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Understanding and Managing Withdrawal Syndromes After Discontinuation of Antidepressant Drugs

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ABSTRACT

Withdrawal symptoms commonly occur during tapering and/or after discontinuation of antidepressant drugs, particularly selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Withdrawal symptomatology does not necessarily subside within a few weeks and may be associated with other manifestations of behavioral toxicity (loss of treatment efficacy, refractoriness, switch into mania/hypomania, or paradoxical reactions). The oppositional model of tolerance provides a pathophysiologic basis for understanding and managing withdrawal syndromes. Reintroducing the antidepressant that was initially used or switching from one antidepressant to another to suppress symptomatology, as suggested by current guidelines, may actually aggravate the state of behavioral toxicity and be detrimental in the long run. Alternative strategies that do not encompass continuation of antidepressant treatment are required, but there is currently lack of adequate research for guiding the clinical approach. Some tentative suggestions are provided.

J Clin Psychiatry 2019;80(6):19com12794

To cite: Fava GA, Cosci F. Understanding and managing withdrawal syndromes after discontinuation of antidepressant drugs. *J Clin Psychiatry.* 2019;80(6):19com12794.

To share: https://doi.org/10.4088/JCP.19com12794

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Withdrawal symptoms following discontinuation of antidepressants were recognized soon after the introduction of these drugs.[1] They have been described with any type of antidepressant, but particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[2–5] The wide variation in their prevalence is due to differences in patient populations, type of drug, duration of treatment, and other clinical variables. We may reasonably expect, however, such an occurrence in 1 out of 2 patients discontinuing an SSRI or SNRI.[4]

Guidelines, such as those of the American Psychiatric Association,[6] have minimized the frequency and seriousness of such reactions:

> Discontinuation-emergent symptoms include both flu-like experiences such as nausea, headache, light-headedness, chills, and body aches, and neurological symptoms such as paresthesias, insomnia, and "electric shock–like" phenomena. These symptoms typically resolve without specific treatment over 1–2 weeks. However, some patients do experience more protracted discontinuation syndromes, particularly those treated with paroxetine, and may require a slower downward titration regimen.[6(p37)]

The term *discontinuation syndrome,* instead of *withdrawal syndrome* as with other psychotropic drugs (eg, benzodiazepines, antipsychotics), has been commonly used in guidelines and reviews, with the aim being to reinforce the conviction that these problems are devoid of important clinical implications and can be prevented by gradual tapering.[6–12] In systematic reviews,[3–5] however, no substantial differences between antidepressants and other psychotropic medications emerged in this regard. As a result, we will use the term *withdrawal syndrome*, which more accurately reflects the dependence potential of antidepressants.

Interpretation of Key Findings

In a recent paper,[12] Jha and associates addressed the clinical challenges that SSRI discontinuation entails. They cited a systematic review[3] stating that "up to 40% of patients reported new onset symptoms after abruptly discontinuing SSRIs." Actually, that systematic review[3] concluded that withdrawal syndromes were likely to occur with both abrupt and gradual tapering, with no significant advantage of the latter. Slow tapering with frequent contacts appears to be a reasonable strategy for many patients. However, the idea that by slowly tapering we can avoid withdrawal syndromes is, in the cases of both SSRIs and SNRIs, simply not supported by the literature.[3–5,13–15] Indeed, it may lead to a misleading assumption: if withdrawal symptoms occur during tapering or after gradual discontinuation, the physician may be driven to interpret them as a sign of relapse. The difficulties in performing such differential diagnosis—keep in mind that differential diagnostic criteria were only published in 2015[16]—are likely to increase the dangers of misinterpretation and inappropriate treatment.[17] Withdrawal symptoms and syndromes are new symptoms

compared to previous symptomatology; they may occur during, and despite, slow tapering and do not magically vanish a couple of weeks after discontinuation.[3–5,16] In a recent review,[18] Horowitz and Taylor claim the literature indicates that slow tapering of SSRIs yields greater success in reducing withdrawal symptomatology. Such a claim, however, is based not on randomized controlled studies but on retrospective analyses and case reports, which lend themselves to problems of interpretation.

