serotonin syndrome
6. Identify three signs of the serotonin syndrome
7. Identify a drug that has been used to treat serotonin syndrome
8. Identify the SSRIS that has produced the most toxic effects.

Introduction

Depression is very common; an estimated 18 million Americans are diagnosed with a major depressive disorder each year and of these, 12 million to 18 million are treated with antidepressants. The exact cause of depression is still not known, although there is strong suspicion that it is inheritable. One theory is that people who are depressed have alterations in brain serotonin levels, and drug therapy for depression has focused on this theory. The tricyclic antidepressants and monoamine oxidase inhibitors were once the commonly used drugs, but today, the selective serotonin reuptake inhibitors are the drugs of choice for treating depression.

The selective serotonin reuptake inhibitors (SSRIs) have become a very popular treatment for depressive illness since the prototypical SSRI, fluoxetine (Prozac®) was introduced in 1988. Between 1998 and 2002, there was an annual increase in use of SSRIs among children and adolescents of 9.2%,[1] and there were over 90 million prescriptions written for fluoxetine in 2002.

The popularity of these drugs is not surprising. Compared to the other antidepressants such as the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs), the SSRIs are much safer and have far fewer distracting and potentially disabling side effects.[2] When taken in overdose, the TCAs and the MAOIs often cause significant morbidity and death is not uncommon. In contrast, an overdose of an SSRI is relatively benign. And most importantly, the SSRIs seem to work. There have been several studies that have strongly suggested that as the prescribing rate of SSRIs has gone up, suicide rates have fallen.[3]

However, abuse of the SSRIs remains a significant problem. The American Association of Poison Control Centers reported over 42,000 exposures to SSRIs in 2002 and 93 deaths (some of the deaths involved multiple medications), and these figures are almost certainly too low.[4] Regardless of their safety, the SSRIs are still prescription drugs and there is potential for harm.

The Serotonergic System

Serotonin is a neurotransmitter that is synthesized from tryptophan. Neurotransmitters are chemical compounds that are released from nerve endings into a synapse in response to depolarization of the pre-synaptic terminal. They are carried by a transport molecule to a receptor on another neuron or an effector organ and produce a specific effect, depending on the effector organ or the location of the neuron. After binding with the receptor, a transporter carries serotonin back to the pre-synaptic terminal where it is packaged in vesicles to be used again or broken down into monoamine oxidase. There are seven serotonin receptors, and this could explain the effects of the different SSRIs. There are serotonin receptors located in the central nervous system, and serotonin is involved in the regulation of mood, sleep, personality, affect, appetite, temperature regulation, sexual activity, and pain perception. Serotonin has been shown to have effects on the cardiovascular and peripheral nervous systems, but the exact mechanisms and function in these systems ha not been clearly outlined.

Pharmacology

The SSRIs are used for depression but they have also been used successfully for treating obsessive-compulsive disorders, panic disorders, dysthmia, eating disorders, alcoholism, and other medical and psychological disorders.[5] As mentioned previously, they have become very popular due to the relatively benign nature of their side effects when compared to older antidepressants and their safety (again, compared to the older antidepressants) in overdose. The most common SSRIs in use today are citalopram, fluvoxmaine, fluoxetine, paroxetine and sertraline.

The SSRIs work by inhibiting the reuptake from the synapse of serotonin by decreasing the serotonin transporter's affinity for serotonin. This increases serotonergic receptor stimulation and may increase serotonergic receptor sensitivity to serotonin. It is also possible (the mechanism is not quite clear) that increased serotonergic activity may have an antidepressant effect by reducing dopamine release.[6] The SSRIs have little direct action on the cholinergic receptors, γ-amino butyric acid receptors, or sodium channels, and do not affect reuptake of norepinephrine.

The SSRIs are completely absorbed after oral administration and the peak plasma concentrations- depending on the drug – are seen in 2-8 hours after ingestion. They have a large volume of distribution and are extensively protein bound. They are metabolized in the liver, primarily by the cytochrome P450 enzyme system. Paroxetine and fluoxetine inhibit the cytochrome P450 enzyme 2D6, so these drugs inhibit their own metabolism. The SSRIs tend to have long half-lives and some of the drugs have active metabolites. The drugs appear to be similar in terms of efficacy. An interesting point is that regardless of the differences between the SSRIs, they all seem to take approximately 2 weeks to have a therapeutic effect; why this happens is not known.

