

# New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal

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Selective serotonin reuptake inhibitors (SSRIs) are widely used in clinical practice, and have advanced the treatment of depression and other mental disorders. However, more studies are needed on the effects of decreasing and discontinuing these medications after their long-term use [1]. Withdrawal symptoms may occur with all SSRIs and serotonin-noradrenaline reuptake inhibitors (SNRIs) [1], similarly to other CNS drugs, including benzodiazepines [2–4] and antipsychotics [5, 6]. Withdrawal from SSRIs and other CNS drugs produces psychiatric symptoms that can be confounded with true relapse or recurrence of the original illness [1, 2, 7]. When discontinuing or decreasing SSRIs, withdrawal symptoms must be identified to avoid prolonging treatment or giving unnecessarily high doses [6, 8].

Different types of syndromes have been described with the withdrawal from SSRIs and other CNS drug classes, including benzodiazepines, antipsychotics, antidepressants, opiates, barbiturates, and alcohol: (1) new withdrawal symptoms (classic withdrawal symptoms from CNS drugs) [1, 4–6, 9–12], (2) rebound [2, 6, 9, 13–16], and (3) persistent postwithdrawal disorders [7, 17, 18] (table 1). These types of withdrawal need to be differentiated from relapse and recurrence of the original illness. Relapse and recurrence are the gradual return of the orig-

inal symptoms at the same intensity as before treatment, entailing a return of the same episode and a new episode of illness, respectively [6, 9]. When treatment with a CNS drug is discontinued, patients can experience classic new withdrawal symptoms, rebound and/or persistent postwithdrawal disorders, or relapse/recurrence of the original illness [6, 9, 14]. New and rebound symptoms can occur for up to 6 weeks after drug withdrawal, depending on the drug elimination half-life [2, 3], while persistent postwithdrawal or tardive disorders associated with long-lasting receptor changes may persist for more than 6 weeks after drug discontinuation. Initial withdrawal symptoms from CNS drugs have been reported to be more frequent and severe when high-potency drugs and drugs with a short elimination half-life have been used [9, 10]. CNS drugs with a shorter elimination half-life and rapid onset of action also carry a higher risk of dependency and high-dose use [9, 10]. Withdrawal symptoms can be relatively short-lasting, lasting for a few hours to a few weeks with complete recovery, while others may persist and last for several months [1, 15, 16].

Fava et al. [1] have proposed using the terminology ‘withdrawal syndrome’ to replace the term ‘discontinuation syndrome’, which has been most often used to describe SSRI withdrawal. They have recommended the

**Table 1.** Types of withdrawal from SSRIs and SNRIs, compared with relapse and recurrence

Type/class	Peak of onset/duration	Outcome	Symptoms
New symptoms	36–96 h, but may also occur later (depending on drug duration of action) Last up to 6 weeks (depending on drug elimination half-life)	Reversible	New symptoms common to CNS drugs: nausea, headaches, sleep disturbances, anxiety, decreased concentration, agitation, dysphoria, aggression, depression Specific serotonin-related new symptoms: flu-like symptoms, dizziness, tachycardia, diarrhea, electric shock sensations, confusion, myoclonus, premature ejaculation
Rebound	36–96 h (depending on drug duration of action) Last up to 6 weeks (depending on drug elimination half-life)	Reversible	Return of original symptoms at greater intensity: anxiety, psychic anxiety, somatic anxiety, panic, agitation, insomnia, depression, dysphoria, obsessions, compulsions
Persistent postwithdrawal disorders	24 h to 6 weeks May last several months or more	Persistent, but remain reversible	(1) Return of original symptoms at greater intensity and/or with additional symptoms (2) Appearance of symptoms related to emerging new mental disorders
Relapse	24 h to 6 weeks	Remission: partial or complete	Same episode returns
Recurrence	6 months or more	Remission: partial or complete	New episode (it is assumed that there was at least partial response to treatment)

use of withdrawal terminology for SSRIs, rather than discontinuation, because the term discontinuation syndrome minimizes the consequences of SSRI withdrawal, separating it from other CNS drug withdrawals [1, 19]. SSRI withdrawal symptoms occur when the drug's pharmacological effects diminish after drug decrease or discontinuation, which indicates an underlying pharmacological mechanism comparable to that of other CNS drug withdrawal symptoms. The terminology discontinuation refers to the medical prescribing act or a patient's self-discontinuation of medication. Furthermore, the term discontinuation syndrome is misleading since withdrawal may occur without discontinuation, for example, in between two doses of rapid-onset and short-acting drugs (e.g. clock watching syndrome) and with a decrease in medication.

