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Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications

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Abstract

Studies on psychotropic medications decrease, discontinuation, or switch have uncovered withdrawal syndromes. The present overview aimed at analyzing the literature to illustrate withdrawal after decrease, discontinuation, or switch of psychotropic medications based on the drug class (i.e., benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, antidepressants, ketamine, antipsychotics, lithium, mood stabilizers) according to the diagnostic criteria of Chouinard and Chouinard [Psychother Psychosom. 2015;84 (2):63–71], which encompass new withdrawal symptoms, rebound symptoms, and persistent post-withdrawal disorders. All these drugs may induce withdrawal syndromes and rebound upon discontinuation, even with slow tapering. However, only selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, and antipsychotics were consistently also associated with persistent post-withdrawal disorders and potential high severity of symptoms, including alterations of clinical course, whereas the distress associated with benzodiazepines discontinuation appears to be short-lived. As a result, the common belief that benzodiazepines should be substituted by medications that cause less dependence such as antidepressants and antipsychotics runs counter the available literature. Ketamine, and probably its derivatives, may be classified as at high risk for dependence and addiction. Because of the lag phase that has taken place between the introduction of a drug into the market and the description of withdrawal symptoms, caution is needed with the use of newer antidepressants and antipsychotics. Within medication classes, alprazolam, lorazepam, triazolam, paroxetine, venlafaxine, fluphenazine, perphenazine, clozapine, and quetiapine are more likely to induce withdrawal. The likelihood of withdrawal manifestations that may be severe and persistent should thus be taken into account in clinical practice and also in children and adolescents.

Introduction

Psychotropic drugs may cause withdrawal reactions which can occur after abrupt discontinuation or gradual tapering [1] with a prevalence of 54% among adults with

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Table 1. New withdrawal symptoms following decrease, discontinuation, or switch of psychotropic medications

Type	New withdrawal symptoms
Peak of onset	36–96 h (or later depending on drug duration of action)
Course	Transient
Duration	Up to 6 weeks (depending on drug elimination half-life)
Outcome	Reversible, with complete recovery
Clinical manifestations	Appearance of new symptoms, that is symptoms which were not experienced before the beginning of the treatment
Diagnostic criteria	(A) Dose decrease, discontinuation, or switch of a psychotropic medications (B) Rapid appearance of at least 2 new symptoms which might be unspecific or specific for the psychotropic medication class (C) Symptoms in criteria B are characterized by a peak of onset within 36–96 h after decrease, discontinuation, or switch of a psychotropic medication (depending on drug duration of action) and last for up to 6 weeks (depending on drug elimination half-life) (D) Symptoms in criteria B cause clinically significant distress (E) Symptoms in criteria B are not due to a general medical condition and are not better accounted for by another mental disorder or substance use

a diagnosis of serious mental illness [2]. A recent review of the literature suggested that benzodiazepines, Z-drugs, ketamine, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), antipsychotics, monoamine oxidase inhibitors (MAOIs), and gabapentin are associated with withdrawal symptoms [3]. Thus, it confirmed what was previously reported in reviews focusing on specific drug classes [4–9]. Regarding SSRIs and SNRIs, the term "discontinuation syndrome" had been used for several years. However, this definition is no longer accepted; the term "withdrawal syndrome" is more appropriate and there are no reasons to believe that there are differences from other classes of psychotropic drugs [3–5, 7, 10].

Based on the literature, Chouinard and Chouinard proposed in 2015 [10] 3 types of withdrawal syndromes for psychotropic medications: new withdrawal symptoms [5, 11–16], rebound symptoms [1, 13, 14, 17–20], and persistent post-withdrawal disorders [21, 22] (Tables 1–3). First, new withdrawal symptoms (Table 1) are usually short-lasting, transient, reversible symptoms, which are new to the patient. New symptoms are usually the same, common to all psychotropic medications during withdrawal [12, 15, 23] (e.g., nausea, headaches, sleep disturbances) [10], but also specific and unique for a drug class (e.g., specific serotonin-related symptoms: flu-like symptoms, diarrhea, confusion) [10]. Second, rebound symptoms (Table 2) are short-lasting, transient, reversible symptoms which represent a rapid return of the primary symptoms usually at a greater intensity than before treatment [13, 14]. Third, persistent post-withdrawal disorders (Table 3) are a set of long-lasting, severe, potentially irreversible symptoms [10] which entitle rebound primary symptoms or primary disorder at greater intensity and/or new withdrawal symptoms and/or new symptoms or disorders that were not present before treatment. They persist >6 weeks.

Withdrawal from psychotropic medications can produce psychiatric symptoms often confounded with relapse (i.e., a return of the same episode) or recurrence (i.e., a new episode) of the original illness [10]. However, both relapse and recurrence have 2 clinical features different from withdrawal syndromes: (1) the gradual onset of the original symptoms and illness, while drug withdrawal produces acute, abrupt return; (2) symptom severity as before drug treatment, while drug withdrawal produces greater severity [10]. On the other hand, Fava et al. [24] suggested that withdrawal from psychotropic medications can be associated with modifications of the illness course such as switching to mania as well as other forms of tolerance [24] such as loss of antidepressant clinical effects [25], resistance when the same medication is administered again [26], and general refractoriness to treatment [25, 27, 28].

The aim of the present overview of the literature was to apply the use of the diagnostic criteria proposed by Chouinard and Chouinard [10] to illustrate withdrawal

Table 2. Rebound symptoms following decrease, discontinuation, or switch of psychotropic medications

Type	Rebound symptoms
Peak of onset	36–96 h (or later depending on drug duration of action)
Course	Transient
Duration	Up to 6 weeks (depending on drug elimination half-life)
Outcome	Reversible, with complete recovery
Clinical manifestations	Return of the original symptoms at a greater intensity than before treatment
Diagnostic criteria	(A) Dose decrease, discontinuation, or switch of a psychotropic medication (B) Rapid return of original symptoms at a greater intensity than before treatment (C) Symptoms in criteria B are characterized by a peak of onset within 36–96 h after decrease, discontinuation, or switch of a psychotropic medication (depending on drug duration of action) and last for up to 6 weeks (depending on drug elimination half-life) (D) Symptoms in criteria B cause clinically significant distress (E) Symptoms in criteria B are not due to a general medical condition and are not better accounted for by another mental disorder or substance use

