Possible Biological Mechanisms of the Serotonin Reuptake Inhibitor Discontinuation Syndrome

Discontinuation Consensus Panel

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Although the number of documented serotonin reuptake inhibitor (SRI) discontinuation reactions is increasing, to date no systematic studies have been completed; therefore the mechanism of action for these reactions is not clearly understood. However, several hypotheses have been proposed. Researchers have postulated that discontinuation events result from a sudden decrease in the availability of synaptic serotonin in the face of down-regulated serotonin receptors. In addition, other neurotransmitters, such as dopamine, norepinephrine, or gamma-aminobutyric acid (GABA), may also be involved, although little research in this area has been published. Individual patient sensitivity, i.e., genetics or cognitive mindset, may also be a factor in SRI discontinuation phenomena. Finally, experts have hypothesized that since some symptoms associated with paroxetine withdrawal are similar to those of tricyclic antidepressant discontinuation, they may be caused by cholinergic rebound.

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Since the efficacy of all available antidepressants is similar, physicians often base their selection of an agent on other factors. One such factor is the likelihood of discontinuation symptoms, which may occur in 30% of patients who discontinue therapy.[1] Both somatic (e.g., problems with balance, nausea and vomiting, sensory and sleep disturbances) and psychological (e.g., anxiety, irritability, crying spells) symptoms have been reported after SRI discontinuation. While available data could suggest that these reactions are more likely to occur with the serotonin reuptake inhibitors (SRIs), such as fluvoxamine, paroxetine, sertraline, and venlafaxine, which have shorter half-lives, than with fluoxetine, which has an extended half-life,[1–3] the exact biological mechanisms of reaction are still unknown. This article will review the existing hypotheses about the mechanisms for these discontinuation symptoms.

MECHANISM OF ACTION FOR SRIs

Serotonin is primarily an inhibitory neurotransmitter utilized by neurons that originate in the raphe nuclei of the brain stem. Each serotonergic neuron sends over 500,000 terminals to the cortex and limbic systems. The diffuse projections of the serotonin pathways allow them to contribute to the regulation of many somatic and psychological functions including appetite, the sleep-wake cycle, sense of pain, mood, anxiety, impulsivity, and aggression. Serotonin also interacts with other neurotransmitter systems, which enhances the capacity of serotonergic systems to influence a broad spectrum of psychobiological functions. For example, the serotonin system has been shown to interact with the gamma-aminobutyric acid (GABA), norepinephrine, and dopamine systems,[4] and a change in the amount of available serotonin may affect these other systems.

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Table 1. Selectivity of Serotonin Reuptake Inhibitors (SRIs) at Blocking Synaptosomal Uptake of Serotonin Over Norepinephrine*

SRI	Selectivity[a]
Sertraline	64
Paroxetine	45
Trazodone	26
Fluoxetine	23
Venlafaxine	5.4
Clomipramine	5.2

*Adapted from reference 5.
[a]Ratio of K_is = K_i uptake norephinephrine/K_i uptake serotonin.

Table 2. Potency of Serotonin Reuptake Inhibitors (SRIs) at Blocking Uptake of Serotonin*

SRI	Potency[a]
Paroxetine	136
Sertraline	29
Clomipramine	18
Fluoxetine	8.3
Venlafaxine	2.6
Trazodone	0.53

*Adapted from reference 5.
[a]10^{-7} x $1/K_i$, where K_i = inhibitor constant in molarity.

Serotonin has been implicated in the mechanisms for affective illness ever since investigators discovered that one of the effects of the tricyclic antidepressants (TCAs) was the blockade of the uptake of serotonin at the presynaptic nerve ending. This discovery became a cornerstone of biogenic amine hypotheses of affective illness, which, in simple terms, suggest that a deficiency or dysregulation of specific biogenic amines at functionally important synapses causes depression. Thus, neuroscientists set out to create a new class of antidepressants that selectively blocked the uptake of serotonin in order to enhance its neurotransmission.