Recently, Fava et al. [1] have conducted the first systematic review of SSRI withdrawal. The authors analyzed 23 studies (15 randomized controlled studies, 4 open trials, 4 retrospective investigations) and 38 case reports of SSRI withdrawal, and found both early and late onset, and short and long duration of withdrawal symptoms. This important report provides substantial evidence for SSRI withdrawal prompting the need for a new classification of withdrawal phenomena associated with SSRIs.

Based on results from Fava et al. [1] and additional reports, we will illustrate three different types of withdrawal occurring when discontinuing SSRI and SNRI antidepressants. We will derive a classification for SSRI withdrawal based on withdrawal symptoms common to different CNS drug classes and specific symptoms common to SSRIs and SNRIs. Existing checklists, such as the Discontinuation-Emergent Signs and Symptoms (DESS) [20], and criteria for SSRI withdrawal symptoms [12, 21] do not differentiate between different types of withdrawal. Thus, we propose diagnostic criteria for the identification of the three different types of withdrawal seen with SSRIs, including new withdrawal symptoms, rebound, and postwithdrawal persistent disorders. We will also present 3 cases, which illustrate postwithdrawal persistent disorders. Moreover, we will focus on SSRI withdrawal, noting that SNRIs produce similar types of withdrawal [1, 22]. Our proposed classification aims to improve the detection and management of SSRI withdrawal, differentiating it from relapse and recurrence of the original illness. To reduce or withdraw from SSRIs with the goal of finding a minimal therapeutic dose, we must more effectively distinguish between the different types of SSRI withdrawal.

**Table 2.** SSRI new withdrawal symptoms: specific serotonin-related symptoms and nonspecific symptoms (adapted from Fava et al. [1])

System involved	Symptoms
Autonomic	
General	Flu-like symptoms <sup>1</sup> , sweating <sup>1</sup> , flushing <sup>1</sup> , chills <sup>1</sup> , fatigue, weakness, tiredness, lethargy
Visual	Visual changes, blurred vision
Cardiovascular	Dizziness <sup>1</sup> , light-headedness <sup>1</sup> , tachycardia <sup>1</sup> , vertigo, dyspnea
Gastrointestinal	Diarrhea <sup>1</sup> , loose stools <sup>1</sup> , abdominal pain <sup>1</sup> , nausea, vomiting, anorexia
Sensory	Paresthesias <sup>1</sup> , electric shock sensations <sup>1</sup> , brain zaps <sup>1</sup> , tinnitus, altered taste, pruritus
Neuromuscular	Myoclonus <sup>1</sup> , restlessness <sup>1</sup> , muscle rigidity <sup>1</sup> , myalgias <sup>1</sup> , neuralgias <sup>1</sup> , jerkiness <sup>1</sup> , ataxia <sup>1</sup> , facial numbness, tremor
Mental	
Cognition	Confusion <sup>1</sup> , amnesia <sup>1</sup> , disorientation <sup>1</sup> , decreased concentration
Affective	Anxiety, agitation, tension, panic, depression, intensification of suicidal ideation, irritability, impulsiveness, aggression, anger, bouts of crying, mood swings, derealization and depersonalization
Psychotic	Visual and auditory hallucinations
Other	
Sleep	Insomnia, vivid dreams, nightmares, hypersomnia
Sexual	Premature ejaculation <sup>1</sup> , genital hypersensitivity <sup>1</sup>

<sup>1</sup> Specific serotonin-related symptoms.

