Physiologic Mechanisms Underlying the Antidepressant Discontinuation Syndrome

Pierre Blier, M.D., Ph.D., and Philippe Tremblay, M.D.

The rate at which serotonin reuptake inhibitor (SRI) treatment is terminated and the duration of treatment appear to be key factors in predicting discontinuation symptoms. The development of animal models to explain the mechanisms of this clinical problem has proved challenging, because less than half of all patients experience any discontinuation symptoms, many of which are subjective in nature. One explanation is that SRI discontinuation symptoms may arise from the rapid decrease in serotonin (5-HT) availability when treatment ends abruptly. Yet, it would appear that discontinuation discomforts may not be mediated exclusively through 5-HT receptors, given the major regulatory role 5-HT exerts on a number of specific chemical receptor systems in the brain. As a result, attempts to explain the determinants of this phenomenon rely on a certain level of speculation. This article examines the possible physiologic bases for the antidepressant discontinuation syndrome and briefly describes these adaptations. It discusses the 3 systems most likely to account for at least part of the symptomatology—the 5-HT, the norepinephrine, and the cholinergic systems—and the possible interactions among them. It also attempts to explain their implications in the therapeutic actions of antidepressants in patients with affective and anxiety disorders.

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Discontinuation symptoms do not occur in all patients who stop taking prescribed medications but may appear following abrupt cessation of many of the serotonin reuptake inhibitors (SRIs) in a substantial proportion of patients. Discontinuation symptoms are, however, rare after discontinuation of fluoxetine, most likely because of the long elimination half-lives of both the drug (2–3 days) and its active metabolite (4–9 days).[1] In general, the shorter the half-life of any medication, the greater the likelihood patients will experience discontinuation symptoms.[2–4] Thus, it appears the rapidity with which serotonin (5-HT) reuptake inhibition is terminated is important to its clinical course. Another factor that seems to predict discontinuation symptoms is duration of SRI treatment. For example, SRI discontinuation syndrome is virtually unheard of in women receiving episodic treatment for premenstrual disorder. This fact suggests that even 2 weeks of exposure (i.e., the second half of the menstrual cycle) to SRIs with short half-lives is not sufficient to produce such symptoms and that prolonged interference with serotonin transporters (5-HTTs) is required.

SRIs rapidly block the high-affinity transporters for 5-HT following their systemic absorption. In this way, they decrease the efficacy of the main inactivating system involved in the termination of 5-HT activity in the extrasynaptic milieu. The best clinical evidence of this phenomenon is the nausea that occurs in about 10% to 20% of individuals shortly after they take an SRI. Presumably, this side effect is due to excess activation of 5-HT_3 receptors, as it can be blocked using agents that antagonize this receptor subtype.[5–7] Prolonging treatment generally abates this side effect within 1 to 2 weeks, providing a first line of clinical evidence that the 5-HT system undergoes adaptive changes after interference with its reuptake transporters. Other plastic changes include alterations in the sensitivity of postsynaptic 5-HT receptors other than the 5-HT_3 receptor subtype, alterations in the presynaptic 5-HT receptors that control function of the 5-HT neurons on which they are located, and even alterations in the function of the 5-HTTs themselves.[8–10]

Before we tackle the possible physiologic bases for the antidepressant discontinuation syndrome in this article, we briefly describe these adaptations and explain their implications in the therapeutic actions of antidepressants in patients with affective and anxiety disorders.

From the Department of Psychiatry, Institute of Mental Health Research, University of Ottawa, Ottawa, Ontario, Canada.