This next generation of antidepressants (serotonin selective reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) is more potent at blocking the uptake of serotonin than of norepinephrine. In 1994, Richelson[5] created a selectivity ratio that defined six drugs that block the uptake of serotonin more than they do the uptake of norepinephrine (Table 1); the agents include the serotonin selective reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline as well as clomipramine (marketed in the United States as an antiobsessional and in Europe as an antidepressant), trazodone, and venlafaxine. Fluvoxamine and citalopram are also SSRIs. Fluvoxamine received Food and Drug Administration approval after Richelson created the list, and citalopram is marketed in Europe. This selectivity ratio is derived from data that establish the potency of antidepressants at blocking uptake of norepinephrine and serotonin into rat brain synaptosomes.

The primary action of these drugs is presumed to be blockade of serotonin uptake, although some (e.g., venlafaxine, clomipramine, trazodone) also have known effects on other uptake sites or receptors. The SSRIs—fluoxetine, paroxetine, sertraline, and fluvoxamine—show high affinity for serotonin reuptake sites. Paroxetine is also the most pharmacologically potent antagonist at the serotonin reuptake site (Table 2). Price et al.[2] suggest that this potency may be a significant factor in the frequency of discontinuation reactions for paroxetine as compared with the other SRIs. The SSRIs, however, differ in other effects. For example, paroxetine is unique because its affinity for muscarinic receptors is similar to that of imipramine. In addition, sertraline alone among the SSRIs is potent at dopamine uptake blockade.[5]

Table 3. Possible Mechanisms for the Serotonin Reuptake Inhibitor Discontinuation Syndrome

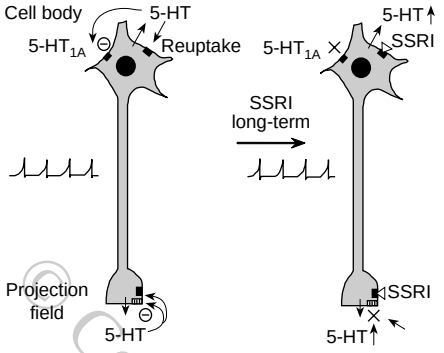
Decrease in available synaptic serotonin in the face of down-regulated serotonin receptors
Secondary effects on other neurotransmitters
Biological or cognitive sensitivity in an individual patient
Cholinergic rebound effect (clomipramine and paroxetine)

During long-term treatment with an SRI, the amount of available serotonin in the frontal cortex increases. Microdialysis studies, which allow for measuring the extracellular levels of transmitter in the frontal cortex and other areas, indicate that low doses of antidepressants with serotonergic action increase the amount of serotonin in the frontal cortex only after repeated treatment.[6] Long-term treatment can also ultimately diminish neurotransmission in the synaptic cleft as the 5-HT postsynaptic receptors undergo compensatory change and become less sensitive to the neurotransmitter (down-regulation).

It has long been recognized that discontinuation symptoms, including gastrointestinal and general somatic distress (sometimes accompanied by anxiety and agitation), sleep disturbances, parkinsonism or akathisia, and paradoxical mania, occur when treatment with tricyclic antidepressants is stopped. Dilsayer[7] suggests that many of these symptoms may be due to cholinergic rebound after cholinergic blockade since tricyclics block cholinergic receptors and induce tolerance. Parkinsonism and akathisia that occur sometimes when TCA therapy is ended may be related to a perturbation of cholinergic/dopaminergic balance. Mania might be a result of cholinergic overdrives that stimulate the limbic activating system.

Symptoms also occur in up to 30% of patients who discontinue treatment with short half-life SRIs. SRI discontinuation reactions may be the result of (1) a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors; (2) secondary effects on other neurotransmitters; or (3) biological or cognitive sensitivity in individual patients. Cholinergic rebound is likely to be a factor in only clomipramine or paroxetine discontinuation since the other SRIs are practically devoid of cholinergic effects (Table 3).

Figure 1. The Serotonin Neuron Before and After Long-Term SSRI Treatment*



*Adapted from reference 8. Abbreviation: SSRI = serotonin selective reuptake inhibitor.