### New Withdrawal Symptoms

New withdrawal symptoms for CNS drugs are classic withdrawal symptoms that are new and not part of the patient's original illness, and occur with a decrease or discontinuation of the drug [3]. They are common to all CNS drugs, including opioids, barbiturates, alcohol, antidepressants, antipsychotics, and benzodiazepines [5, 10, 11]. Withdrawal has been classically divided into minor and major new symptoms [4]. Different classes of CNS drugs may share common withdrawal symptoms, but may also have their own specific withdrawal symptoms. Some initial new withdrawal symptoms common to all CNS drug classes include nausea, headaches, tremor, sleep disturbances, decreased concentration, anxiety, irritability, agitation, aggression, depression, or dysphoria. Other new withdrawal symptoms that may be more specific to a certain class of CNS drugs include lacrimation, rhinorrhea, and sneezing for opiates, paroxysmal sweats for alcohol, and increased appetite for nicotine [10, 23, 24]. These symptoms are typically transient, reversible and usually last <6 weeks, depending on the drug elimination half-life [2, 9–11]. However, major complications of withdrawal may occur, such as seizures, suicide and psychoses [10], and, in cases of barbiturate or alcohol abuse,

even death [25]. The term 'severe complications' has replaced the term 'major withdrawal symptoms' [10, 25]. The appearance or onset of withdrawal symptoms depends on the duration of action; for example, short-acting drugs have an early peak of onset [10]. High potency and short and intermediate half-life compounds tend to carry greater risks for withdrawal symptoms, in addition to drug dependence [6, 9, 10].

New withdrawal symptoms reported with SSRIs include a wide range of symptoms, both physical and psychological [1], and are found throughout different systems in the body (table 2). New withdrawal symptoms described in the literature include flu-like symptoms, headaches, nausea, diarrhea, dizziness, decreased concentration, sleep disturbances, dysphoria, irritability, and restlessness [1, 12, 22]. A recurrent disabling withdrawal symptom described in the literature and online by patients is a sensory symptom of electric shock sensations and electric-like waves [1, 12, 22, 26]. In table 2, we present withdrawal symptoms from the recent systematic review by Fava et al. [1] and indicate new symptoms during SSRI withdrawal that seem to be specifically related to serotonergic pharmacology [27, 28]. These specific serotonin-related symptoms include diarrhea, flu-like symptoms, dizziness, myoclonus, electric shock sensations, and premature ejaculation.

**Table 3.** Diagnostic criteria for SSRI and SNRI new withdrawal symptoms

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- (A) Cessation of (or reduction in) SSRIs/SNRIs after at least 6 months of continuous use
- (B) One or more of the following new symptoms: nausea, headaches, tremor, sleep disturbances, decreased concentration, anxiety, irritability, agitation, aggression, depression, or dysphoria
- (C) Two or more specific serotonin-related new symptoms, each in a different domain as follows:
- (1) Flu-like symptoms, sweating, or chills (general)
  - (2) Dizziness, light-headedness, or tachycardia (cardiovascular)
  - (3) Diarrhea, loose stools, or abdominal pain (gastrointestinal)
  - (4) Myoclonus, restlessness, myalgias, or rigidity (neuromuscular)
  - (5) Paresthesias, electric shock sensations, or zaps (sensory)
  - (6) Confusion, disorientation, or amnesia (cognition)
  - (7) Premature ejaculation, or genital hypersensitivity (sexual)
- (D) Symptoms in criteria B and C are characterized by a peak of onset within 36–96 h after cessation of or reduction in SSRIs/SNRIs (depending on drug duration of action), and last for up to 6 weeks (depending on drug elimination half-life)
- (E) Symptoms in criteria B and C cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- (F) Symptoms are not due to a general medical condition and are not better accounted for by another mental disorder or substance use
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New SSRI withdrawal symptoms have been found to occur after drug discontinuation with variable frequency and duration, depending on the SSRI which is discontinued [1, 12, 22]. They usually reach a peak of onset between 36 and 96 h after SSRI reduction or discontinuation, and are reversible, lasting from a few hours up to 6 weeks [1, 12, 22]. Data from controlled trials [15, 20, 29], case reports [16], and online patient reports [26] show that paroxetine is most likely to be associated with new withdrawal symptoms, and fluoxetine the least. Severity may also vary mainly according to the SSRI used [1, 20].