Although most of the side effects of the SSRIs are relatively benign, they can still be troublesome. Common ones include

- Anorexia,
- Nausea,

- Vomiting,
- Diarrhea,
- Headache,
- Dizziness,
- Fatigue, and
- Sedation

More serious ones include

- Sexual side effects: Sexual dysfunction is a common side effect of SSRIs; one author estimated it occurs in 30-70% of patients taking SSRIs.[7] Decreased libido, erectile dysfunction, ejaculatory dysfunction and inhibition of orgasm have been reported, and may be due to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects, nitric oxide synthetase inhibition, or accumulation of the drug/metabolites over time.[8] Some patients develop a tolerance, some do not. Most cases of sexual dysfunction stop after 1-3 days if the medication has been stopped. Patients can also try drug "holidays" or reduced doses. Some physicians have reported success treating SSRI-induced sexual dysfunction with bupropion, cyproheptadine, granisetron, methylphenidate, sildenafil, or yohimbine.
- Suicide: Whether or not the SSRIs increase suicide rates – especially in adolescents – has been a matter of contention for many years. A 2006 study by the American College of Neuropharmacology examined all the relevant studies and came to the conclusion that there is only strong statistical evidence for the efficacy of fluoxetine in treating depression in adolescents, and that the use of SSRIs has been associated with a small increase in the number of adverse event reports of suicide in youth. However, epidemiological studies, autopsy reports and cohort studies contradict this finding.
- Extrapyramidal side effects: Movements disorders such as akasthisia and dystonia have been noted: an incidence as high as 10-20% has been reported.[9] The disorder may be caused by serotonergic modulation of the nigrostriatal dopamine system.
- SIADH: SIADH is a relatively infrequent (one author estimated its occurrence in with fluoxetine as 6.3 cases in 1000) complication of SSRI use.[10] The risk appears to increase with age. The mechanism of action is not clear, but it may be due to inhibition of metabolism of the SSRIs and accumulation of the drug/metabolite, or a direct effect on ADH secretion by serotonin.[11]
- Gastrointestinal bleeding: Several studies have strongly suggested that the SSRIs have a causal role in gastrointestinal bleeding.[12]
- SSRIs and platelets: Platelets are apart of the uptake and transport system of serotonin, and there are reports in the literature that suggests that prolonged use of some SSRIs can decrease platelet serotonin. This can decrease the stabilization of a platelet clot in an injured vessel and decrease the vasodilating effect of serotonin. It may also lead to bleeding disorders, and there is growing evidence that this may be the case.[13]

Serious side effects of specific drugs include

- Citalopram: Bradycardia, postural hypotension, tachycardia,
- Fluoxetine: QT prolongation, bradycardia, tachycardia, hypertension,
- Fluvoxamine: QT, QTc, and R-R prolongation,
- Paroxetine: Postural hypotension, extrapyramidal effects, and
- Sertraline: Hyponatremia

Serotonin syndrome

As mentioned several times previously, the SSRIs are – relatively – benign in overdose. But there is one effect of these drugs that can happen with therapeutic use and after an overdose that is not so harmless: serotonin syndrome.

The serotonin syndrome is a condition in which there is *excess stimulation of the serotonergic receptors*. No single serotonin receptor appears to be involved in the serotonin syndrome. It is most commonly seen after two drugs have been given that both affect serotonin reuptake, but it has rarely been reported to occur after one therapeutic doses and has been reported after overdose of single agents.[14] The exact incidence of serotonin syndrome is not certain: post-marketing surveillance reported an incidence of 0.4 cases per 1000 patients months for patients taking nefazadone[15] and one author estimates that 14 to 16 percent of patients that overdose on an SSRI will have serotonin syndrome.[16]

What causes serotonin syndrome? Any drug that 1) inhibits the breakdown of serotonin, 2) blocks the reuptake of serotonin, 3) acts as an agonist at serotonin receptors, and 4) causes release of serotonin. Specific drugs include[17]

- SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline,
- Antidepressnats: Buspirone, clomipramine, nefazodone, trazodone, and venlafaxine,
- MAOIs: Clorgiline, isocarboxazid, moclobemide, and phenelzine,
- Anticonvulsants: Valproic acid,
- Analgesics: Fentanyl, meperidine, pentazocine, and tramadol,
- Antiemetics: granisteron, metoclopramide, and ondansetron,
- Antimigraine drugs: Sumatriptan,
- Antibiotics: Linezolide and ritonavir,
- OTC drugs: Dextromethorphan,
- Drugs of abuse: LSD, MDMA,
- Herbal products: Panax ginseng, St John's wort, tryptophan, and
- Lithium

The serotonin syndrome can also happen when one serotonergic drug is discontinued and another is started before sufficient time has elapsed.[18] This may be due to residual effect of the previous drug, changes in receptor sensitivity or active metabolites (eg, fluoxetine has a pharmacologically active metabolite that has a long half-life).