Table 3. Persistent post-withdrawal disorder following decrease, discontinuation, or switch of psychotropic medications

Type	Persistent post-withdrawal disorder
Peak of onset	24 h to 6 week (or later depending on drug duration of action)
Course	Persistent
Duration	More than 6 weeks (depending on drug elimination half-life)
Outcome	Potentially irreversible
Clinical manifestations	Return of original symptoms at greater intensity and/or new withdrawal symptoms that persist over 6 weeks and/or appearance of new symptoms that were not present before
Diagnostic criteria	(A) Dose decrease, discontinuation, or switch of a psychotropic medication (B) Rapid return of original symptoms at a greater intensity than before treatment and/or rapid appearance of new withdrawal symptoms which can be unspecific or specific for the psychotropic medication class (C) Symptoms in criteria B are characterized by a peak of onset within 24 h and 6 weeks after decrease, discontinuation, or switch of a psychotropic medication (depending on drug duration of action), and last more than 6 weeks (depending on drug elimination half-life) (D) Symptoms in criteria B cause clinically significant distress (E) Symptoms in criteria B are not due to a general medical condition and are not better accounted for by another mental disorder or substance use

after decrease, discontinuation, or switch of psychotropic medications based on the drug class (i.e., benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, antidepressants, ketamine, antipsychotics, lithium, mood stabilizers) and different molecules. The ultimate purpose is to organize the data in a clinically useful way.

Methods

Eligible articles included papers in English published in peer-review journals reporting data on adult subjects who decreased, discontinued, or switched psychotropic medications.

MEDLINE was comprehensively searched from inception to January 2020. In addition, a manual search of reference lists from all articles selected, for full-text re-

views, and relevant reviews were done. Search terms were "discontinuation/withdrawal," combined using the Boolean "AND" operator with "benzodiazepine/nonbenzodiazepine benzodiazepine receptor agonist/Z-drug/antidepressant/ketamine/esketamine/antipsychotic/neuroleptic/lithium/mood stabilizer."

Titles and abstracts were screened by 1 reviewer (F.C.). Articles appearing potentially relevant were retrieved and 2 reviewers (F.C. and G.C.) independently assessed each of the full reports, arriving at consensus regarding eligibility.

When information about the methods or results was omitted, the writers of the report were contacted to obtain the missing information. In case of the suspect of duplicate publications, the authors of the reports were contacted to receive further details.

Since new withdrawal symptoms have been described in the literature in several ways and using different words, a categorization used previously for antidepressant discontinuation symptoms [5, 6, 10] was adopted. It includes general symptoms; cardiovascular symptoms; gastrointestinal symptoms; genitourinary symptoms; sensory-related symptoms; neuro-muscular symptoms; sexual symptoms; central nervous system symptoms (which were articulated as: neurological, cognitive, affective, psychotic, behavioral, sleep-related symptoms).

Benzodiazepines and Nonbenzodiazepine Benzodiazepine Receptor Agonists

The first systematic review on withdrawal symptoms associated with benzodiazepine discontinuation was published in 1980 by the Committee on the Review of Medicines [29]. Interestingly, they concluded that the true addiction potential of benzodiazepines was low, since a dependence rate of 5–10 cases per million patient months was estimated [30]. Such cases of addiction were more frequent in drug misusers. Few reports described dependence during medically supervised treatment which occurred when high doses were used for extended periods [29].

As for nonbenzodiazepine benzodiazepine receptor agonists (i.e., eszopiclone, zaleplon, zolpidem, zopiclone), or Z-drugs, when they are discontinued, patients also report new withdrawal and rebound symptoms. Based on our review of what has been published in the literature, we found: (1) one report of eszopiclone cessation produced new withdrawal symptoms (i.e., abnormal dreams, nausea, upset stomach) and rebound anxiety [31]; (2) two reports of abrupt discontinuation of zolpidem were associated with rebound insomnia [32, 33]; (3) three reports of 2 cases of zolpidem withdrawal seizure were described [34, 35]; (4) zopiclone, the S-isomer of eszopiclone, was found to induce daytime inter-dose rebound anxiety [36]. There is no reason to believe that Z-drugs are any different than benzodiazepines. Short-acting and short elimination half-life Z-drugs with high potency are predicted to be similar to their benzodiazepine counterpart to produce withdrawal symptoms. Up to now, no data on persistent post-withdrawal disorders are published for Z-drugs. Apparently, little is still known on these recently marketed molecules, and no studies evaluated how to manage withdrawal syndromes after their decrease or discontinuation. Published data so far have been linked directly or indirectly with pharmaceutical companies.

New Withdrawal Symptoms after Benzodiazepine Discontinuation

Benzodiazepine discontinuation is known to produce minor as well as major new withdrawal symptoms. Table 4 reports most frequent minor new withdrawal symptoms [37–41], among them sweating, tachycardia, nausea, visual changes, tremor, confusion, restlessness. Major withdrawal symptoms, such as seizure [42, 43] and psychosis [43], are rare. Seizure usually occurs in predisposed subjects (i.e., history of brain damage, alcohol addiction, abnormal electroencephalograms) [44] or in those treated with drugs which lower the seizure threshold (i.e., TCAs, bupropion, antipsychotics) [45].

New withdrawal symptoms are generally mild, transient, and subside within 2–4 weeks [46, 47]. They appear more frequently [37, 44, 48] and are more severe [49] with high-potency benzodiazepines with short to medium elimination half-life. More new withdrawal symptoms were found upon discontinuation of lorazepam (high potency and short-acting) than with diazepam [38]. Elimination rates of benzodiazepines also predict the time of onset [15] of new withdrawal symptoms: after discontinuation of rapidly eliminated benzodiazepines (i.e., lorazepam, oxazepam) [50], new withdrawal symptoms occurred within 48 h; with slowly eliminated benzodiazepine (i.e., diazepam) new withdrawal symptoms occurred after 5 days with peak severity after 9.6 days. However, 75% of patients who withdrawn after long-term use of benzodiazepines developed new withdrawal symptoms regardless of rapidly eliminated or slowly eliminated compounds [51].