The diagnostic criteria that we propose for new SSRI withdrawal symptoms require a duration of at least 6 months of continuous SSRI use prior to reduction or discontinuation (table 3, criterion A). We deem this treatment duration requirement necessary, so that the pharmacologic effect of the drug is well established, allowing for differentiation between withdrawal phenomena and relapse or recurrence of the original illness. If a patient

has taken an SSRI for <6 months, the clinician may use a checklist, such as the DESS [20], to assess new withdrawal symptoms. Criterion B requires  $\geq 1$  new symptom, common to CNS drugs, including nausea, headaches, tremor, sleep disturbances, decreased concentration, anxiety, irritability, agitation, aggression, depression, or dysphoria. Criterion C requires  $\geq 2$  specific new symptoms related to the serotonergic system, in particular 5HT<sub>2A</sub> and 5HT<sub>1A</sub> receptors [28], which may be involved in SSRI withdrawal. In addition, noradrenergic CNS hyperactivity [28] likely contributes to SSRI withdrawal symptomatology. Symptoms in criteria B and C should also be characterized by a peak of onset within 36–96 h (depending on the drug duration of action) and by a symptom duration of up to 6 weeks (depending on drug elimination half-life). Symptoms cause clinically significant distress or impairment in important areas of functioning, and cannot be due to a general medical condition, another mental disorder, or substance use.

### Rebound Symptoms

Rebound symptoms are a rapid return of the patient's original symptoms at a greater intensity than before treatment [6, 9]. CNS drug rebound was first reported as REM rebound, consisting of an increase in REM sleep following abrupt withdrawal of barbiturates and nonbenzodiazepine hypnotics [30, 31]. These reports were followed by the demonstration of rebound insomnia in individuals with insomnia upon withdrawal of short and intermediate half-life benzodiazepines [13] and early morning insomnia with rapidly eliminated benzodiazepines [32]. Rebound anxiety [2, 14] and rebound panic [15] were then reported with abrupt benzodiazepine discontinuation [9]. It has been clearly demonstrated with benzodiazepines that patients often respond rapidly to the reinstatement of the drug, which may lead to a false sense of efficacy and need for the drug. The reinforcing properties of short-acting and short-elimination half-life CNS drugs appear to be the same for all CNS drug classes [6, 9]. Rebound with short-acting drugs may be best illustrated by withdrawal from cocaine and heroin, which both have a rapid onset and brief duration of action [10, 23]. The prevalence of rebound is greater among patients taking benzodiazepines with short to intermediate half-lives (e.g. triazolam, lorazepam, and alprazolam) than among those taking agents with long half-lives [9, 14]. This is also true for short-acting antipsychotics, such as clozapine and quetiapine, which have a fast dissociation from do-

**Table 4.** Diagnostic criteria for SSRI and SNRI rebound withdrawal

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- (A) Cessation of (or reduction in) SSRIs/SNRIs after at least 6 months of continuous use
  - (B) Return of original symptoms (e.g. anxiety, psychic anxiety, somatic anxiety, panic, agitation, insomnia, depression, dysphoria, obsessions, compulsions) and  $\geq 4$  of the following criteria:
    - (1) Greater intensity of symptoms than before treatment
    - (2) Rapid appearance of symptoms
    - (3) Transient
    - (4) Reversible
    - (5) Psychological belief of the need for drug
    - (6) Rapid improvement of symptoms after reintroduction of the drug
  - (C) Symptoms in criterion B are characterized by a peak of onset within 36–96 h after cessation of or reduction in SSRIs/SNRIs (depending on drug duration of action), and last for up to 6 weeks (depending on drug elimination half-life)
  - (D) Symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
  - (E) Symptoms are not due to a general medical condition and are not better accounted for by another mental disorder or substance use
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pamine D<sub>2</sub> receptor, and have been shown to have a greater risk of rebound [6, 33].