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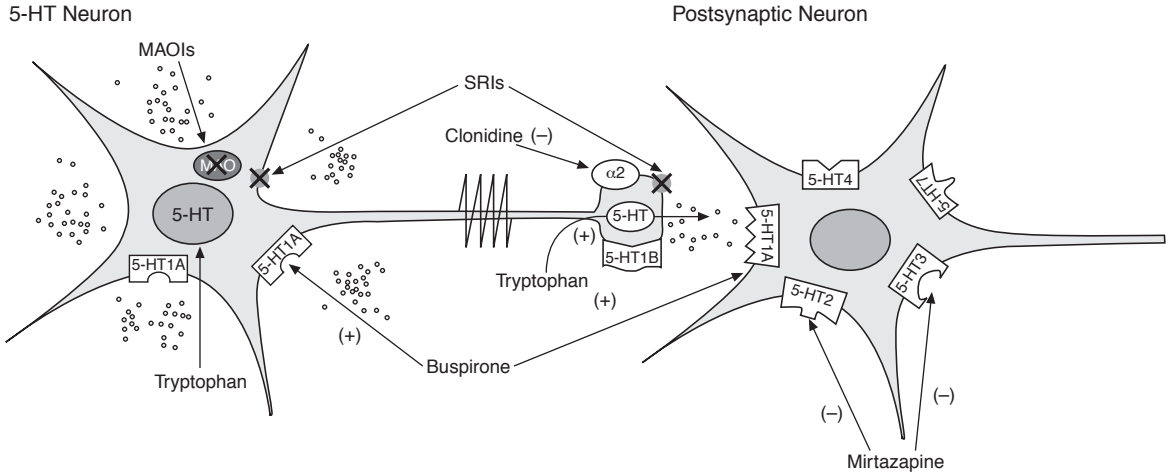
Corresponding author and reprints: Pierre Blier, M.D., Ph.D., Department of Psychiatry, Institute of Mental Health Research, University of Ottawa, 1145 Carling Ave., Suite 2053, Ottawa, Ontario, Canada K1Z 7K4.

Figure 1. The Serotonin (5-HT) System and Sites of Action of Selected Modifying Agents[a]



[a]The small dots represent serotonin molecules being released both at the cell body and terminal levels. The spikes on the axon represent action potentials; the faster the firing, the greater the release of 5-HT. Tryptophan is the essential amino acid precursor of 5-HT; tryptophan hydroxylase is not saturated under basal condition, so 5-HT synthesis can be increased by administering tryptophan. (+) signs represent an activation and (–) signs an inhibition. 5-HT_{1A} receptors exert an inhibitory action on firing activity, whereas 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7 exert an excitatory action.
Abbreviations: MAOIs = monoamine oxidase inhibitors, SRIs = serotonin reuptake inhibitors.

THE DELAYED THERAPEUTIC ACTION OF SRIs

Numerous positron emission tomography studies have shown that 5-HTTs are rapidly occupied by SRIs in the animal and the human brain, as demonstrated by a decreased binding of specific radiotracers for the 5-HTTs.[11] In vivo laboratory studies have shown that increased (albeit generally transient increases) 5-HT levels in microdialysis experiments prolonged actions of exogenous 5-HT on postsynaptic neurons and suppressed firing activity of the 5-HT neurons themselves.[9] The latter change is thought to be responsible, at least in part, for the drugs' therapeutic actions, because suppressed firing activity of the 5-HT neurons limits the effect of reuptake inhibition on 5-HT levels in many brain structures. Indeed, the increased activation of cell body 5-HT_{1A} autoreceptors in the brain stem attenuates the firing rate of 5-HT neurons, thereby decreasing release of 5-HT in projection areas (Figure 1). Prolonging treatment sustains 5-HT reuptake inhibition, allowing these autoreceptors to desensitize and 5-HT neurons to recover a normal firing rate. Moreover, autoreceptors of the 5-HT_{1B} subtype on 5-HT terminals, which inhibit 5-HT release, also desensitize. These changes occur gradually over time and lead to a progressive increase in 5-HT transmission.

The time required for the autoreceptors to adapt varies in different brain regions and is reflected in the delays in onset of therapeutic action of the SRIs. For example, the 5-HT_{1A} autoreceptors in the raphe and the 5-HT_{1B} autoreceptors in the hippocampus (a brain structure intimately implicated in depression and the antidepressant response) take 2 weeks to desensitize, whereas the 5-HT_{1B} autoreceptors in the orbitofrontal cortex (a brain region involved in obsessive-compulsive disorder [OCD]) take 2 months to desensitize. This difference is consistent with the longer delay for SRIs to act in OCD than in depression.[12]

Not all postsynaptic 5-HT receptors desensitize in all brain structures and thereby mediate an enhanced 5-HT signal transfer resulting from increases in 5-HT levels. For example, 5-HT_3 receptors desensitize,[13] and this action may account for the disappearance of the nausea mentioned above. Some 5-HT_2 receptors also adapt during long-term exposure to SRIs,[14] possibly contributing to the gradual decrease of the agitation that sometimes occurs with SRI initiation in selected populations, such as patients with panic disorder and perhaps children.