When phenomena are complex and clinical presentations are quite variable, as during antidepressant tapering and after discontinuation,[17] the conceptual model the clinician uses very much affects the interpretation of phenomena and the selection of management strategies.

The pharmacokinetic model. Withdrawal syndromes are particularly frequent with short-elimination half-life antidepressants, such as paroxetine and venlafaxine, and less frequent with long elimination half-life medications, such as fluoxetine.[3–5,18,19] Thus, a pharmacokinetic model may provide the conceptual background for gradual tapering and/or switch from short-elimination half-life antidepressants to fluoxetine.[7–12,18] Gradual reduction of antidepressants may allow time for the adaptation of the system to lowered levels of the ligand, limiting withdrawal symptomatology.[18] The pharmacokinetic model, however, is unable to explain a number of clinical phenomena that are associated with antidepressant reduction or discontinuation. Withdrawal syndromes may typically appear within 3 days of antidepressant reduction or discontinuation and are characterized by new symptoms (that is, psychological/physical symptoms that were never experienced before by the patient) with a wide range of severity. In some cases, these withdrawal syndromes resolve spontaneously in 1 to 6 weeks. However, in other cases, the withdrawal syndrome is characterized by the return of the original illness at a greater intensity than before treatment, with additional clinical features and/or the occurrence of psychiatric disorders that never occurred before.[16] This latter symptomatology may persist for months or even years, leading to what has been termed *persistent post-withdrawal disorder*,[16] which has been described after both SSRI and SNRI discontinuation.[3–5] Withdrawal and post-withdrawal symptoms may be associated with modifications of the illness course, such as onset of hypomania, loss of clinical effects, and refractoriness to treatment.[17] When hypomania occurs, it may be self-limiting, may abate with reinstitution of antidepressant drugs, or may require specific antimanic treatment.[20] Loss of clinical effects (also referred to as *tachyphylaxis*) involves the return of depressive symptoms during maintenance antidepressant treatment that only temporarily respond to dose increase.[21] Refractoriness to treatment, that is, the lack of response to a previously effective pharmacologic treatment when it is started again after a drug-free period, is another phenomenon that may occur[21]; interestingly, it took place in the clinical case presented by Jha and associates.[12]

An essential issue in interpreting these clinical data is whether we view withdrawal syndromes only as isolated, self-limiting manifestations, which in due course subside, or also as one of the possible manifestations of behavioral toxicity, that is, the pharmacologic actions of a drug that, within the dose range in which it has clinical utility, may produce alterations in mood, perceptual, cognitive, and psychomotor functions that limit the capacity of the individual or constitute a hazard to his/her well-being.[22] Behavioral toxicity, in addition to withdrawal symptomatology, may manifest as switch to hypomania and bipolar course, loss of treatment effect, refractoriness to a treatment that was effective in the past, or paradoxical responses (eg, deepening of depression).[21]

As Grahame-Smith remarked: "Chronic drug therapy may induce a sleeping tiger, which awakens when the drug therapy is stopped and results in rebound withdrawal effects with serious consequences, as with many drug addictions."[23(p227)] But what *is* this "sleeping tiger"?