Due to the lack of classification for SSRI withdrawal, rebound symptoms in SSRI withdrawal have not been described as such in the literature. However, examination of various studies [20, 34, 35] shows us that this type of withdrawal occurs with SSRIs as well as with other CNS drugs. Rosenbaum et al. [20] demonstrated rebound major depression, although the authors did not describe it as such, in a double-blind withdrawal trial (5–8 days) conducted in 242 patients with major depression who had their maintenance paroxetine, sertraline or fluoxetine treatment interrupted [20]. In this study, patients taking paroxetine and sertraline developed worsened depressive symptoms on the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale after treatment interruption, and returned to baseline depression measurements after reinstatement of the treatment. New withdrawal symptoms, measured using the DESS, also appeared after paroxetine and sertraline discontinuation. Rebound depression has also been shown in another double-blind placebo-controlled paroxetine, sertraline and fluoxetine withdrawal study (5 days) [34], in which paroxetine-treated patients ( $n = 36$ ) had significantly higher scores on the Hamilton Depression Rating Scale, the State Anxiety Inventory, and an adverse events checklist after drug discontinuation. Pa-

tients taking sertraline ( $n = 34$ ) and those taking fluoxetine ( $n = 37$ ) did not have rebound depression. In this study and the study by Rosenbaum et al. [20], the drug interruption was short (5–8 days), and it is unlikely that rebound with fluoxetine would be seen. However, as fluoxetine has a long half-life, it is also less likely to cause rebound.

The proposed diagnostic criteria for SSRI rebound withdrawal (table 4) requires at least 6 months of continuous SSRI use prior to cessation or reduction, for the same reasons discussed with regard to new withdrawal symptoms. Cessation or reduction is followed by a return of the original symptoms of the illness, such as anxiety, depression, or obsessions and compulsions. The symptoms must be characterized by the presence of at least 4 of the following criteria: greater intensity of the symptoms than before treatment, rapid appearance of the symptoms, reversible, transient, psychological belief in the need for the drug, or rapid improvement of the symptoms after reintroduction of the drug. The peak of onset and the duration of symptoms are the same as for the criteria of the new withdrawal symptoms.

### Postwithdrawal Disorders

Persistent postwithdrawal disorders or tardive receptor supersensitivity disorders have been described with the use of antipsychotic medication [7, 17, 18]. Tardive dyskinesia and supersensitivity psychosis are well-known postwithdrawal disorders (also called supersensitivity syndromes) [7, 17, 18]. Persistent postwithdrawal disorders have been described with different classes of CNS drugs (e.g. protracted insomnia for alcohol and benzodiazepine withdrawal [10, 36] and major depression/dysphoria for cocaine and amphetamine withdrawal [10, 23]), and even more so with specific drugs (e.g. quetiapine and paroxetine) within a drug class [6, 15, 16, 33]. We now have increasing evidence for postwithdrawal disorders with SSRI long-term use [6, 15, 16, 26, 37]. This type of withdrawal consists of: (1) the return of the original illness at a greater intensity and/or with additional features of the illness, and/or (2) symptoms related to emerging new disorders. They persist at least 6 weeks after drug withdrawal and are sufficiently severe and disabling to have patients return to their previous drug treatment. When the previous drug treatment is not restarted, postwithdrawal disorders may last for several months to years. They may resemble rebound symptoms being more severe than the original symptoms, but these disorders persist at least 6 weeks in contrast to rebound symptoms and

may include new illness features. With SSRI withdrawal, persistent postwithdrawal disorders may appear as new psychiatric disorders, in particular disorders that can be treated successfully with SSRIs and SNRIs [6, 15, 16, 26, 37]. Significant postwithdrawal illnesses found with SSRI use include anxiety disorders, tardive insomnia, major depression, and bipolar illness.

