Antidepressant Discontinuation Syndrome: Consensus Panel Recommendations for Clinical Management and Additional Research

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Objective: Currently, no evidence-based guidelines exist for the management of serotonin reuptake inhibitor (SRI) discontinuation syndrome. This article summarizes recommendations with respect to future research as well as clinical management recommendations for SRI discontinuation syndrome. ***Participants:*** In April 2004, a panel of physicians convened in New York City to discuss recommendations for clinical management of and additional research on SRI discontinuation syndrome. ***Evidence:*** Previous guidance for management of SRI discontinuation syndrome was proposed in 1997 in a consensus meeting also chaired by Alan F. Schatzberg. A literature search of the PubMed database was conducted to identify articles on SRI discontinuation syndrome that have been published since 1997. ***Consensus Process:*** The 2004 panel reviewed important preclinical and clinical studies, discussed prospective investigation of this syndrome in clinical trials, and suggested the establishment of a research network to collect data in naturalistic settings. The panel also reviewed the management recommendations published in 1997 and subsequently updated the recommendations, taking into account the latest clinical data as well as the personal experience of its members with patients. ***Conclusions:*** Additional preclinical and clinical studies are necessary to further elucidate the underlying biological mechanisms of SRI discontinuation syndrome and to identify the patient populations and agents that are most affected by this phenomenon. Management strategies include gradual tapering of doses and should emphasize clinical monitoring and patient education.

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In 1997, a consensus panel reviewed the data on serotonin reuptake inhibitor (SRI) discontinuation syndrome and made a number of recommendations for clinical management. In April 2004, a panel of physicians convened in New York City and made recommendations for clinical management of and additional research on SRI discontinuation syndrome. These recommendations included outlining important preclinical and clinical studies to understand biological mechanisms, discussing prospective investigation of this syndrome in clinical trials, and proposing the establishment of a research network to collect data in naturalistic settings. Importantly, the panel also reviewed the management recommendations published in 1997[1] and updated its recommendations according to the latest clinical data as well as the personal experiences of the members with patients.

Since the original panel met in 1997, interest in SRI discontinuation syndrome has greatly increased. A literature search of the PubMed database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?) reveals that more than 30 review articles on SRI discontinuation syndrome have been published since 1997. Notably, diagnostic criteria for this syndrome were proposed by Haddad[2] in 1998 and Black et al.[3] in 2000 and are described in this supplement by Shelton.[4]

However, few studies have investigated the underlying biological mechanisms of this phenomenon. Some studies have better characterized the patient populations that are affected by SRI discontinuation syndrome and have compared effects elicited by discontinuation of different SRIs, but the panel concurred that much work remains to be

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done in this area. In 2000, results of a double-blind, placebo-controlled study investigated the effects of a short (4 to 7 days) SRI discontinuation in 87 patients and showed that discontinuation symptoms were more frequent and more severe in patients who were receiving paroxetine compared with those who were being treated with fluoxetine, sertraline, or citalopram.[5] Two further studies[6,7] with a similar design, published in 2000 and 2002, also found that SRI discontinuation syndrome was more common in paroxetine-treated patients than in fluoxetine-treated patients. Another 2002 study[8] revealed that discontinuation of paroxetine is also associated with a higher incidence of SRI discontinuation syndrome than is discontinuation of fluoxetine in dysthymic patients and that discontinuation syndrome is also more likely in patients who were diagnosed at an earlier age and in females. The higher frequency of discontinuation effects with paroxetine, in contrast with other selective SRIs, may be attributable to its high affinity for the serotonin (5-HT) transporter and short half-life.

In this supplement, Shelton[4] reviews recent studies that assess the prevalence of adverse events in neonates exposed to maternal antidepressant use during pregnancy.[9–11] A high prevalence of such symptoms has been reported, but there is debate as to whether such symptoms represent a neonatal-selective SRI discontinuation phenomenon or 5-HT toxicity.[12] These are not mutually exclusive, and each may apply to different cases. Tapering expectant mothers from SRI therapy before delivery has the potential to reduce the occurrence of such symptoms irrespective of the mechanism by which the antidepressant use causes them. However, the downside is that the mother is at increased risk for depressive relapse. More data are needed to confirm the optimal management strategy for this unique patient population.

This article summarizes the recommendations of the 2004 consensus panel with respect to future research as well as its clinical management recommendations of SRI discontinuation syndrome.