The pharmacodynamic model. A pharmacodynamic consideration of the clinical phenomena related to antidepressant discontinuation was presented in this journal in 2003.[24] According to the oppositional model of tolerance, continued drug treatment may recruit processes that oppose the initial acute effects of a drug. This may explain loss of treatment efficacy and the fact that certain side effects (such as increased appetite and weight gain) tend to ensue only after a certain time.[25] These processes may also propel the illness to a more malignant and treatment-unresponsive course, as with bipolar manifestations or paradoxical reactions. When drug treatment ends, oppositional processes may encounter no more resistance, resulting in the appearance of new withdrawal symptoms, rebound symptomatology, persistent post-withdrawal disorders, hypomania, or resistance to treatment if it is reinstituted (Figure 1). In the long run, antidepressants may increase chronicity, vulnerability to depressive disorders, and comorbidity.[24] The model is complex and multifactorial and is influenced by duration of and prior exposure to antidepressant treatment as well as by psychosocial and genetic factors.[24] The duration of the oppositional process when drug treatment ends may be variable, from a few weeks to months or years. The number of clinical studies supporting the oppositional model of tolerance[24] has progressively increased over the years.[21,26]

The delayed effects of antidepressant drugs on serotonin function have long been established.[23,27] If it is an adaptive response that mediates therapeutic actions at 2–4 weeks, it is also conceivable that further adaptive changes may occur at some later point in time. Such adaptive changes may take place through 5-HT_{1A} autoreceptor activity[17] and/or be associated with the allosteric modulation of the serotonin transporter protein, which was recently detected with SSRIs such as paroxetine and escitalopram.[28] Genetic polymorphism in serotonin receptors such as 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 may modulate the extent of opposing and compensatory processes to the initial effects of drugs.[29] However, factors such as duration and type of treatment, prior history of antidepressant exposure, and augmentation and switching strategies that have taken place may carry

Figure 1. The Oppositional Model of Tolerance

DURING TREATMENT	POST-TREATMENT
• Loss of clinical effects	• New withdrawal symptoms
• Paradoxical reactions	• Rebound symptomatology
• Hypomania/mania	• Hypomania/mania
• Delayed side effects	• Persistent post-withdrawal disorders
	• Refractoriness to treatment

much more weight than genetic predispositions.[21] Such factors can be subsumed under the rubric of iatrogenic comorbidity: the unfavorable modifications in the course, characteristics, and responsiveness to a treatment of an illness that may be related to treatments previously administered.[30]

Clinical Challenges

Management of withdrawal syndromes that may be associated with antidepressant dose reduction or discontinuation is a complex task that requires considerable skills.

A first challenge comes from the differentiation among symptoms of relapse and recurrence (the gradual return of the original symptoms at the same intensity as before treatment, entailing a return of the same episode and a new episode of illness, respectively), new withdrawal symptoms (new for the patient and not part of the patient's original illness), rebound symptoms (a rapid return of the patient's original symptoms at a greater intensity than before treatment), and persistent post-withdrawal disorder (return of the original illness at a greater intensity than before treatment and additional clinical features of the illness/additional psychiatric disorders).[16] The clinician should be familiar with these clinical phenomena and investigate withdrawal syndromes that appear with SSRI and SNRI discontinuation.[3–5,30,31] Yet, assessment does not involve simply careful collection and discrimination of symptoms. It depends very much upon whether the clinician collects medical history and current symptoms related to the concept of behavioral toxicity.[21,22,30]

The discrepancies that may arise among the conceptual models of interpretation of symptoms (pharmacokinetic versus pharmacodynamic) become larger with regard to the management of withdrawal syndromes. Jha et al[12] supported previous reviews[7–11] in suggesting that antidepressants should be tapered as slowly as possible, over at least 4 weeks or longer, and that the same antidepressant should be prescribed if withdrawal symptoms occur. Horowitz and Taylor[18] observed that decreasing medication by constant amounts (linear tapering) may cause increasingly severe symptoms over time and suggested dose reductions with exponential tapering programs that consist of very small doses over months. Another procedure that is advised[7–12] is to switch to fluoxetine, which is less likely to induce withdrawal problems.[19] However, there are a number of clinical situations (occurrence of side effects such as gastrointestinal symptoms or bleeding; pregnancy and breastfeeding; onset of hypomania or mania; lack or loss of efficacy of the antidepressant; improved clinical conditions) that may suggest antidepressant interruption.[17,25] Such situations require alternative methods.