Persistent postwithdrawal panic disorder [15, 38] has been shown to occur following withdrawal of paroxetine, and paroxetine has also been associated with other postwithdrawal disorders [6, 15, 16]. Fava et al. [16] conducted a study of gradual SSRI discontinuation in panic disorder and found that 9 of 20 patients (45%) experienced new withdrawal symptoms, and that 3 of the 9 (33%) patients treated with paroxetine had postwithdrawal disorders at 1 year of follow-up, including bipolar spectrum disorder ( $n = 2$ ) and major depressive disorder ( $n = 1$ ). We previously reported two types of persistent postwithdrawal psychiatric disorders (pathological gambling and generalized anxiety) with paroxetine that were treated successfully with specific cognitive behavioral therapy (CBT) and medications [37]. In another study, we analyzed online reports from individuals who described postwithdrawal disorders after SSRI discontinuation [26]. The most frequent persistent postwithdrawal disorder symptoms reported online were disturbed mood, depression, emotional lability, mood swings, irritability, anxiety, insomnia, impaired concentration, and impaired memory. There were online cases of persistent postwithdrawal disorders found after the discontinuation of paroxetine, citalopram, escitalopram, and fluvoxamine, but not sertraline or fluoxetine [26].

We will now present 3 cases which further illustrate persistent postwithdrawal disorders.

#### *Case 1: Persistent Postwithdrawal Generalized Anxiety Disorder*

A woman psychiatrist had a first major depressive episode (MDE) at the age of 48. She self-diagnosed her MDE (which was later confirmed by another psychiatrist) and self-prescribed citalopram 20 mg/day for 2 years; after this time, she started tapering it to 10 mg/day. After 1 month of 10 mg/day, she discontinued citalopram. A few days later, she started to have severe symptoms of nervousness, irritability, insomnia, and hot flushes, meeting the symptom criteria for generalized anxiety disorder (GAD), except for the duration of symptoms. She had never had GAD previously. She interpreted these symptoms as a relapse of her depression, restarted citalopram 20 mg/day, and decided to ask for a consultation.

She was seen by a psychiatrist after 12 weeks of reinitiating citalopram 20 mg/day, and at that time continued to have GAD symptoms. Clonazepam 0.25 mg twice a day was started to treat her withdrawal anxiety, while continuing citalopram 20 mg/day. Citalopram was reduced to 10 mg/day after 2 weeks, while clonazepam remained unchanged. After 2 weeks on citalopram 10 mg/day, citalopram was discontinued and clonazepam was increased to 0.5 mg twice a day. The acute anxiety symptoms disappeared after 1 month of citalopram discontinuation, but some GAD symptoms persisted, such as irritability and hot flushes. For the last 3 years, she had been on clonazepam 0.25 mg twice a day, in addition to undergoing CBT, targeting anxiety and interpersonal sensitivity. The patient believes that her GAD, which she had previously never experienced, was induced by citalopram withdrawal. She is currently in remission with residual anxiety but without functional impairment. This case illustrates a persistent postwithdrawal disorder with GAD, which responded to CBT and clonazepam, but without complete recovery, still requiring clonazepam despite the completion of the CBT.

#### *Case 2: Persistent Postwithdrawal Cyclothymic Disorder*

A 37-year-old man was treated for panic disorder with agoraphobia with paroxetine 20 mg/day for 7 years. Panic disorder and agoraphobia persisted despite treatment, and any attempt to reduce paroxetine was unsuccessful. He could only leave the house to go to work, and limited his activities to what he could not refuse for work, declining any other outings for leisure, including out-of-town opportunities. When the patient sought a new consultation, he was first treated for agoraphobia with CBT. A specialized psychologist guided him with homework exposure, consisting of 10 sessions every other week. His agoraphobia improved, and a paroxetine taper was then initiated. It was first tapered to 10 mg nightly, which immediately resulted in nervousness, headache, tension, and diarrhea. After 1 week of this paroxetine dose reduction, the patient was switched to fluoxetine 20 mg/day, which resulted in new withdrawal symptoms. After 2 months, these new symptoms improved, and fluoxetine was tapered to 10 mg/day for 1 week and then discontinued. Subsequently, he developed significant cyclothymic disorder, with greatly increased reactivity to environmental stimuli and anxious distress, which lasted for 3 years. It is important to note that he had no previous history of mood disorder. He was prescribed clonazepam without a decrease in his symptoms. Three years after the