RESEARCH RECOMMENDATIONS

Preclinical Studies

To further elucidate the biological and pharmacologic mechanisms of SRI discontinuation syndrome, a number of different types of preclinical studies are needed. First, the relationship between 5-HT receptor desensitization and SRI discontinuation syndrome should be investigated. (See Blier and Tremblay.[13]) Sustained blockade of 5-HT reuptake during exposure to SRIs has been shown to produce a subsequent desensitization of postsynaptic 5-HT_{1A} receptors in some, but not all, brain structures.[14–16] Restoration of 5-HT reuptake activity occurs following discontinuation of SRI treatment, which, in combination with such desensitized postsynaptic 5-HT_{1A} receptors, could lead to an acute hyposerotonergic state. This state could, in turn, potentially alter the function of several other interacting neurotransmitter systems, resulting in the symptoms associated with SRI discontinuation syndrome.[17,18] Thus, the restoration of enhanced synaptic 5-HT availability over time would correspond to the gradual improvement of discontinuation symptoms. In 1999, Raap and colleagues[19] investigated the time course and mechanism of this desensitization after discontinuation of fluoxetine administration and found that desensitization of 5-HT_{1A} receptors lasted for at least 60 days in rats and appeared to be due to altered interactions among various components of the 5-HT_{1A} receptor system. It was agreed that similar studies should be performed with other shorter-acting SRIs.

Serotonin transporter (5-HTT) density should also be investigated; specifically, does the density of 5-HTTs increase above the prior normal level following cessation of treatment, and is there a rebound effect in 5-HTT levels after discontinuation of sustained treatment? Finally, considering the cross talk between different neurotransmitter systems, it would be interesting to define the roles of other neurotransmitter systems in SRI discontinuation syndrome. Some researchers have found that the norepinephrine and dopamine systems are affected in patients with SRI discontinuation syndrome, but, to our knowledge, the reverse situation has not yet been examined. With respect to the norepinephrine system, studies should be conducted to evaluate whether a rebound in noradrenergic activity, caused by the removal of the enhanced inhibitory 5-HT tone exerted by the SRI, contributes to discontinuation phenomena. In addition, effects of the dopamine system should also be assessed using microdialysis techniques, particularly with respect to the ventral tegmental area and substantia nigra firing activity and the levels of dopamine in their projecting regions. Depending on results of preclinical studies evaluating the role of other neurotransmitter systems in SRI discontinuation syndrome, antidote studies could be performed to determine whether and which specific drugs would abate or prevent some symptoms of discontinuation.

Pharmacogenetic and Clinical Pharmacology Studies

Pharmacogenetic/pharmacogenomic studies investigating the relationship between polymorphisms in genes encoding proteins that participate in the serotonergic system and SRI discontinuation syndrome could potentially shed light on which patients might be more susceptible to this phenomenon. Indeed, at least one researcher has proposed that genetics may play a role in SRI discontinuation syndrome.[20] Shelton and colleagues have developed a "short" list of approximately 120 genes in this system that each have about 3 to 5 polymorphic variants (R.C.S., unpublished data). While polymorphisms in the 5-HTT promoter and the 5-HT_{2A} receptor are the 2 leading candidates for influencing discontinuation reactions, analysis of other genes is expected to yield additional information.

Although the role of a drug's half-life in SRI discontinuation syndrome has been well accepted, it would be interesting to investigate whether other pharmacokinetic or transport parameters could serve as predictors of SRI discontinuation syndrome, e.g., medication drug resistance and glycoprotein.

Clinical Studies

The symptom profile of SRI discontinuation syndrome is quite complex, so a critical analysis of how the symptoms associated with this syndrome are related to its underlying biology would greatly facilitate our understanding of this phenomenon. Positron emission tomographic studies similar to those performed in tryptophan depletion studies (see Delgado[21]) could be used to evaluate the time course of symptom onset following discontinuation as a function of transporter density. Investigation of whether certain symptoms tend to occur earlier versus later following discontinuation, both within and across patient populations, could enable clinicians to better distinguish SRI discontinuation syndrome symptoms from those of other conditions. It would also be useful to investigate whether different SRIs are associated with different symptom profiles. In addition, determining whether different symptoms, particularly psychological symptoms, are observed in nondepressed patient populations who rapidly discontinue their SRIs might reveal if certain symptoms are related to the underlying disease rather than the treatment. Discontinuation characteristics as a function of treatment duration should also be determined; that is, do discontinuation syndrome characteristics differ between patients treated for shorter versus longer periods? Finally, any differences in SRI discontinuation syndrome severity or occurrence should be compared in patients who have a successful versus unsuccessful response to treatment.

Other suggested research includes naturalistic studies to determine how frequently discontinuation syndrome prevents stoppage of antidepressants: studies to determine the most effective antidepressant taper for minimizing discontinuation symptoms and studies of neonates exposed to antidepressants in the third trimester up to delivery to determine the incidence of adverse neonatal symptoms and to clarify whether the responsible mechanism is 5-HT toxicity or discontinuation syndrome. (Both mechanisms may apply in different cases.)