If one subscribes to the oppositional model of tolerance,[24] reintroducing the antidepressant that was initially used or switching from one antidepressant to another (such as fluoxetine) to suppress clinical manifestations of withdrawal are both highly questionable suggestions. It is one thing to reintroduce an antidepressant after a drug-free period if relapse has occurred. It is another thing to do so if withdrawal has ensued: we should be aware that, by doing this, we are simply postponing, and most likely aggravating, the problem. Tolerance does not necessarily develop to a specific drug but may occur as a reaction to particular effects of a drug, which may be shared by medications of the same class.[17] As a result, if we administer an antidepressant, regardless of whether it is the same or a different one, we may worsen the state of behavioral toxicity that is associated with withdrawal phenomena as well as other manifestations of oppositional tolerance.[30] The use of alternative classes of medications (such as clonazepam) has been suggested.[17] Cognitive behavioral therapy has failed to prevent the onset of withdrawal syndromes compared to treatment as usual in a randomized controlled trial.[32] A strategy that consists of the sequential combination of explanatory therapy,[33] cognitive behavioral therapy, and Well-Being Therapy[34] has been suggested[17,35] but awaits proper validation studies.

A clinical issue that has attracted insufficient attention concerns the medical consequences of SSRI and SNRI discontinuation, since these medications may interact with a number of drugs, such as anticoagulants, β-blockers, antihypertensive drugs, and tamoxifen.[36] For instance, if a patient is taking antihypertensive medication, changes in antidepressant dosages may affect blood pressure and may require readjustments of antihypertensive therapy.[17] The presence of multiple drugs that cause both pharmacokinetic and pharmacodynamic interactions may further complicate the issue.[17] Discontinuing antidepressants may indeed require the availability of close medical consultation and cooperation.[17] It has been argued that antidepressant discontinuation, when performed without medical consultation and adequate psychotherapeutic support, entails substantial risks for the patient and is often bound to fail.[17]

What clearly emerges is the lack of appropriate research for guiding the clinician in this area.

Urgent Research Agenda

There are important issues that need to be explored. The most urgent are as follows.

Neurobiological studies. We need neurobiological investigations that may shed some light on why, with the same treatment for the same duration of time, certain patients develop withdrawal syndromes and others do not. This research should take place at both preclinical[37] and clinical[12] levels.

The course of withdrawal symptomatology. Longitudinal studies exploring the occurrence, clinical features, and neurobiological correlates of persistent post-withdrawal disorders are needed. In a pilot investigation,[38] 20 subjects who had been successfully treated with a standardized behavioral protocol for panic disorder with agoraphobia and were taking an SSRI had their medications gradually tapered (at the slowest possible pace) and discontinued. Patients were panic free after a type of psychotherapy that is generally associated with enduring effects[39] and received individual attention with opportunities for clarification and discussion of any symptoms that might have appeared. Nonetheless, 9 of the patients (45%) experienced a withdrawal syndrome, which subsided within a month in all but 3 patients who had been taking paroxetine. At 1-year follow-up, these 3 patients developed cyclothymia, which they had never experienced before, and presented with a syndrome that was later defined as persistent post-withdrawal disorder[16,35] and was also reported by other investigators.[3–5] We lack large studies exploring the frequency and course of persistent post-withdrawal disorders that are described in the literature,[3–5] and we lack studies showing whether specific individual patient characteristics may predict who might develop withdrawal.

In a recent longitudinal epidemiologic study,[40] mood disorders were found to be associated with an increased risk of developing other mental disorders. A possibility that needs to be explored, and was not entertained by the authors, is that antidepressant treatment, more than depression itself, might have caused persistent post-withdrawal disorders and be, at least in part, responsible for the increased comorbidity. Such studies are now feasible since diagnostic criteria are available.[16,41] The variability in the course of major depressive disorders may confound the identification of iatrogenic effects (eg, nonmedicated patients who have anxiety symptoms early in life and mood disturbances at a later time).[39] Longitudinal studies may also clarify the relationships between withdrawal syndromes and other manifestations of behavioral toxicity (eg, refractoriness, loss of effects), as well as distinguishing whether a specific treatment worsened the symptoms or was simply ineffective and the clinical picture would have deteriorated irrespective of treatment.