**Table 5.** Diagnostic criteria for SSRI and SNRI persistent postwithdrawal disorder

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- (A) Cessation of (or reduction in) SSRIs/SNRIs after at least 6 months of continuous use
- (B) One or more of the following two criteria must be present:
- (1) Return of original illness at a greater intensity than before treatment and/or return of the original illness with additional symptoms (e.g. melancholic features for depression)
  - (2) Appearance of symptoms related to emerging new mental disorders; if treated, these may not necessarily meet DSM criteria for duration of illness; one or more of the following must be present: major depression, premenstrual dysphoria, generalized anxiety, panic attacks, insomnia, obsessive-compulsive and related illness, pathological gambling, posttraumatic stress, bulimia, bipolar spectrum illness, or symptoms of other DSM mental disorders
- (C) Symptoms in criterion B persist longer than 6 weeks after drug reduction or cessation, and are characterized by two or more of the following criteria:
- (1) Greater severity of illness than before treatment
  - (2) Reversible with partial or total remission
  - (3) Partial or total response to reintroduction of discontinued drug
- (D) Symptoms in criterion B are characterized by peak of onset ranging from 24 h to 6 weeks after cessation of or reduction in SSRIs/SNRIs (depending on duration of action and pharmacology of the discontinued drug), and may last several months or more
- (E) Symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- (F) Symptoms are not due to a general medical condition and are not better accounted for by another mental disorder or substance use
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discontinuation of paroxetine, the patient started to improve, and the postwithdrawal cyclothymic disorder remitted, but without complete recovery.

### *Case 3: Persistent Postwithdrawal MDE with Melancholic Features*

A 50-year-old woman with a prior history of social phobia was prescribed citalopram 20 mg/day for a period of 5 years to treat an MDE. She had no previous history of mood disorder or family history of mood disorder. She then presented to her primary care physician with increased symptoms of depression, and citalopram was increased from 20 to 40 mg/day. She reported feeling worse with 40 mg/day, and decreased the citalopram dose back to 20 mg/day. At that time, the patient was referred for psychiatric consultation, and it was decided to discon-

tinue citalopram. First, clonazepam was initiated at 0.5 mg twice a day to aid in the tapering of citalopram. Citalopram was tapered to 10 mg/day for 2 weeks, and then discontinued, while clonazepam was increased to 0.5 mg three times a day. After the discontinuation of citalopram, she reported new symptoms, such as sweating, agitation, and nausea, for 2 weeks. However, she also developed MDE with melancholic features accompanied by deep anhedonia, depressed mood with diurnal variation, loss of energy, guilt, and suicidal thoughts, which she had never had before. The patient was observed for an additional week, and while other withdrawal symptoms disappeared, the melancholic depression persisted. Nortriptyline 25 mg/night was added to clonazepam to treat her depression, and was gradually increased to 100 mg/day. Her depression improved after 6 weeks. After 3 months of treatment with nortriptyline, CBT was introduced to treat her social phobia. She interrupted psychotherapy after 3 sessions, but continued to take nortriptyline. After 2 years, she is still on nortriptyline 100 mg/day and clonazepam 0.5 mg three times a day. Any attempt to taper both drugs (one at the time) has been unsuccessful.

The proposed diagnostic criteria for persistent postwithdrawal disorders are presented in table 5. Criterion A requires a reduction in or discontinuation of SSRIs/SNRIs after at least 6 months of continuous use. Criterion B requires either (1) the return of the original illness at a greater intensity than before treatment and/or the return of the original illness with additional symptoms (e.g. melancholic features for depression) or (2) the appearance of symptoms related to emerging new mental disorders, including  $\geq 1$  of the following: major depression, premenstrual dysphoria, generalized anxiety, panic attacks, insomnia, obsessive-compulsive and related illness, pathological gambling, posttraumatic stress, bulimia, bipolar spectrum illness, or symptoms of other DSM mental disorders. Of note, if treated, the symptoms may not necessarily meet the DSM criteria for the duration of illness. Symptoms must persist longer than 6 weeks after drug discontinuation, and are characterized by two of the following criteria: greater severity of illness than before treatment, reversible with partial or total remission, or partial or total response to the reintroduction of the discontinued drug. In addition, the symptoms are characterized by a peak of onset ranging from 24 h to 6 weeks, depending on the duration of action and pharmacology of the discontinued drug, and may last for several months or more. Finally, the symptoms cause clinically significant distress or impairment, and cannot be due to a general medical condition, another mental disorder or substance use.