Prospective Investigation of SRI Discontinuation Syndrome in Clinical Trials

Because all psychotropic agents have potential discontinuation issues, the panel recommends that formal assessment of discontinuation syndromes should be conducted in phase III clinical studies when new compounds are developed. Characteristics of onset, duration, and severity of any discontinuation symptoms should be compared with those of the active comparator in these studies. The recommended instrument for evaluating symptoms is the Discontinuation-Emergent Signs and Symptoms (DESS) Checklist, a 43-item scale that can be administered in a clinician-rated form, a self-rated form, or an interactive voice-response form. (See Fava.[23]) Members of the panel recommended that the 43-item DESS Checklist be used, as shorter versions may not be sensitive enough to detect discontinuation reactions, with the understanding that the DESS Checklist itself may require further tweaking, since this scale has not yet been validated. Use of a single version of the DESS also has the advantage of facilitating comparison between studies.

Establishment of a Research Network to Collect Data in Naturalistic Settings

Capturing information from patients as they go through treatment in the community, using standardized measures that become part of the national practice, would help to answer some of the questions that might be difficult to address in the context of clinical trials. The National Institute of Mental Health is establishing a research network to accomplish these goals (R.C.S., unpublished observation). The panel also recommends that quality improvements and tracking as well as outcomes assessment be merged with systems and health services research.

RECOMMENDATIONS FOR CLINICAL MANAGEMENT

Following the 1997 panel meeting, Rosenbaum and Zajecka[1] published clinical management strategies for the treatment of SRI discontinuation syndrome. These included (1) reassuring patients that the symptoms associated with SRI discontinuation syndrome are likely to be short-lived and mild; (2) for severe and distressing symptoms, the dosage of the drug prescribed immediately before the dose decrease that led to the onset of discontinuation symptoms should be reinstituted and the rate of taper should be slowed; (3) all SRIs, with the exception of fluoxetine, should be gradually tapered; and (4) using or switching to agents with an extended half-life, such as fluoxetine, can help reduce the incidence of SRI discontinuation syndrome.[1]

The panel reviewed the 1997 treatment recommendations and agreed that slow tapering and drug substitution with longer-acting drugs, such as fluoxetine, were still among the best management strategies for minimizing and/or preventing SRI discontinuation syndrome. In addition, the importance of careful patient monitoring was discussed. Clinicians should be able to distinguish between the onset of discontinuation symptoms versus the return of depressive symptoms. In addition, monitoring should be open-ended during the usual window for onset of discontinuation symptoms (i.e., from the time of discontinuation through about 2 weeks afterward). Clinicians or members

of their team should be available by phone and/or e-mail during the tapering period and weeks immediately after stopping. Clinicians may want to check on their patients during this critical period, particularly if there is a history of severe discontinuation symptoms.

Patient education is still considered a key factor in the management of SRI discontinuation syndrome, and clinicians should reassure their patients that this syndrome is easily manageable. Prior to initiating treatment or early in its course, clinicians should educate patients about the possibility and nature of discontinuation symptoms, the importance of taking medication consistently, and the general need to taper medication at the end of a course of treatment of 3 to 4 weeks or longer to minimize the occurrence of such symptoms. Because antidepressants are generally used long-term, patients should be reminded frequently about these issues during treatment and especially that discontinuation symptoms may occur if the antidepressant is abruptly stopped, doses are missed, or the prescription is not refilled. This is particularly relevant given data that suggest a significant proportion of patients surreptitiously discontinue antidepressants without telling their prescribing clinician.[24] Patients should also be informed that discontinuation-like syndromes are not unique to antidepressants and can frequently occur with medications used for other conditions (e.g., β-blockers for hypertension, lithium in bipolar disorder). Importantly, clinicians should emphasize that SRI discontinuation does not indicate addiction or dependence. Finally, it is common practice in psychiatry to involve a key carer (e.g., spouse, partner, family member, close friend of the patient) in the patient's management plan, assuming the patient agrees. In this situation, the panel members supported the potential benefit of educating the carer about the importance of the patient's taking medication consistently not only for its therapeutic effects but also to prevent discontinuation symptoms.

It is important that health professionals are educated about discontinuation syndrome so that they are familiar with the concept and can provide appropriate advice to patients, recognize discontinuation symptoms when they occur, and provide appropriate management.

CONCLUSION

A number of preclinical and clinical studies are necessary to further elucidate the underlying biological mechanisms of SRI discontinuation syndrome as well as the patient populations and agents that are most affected by this phenomenon. The management strategies that were developed build on those drafted by the 1997 panel and place particular emphasis on monitoring and patient education. Implementing these recommendations in the near future may minimize the occurrence of SRI discontinuation syndrome.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft).

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