Initially, experiments in animals failed to document any changes in the density of 5-HTTs resulting from repeated and long-term administration of SRIs.[15] However, using osmotic minipumps implanted subcutaneously in rats, Pineyro et al.[8] demonstrated that 5-HTTs down-regulate with sustained exposure to a selective SRI (SSRI). Indeed, rats metabolize SRIs much faster than humans, and the sustained levels of these drugs that occur in humans cannot be replicated by repeated injections in rats. For example, the elimination half-life of citalopram is 3 hours in rats but 33 hours in humans.[16,17] Importantly, the decreased number of 5-HTTs in the raphe and forebrain following SRI administration was later replicated by Frazer's group.[10,18] Such a lesser density of 5-HTTs on 5-HT neurons has a significant physiologic effect, because it decreases 5-HT clearance from the extracellular space even

after a drug washout.[10] Therefore, 5-HTTs, like 5-HT receptors, may undergo drastic changes upon sustained occupation by SRIs.

TREATMENT DURATION AND DISCONTINUATION SYNDROME: TOO LITTLE OR TOO MUCH 5-HT?

It is presumed that the adaptive changes of 5-HT neuronal elements documented in rats also occur in humans, although perhaps delays are somewhat longer with most drugs, given that steady-state levels take longer to achieve in humans. Therefore, it is possible the consequences of such adaptations contribute to the manifestations of the SRI discontinuation syndrome. This possibility will be discussed later in this article. However, before examining which alterations may account for these symptoms, we must determine if an increase or a decrease in 5-HT transmission triggers the SRI discontinuation syndrome (Figure 1).

On one hand, it can be postulated that, in the presence of 5-HT_{1A} autoreceptor desensitization[19] immediately or shortly after the washout of the SRI, the firing rate of 5-HT neurons could rebound or increase markedly. Thus, an enhanced level of endogenous 5-HT in the raphe, normally produced by reuptake inhibition, would no longer maintain the firing rate of 5-HT neurons within the normal range after an SRI washout. Theoretically, such events could lead to an excessive amount of synaptic 5-HT in projection areas. This scenario is unlikely, because 48 hours after the interruption of a 14-day treatment with a 5-HT_{1A} agonist, the 5-HT_{1A} autoreceptor is still desensitized, the exogenous 5-HT_{1A} agonist is no longer present, and the firing rate of 5-HT neurons is within the normal range.[20] On the other hand, given that discontinuation symptoms can be promptly reversed by the reintroduction of the SRI, it is thus likely that an abrupt decrease in 5-HT availability is responsible for the problem. Indeed, after long-term administration of SRIs, presynaptic 5-HT_{1A} and 5-HT_{1B} receptors are desensitized, a change that can be demonstrated in the presence of the drug and immediately after SRI washout. In such a pharmacologic situation, the injection of an SRI increases 5-HT availability (and in the clinic, this reintroduction makes the symptoms disappear) because the negative feedback action exerted by the autoreceptors is dampened.[10,21] In support of this conclusion is the observation that the increase in 5-HT availability produced by SRI administration is potentiated by the pharmacologic antagonism of these autoreceptors.[22] Finally, in mice lacking either 5-HT_{1A} or 5-HT_{1B} autoreceptors, again the enhancing action of SRIs on the availability of 5-HT is potentiated.[23–25] Consequently, discontinuation symptoms in all likelihood result from a decrease, not an increase, in 5-HT availability and transmission.

Since fewer than half of patients present any discontinuation symptoms, and many of these symptoms are subjective in nature,[26] it is virtually impossible to develop animal models that can generate strong evidence for the mechanisms underlying this clinical problem. Consequently, we are left only with the possibility of speculating on the determinants of the phenomenon. The 3 systems most likely to account for at least part of the symptomatology will be examined, namely the 5-HT, the norepinephrine (NE), and the cholinergic systems and the possible interactions among them.