## Clinical Strategies for the Management of SSRI Withdrawal

First, the management of SSRI withdrawal should begin by identifying the different types of SSRI withdrawal. The proposed diagnostic criteria will assist in distinguishing between new withdrawal symptoms, rebound, and persistent postwithdrawal disorders, and relapse or recurrence of the illness. Checklists, such as the DESS [20], are also helpful to ensure that all new withdrawal symptoms are inquired about, particularly if the medication is withdrawn before 6 months of continuous intake. It is important to note that our proposed criteria require this minimal length of drug treatment.

Second, we recommend gradual tapering over a long period of time to discontinue an SSRI, for example, over several months if clinically appropriate. According to most studies [1, 15, 16, 20, 29], even with gradual tapering, withdrawal symptoms still occur. However, gradual tapering, rather than abrupt discontinuation, can help to control the severity of withdrawal symptoms. Furthermore, by reducing the dose gradually, a plateau period develops that can help to distinguish the development of new withdrawal symptoms, rebound, or recurrent symptoms. Of note, it may be that gradual withdrawal reduces new withdrawal and rebound symptoms, but has no effect on persistent postwithdrawal disorders.

Third, the same principles recommended for the management of alcohol, opiate and benzodiazepine withdrawal should apply to SSRIs, including the use of long half-life drugs [9, 10], such as fluoxetine. Long-acting drugs with a lower potential for withdrawal, abuse, or overdose, and with a low incidence of side effects should be used. Importantly, if the patient is not already taking fluoxetine, it should be started during the tapering of the SSRIs to aid in withdrawing from it. Given the evidence for the high risk of disabling withdrawal with paroxetine, thought to be related to noradrenergic and cholinergic supersensitivity [15, 35], its shorter half-life (19 h compared with 45 h for fluoxetine), and earlier steady-state concentration (7–14 days for paroxetine compared with 28–35 days with fluoxetine) [35], we recommend that paroxetine should not be given before exploring other treatment alternatives.

Fourth, optimal maintenance drug treatment consists in reducing the dose to find a minimal therapeutic dose. Clinicians should understand why it is difficult to decrease a given drug treatment for a patient, for example, due to the presence of a persistent postwithdrawal disorder. Giving low doses of SSRIs and decreasing the lengths

of SSRI maintenance treatment by using adjunct treatments, such as CBT, should be considered whenever possible to try to minimize long-term receptor changes. After 2 years of maintenance treatment, many types of persistent postwithdrawal disorders may be observed. We recommend re-evaluation of overall treatment and management after 2 years of continuous SSRI use, considering the possible use of other therapies, whether as adjunct or alternative treatment.

Fifth, we previously proposed treating SSRI withdrawal with anticonvulsants [6], particularly the anticonvulsants gabapentin and lamotrigine. Anticonvulsants may be used with an antipsychotic or SSRI in order to decrease or discontinue these medications. One proposed mechanism explaining the beneficial effects of using an anticonvulsant as an adjunct to an antipsychotic in schizophrenia is its antkindling effect [39, 40]. Lamotrigine may also be beneficial as an adjunctive therapy with SSRIs to treat depression as it has a depression-stabilizing effect.

## Conclusion

SSRIs have provided major therapy advancement in the treatment of depression and other mental disorders. Withdrawal symptoms may occur with SSRIs, similarly to other CNS drugs, and they must be identified and differentiated from relapse and recurrence of the original illness. The proposed diagnostic criteria will permit the identification of three types of withdrawal associated with SSRIs. Differentiating withdrawal from relapse and recurrence of the original illness will allow clinicians to more effectively reduce and withdraw SSRIs, and find a minimal therapeutic dose. It is most important to recognize persistent postwithdrawal disorders to prevent unnecessarily high doses and prolonged treatment.

## Disclosure Statement

G.C. has received conference honoraria within the last 3 years from Otsuka Pharmaceutical.

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