In the 12-year Luxemburg study (n = 214,170 subjects), all available hypnotics (including triazolam) and

Table 4. New withdrawal symptoms after decrease or discontinuation of psychotropic medications

System involved	Benzodiazepines	Nonbenzodiazepine benzodiazepine receptor agonists	SSRI/SNRI	Tricyclics, MAOIs, other antidepressants	Antipsychotics	Lithium	Mood stabilizers
General	Sweating		Sweating	Sweating	Sweating		Sweating
	Flu-like symptoms		Flu-like symptoms	Flu-like symptoms	Flu-like symptoms		Flu-like symptoms
	Headache		Headache	Headache	Headache		Headache
	Flushing		Flushing Chills	Chills	Chills		
	Fatigue		Fatigue	Fatigue			
	Weakness		Weakness				Weakness
	Pain		Pain				Pain
	Malaise		Malaise				
	Perceptual ataxia						
	Itching, skin rash						
			Tiredness				
			Lethargy				
			Infection				
					Hypothermia		
				Dizziness			Dizziness
				Lacrimation			
Cardiovascular	Tachycardia		Tachycardia	Tachycardia	Tachycardia		Tachycardia
	Dizziness		Dizziness		Dizziness		
	Lightheadedness, vertigo		Lightheadedness		Lightheadedness		
	Chest pain		Chest pain		Chest pain		
			Hypertension		Hypertension		Hypertension
	Postural hypotension		Postural hypotension				Hypotension
			Vertigo				
			Syncope		Pre-syncope		
			Dyspnea				
					Angina pectoris		
					Risk of myocardial infarction		
				Arrhythmia			
Gastrointestinal	Nausea	Nausea	Nausea	Nausea	Nausea		Nausea
	Vomiting		Vomiting	Vomiting	Vomiting		Vomiting
	Anorexia, weight loss		Anorexia, appetite problems	Low appetite	Anorexia		Anorexia
	Diarrhea		Diarrhea	Diarrhea	Diarrhea		
	Abdominal pain/cramp		Abdominal pain/cramp/ distention		Abdominal pain/cramp		
			Loose stools		Loose stools		
					Salivation		
			Esophagitis				
			Increased bowel movements				
	Constipation						
	Dry mouth						
	Gastrointestinal problems	Gastric problems		Gastrointestinal problems			Gastrointestinal problems

Table 4 (continued)

System involved	Benzodiazepines	Nonbenzodiazepine benzodiazepine receptor agonists	SSRI/SNRI	Tricyclics, MAOIs, other antidepressants	Antipsychotics	Lithium	Mood stabilizers
Genitourinary	Increased urinary frequency						
Sensory	Electric shock sensations		Electric shock sensations		Electric shock sensations		
	Tinnitus		Tinnitus				
	Blurred vision, visual changes		Blurred vision, visual changes				Photophobia
			Brain zaps	Zaps	Zaps		
	Hypersensitivity to touch/sound/smell		Hyperesthesia				
	Taste/smell disturbances, metallic taste in mouth		Altered taste				
	Perceptual distortions (e.g., sensation of the floor undulating)						
			Pruritus				
			Crowling/pricking sensations				
			Buzzing noise within the head				
Neuromuscular	Paresthesia		Paresthesia	Paresthesia	Paresthesia		
	Myoclonus		Myoclonus		Inducible clonus		
	Tremor		Tremor	Tremor	Tremor		Tremor
	Coordination problems		Coordination problems		Coordination problems		Coordination problems
	Numbness		Numbness				
	Stiffness		Stiffness		Stiffness		
	Myalgia		Myalgia		Myalgia		Myalgia
	Ataxia		Ataxia	Ataxia			Ataxia
	Muscular spasm		Muscular spasm				
	Fasciculation						
	Twitches cramps						Twitches cramps
			Neuralgias				
			Jerkiness				
			Arthralgias				
			Cramp				
			Hemiplegia				
					Myosis		
					Hyperreflexia		Hyperreflexia
				Dystonia			
Sexual			Premature ejaculation		Premature ejaculation		
			Genital hypersensitivity		Genital hypersensitivity		
Central nervous system							
Neurological	Seizures	Seizures	Seizures	Seizures	Tonic clonic seizures		
			Stroke-like symptoms				
					Coma		
				Akathisia	Akathisia		
				Parkinsonism	Parkinsonism		

Table 4 (continued)

System involved	Benzodiazepines	Nonbenzodiazepine benzodiazepine receptor agonists	SSRI/SNRI	Tricyclics, MAOIs, other antidepressants	Antipsychotics	Lithium	Mood stabilizers
Cognitive	Confusion		Confusion		Confusion		Confusion
	Amnesia		Amnesia		Amnesia		Ipomnesia
	Decreased concentration		Decreased concentration				Decreased concentration
			Disorientation		Disorientation		
	Lethargy		Lethargy, drowsiness		Lethargy		
			Attention difficulties		Attention difficulties		
	Indecision						
			Slurred speech				
Affective	Anxiety		Anxiety	Anxiety	Anxiety	Anxiety	Anxiety
	Agitation		Agitation	Agitation	Agitation		Agitation
	Depression		Depression	Depression	Depression		Depression
	Irritability		Irritability	Irritability	Irritability	Irritability	Irritability
	Panic		Panic	Panic			
	Derealization		Derealization				
	Depersonalization		Depersonalization	Depersonalization			Depersonalization
	Dysphoria		Dysphoria	Dysphoria	Dysphoria		Dysphoria
			Mood swings				
			Suicidal ideation				
			Hypomania, euphoria	Hypomania, mania			
							Anhedonia
			Fear				
	Nervousness		Nervousness				
			Tension				Tension
			Anger				
	Feeling of imminent death						
	Terror						
	Agoraphobia						
Psychotic	Hallucinations		Visual/auditory hallucinations	Hallucinations			Hallucinations
	Delirium		Delirium				
			Catatonia		Catatonia		
	Paranoia			Paranoia			Paranoia
	Distortion of body image						
	Psychosis						
				Delusions			
Behavioral	Restlessness		Restlessness	Restlessness	Restlessness		
	Aggressive behavior		Aggressive behavior		Aggressive behavior		
			Impulsivity				
			Bouts of crying/outbursts of anger				

Table 4 (continued)

System involved	Benzodiazepines	Nonbenzodiazepine benzodiazepine receptor agonists	SSRI/SNRI	Tricyclics, MAOIs, other antidepressants	Antipsychotics	Lithium	Mood stabilizers
Sleep	Insomnia		Insomnia	Insomnia	Insomnia		Insomnia
	Nightmares		Nightmares	Nightmares			
	Sleep problems		Sleep problems	Restless sleep		Sleep problems	
		Abnormal dreams	Vivid dreams	Vivid frightening dreams			
			Hypersomnia				

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor; MAOIs, monoamine oxidase inhibitors.

triazolo benzodiazepine, alprazolam, were found to be at higher risk of continuous and high-dose use. In contrast, anxiolytic benzodiazepines, in particular, clobazam and clonazepam, were found to be significantly less problematic having lower risk of high-dose use [52].