THE 5-HT SYSTEM

Down-regulation of the 5-HTTs by SRIs tends to enhance synaptic levels of 5-HT in the brain. In fact, it was reported that this adaptive change produces a greater effect on its own than the pharmacologic blockade of the 5-HTT.[10] The reasons for this apparent difference remain unclear. Nevertheless, this down-regulation appears to take about 1 week to return to normal in rats after stopping the selective SRI sertraline. Therefore, progressive recovery of normal 5-HTT activity following SRI cessation could contribute to decreases in synaptic availability of 5-HT. Possibly counteracting this downward trend in 5-HT transmission are alterations of the presynaptic 5-HT autoreceptors. The length of time that these changes persist after stopping the antidepressants that modify their function has not been thoroughly studied. For example, 5-HT_{1A} autoreceptors remain desensitized for 48 hours following the cessation of the antidepressant,[20] but longer time courses have not been examined. Although the messenger RNA levels for 5-HT_{1B} receptors in the rat dorsal raphe nucleus are already back to normal after 3 days, evidence shows that the function of 5-HT–releasing modulating autoreceptors is still decreased after a 2-day SRI washout.[9,27] Nevertheless, even if desensitization of the autoreceptor were to persist beyond that of the 5-HTTs, it would not enhance 5-HT transmission, because on its own, in the absence of reuptake or monoamine oxidase inhibition, desensitization of the autoreceptor does not enhance 5-HT transmission.[28]

A decrease in the activation of postsynaptic 5-HT receptors would therefore account for the manifestation of discontinuation symptoms. The question then is which receptor(s) from among the 7 families of 5-HT receptors and the multiple subtypes within each family is/are responsible? Apart from restoring the SRI, no serotonergic antidotes consistently counteract discontinuation symptoms. Few 5-HT agonists are available for use in humans that could help determine which 5-HT receptor(s) might be responsible for the effects of SRI cessation. For example, 1 case report describes an exacerbation of discontinuation symptoms using the 5-HT_{1A} agonist buspirone.[29] In contrast, blocking certain 5-HT receptor subtypes to trigger discontinuation symptoms could appear a worthwhile strategy, based on the contention that a decrease in 5-HT

transmission mediates this phenomenon. However, the question remains about which 5-HT receptors, or combination thereof, must be blocked for symptoms to develop. The authors have observed clear discontinuation symptoms 3 days after a gradual decrease and finally cessation of venlafaxine therapy in patients who had remitted earlier while receiving combination therapy with venlafaxine and the 5-$HT_{2/3}$ antagonist mirtazapine (P.B., unpublished observations, 2005). Although this sample includes few patients, these reports suggest that the 5-$HT_{2/3}$ receptors are not important.

An interesting question remains: why doesn't lowering synthesis by depleting tryptophan produce SRI-like discontinuation phenomena in SRI-naive individuals? (Pedro Delgado, M.D., addresses this question in depth in this supplement.) Perhaps a first question would be whether the absolute decrease in synaptic 5-HT availability achieved with tryptophan depletion is the same as that obtained with a rapid SRI washout after a prolonged treatment. Second, one may wonder if the level of 5-HT transmission from which the sudden drop is triggered is also an important factor. Therefore, the manifestation of discontinuation symptoms following the abrupt cessation of 5-HT reuptake inhibition may result not only from a given decrease in 5-HT transmission but also from the set point at which it occurs.

The 5-HTTs are reported to be linked to protein kinase C, as the activation of this key protein in signal transduction for membranal receptors leads to a decrease in 5-HT transport. In fact, transporters seem to be under the control of a variety of signal transduction pathways that are shared with many receptors.[30] Therefore, long-term inhibition of 5-HTTs potentially alters the transduction mechanisms of presynaptic receptors. For example, the SRIs citalopram and paroxetine lower the responsiveness of the α_2-adrenergic heteroreceptors on 5-HT terminals to the α_2-adrenoceptor agonists.[31] Similarly, sustained activation of postsynaptic 5-HT receptors may also alter transduction pathways common among the neurotransmitters,[32] giving rise to the array of signs and symptoms of the SRI discontinuation syndrome, upon abruptly diminishing 5-HT signal transfer.