Serotonin syndrome has classically been described as a syndrome characterized by autonomic, cognitive, and neuromuscular signs and symptoms, but the patient may have findings of one but not the others. It can be mild (in which case it may not be detected) or dramatic and life threatening. One of the difficulties of serotonin syndrome is making the diagnosis, and there have been several attempts to standardize diagnostic criteria. Sternbach's criteria was one of the first. He described serotonin syndrome as the presence of mental status changes, agitation, mycoclonus, hyperreflexia, diaphoresis, diarrhea, tremor, fever, and incoordination. These criteria were in use for some time, but have since been rejected as too limiting as there was the possibility that when using these criteria, severe cases would be missed. A more recent diagnostic algorithm has been proposed.[19] This has shown to be, compared to the Sternbach criteria, more sensitive (85% to 75%) and more specific (97% to 96%).

- Has the patient been started on a serotonergic drug in the past 5 weeks?
- If *no*, the patient does not have serotonin syndrome.
- Can metabolic and infectious processes be ruled out as causes for the signs and symptoms?
- If *no*, the presence/absence of these must be determined and the patient does not have serotonin syndrome.
- If yes, are any of the following present?

  Tremor and hyperreflexia
  Spontaneous clonus (more common in the lower extremities)
  Muscle rigidity
  Temperature > 38° C
  Agitation
  Diaphoresis
  Ocular clonus
  Inducible clonus

- If *no*, the patient does not have serotonin syndrome. If *yes*, he/she has serotonin syndrome.

And not only is serotonin syndrome difficult at times to detect, it may be difficult to distinguish it from other toxic syndromes. Other conditions can present with signs that closely approximate those of the serotonin syndrome. The sympathomimetic syndrome, the anticholinergic syndrome, and the neuroleptic malignant syndrome can all mimic – or vice versa – serotonin syndrome. Important differences in the clinical presentation of these syndromes include

- Medication history: Did the patient take an anticholinergic agent, a sympathomimetic drug, or a dopamine antagonist (neuroleptic malignant syndrome)?
- Onset of the condition: The serotonin syndrome, the sympathomimetic syndrome and the anticholinergic syndrome all start soon after the drug is taken. Neuroleptic malignant syndrome takes days to develop.

- Mucosa: In serotonin syndrome, sympathomimetic syndrome and neuroleptic malignant syndrome, the mucosa will be wet: with the anticholinergic syndrome, the mucosa will be dry.
- Skin: The skin will be diaphoretic in the serotonin syndrome, neuroleptic syndrome, and the sympathomimetic syndrome, dry in the anticholinergic syndrome.
- Neuromuscular tone: This will be increased (mostly in the lower extremities) in the serotonin syndrome, normal in the symapthomimetic and anticholinergic syndrome and there will be a "lead pipe" rigidity in all extremities in the neuroleptic malignant syndrome.
- Reflexes: There will be hyperreflexia and clonus in the serotonin syndrome reflexes will be normal in the sympathomimetic and anticholinergic syndromes and there will be bradyreflexia in the neuroleptic malignant syndrome

Instant feedback: It can be confusing trying to remember the differences between these 4 syndromes, but the hallmarks of the serotonin syndrome are hyperreflexia (especially in the lower extremities), and increased neuromuscular tone (also predominantly in the lower extremities).

Instant feedback: If the patient appears to have serotonin syndrome, determine if they have been started on a serotonergic drug, discontinued a serotonergic drug, or had the dose of a serotonergic drug changed within the past 24 hours.

Instant feedback: There are no confirmatory tests for serotonin; it is a clinical diagnosis.