DECREASE IN AVAILABLE SEROTONIN

During long-term SRI treatment, serotonin autoreceptors and postsynaptic receptors are exposed to a high concentration of serotonin because of blockade of the serotonin reuptake pump (Figure 1),[8] which may result in desensitization of the receptors. When SRI therapy is discontinued, serotonin concentrations at the receptors may be decreased, abruptly or slowly, depending on the rate of taper and the half-life of the agent being withdrawn, and there may be a temporary relative deficiency of serotonin in the synapse (lasting from 48 hours to 10 days). Lane[9] proposes that these receptor changes in the serotonin system may correlate with the withdrawal symptoms that have been reported. Coccaro,[10] for example, reported that reduced activity of postsynaptic receptors may correlate with impulsive and aggressive behavior, which have been described during SRI discontinuation.[11]

Many symptoms of SRI discontinuation can be linked to the place of serotonin in biological and psychological function. For example, dizziness and paresthesia may be connected to the purported role of serotonin in coordinating sensory and autonomic functions with gross motor function. Jacobs and Fornal[12] pointed out that the distribution of serotonergic neurons is linked with the structures that are involved in controlling movements that require gross skeletal muscles as well as facial muscles. Paresthesias that have been reported during SRI discontinuation involved the face, neck, or upper body rather than the extremities.[13,14] The serotonergic neurons fire at the same time as or in anticipation of gross movements and are quiescent during REM sleep and orientation. The suppression of some aspects of sensory processing by serotonin could also be a mechanism that underlies the similar suppression during movement, according to Jacobs and Fornal. In support of this theory, many reported withdrawal symptoms intensify upon movement.

Table 4. Half-Life and Active Metabolites of Serotonin Reuptake Inhibitors (SRIs)*

SRI	Half-life (h)	Active Metabolite	Half-Life
Clomipramine	17–28	Desmethylclomipramine	…
Fluoxetine	84	Norfluoxetine	4–16 d
Fluvoxamine	15	None	…
Paroxetine	21	None	…
Sertraline	26	Desmethylsertraline	66 h
Trazodone	4–9	*m*-Chlorophenylpiperazine	…
Venlafaxine	5	O-desmethylvenlafaxine	11 h

*Data from reference 17.

For example, Pyke[15] described a patient in whom eye movement produced visual lag, dyscoordination, and an unpleasant occipital feeling of movement. Dizziness, the most common symptom of SRI withdrawal, is often triggered by slight head or eye movements that could also be related to a disruption of the usual decrease in serotonergic activity during orienting responses.

Coupland et al.[1] suggest that one clue about the nature of the disruption of serotonergic function during SRI withdrawal may be provided by the overlap of dizziness, nausea, lethargy, and visual symptoms with the signs of motion sickness. Motion sickness has been suppressed in animals by 5-HT_{1A} agonists.[16] During chronic treatment with SRIs, desensitization of 5-HT_{1A} receptors in the raphe nuclei occurs,[6] which may lead to greater excitability of serotonergic neurons, mimicking that inferred to occur in motion sickness.

The half-life of the agent being discontinued and the presence of active metabolites may affect the amount of available synaptic serotonin, as suggested by the fact that discontinuation events are more frequent after paroxetine, venlafaxine, and fluvoxamine termination than they are when fluoxetine is discontinued (Table 4).[1,2]

Dominguez[3] noted that the relationship between the frequency of discontinuation reactions and the pharmacologic profiles of the SRIs follows a pattern similar to clinical experience with the benzodiazepines. Withdrawal symptoms are more likely to occur with benzodiazepines that have relatively short half-lives and those without active metabolites (e.g., lorazepam, alprazolam). When Rauch et al.[29] reported on four of nine patients who experienced venlafaxine discontinuation symptoms, they noted that venlafaxine, like paroxetine, has a short half-life. Fluvoxamine also has a short half-life and has been reported to be associated with discontinuation reactions.