THE NE SYSTEM

Long-term administration of SSRIs leads to a progressive decrease in firing activity of NE neurons in the locus ceruleus.[33,34] This decrease results from an enhanced inhibitory 5-HT tone on NE neurons.[35] It is therefore conceivable that, after the abrupt lifting of this inhibitory tone on NE neurons, there is a hyperadrenergic drive that contributes to some discontinuation symptoms. Indeed, upon discontinuation of the α_2-adrenergic agonist clonidine, which normally inhibits the firing activity of NE neurons, a rebound hypertension and symptoms such as weakness, restlessness, and headaches may ensue.[36,37] Similarly, long-term opiate administration attenuates the firing activity of NE neurons, and opiate withdrawal leads to a robust increase in the firing activity of these neurons.[38] The latter electrophysiologic rebound phenomenon is believed to contribute to the symptomatology reported in laboratory animals and humans undergoing discontinuation of opiate administration, with the reservation that other transmitters may also be involved, because clonidine only partially attenuates this syndrome.[39,40] Using clonidine to dampen the SRI discontinuation syndrome, by reducing a putative noradrenergic drive, may also appear futile. Indeed, α_2-adrenoceptor agonists suppress the firing rate of 5-HT neurons and decrease the release of 5-HT directly through the activation of inhibitory α_2-adrenoceptors on 5-HT terminals.[9,31] These 2 alterations could contribute to further reducing 5-HT transmission during an abrupt SRI washout.

THE CHOLINERGIC SYSTEM

Discontinuation symptoms following cessation of tricyclic antidepressant therapy have long been known to occur with a notable incidence.[41,42] However, they are somewhat different from symptoms observed with discontinuation of SRIs, most often consisting of headaches and gastrointestinal symptoms. This atypical presentation is not surprising because, with the exception of clomipramine, tricyclics are not potent blockers of 5-HT reuptake. It is unlikely that a rebound noradrenergic action would contribute to the discontinuation symptoms associated with the tricyclics, because cessation of the nontricyclic but potent NE reuptake inhibitors reboxetine and atomoxetine has not been linked to such problems.[43,44] In contrast, most tricyclics are relatively potent antagonists of the cholinergic muscarinic receptors, as is the case with clozapine, a drug with a known potential for causing discontinuation phenomena.[45] In this context, it is possible that the more frequently reported occurrence of discontinuation symptoms with paroxetine than with other SSRIs could be attributed in part to its moderate affinity for muscarinic receptors.[46] This observation emphasizes the possibility that discontinuation symptoms occurring with a given agent may be due to more than 1 system. For example, long-term administration of paroxetine appears to produce a greater reduction of the firing rate of NE neurons than other SSRIs,[33,34] possibly producing a greater alteration in NE neuronal firing after its cessation, in addition to a cholinergic and 5-HT contribution to the problem. Such multiple causality might explain the discontinuation phenomena frequently accompanying the cessation of paroxetine.

CONCLUSION

Symptoms of SRI discontinuation may be attributable to a rapid decrease in 5-HT availability. Such discomforts may not be mediated exclusively through 5-HT receptors,

given the major regulatory role 5-HT exerts on a multitude of chemospecific systems in the brain. Nevertheless, it would be useful to determine which 5-HT receptor subtype(s) is/are responsible for this cumbersome clinical phenomenon. A clear answer to this question may come only from attempts to reverse these symptoms with specific 5-HT receptor ligands in humans, since there are no means to ascertain the validity of animal models, given the subjective nature of the problem. This effort will remain hampered in the near future by the paucity of 5-HT ligands available to attempt reversing these symptoms in humans.

From a heuristic point of view, it would be useful to determine if any biological parameter could help predict the occurrence of the SRI discontinuation syndrome. For example, it would be interesting to examine whether the syndrome occurs more often in individuals with the 2 long or the 2 short alleles of the 5-HTT, genotypes that confer a normal and a dampened activity of the 5-HTTs, respectively.[47] It may also be useful to explore if pharmacologic strategies aimed at decreasing overall brain excitability help reverse discontinuation symptoms. Although benzodiazepines, which enhance inhibitory γ-aminobutyric acid activity, are not helpful,[48] it is possible that drugs aimed at decreasing excitatory glutamatergic transmission may be of significant use. In support of the latter possibility, it has been reported that the density of *N*-methyl-D-aspartate binding sites, an important subtype of glutamate receptors, increases following withdrawal of an antidepressant—imipramine—with some 5-HT activity.[49] Considering that 5-HT can exert an inhibitory role on glutamate pyramidal neurons in the rat cortex[50] and that SRI discontinuation increases markers of stress response in humans,[51] it is possible that SRI discontinuation leads to an increased glutamate release.[52–54] Clearly, more research is necessary to shed light on the pathophysiology of this clinical problem.

Drug names: atomoxetine (Strattera), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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