The onset of symptoms is usually rapid; most patients will begin to become symptomatic within 6 hours of an overdose, or a change in dose or medication.[20] Patients with mild cases may simply be tachycardic and have diaphoresis. Other signs that may be seen are diarrhea, delirium, myoclonus, and mydriasis. Patients with florid cases will have all of the above signs. Severe cases may present with hypertension and tachycardia that may progress to shock. Hyperthermia – core temperatures as high as 41.1° C – is possible. Metabolic acidosis (due to poor tissue perfusion), rhabdomyloysis, elevations of liver transaminases and serum creatinine, seizures, renal failure, and disseminated intravascular coagulation are all possible. ARDS has also been described. [21]

Treatment of the serotonin syndrome is primarily symptomatic and supportive. Special attention should be paid to hydrating the patient. The temperature should be closely monitored and if hyperthermia is present, make vigorous attempts to lower it; this may require sedation, neuromuscular paralysis, and intubation (If this is the case, succinylcholine should be avoided. It can cause hyperkalemia and patients who are hyperthermic may have rhabdomyolysis and hyperkalemia). Antipyretics will not be effective. Benzodiazepines can be used for agitation and tachycardia. Given the autonomic instability, attempts to control blood pressure and/or pulse should be done cautiously and with short-acting agents. Most cases of serotonin syndrome resolve within 24 hours, but if the case involves a drug with a long half-life, it may take longer.

Some clinicians have reported success treating the serotonin syndrome with cyproheptadine.[22] Cyproheptadine is a serotonergic receptor ($5\text{-}HT_{2a}$) antagonist, and its

use makes sense from a pharmacological standpoint. However, at this time, there are only anecdotal case reports; there have been no controlled studies that have evaluated its effectiveness. Side effects would include sedation. Other authors have reported success with chlorpromazine[23] and olanzipine[24] but these are anecdotal reports. Also, chlorpromazine can cause severe orthostatic hypotension.

SSRI Overdose

As mentioned previously, the SSRIs have become popular because the side effects they cause are usually minor when compared to the older antidepressants, the TCAs and the MAOIs. They have also become popular because they have been proven to be much safer when taken in overdose. The TCAs, when taken in excess, can cause coma, seizures, hypotension and arrhythmias – and these effects are not uncommon in an overdose with a TCA. The MAOIs can cause delirium, seizures and severe hypotension.

The SSRIs, by contrast, are relatively benign. One study showed a comparative incidence of death after overdose with SSRIs to be less than half of that of the TCAs.[25] Patients with an SSRI overdose will experience nausea, vomiting, dizziness, blurred vision, and occasionally central nervous system depression and sinus tachycardia.[26] However, serous effects can be seen.

- Coma: This has been reported after fluvoxamine overdose.[27]
- ARDS: This has been reported after citalopram overdose.[28]
- Left bundle branch block: This has been reported after citalopram overdose.[29]
- Rhabdomyolysis: This has been reported after sertraline overdose.[30]
- Bradycardia: This has been reported after citalopram overdose.[31]
- Renal failure and DIC: Fluvoxamine.[32]
- Seizures: Seizures have been reported after fluvoxamine and citalopram overdose.[33,34]
- Syncope: This has been caused by citalopram overdose.[35]
- QRS/QTc prolongation: This has been caused by citalopram overdose.[36]
- Hypotension. This has been reported after citalopram and fluvoxamine overdose.[37]

It should be stressed that serious effects such as these are unusual. Given the widespread use of SSRIs and the large number of overdoses, this handful of case reports from more than 10 years of experience with the drugs suggest that the SSRIs are less harmful when taken in an overdose.

Is one SSRI more dangerous than the others? There seem to have been more serious effects attributed to citalopram and a 2004 study tended to support this view. The authors examined more the hospital records of more than 400 patients with serotonin overdoses. They checked the incidence of seizures, coma, serotonin syndrome, arrhythmias, conduction blocks, bradycardia, tachycardia, hypotension, a QTC > 440 msec, and a QTc of > 500 msec. In every category except the incidence of serotonin syndrome (The incidence of serotonin syndrome for citalopram was 9%; the incidences for sertraline,

paroxetine, and fluvoxamine were 20%, 18%, and 17% respectively), citalopram overdoses produced more toxic effects.

Treatment for an overdose of an SSRI is basically symptomatic and supportive. The patient should receive a dose of activated charcoal if they present to the hospital within an hour of taking the drug. Lavage is not indicated, whole bowel irrigation and multiple doses of activated charcoal would not be effective, and syrup of ipecac would be contraindicated. A baseline ECG should be obtained and this should be repeated in 2-4 hours. Blood for aspirin and acetaminophen levels and electrolytes should be obtained. The patient should be monitored for hyponatremia and monitored closely for the development of serotonin syndrome.

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