The half-life of paroxetine is 21 hours, of fluvoxamine is 15 hours, and of fluoxetine is more than 3 days.[17] The half-life of venlafaxine is 5 hours and of its active metabolite O-desmethylvenlafaxine, 11 hours.[17] Fluoxetine has an active metabolite norfluoxetine, which has a half-life of from 4 to 16 days, while fluvoxamine and paroxetine lack active metabolites.[17] Lazowick[18] proposed that the extended half-life of fluoxetine may prevent the appearance of discontinuation symptoms.

Table 5. Affinities of the Serotonin Reuptake Inhibitors (SRIs) for the Muscarinic Receptor of Human Brain*

SRI	Affinity[a]
Amitriptyline[b]	5.6
Clomipramine	2.7
Imipramine[b]	1.1
Paroxetine	0.93
Sertraline	0.16
Fluoxetine	0.05
Trazodone	0.00031
Venlafaxine	0

*Data from reference 5.
[a] 10^{-7} x $1/k_d$, where K_d = equilibrium dissociation constant in molarity.
[b] Amitriptyline and imipramine, tricyclic antidepressants that have a high affinity for the muscarinic receptor in brain, are shown for comparison.

SECONDARY EFFECTS ON OTHER NEUROTRANSMITTERS

Although little research has been done, there may be secondary effects of discontinuing SRI treatment on other neurotransmitters. For example, Lejoyeux et al.[19] suggested that the extrapyramidal symptoms that have been reported upon fluoxetine discontinuation[20] could be related to serotonin-mediated inhibition of dopamine neurotransmission. Louie et al.[21] theorized that the binding of sertraline to the sigma opioid receptor may be involved in sertraline discontinuation symptoms. Norepinephrine or GABA may also be involved.

INDIVIDUAL DIFFERENCES IN PATIENTS

Individuals may have specific genetic or psychological differences that place them at risk for discontinuation symptoms. When Rosenstock[14] reported on two brothers who experienced similar symptoms when they stopped sertraline treatment, he noted there may be a genetic factor in SRI discontinuation symptoms. For example, 15% of the population lack a serotonin transporter gene; therefore, the perturbing effects of treatment and its discontinuation are likely to be different for these individuals. In addition, cognitive mindset certainly varies among patients. Although several patients may experience similar discontinuation symptoms, some may report these symptoms to a physician while others may tolerate them and not report them.

CHOLINERGIC REBOUND

Several investigators[15,22–24] have suggested that discontinuation symptoms, which have been reported much more often for paroxetine than for the other SSRIs[25] may be the result of cholinergic rebound. Headache, abdominal cramping, and nausea, which occur frequently when tricyclic treatment is ended, have been reported after paroxetine discontinuation.[22,26,27] Unlike the affinity profile for the muscarinic receptor of the other SSRIs, the affinity profile of paroxetine resembles that of the tricyclics (Table 5). However, Fava and Grandi[28] reported on two patients who experienced symptoms after paroxetine discontinuation despite the fact that they had been switched to desipramine, which binds to the muscarinic cholinergic receptor with about the same affinity as paroxetine, which suggests that cholinergic rebound may account for only a part of this phenomenon.

CONCLUSION

SRI discontinuation phenomena are probably due to a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors. However, other neurotransmitters such as dopamine, norepinephrine, or GABA may also be involved. Genetics and cognitive mindset of individual patients are likely to also play a role in the severity of the SRI discontinuation symptoms. Published data suggest that withdrawal symptoms are more likely to occur after paroxetine discontinuation. This increased frequency with paroxetine may in part be due to its being introduced later into the market or to intrinsic pharmacological properties—cholinergic effects, shorter half-life, or pharmacological potency at the serotonin uptake site. Other shorter half-life SRIs (e.g., venlafaxine and fluvoxamine) also appear to be more commonly associated with discontinuation phenomena. Thus, the frequency and severity of symptoms that appear may depend on the pharmacologic profile of a particular drug. Future research is needed to better describe the mechanisms of SSRI withdrawal and to more clearly define the characteristics of this phenomenon.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), chlordiazepoxide (Librium and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor)

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