Monoamine Depletion Studies: Implications for Antidepressant Discontinuation Syndrome

Pedro L. Delgado, M.D.

The likelihood of a connection between serotonin reuptake inhibitor (SRI) discontinuation and an acute reduction in synaptic serotonin (5-HT) has ignited interest in the similarities between SRI discontinuation syndrome and the symptoms observed after acute tryptophan depletion, which reduces synaptic 5-HT levels. An open question is whether these 2 phenomena have shared characteristics because of a similar underlying mechanism. The evidence in support of a similar underlying mechanism includes the observation that comparable proportions of SRI-treated patients experience depressive symptoms following tryptophan depletion and SRI discontinuation. Furthermore, the proportion of people who have emotional changes with rapid antidepressant discontinuation may be parallel to the proportion of people who experience those changes with rapid tryptophan depletion.

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The involvement of the monoamine neurotransmitters serotonin (5-hydroxytryptamine [5-HT]), norepinephrine (NE), and dopamine (DA) in the pathogenesis and treatment of major depressive disorder (MDD) and other psychiatric conditions is now well established. Most antidepressant medications currently available increase synaptic levels of 5-HT and/or NE, and this is thought to be the first step in the cascade of effects that underlies their therapeutic effects in MDD. Emerging awareness of the frequency and severity of serotonin reuptake inhibitor (SRI) discontinuation syndrome[1] has elevated the importance of understanding the underlying neurobiology of this syndrome. The possibility that SRI discontinuation may be related to an acute reduction in synaptic 5-HT has prompted interest in comparing this syndrome with the symptoms observed following acute tryptophan depletion. Tryptophan depletion effectively and rapidly reduces synaptic 5-HT levels (described below). Although it has yet to be demonstrated definitively, discontinuation of SRIs presumably decreases the amount of available synaptic 5-HT levels as well.[2–4] This article will discuss the relevance of monoamine depletion studies, particularly tryptophan depletion, to SRI discontinuation syndrome. The results of several monoamine depletion studies will be reviewed, including the proportion of patients with a return of symptoms, differences observed in depressed versus nondepressed individuals, and the nature and time course of these symptoms. Similarities and differences between the symptoms that emerge following tryptophan depletion and those that comprise SRI discontinuation syndrome will also be discussed.

From the Department of Psychiatry, The University of Texas Health Sciences Center at San Antonio, San Antonio.

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Corresponding author and reprints: Pedro L. Delgado, M.D., Department of Psychiatry, The University of Texas Health Sciences Center at San Antonio, Mail Code 7792, 7703 Floyd Curl Dr., San Antonio, TX 78229–3900 (e-mail: delgadop@uthscsa.edu).

MONOAMINE DEPLETION

The monoamine hypothesis of depression proposes that depression results from a depletion in central nervous system levels of 5-HT, NE, and/or DA in depressed patients.[5] However, clarifying the relationship of monoamine systems to antidepressant responses and the neurobiology of depression has been challenging due to the inability to directly measure monoamine levels in humans.

Monoamine depletion studies have provided the first mechanistic evidence that 5-HT and NE might be implicated in distinct symptoms common to mood disorders.[6] Monoamine depletion can reduce the amount of the presynaptic levels of monoamine neurotransmitters by either inhibiting their synthesis,[7] as has been done for NE and DA, or restricting their precursor levels,[8] as has been done for 5-HT. Precursor restriction strategies are more rapid, while synthesis inhibitor strategies tend to be slower due to the pharmacokinetics and absorption of the drugs used to inhibit synthesis.[9]

Tryptophan Depletion

The synthesis of 5-HT is entirely dependent on the availability of its precursor, the essential amino acid tryp-

tophan. Several studies have shown that tryptophan depletion specifically reduces brain 5-HT levels.[10–14] Tryptophan depletion is achieved through administration of a tryptophan-free amino acid drink.[14] The tryptophan depletion paradigm has been used in a variety of patient populations, including healthy people without personal or family history of depression,[8,15–22] medication-free people with a history of depression who were not clinically depressed,[19,23,24] symptomatic depressed patients,[25–27] SRI-treated depressed patients,[6,28–30] and norepinephrine reuptake inhibitor (NRI)–treated depressed patients.[6,28–30] The majority of studies have been relatively short term, although one longer-term study investigated tryptophan depletion in fluoxetine-treated patients for 1 year.[31] Tryptophan depletion has also been examined in patients receiving nonpharmacologic treatments, including patients receiving cognitive-behavioral therapy[32] and patients with seasonal affective disorder receiving light therapy.[33–35]

Acute tryptophan depletion leads to rapid changes in brain 5-HT synthesis. In animal studies, it has been shown to be associated with a rapid decrease in 5-HT and/or the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels.[13,14,36–38] A positron emission tomography (PET) study using α–[^{11}C]methyl-L-tryptophan as a tracer showed that the rate of 5-HT synthesis was reduced by 87% in males and 97% in females within 5 hours of ingestion of the tryptophan-free drink.[17] In addition, in cerebrospinal fluid sampling studies, tryptophan depletion has been shown to reduce levels of 5-HIAA by 24% to 40%.[39,40]