Rebound Symptoms after Benzodiazepine Discontinuation

Kales et al. [17] first reported rebound insomnia upon abrupt cessation of a nightly single dose of benzodiazepines after short-term use. This was confirmed by other studies [53–59]. Rebound anxiety was also observed [1, 38, 50]. It is an acute return of pretreatment anxiety above baseline following benzodiazepine withdrawal, even after short-term use. The symptoms are transient but may last 3 weeks after drug cessation [20].

The prevalence of rebound insomnia was found to be significantly lower in all benzodiazepines compared to triazolam [52, 60–69] and was lower than that with triazolam. Thus, similarly to rebound anxiety, the risk seems related to benzodiazepine elimination half-life and potency [20, 23] and independent form the length of treatment [1].

Short and intermediate elimination half-life benzodiazepines are at a greater risk of rebound anxiety compared to long elimination half-life agents [20, 44, 70]. In a placebo-controlled double-blind study [1], abrupt withdrawal resulted in 7 cases of rebound anxiety: 5 of 7 (71.4%) treated with bromazepam and 2 of 7 (28.6%) treated with diazepam, bromazepam is a high potency benzodiazepine with intermediate elimination half-life, whereas diazepam is a medium potency benzodiazepine with long elimination half-life [14]. Rebound anxiety can also occur during ongoing treatment with rapidly eliminated benzodiazepines when their pharmacological effects decrease. For example, increased daytime anxiety following a bedtime dose of triazolam [71], daytime interdose rebound anxiety in triazolam- and zopiclone-treated patients for insomnia in generalized anxiety disorder [36], clock-watching rebound anxiety 3–4 h after the last dose in lorazepam- and alprazolam-treated panic disorder patients [72].

Clonazepam [73–76] has a long elimination half-life, induced less frequently rebound anxiety than alprazolam [77].

Persistent Post-Withdrawal Disorders after Benzodiazepine Discontinuation

The literature on persistent post-withdrawal disorders after long-term benzodiazepine use and discontinuation is hardly existent. Notwithstanding this, anxiety, depression, psychosis, cognitive impairment, insomnia, sensory phenomena (i.e., tinnitus, tingling, numbness, paresthesia, deep or burning pain in limbs, feeling of inner trembling or vibration, strange skin sensations), motor phenomena (i.e., muscle pain, weakness, painful cramps, tremor, jerks, spasms, shaking attacks), and gastrointestinal disturbances (patients complain of food intolerance and gaseous abdominal distension) have been described [41]. Length of treatment and high potency with short to intermediate elimination half-life seem important to favor the occurrence of persistent post-withdrawal disorders [41]. It has been observed that withdrawal symptoms after discontinuation of low-dose benzodiazepine may take 6–12 months to subside completely [47] and in some cases they persist for years [41].

Associated Clinical Manifestations

We found no evidence in the literature for clinical symptoms or disorders associated to withdrawal due to benzodiazepine decrease or discontinuation.

Management of Benzodiazepine Discontinuation

Slow tapering, often extending over a year or more, has been suggested to manage new withdrawal symptoms [78]. However, even a more flexible tapering at a rate that the patient can tolerate, typically in about 3–6 months, has shown to be appropriate [37]. Some authors suggested tapering from other BZDs such as lorazepam after substituting diazepam [79], according to Murphy and Tyrer [80] such substitution has shown little evidence to support its efficacy.

The adjunct of cognitive behavioral therapy to a careful tapering schedule was found of limited value by Voshaar et al. [81], although 2 trials showed that cognitive behavioral therapy facilitated tapering among chronic benzodiazepine users [82, 83]. In addition, it has been suggested that gradual discontinuation can reduce both rebound insomnia [84, 85] and rebound anxiety [1]. In contrast, in a randomized controlled trial evaluating the relative efficacy of 3 interventions for benzodiazepine discontinuation among panic disorder patients (i.e., taper alone, taper plus relaxation, and taper plus exposure-based cognitive-behavioral therapy), the rate of successful discontinuation of benzodiazepine treatment was significantly higher for those receiving the cognitive-behavioral program (13 of 17; 76%) than for those receiving the slow taper program alone (4 of 16; 25%); the results were confirmed at a 3-month follow-up [86]. These findings suggest that cognitive behavioral therapy may help benzodiazepine discontinuation. They were confirmed by Fava et al. [87] who observed an improvement in anxiety and anxiety sensitivity after stopping long-term benzodiazepines in patients who had recovered from panic disorder and agoraphobia after a successful behavioral treatment. However, when Otto et al. [86] attempted to replicate their own results published in 1993, the effect size was used instead of *p* values, since significance levels did not allow to identify differences between groups, only the number of years of benzodiazepine use emerged as a significant predictor of benzodiazepine discontinuation in the regression models, only in the context of this single covariate the cognitive-behavioral therapy demonstrated significantly better outcome for benzodiazepine-free status than both relaxation and taper alone at 6-month follow-up [88].

On the other hand, we did not find studies which investigate strategies to manage benzodiazepine persistent post-withdrawal disorders.

Antidepressants

The literature indicates that antidepressant withdrawal reactions are frequent, with incidence rates ranging from 27 to 86% (weighted average of 56%) [7]. Even though discontinuation symptoms were mostly reported after abrupt discontinuation, they were found to occur after gradual tapering [5, 6] and differ in prevalence according to the pharmacological profile of the antidepressant [89].

New withdrawal symptoms from TCAs were first reported with imipramine in 1959, described in 1961 [90], and later confirmed [91]. In 1980 and 1990s, Dilsaver documented general somatic and gastrointestinal distress; sleep disturbances characterized by initial and middle insomnia or excessively vivid and frightening dreams; akathisia or parkinsonism; hypomania or mania as manifestations of new withdrawal symptoms due to TCA discontinuation [92–95]. Cardiac arrhythmia rebound after discontinuation of imipramine was described [96] and persistent insomnia following discontinuation or decrease of amitriptyline documented [13, 14].