Exploring tapering. The hypothesis that very gradual tapering may yield a lower likelihood of withdrawal phenomena cannot be completely discarded, even though there are no data available to support it. We still need well-designed studies with appropriately titrated doses of medication comparing different strategies. Studies based on serotonin transporter occupancy suggest that SSRI dosage strengths in capsules or tables may be too large for allowing appropriate tapering[29]; liquid formulations have been advocated.[12,29]

Comparing different management strategies. There is a pressing need for randomized controlled trials comparing different methods of managing withdrawal syndromes. Examples may be very slow versus more rapid tapering, readministration of the antidepressant versus placebo, use of clonazepam versus antidepressant versus placebo, and adjunctive role of psychotherapeutic strategies.

Reassessing the protective effect of antidepressants against relapse. We need randomized controlled trials that consider the possibility that withdrawal syndromes may be confounded with relapses in long-term drug/placebo continuations studies[42]; the efficacy of antidepressants to prevent relapse in depression and anxiety disorders may have been overstated.

There is clearly the need of a paradigm shift in research on antidepressants. There are major conceptual and clinical issues that may originate from research on behavioral toxicity of antidepressant drugs, including withdrawal syndromes. A hidden conceptual assumption of a large body of research on treatment in depression is that, with appropriate treatment, depressive disturbances will go back to a premorbid state; that is, the receptor changes that are induced by antidepressants are limited to their time of administration or shortly afterward and that it is just a matter of allowing time for adaptation of the system to antidepressant discontinuation.[18] This naive assumption runs counter to current concepts on the plasticity of the brain.[43] The literature that we surveyed and, in particular, the oppositional model of tolerance, suggest that remission and recovery in mood disorders are a one-way street, characterized by structural remodeling of neural architecture and continually changing patterns of gene expression mediated by epigenetic mechanisms.[43]

This perspective may indicate the futility of looking for pretreatment biological predictors,[44] since the neurobiological assets change throughout the course of illness.[45] Major clinical challenges are left without appropriate independent research supported by public sources. Withdrawal symptoms and syndromes have been neglected with regard to proper funding and consideration. As a result, patients experiencing the anguish and mental pain of withdrawal syndromes have not received appropriate medical attention and have been forced to refer themselves to websites, groups, and associations, which had the recognized merit of providing support but could not offer the medical competence that was required.[17]

CONCLUSIONS

The time has come to initiate research on withdrawal phenomena related to antidepressants and to redefine the use and indications of these medications, including their differential likelihood of inducing behavioral toxicity.[46] We should become aware that when we prolong treatment with antidepressants over 6–9 months, we may trigger phenomena of oppositional tolerance.[24] It has been argued that antidepressant drugs should be targeted only to the most severe and persistent cases of depression, limiting their use to the shortest possible time and at the lowest possible dosage.[21] Augmenting or switching strategies (ie, adding a new antidepressant to the regimen) would need to be carefully weighed because of their strong link with behavioral toxicity.[17] The use of antidepressants in anxiety disorders would also have to be evaluated, and benzodiazepines could be reconsidered.[47]

In the meanwhile, in light of the evidence that is now available,[3–5,17] the prescribing physician should inform the patient about the possibility of dependence and withdrawal effects of antidepressants.[4] The clinician should monitor the occurrence of potential manifestations of behavioral toxicity, in addition to withdrawal symptoms, during and after antidepressant treatment. A simple checklist is now available.[48]

Published online: November 26, 2019.
Potential conflicts of interest: None.
Funding/support: None.

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