The most common behavioral effect of tryptophan depletion is no effect.[16,41] Across different study samples (excluding women with premenstrual dysmorphic disorder), more people are unaffected by this paradigm than are affected, notably healthy subjects and depressed patients not taking any medication.[5,32] An important exception is depressed patients taking either SRIs or dual serotonin-norepinephrine reuptake inhibitors (SNRIs): an estimated 50% to 80% of these patients experience a transient return of depressive symptoms during tryptophan depletion, as assessed by an increased Hamilton Rating Scale for Depression (HAM-D) total score.[28] It is worth noting that the profile of depressive symptoms emerging during depletion tends to be characteristic for each patient.[6,28] In contrast, there is a relative absence of new or reemerging symptoms associated with tryptophan depletion in depressed patients taking agents that inhibit NE uptake.[6,42]

Tryptophan depletion effects appear to be more common in people with affective disorders. For example, in patients with obsessive-compulsive disorder (OCD), tryptophan depletion has no effect on OCD symptoms and only a minor effect on depressive symptoms.[43–45] In patients with panic disorder, tryptophan depletion does not appear to affect resting anxiety but does cause a greater anxiogenic response and an increased rate of panic attacks following 5% CO_2 challenge[46]; however, it has no effect on depressive symptoms.[46] In addition, tryptophan depletion alone produces no exacerbation of anxiety.[46]

Genotyping of patients in remission from a major depressive episode who underwent tryptophan depletion revealed that homozygotes for the long allele (*l*) of a functional polymorphism of the promoter region of the 5-HT transporter gene (*SLC6A4*) were more likely to experience depressive symptoms on depletion than either heterozygotes for *l* and the short allele (*s*) or *s* homozygotes.[47] This difference could serve as a possible explanation for the percentage of depleted patients who experience mood symptoms.

While the somatic symptoms associated with depletion have not been extensively studied, a few have been noted. The most consistent and common symptom across all groups is nausea, although this may be nonspecific since consumption of a balanced mixture of amino acids also causes nausea. The second most common side effect is gastrointestinal discomfort. In an unpublished study, this author observed that healthy patients who underwent "super depletion" with tryptophan depletion plus the 5-HT antagonist methysergide experienced severe nausea/vomiting, and patients taking monoamine oxidase inhibitors who underwent tryptophan depletion experienced severe nausea and myoclonus (P.L.D., unpublished data, 1996).

Catecholamine Depletion

Depletion of central NE and DA is conducted in a slightly different manner than depletion of 5-HT, although the underlying principles are similar. The rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase, is responsible for the conversion of tyrosine to L-3,4-dihydroxyphenylalanine (L-dopa). Oral administration of the reversible tyrosine hydroxylase inhibitor α-methyl-*para*-tyrosine (AMPT) effectively reduces both NE and DA levels.[48] Catecholamine depletion occurs over a longer time period (24–48 hours)[48,49] than does tryptophan depletion, which occurs in just over 5 hours.[17]

Analogous to the results of tryptophan depletion studies, in AMPT studies in depressed patients, NRI responders were at a much greater risk (~80%) for a relapse of depressive symptoms, as measured by an increased HAM-D total score, compared with only 20% to 25% of patients receiving SRIs.[28,30] Patients who receive AMPT exhibit a more consistent set of symptoms, including lethargy or lack of energy (frequently described as feeling sleep-deprived) as well as some level of irritability, which is consistent with symptoms modulated by noradrenergic drugs.[9,50,51] Compared with 5-HT depletion, catecholamine depletion results in less anxiety and greater increases in concentration problems, lack of interest, and psychomotor retardation.[9,52]

Table 1. Comparison of Effects of Tryptophan Depletion and SRI Discontinuation in SRI-Treated Patients[a]

Tryptophan Depletion[b]	SRI Discontinuation[c]
Neuropsychiatric	Neuropsychiatric
Depressed mood*	Depressed mood*
Psychic anxiety*	Anxiety*
Loss of energy	Intensification of suicidal ideation
Loss of interest	Irritability
Loss of pleasure	Impulsiveness
Decreased concentration	
Ruminative thinking	
Feelings of worthlessness/failure	
Gastrointestinal	Gastrointestinal
Nausea*	Nausea*
Vomiting*	Vomiting*
Gastrointestinal discomfort	Diarrhea
Other neurologic	Other neurologic
Terminal insomnia*	Insomnia*
Anorexia*	Anorexia*
	Vivid dreaming
	Asthenia/fatigue
	Chills
	Neuromotor
	Myoclonus
	Tremor
	Ataxia
	Visual changes
	Neurosensory
	Vertigo
	Paresthesias
	Shock-like reactions
	Myalgias
	Other neuralgias
	Vasomotor
	Diaphoresis

[a]Symptoms that are shared by these 2 patient groups are designated by an asterisk.
[b]Data from Delgado et al.[28]
[c]See Shelton.[53]
Abbreviation: SRI = serotonin reuptake inhibitor.

