

Antidepressant Discontinuation Syndrome

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Discontinuation syndromes occur with many psychotropic agents. Withdrawal syndromes have been sporadically reported with the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), although these are generally thought to affect a minority of patients.^{1,2} In contrast, drugs that act as central nervous system (CNS) depressants, such as sedative hypnotics, opiates, and ethanol, have prominent and potentially severe withdrawal effects. For example, habituation and pharmacologic dependence to benzodiazepines led to difficulty in stopping treatment with these agents and ultimately resulted in their listing as scheduled substances.³

More recently, concerns have centered on recently reported withdrawal effects of antidepressants with serotonin reuptake inhibitor (SRI) properties. It is now recognized that these new-generation SRIs commonly cause untoward posttreatment effects, necessitating a gradual tapering of dose when stopping or changing drugs.^{4,5} While discontinuation syndromes have been linked to essentially all classes of antidepressants, SRIs are thought to have a higher incidence of withdrawal effects, especially agents with relatively short elimination half-lives.^{5,6} Estimates of the incidence of SRI withdrawal phenomena vary widely, but most likely a majority of patients are affected.

CHARACTERISTICS OF ANTIDEPRESSANT DISCONTINUATION SYNDROMES

The antidepressant discontinuation syndrome is manifested by a wide array of symptoms. Onset of symptoms occurs shortly after stopping drug or reducing the dose. Common symptoms include dizziness, anxiety, irritability, panic attacks, mood lability, decreased concentration, and insomnia. Nausea, occasionally associated with vomiting, and other gastrointestinal symptoms are frequent.

The SRI discontinuation syndrome differs from the classical withdrawal syndrome associated with CNS depressant drugs, such as alcohol, sedative hypnotics, and opiates. The latter is characterized by craving and drug-seeking behavior, along with prominent symptoms such as extreme diaphoresis, papillary

dilation, tachycardia, restlessness, and potentially withdrawal seizures. Unlike the withdrawal syndrome for CNS depressants, the antidepressant discontinuation syndrome is not manifested by drug craving. It is associated with a broad range of somatic symptoms, including dizziness, headache, fatigue, sleep disturbances, and gastrointestinal complaints. The diverse symptomatology of the SRI discontinuation syndrome led to development of the Discontinuation-Emergent Signs and Symptoms (DESS) rating scale for use by clinicians and patients.⁷ This 43-item rating scale spans a broad spectrum of discontinuation symptoms and can be helpful in documenting symptoms of depressed patients in order to diagnose the likely cause of distress.

PROSPECTIVE STUDIES OF ANTIDEPRESSANT DISCONTINUATION SYNDROMES

It was not until the advent of the SRIs that the first prospective studies were carried out to determine the incidence of the antidepressant withdrawal syndrome, prompted by the growing numbers of reports. In an early report about possible posttreatment effects of SRIs, Mallya and colleagues⁸ postulated the existence of a serotonergic withdrawal syndrome. The first prospective study compared the incidence of posttreatment symptoms following a 12-week course of the SRI paroxetine or placebo and found during a 2-week follow up period that the incidence of adverse events (AEs) was 34.5% for paroxetine versus 13.5% for

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placebo treatment.⁹ Dizziness was the AE of greatest frequency as compared with placebo. A subsequent prospective, placebo-controlled study of the serotonin norepinephrine reuptake inhibitor venlafaxine found a similar higher incidence of AEs over a 2-week period of rapid tapering of the antidepressant following an 8-week clinical trial as compared with placebo.¹⁰

In a double-blind, randomized, placebo-substitution trial, patients completing long-term maintenance treatment with either fluoxetine, sertraline, or paroxetine underwent evaluation during a 5–8-day period of treatment interruption.⁷ Both the sertraline- and paroxetine-treated patients experienced significantly more symptoms as rated by the DESS than did fluoxetine patients. With this treatment paradigm, paroxetine, but not sertraline or fluoxetine, produced significant increases in AEs as early as the fourth day of treatment.¹¹ Dizziness was more frequent following paroxetine or sertraline as compared with fluoxetine treatment. Two other similar studies of brief treatment interruption reported deleterious effects following paroxetine administration but not other SRIs.^{12,13}

PHYSIOLOGIC MECHANISMS UNDERLYING THE ANTIDEPRESSANT DISCONTINUATION SYNDROME

It is unclear why many but not all patients experience discontinuation symptoms when stopping SRIs. Both the duration of SRI treatment and the rapidity with which reuptake inhibition is terminated contribute to the likelihood of incurring the antidepressant discontinuation syndrome.¹⁴ Unlike other SRIs, discontinuation symptoms are rare following fluoxetine treatment, presumably because of the prolonged elimination half-lives of parent drug and active metabolite. SRI discontinuation syndromes are rare in women receiving episodic treatment of premenstrual disorder, suggesting that 2 weeks of drug exposure is insufficient, and uninterrupted interference with the serotonin norepinephrine transporter is necessary to invoke symptoms.

By rapidly decreasing the efficiency of the primary inactivating system (serotonin reuptake), SRIs initially can cause nausea, which may be blocked with agents that inhibit serotonin (5-HT)₃ receptors.^{15,16} Adaptation to this SRI side effect occurs during initial weeks of treatment along with other changes in neuronal function. Gradual desensitization of autoreceptors during SRI treatment allows serotonin neurons to recover normal firing rates and to progressively increase 5-HT neuronal transmission, perhaps accounting for the delay in onset of their therapeutic effects.

Because of diverse effects of serotonin on brain neurotransmitters, it has been postulated that multiple neuronal systems, including the 5-HT, norepinephrine (NE), and cholinergic systems, may be implicated in the discontinuation syndrome.¹⁷ Downregulation of the 5-HT transporter occurs as an adaptive effect, and recovery of normal transport activity takes several days in rodents.

Long-term administration of SRIs have also been shown to lead to a decrease in firing activity of NE neurons.¹⁸ It has also been speculated that the adaptive phenomena of enhanced inhibitory 5-HT tone on NE neurons, on abrupt discontinuation, could lead to loss of inhibition with resultant rebound hypertension or symptoms such as headache or restlessness. The cholinergic system might also be involved in discontinuation syndromes, as appears likely to be the case with TCAs and the SRI paroxetine, both of which exhibit moderate affinities for muscarinic receptors, in addition to effects on serotonin reuptake.¹⁴

CONCLUSION

Discontinuation syndromes have been associated with habituation to many psychotropic drugs, including CNS depressants such as sedatives hypnotics, opiates, and alcohol. Aftereffects of long-term antidepressant therapy have been described with TCAs and MAOIs. Abrupt discontinuation of SRIs may carry a higher liability for this syndrome than other antidepressants, possibly due to greater potency on the serotonin transporter. In prospective controlled trials, paroxetine has been found to have the highest incidence of posttreatment AEs compared with other SRIs. Fluoxetine, by contrast, has the lowest reported incidence of discontinuation symptoms, presumably due to the long elimination half-lives of parent drug and its active metabolite. **PP**

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