Following abrupt discontinuation of MAOIs, severe rebound panic was described [73] and subsequent studies reported that new withdrawal symptoms may occur [97]. Overall, TCAs and MAOIs aroused little interest [97], since withdrawal was seen in those days as part of a drug treatment necessary for the patient illness and a progress compared to previous treatments.

Case reports of new withdrawal symptoms (i.e., hypomania, anxiety, restless sleep, nightmares, depersonalization, formication, headache) after discontinuation of trazodone were published [98–101].

Among noradrenergic and specific serotonergic antidepressants (i.e., mirtazapine, mianserin, setiptiline), clinical case reports described new withdrawal symptoms (i.e., panic, anxiety, restlessness, irritability, hypomania, insomnia, dizziness, paresthesia, nausea, vomiting) and rebound mania after decrease or discontinuation of mirtazapine [102]. One case of seizure [103] and one case of panic attacks [104] were described after the abrupt discontinuation of mianserin, while no data were reported for setiptiline.

One study found acute dystonia as new withdrawal symptom resulting from abrupt discontinuation of bupropion [105].

The literature on the withdrawal of the more recently introduced antidepressants other than SSRI/SNRI is limited. The discontinuation of agomelatine was investigated in a 24-week randomized double-blind placebo-con-

trolled study, after a brief 8- to 10-week open treatment [106]. The authors looked at adverse events "suggestive of withdrawal symptoms" within the first month after randomization in placebo-treated patients withdrawn from agomelatine. They found 3 emergent potentially withdrawal symptoms (i.e., depression, irritability, palpitations). However, they did not study withdrawal at the end of the 24-week randomized placebo-controlled study. In Stein et al. [107] and in Montgomery et al. [108], discontinuation symptoms in patients switched to placebo were similar to those of patients maintained on agomelatine.

No case reports after vilazodone or vortioxetine decrease or discontinuation are available. However, we should keep in mind that new antidepressants have a mechanism of action similar to that of first- and second-generation antidepressants. The difference is that they have new, or different, receptor targets, but the approach of looking for antidepressants which inhibit neurotransmitters reuptake is repeated [109]. Thus, future reviews of the literature might report more evidence on withdrawal syndromes after decrease or discontinuation of new antidepressants; this is likely because of their relatively recent release: the delay between the placing on the market of a drug and the publication of the first reports on adverse events is widely known for every new molecule.

SSRIs are the leading cause of withdrawal, followed by SNRIs [7]. The first systematic review of SSRIs withdrawal reactions was published in 2015 [5] and a few years later, Fava et al. [6] published the first systematic review on SNRIs.

New Withdrawal Symptoms after SSRIs/SNRIs Discontinuation

New withdrawal symptoms following decrease or discontinuation of SSRIs have been widely documented and include a wide range of symptoms [5] which are listed in detail in Table 4.

Peaks of onset occur 36 h to 10 days after dose decrease or discontinuation, they are usually reversible and last from a few hours to 6 weeks [5, 16, 97]. Their frequency and duration depend on the drug discontinued [5, 16, 97]. A bulk of literature, derived from controlled trials [18, 110, 111], case reports [19], and patients' online reports [112], showed that new withdrawal symptoms may occur with any type of SSRI, but paroxetine is the most likely to be associated with new symptoms, while fluoxetine being the least associated. Severity varies according to the SSRI, paroxetine being the most likely to be associated with severe depressive and somatic symptoms, and fluoxetine being the least likely to be associated with severe depressive and somatic symptoms [5, 111].

A systematic review of the literature [6] indicated that new withdrawal symptoms may occur also after discontinuation of SNRIs (i.e., venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran). Once again, new withdrawal symptoms include a wide range of clinical manifestations which are described in detail in Table 4. They occur irrespective of whether gradual or abrupt discontinuation is implemented and are similar to those observed after discontinuation of SSRIs [5]. They typically appear within a few days from drug discontinuation and last a few weeks. The prevalence of new withdrawal symptoms vary among the different drugs but was highest after the discontinuation of venlafaxine (rates of withdrawal from controlled trials and open trials rage from 23 to 78%) and lowest after the discontinuation of levomilnacipran (rates of withdrawal from controlled trials and open trials rage from 9 to 10%) [6].

Rebound Symptoms after SSRIs/SNRIs Discontinuation

Controlled discontinuation studies [111, 113, 114] showed that rebound may occur following SSRI discontinuation. Rebound depression has been observed at a greater frequency with paroxetine or short-acting SSRIs [10, 13]. In 2 double-blind placebo studies, patients with major depression had their maintenance medications (paroxetine, sertraline or fluoxetine) discontinued after 4–24 months and replaced with placebo and then reinstituted [111, 113]. In one of the studies [111], patients taking paroxetine or sertraline had a sudden worsening of depressive symptoms upon drug discontinuation with a return to pre-placebo measurements following re-institution of the drug. In both studies [111, 113], patients treated with paroxetine had acute return of pre-treatment symptoms [10, 111, 113], while patients taking fluoxetine did not.

Few studies also reported on rebound anxiety after venlafaxine discontinuation [115, 116].

Persistent Post-Withdrawal Disorders after SSRIs/SNRIs Discontinuation

After SSRIs long-term use, persistent post-withdrawal disorders have been described [10, 13, 18, 19, 112, 117, 118]. Following discontinuation of a long-term treatment with paroxetine, Shoenberger [117] first reported the emergence of persistent post-withdrawal panic disorder, which was some years later also documented by Bhanji et al. [18]. Fava et al. [19] conducted a study of gradual SSRI

discontinuation in panic disorder and found that 3 out of the 9 patients treated with paroxetine had persistent post-withdrawal disorders after 1-year post-withdrawal. Belaise et al. [112] analyzed online reports from individuals who described persistent post-withdrawal disorders after SSRI discontinuation; the most frequent disorders were: disturbed mood, depression, emotional liability, mood swings, irritability, anxiety, insomnia, impaired concentration, impaired memory. In another study, following paroxetine cessation, Belaise et al. [118] reported the emergence of persistent post-withdrawal disorders such as pathological gambling and generalized anxiety. Stockmann et al. [119] analyzed the content of a sample of posts on an antidepressant withdrawal website and found that patients assessing antidepressant withdrawal websites report experienced persistent post-withdrawal disorders more frequently with SSRIs than SNRIs, with neurological symptoms more common among SNRI users and psychosexual/genitourinary symptoms more common among SSRI users. Finally, Chouinard and Chouinard [10] illustrated 3 cases of persistent post-withdrawal disorders: one had generalized anxiety disorder, one cyclothymic disorder, and one had major depressive episode with melancholic features. Overall, based on the literature here described, which is still limited, paroxetine seems at higher risk to induce persistent post-withdrawal disorders than other SSRIs.