SRI Discontinuation Syndrome

The characteristics of SRI discontinuation syndrome are discussed at length elsewhere in this supplement (see Shelton[53]) and hence will be addressed only briefly here. This increasingly documented phenomenon has been observed following abrupt discontinuation, intermittent nonadherence, and, less frequently, dose reduction of an SRI or SNRI.[1] At least 53 different somatic and neuropsychiatric symptoms have been reported following discontinuation of fluoxetine, fluvoxamine, paroxetine, or sertraline[54]; these symptoms have been alternately grouped into 5 clusters of core somatic symptoms[1] or 6 syndromic features (see Shelton[53]). The most commonly reported symptoms were dizziness, nausea/vomiting, fatigue, headache, gait disturbance (ataxia), paresthesias, shock-like sensations, and visual changes, although the majority of patients have many additional symptoms, and each patient tends to have a unique set of symptoms.[54]

The half-life of the SRI appears to be key to the degree and duration of SRI discontinuation syndrome.[55,56] Agents such as fluoxetine that have a relatively long half-life (3 days) are rarely associated with SRI discontinuation syndrome, while patients treated with SRIs with shorter half-lives (e.g., paroxetine; $t_{1/2}$ = 21 hours) are more likely to experience discontinuation symptoms.[56] Discontinuation symptoms can be rapidly reversed by reintroduction of the original drug or substitution with another SRI, preferably one with a longer half-life, and symptoms also can be minimized by slow tapering.[1] SRI discontinuation syndrome generally lasts for about 2 weeks, which is consistent with the time frame for reregulation of receptors and 5-HT transporters.[54]

Estimating the true incidence of SRI discontinuation syndrome has proven to be difficult due to a lack of large studies prospectively assessing the issue as well as uniform diagnostic criteria and assessment instruments. Current estimates of frequency range from ~0% for fluoxetine and 17% to 78% for SRIs with shorter half-lives.[57,58]

Symptoms Associated With Tryptophan Depletion vs. SRI Discontinuation Syndrome

Presynaptic levels of 5-HT have been shown to decrease following tryptophan depletion,[10–14] and they presumably decrease following SRI discontinuation as well.[2–4] This apparent parallel raises the question of whether there are shared features of these 2 phenomena due to a similar underlying mechanism. Supporting evidence for a similar underlying mechanism includes the observation that comparable proportions of SRI-treated patients experience depressive symptoms following tryptophan depletion and SRI discontinuation.[6,28,57,58] However, closer inspection of the symptoms that occur following tryptophan depletion versus SRI discontinuation syndrome suggests that these are more likely to involve distinct mechanisms (Table 1). The majority of SRI-treated patients who undergo tryptophan depletion generally experience a return of depressive symptoms.[5,6,28] In contrast, patients who have discontinued SRI treatment tend to experience a wide range of somatic symptoms that are not observed during tryptophan depletion, as shown in Table 1.[28] It should be noted that, at a clinical level, there are fewer discontinuation data to draw from regarding specific symptoms as well as the actual prevalence of specific mood symptoms. Compared with the extensive analysis of tryptophan depletion in healthy subjects, no studies have been performed to determine whether healthy patients, or other nondepressed patients, receiving SRIs would experience a discontinuation phenomenon after discontinuing treatment.

The duration of reduction in monoamines in research studies of neurotransmitter depletion (especially tryptophan depletion) is usually short (4 to 24 hours) in order to diminish the likelihood of adverse effects. It is possible that the length of time that monoamines are diminished after abrupt discontinuation of antidepressants may be longer, causing a different constellation of symptoms

to emerge. Research using a longer duration of neurotransmitter depletion could be used to determine whether discontinuation-like symptoms emerge. This research would be impossible for tryptophan depletion, since the body begins catabolizing muscle proteins to restore tryptophan levels when levels have been low for longer than 6 to 12 hours.[59] Studies employing the 5-HT synthesis inhibitor *p*-chlorophenylalanine (pCPA), which can be used to deplete 5-HT for a longer period of time, could potentially help to further elucidate this issue. However, due to toxicity, pCPA cannot be used in humans, so such studies would be limited to animal subjects.

The observed differences in symptoms could also be explained by different magnitudes of 5-HT being depleted, differences in 5-HT availability between depleted patients versus discontinued patients, or differences in the brain regions affected by tryptophan depletion versus SRI discontinuation. In depletion studies, neurotransmitter levels drop relatively quickly and return to normal quickly. The time frame, regional specificity, and magnitude of neurotransmitter changes in discontinued patients need to be investigated before any conclusions can be drawn.

CONCLUSION

The spectrum of predominantly emotional symptoms associated with neurotransmitter depletion differs from the somatic and psychic symptoms that are seen with the SSRI discontinuation syndrome. However, the proportion of people who have emotional changes with rapid antidepressant discontinuation may be parallel to the proportion of people who experience those changes with rapid tryptophan depletion. Given that only a subset of people seem vulnerable to either of these phenomena, it will be important to assess genetic similarities and differences that may contribute to them.

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

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