Episodes of long duration of withdrawal symptoms (i.e., depression, anxiety, mania, tinnitus, nausea, unexplained fear, and dizziness) were described after SNRIs discontinuation, suggesting the occurrence of persistent post-withdrawal disorders [120–123]. To be noted that 3 out of the 4 studies reporting SNRI persistent post-withdrawal disorders were on venlafaxine [120–122] and 1 was on duloxetine [123].

Finally, since 2006, persistent sexual side effects after SSRIs and SNRIs discontinuation have been described [124]. These sexual manifestations have been rapidly identified as a syndrome called post-SSRI sexual dysfunction (PSSD) [125], that is a sexual dysfunction, caused by both SSRIs and SNRIs, characterized by a decrease or absence of libido, genital anesthesia, numbness in nipples, orgasmic disorders (i.e., anorgasmia or anhedonic orgasm), erectile dysfunction, delayed or premature ejaculation, testicular pain or atrophy (in males), lack of lubrication (in females) and by psychological symptoms such as anhedonia, difficulty in concentrating, memory problems, inability to experience sexual attraction to the sight, touch, or idea of a sexual partner [125–127]. The symptoms may last months or even years [127, 128]. Recently, it has been described the case of a patient in which PSSD symptoms were part of a broader syndrome which was diagnosed as persistent post-withdrawal disorder [129]. This case rises the suspicion that PSSD might be a withdrawal syndrome occurring after decrease/discontinuation of SSRIs or SNRIs and that withdrawal symptoms might include a wider variety of sexual manifestations which are under-reported, probably due to a poor attention of clinicians toward sexual symptoms and a lack of investigations by clinicians as well as researchers [129].

Associated Clinical Manifestations

Withdrawal syndromes after decrease or discontinuation of antidepressants may be associated with additional clinical manifestations. They include modifications of the illness course, such as switching to mania or other forms of excessive behavioral activations [24], but also loss of clinical effects and refractoriness to treatment; they have been reported with SSRI and SNRI [5, 6, 27]. When mania or other forms of excessive behavioral activations occur, it may be self-limiting or may require specific anti-manic treatment [130]. Loss of clinical effects involves the return of symptoms during maintenance treatment that only temporarily respond to dose increase [25]. Refractoriness to treatment is the lack of response to a previously effective pharmacological treatment when it is started again after a drug-free period [25], as was reported in the case illustrated by Jha et al. [89].

Management of SSRIs/SNRIs Discontinuation

An initially hypothesized strategy to manage antidepressant withdrawal was restarting the antidepressant [97]; of course this meant for the patients never being able to decrease or discontinue the drug which was responsible for the withdrawal manifestation. Thereafter, it was proposed to switch to a longer half-life SSRI (i.e., fluoxetine) [111], since it is less likely to induce withdrawal problems; however, this switch may favor subsequent episodes of illness deterioration [27]. Another suggested option was slow tapering; however, it was shown that withdrawal symptoms and syndromes may occur during and despite slow tapering [5, 6]. A hyperbolically decreasing pattern of SSRI dose decrease has been recently proposed to produce a linear reduction of pharmacological effect [131], but its validity needs to be tested in randomized controlled trials. A multistep dose reduction paradigm was suggested by Ruhe et al. [132]. In this paradigm, the initial step is to reduce the dose to half of the minimally effective dose in 1 week and then reduce very gradually. However, even this approach has not been tested yet.

Regarding non-pharmacological interventions, when a group cognitive-behavioral therapy aimed at relapse prevention was proposed to patients who were tapering antidepressants within 4 months according to a fixed schedule, only 37% (n = 26) of the subjects succeeded in discontinuing the drug and only 28% (n = 20) succeeded in discontinuing without recurrence. This finding suggests that cognitive behavioral therapy does not help with antidepressants withdrawal. However, the results might be partly due to the timing of administration of the cognitive-behavioral therapy, which was simultaneous with the discontinuation period, although it is known that the right timing of cognitive-behavioral therapy is crucial [118], as well as to the vulnerability of the sample under study, the majority had unsuccessfully tried to discontinue before [133].

Fava and Belaise [27] proposed pharmacological (i.e., lessen withdrawal symptomatology by the use of psychotropic drugs that are not antidepressants, for instance clonazepam) and non-pharmacological (i.e., a 3-module intervention which includes explanatory therapy, cognitive behavioral treatment, and well-being therapy) strategies to manage SSRI withdrawal which are, however, based on their extensive clinical experience and in need of being tested in randomized clinical trials.

Ketamine and Esketamine

Esketamine, the enantiomer of ketamine and an NMDA receptor antagonist, has been marketed as nasal spray approved by the Food and Drug Administration (FDA) in 2019 for intranasal treatment of treatment-resistant depression in conjunction with an oral antidepressant [134, 135].

Ketamine (intravenous anesthetic) and esketamine (nasal spray) potentially produce psychological dependence and rapidly induce pharmacological tolerance [136–139]. Ketamine is used for recreational purposes because it produces mental and behavioral changes, such as euphoria, perceptual changes, dissociation, and hallucinations [140]. These effects, together with a risk of abuse and misuse, made ketamine a popular street drug, also known as "Special K" [141]. In addition, a prolonged exposure to ketamine may predispose to neurotoxicity [142].

Studies showing that esketamine has less risks of abuse than ketamine are lacking. Before approval, the FDA committee wrote in its documentation that "data on safety of ketamine may be considered relevant to discussions regarding the safety of esketamine […]. The risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and post marketing surveillance for esketamine" [143]. Additionally, the FDA reported that the safety concerns for esketamine are misuse, abuse, dissociation, and sedation, for which a Risk Evaluation and Mitigation Strategy was planned [143, 144].

New acute withdrawal symptoms after ketamine discontinuation have been described. They are craving, dysphoria, shaking, sweating, palpitations, tiredness, low appetite, low mood, chills, autonomic arousal, lacrimation, restlessness, anxiety, nightmares, paranoia, delusions, and hallucinations [145–147]. Addiction websites (i.e., American Addiction Centers and Addiction Center) also mentioned agitation, confusion, loss of motor skills, rage, nausea, decreased respiratory and cardiac functions, insomnia, cognitive impairment, tremors [3]. New withdrawal symptoms typically begin within 24 h of discontinuation and last approximately 3 days, although in some cases, they may persist for 2 weeks and thereafter stabilize [3].

In view of the inevitable decay of the response to ketamine due to pharmacological tolerance [148] and its possible benefit as maintenance therapy in treatment-resistant depression [142], and considering that some clinicians use ketamine formulations for chronic use despite the alarm regarding "the rapid proliferation of off-label ketamine administration in the absence of evidence of lasting therapeutic benefit or safety with long-term administration" [p. 686 in 142], the use of ketamine in psychiatry is at risk of replicating the 2016 opioid US epidemic abuse [149] with the risk to induce neurotoxicity, which might be associated with persistent post-withdrawal disorders.

Antipsychotics

Chouinard et al. [9] described withdrawal reactions due to antipsychotics dose decrease, discontinuation, or switch and concluded that acute withdrawal symptoms, rebound, and persistent post-withdrawal disorders may occur and that 2 persistent post-withdrawal disorders, tardive dyskinesia and supersensitivity psychosis, were specifically induced by antipsychotics [21, 22, 150, 151]. Studies on withdrawal reactions associated with antipsychotics switch were extensively reviewed also by Cerovecki et al. [8] and similar conclusions were reached.

In the era of first-generation antipsychotics (FGAs) both supersensitivity psychosis and tardive dyskinesia were widely studied [9]. Second-generation antipsychotics (SGAs) decreased the prevalence of drug-induced movement disorders, including tardive dyskinesia [13], but concerns [13] have remained about supersensitivity psychosis [9]. Since both FGAs and SGAs have shown to trigger withdrawal at decrease, switch, or discontinuation, we will here describe the literature on antipsychotics withdrawal using Chouinard and Chouinard [10] diagnostic criteria and highlighting the different impact, when present and available, of FGAs and SGAs.

New Withdrawal Symptoms after Antipsychotic Discontinuation

New withdrawal symptoms following dose decrease, discontinuation, or switch may occur with any type of antipsychotic and include a wide range of symptoms [8, 9] which are reported in Table 4.

Chouinard et al. [9] described them as serotonin withdrawal syndrome (i.e., flu-like symptoms, sweating, chills; dizziness, light-headedness, tachycardia; diarrhea, loose stools, abdominal pain; restlessness, myalgia, rigidity, hyperreflexia, inducible clonus; paresthesia, electric shock sensations, zaps; confusion, disorientation, amnesia, coma; premature ejaculation, genital hypersensitivity), as muscarinic cholinergic withdrawal syndrome (i.e., agitation, insomnia, anxiety, depression; dizziness, light-headedness, tachycardia; nausea, vomiting, salivation, diarrhea, loose stools, abdominal cramp; tremor, parkinsonism, restlessness, myalgia, rigidity, myosis; paresthesia; confusion, disorientation; hypothermia, sweating, diaphoresis), as adrenergic withdrawal syndrome (i.e., headache, anxiety, agitation; increased blood pressure, increased heart rate, risk of myocardial infarction, angina pectoris, palpitations, chest pain; pre-syncope, tremulousness; sweating), and as histaminic withdrawal syndrome (i.e., irritability, depressed affect, insomnia, agitation; loss of appetite, nausea; tremulousness, incoordination, increased inducible seizure; lethargy, amnesia) [9].

Peaks of onset occur 36–96 h after decrease, discontinuation, or switch from and to SGAs, the symptoms are usually reversible and last from a few hours to 6 weeks [9].

Cerovecki et al. [8] summarized the studies reporting new withdrawal and rebound symptoms associated with switching from first- (mainly chlorpromazine, haloperidol, fluphenazine, amisulpride, sulpiride, zuclopenthixol) or SGAs (i.e., aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) to SGAs (i.e., aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone). They evaluated 61 studies and 7 case reports. Among the 61 studies, 32 (52%) did not report withdrawal or rebound symptoms, while 14 reported new withdrawal symptoms. Among the case reports, 5 did not report new withdrawal or rebound symptoms. In 1 case, the switching from clozapine triggered new withdrawal symptoms.

Overall, SGAs are associated as frequently with new withdrawal symptoms as FGAs, when we take into consideration the early 1960–1970 studies of FGAs.

Rebound Symptoms after Antipsychotic Discontinuation

Rebound symptoms have been described during discontinuation and switch [9]. Rebound psychosis is a rapid return above pretreatment levels of original symptoms (i.e., illusion, hallucination, catatonia, passivity experience, delusion) [152, 153]. It is generally short lasting (i.e., <6 weeks after peak onset) [13] and is considered a reversible form of supersensitivity psychosis, equivalent to reversible withdrawal tardive dyskinesia [13].

In their review, Cerovecki et al. [8] reported even rebound symptoms associated with switching from first- or SGAs to SGAs. Among the 61 studies evaluated, 22 (36%) reported rebound symptoms. Among the 7 case reports, no case reports documented rebound symptoms. Rebound psychosis appears as frequently with SGAs than with FGAs.

Among, SGAs, the phenomenon was first recognized to occur with clozapine [9, 13, 154–156] and quetiapine monotherapy [157], later with other SGAs [158–160], overt frequency depending of their elimination half-life and potency. Antipsychotics rapidly eliminated or rapidly dissociated from the D2 receptors (i.e., clozapine, quetiapine) [161, 162] are known to have greater risks of rebound when medication is decreased, switched, or discontinued [13, 154, 156, 157, 163].

Patients on clozapine monotherapy taken as a single dose at bedtime report late afternoon return of symptoms [13]. For quetiapine, it is common clinical practice to have difficulty to decrease the drug, having first rebound anxiety and rebound insomnia, and later an in-between dose clock watching for return of symptoms (i.e., patient watches the clock to make sure the next dose is not missed for fear that symptoms might return) [9, 10, 13, 163].

Persistent Post-Withdrawal Disorders after Antipsychotic Discontinuation

Persistent post-withdrawal disorders, that is a condition in which rebound symptoms and/or new withdraw-

al symptoms and/or emerging new psychotic symptoms of another type, such as disorganized behavior, persist longer than 6 weeks, have been described after discontinuation of antipsychotics. In addition to the several clinical manifestations of persistent post-withdrawal disorders which have been observed also for other psychotropic medication classes, 2 specific persistent post-withdrawal disorders, named persistent post-withdrawal tardive dyskinesia and persistent post-withdrawal supersensitivity psychosis, have been well described [21, 22, 150, 151]. Thus, when dyskinesia or psychosis last <6 weeks after discontinuation, they are considered new withdrawal dyskinesia/psychosis or rebound psychosis, and when they last longer than 6 weeks, they become persistent post-withdrawal disorders [9, 13].

Persistent post-withdrawal tardive diskinesia is characterized by a hyperkinetic, involuntary, and purposeless movement disorder [10] occurring after decrease, discontinuation, or switch of antipsychotics. It has been documented to occur after short-term use (1-month) of chlorpromazine in a patient with schizophrenia [164], and in a non-psychiatric patient after a 4-month treatment with a gastric preparation containing trifluoperazine and an anticholinergic drug. In the latter case, 7 weeks after the termination of the treatment, continuous movements of the patient's face, lips, and tongue appeared; they were irreversible and extremely severe [165].

Persistent post-withdrawal supersensitivity psychosis is characterized by rebound and/or new withdrawal psychosis occurring after decrease, discontinuation, or switch of antipsychotics which is associated with rapid appearance or reappearance of positive symptoms (i.e., illusion, hallucination, catatonia, Schneider passivity experience, delusion) and with the emergence of one definite drug-induced movement disorder, including tardive dyskinesia or prior movement disorder. Drug tolerance is present since positive symptoms cannot be controlled by an increase or by the re-introduction of the antipsychotic. The peak onset is within 24 h to 6 weeks after decrease, discontinuation, or switch for oral medications; for long-acting injectable antipsychotics, the peak onset occurs 1–7 days before receiving the next injection or end of injection dosing interval determined by terminal plasma half-life [166]. Positive symptoms last >6 weeks after peak onset [22]. Kimura et al. [158] studied long-acting injectable risperidone as adjunctive therapy to treatment-resistant schizophrenia in a 1-year multicenter prospective follow-up study, the mean dose was equivalent to 1,000 mg/day chlorpromazine. They found a prevalence of SP of 65%. At baseline, schizophrenia patients with SP had higher total scores for drug-induced movement disorders on the Extrapyramidal Symptom Rating Scale and higher scores on the negative symptoms sub-scale of the Brief Psychiatric Rating Scale. The SP group showed significantly greater improvement on the Brief Psychiatric Rating Scale total score than non-SP group. Kimura et al. [167] did a second-year follow-up, similar results were found. Patients with SP showed greater improvement on positive and negative symptoms and significantly less relapses during the first- and second-year follow-up, compared to treatment-resistant patients without SP. Takase et al. [159] retrospectively examined the clinical characteristics of schizophrenic patients with supersensitivity psychosis who had their antipsychotic treatment gradually switched to aripiprazole. They found a prevalence rate of supersensitivity psychosis of 26.5%, that significantly more patients with supersensitivity psychosis had worsening of their positive symptoms compared to non-supersensitivity psychosis patients, and that significantly less patients with supersensitivity psychosis were able to continue aripiprazole compared to non-supersensitivity psychosis patients. Suzuki et al. [160] examined supersensitivity psychosis in treatment-resistant schizophrenic patients and found a prevalence of 72% for at least one supersensitivity psychosis episode among those treated with SGAs (i.e., olanzapine, paliperidone, perospirone, quetiapine, and risperidone).

The Kimura et al. [167] and the Suzuki et al. [160] studies highlight the clinical characteristics of supersensitivity psychosis patients in the era of SGAs: high prevalence of drug-resistance, increased risk for drug-induced movement disorders, use of high chlorpromazine-equivalent doses, and a better clinical response in patients with supersensitivity psychosis compared to patients without supersensitivity psychosis.

Drugs such as fluphenazine, perphenazine, quetiapine, and clozapine permitted the identification of persistent post-withdrawal disorders [10, 13, 18, 19, 156, 157]. The manifestation and persistence of the supersensitivity psychosis depend on the specific antipsychotics used (i.e., fluphenazine, perphenazine, clozapine, quetiapine) [10, 13], the duration of D2-receptor blockade [168], and the continuous use.

Associated Clinical Manifestations

Persistent post-withdrawal tardive diskinesia and persistent post-withdrawal supersensitivity psychosis may be associated with additional clinical manifestations. They include loss of clinical effects, modifications of the illness course, and refractoriness to treatment [169, 170].

Loss of clinical effects implies the occurrence of relapse in treatment adherent schizophrenic patients who did not discontinue or decrease or switch the drug [169, 170]. Relapse is also characterized by modifications of the illness course: positive psychotic symptoms are more severe [169], the duration of the episode is longer [169], and more residual negative symptoms occur [170]. Refractoriness to treatment is another possible manifestation since relapse occurs when the patients are treated with higher doses of antipsychotics [169].

Management of Antipsychotic Discontinuation

A gradual decrease over a long period of time, over several months when clinically appropriate, was suggested to reduce the severity of new withdrawal and rebound symptoms [1], however this strategy does not reduce the risk of occurrence of new withdrawal and rebound symptoms and has not shown effects on persistent post-withdrawal disorders [9]. The use of adjunctive long half-life drugs, such as long-acting injectable SGAs, and antiseizure drugs has been proposed for the treatment of withdrawal syndromes [9]. Lamotrigine and antiseizure drugs (in particular valproic acid, carbamazepine, phenytoin) have been suggested as useful for supersensitivity psychosis [171], while clozapine and risperidone were considered palliative treatment [158–160]. Limited data are presently available for other potential pharmacological intervention of supersensitivity psychosis (e.g., clozapine, asenapine, blonanserin) [9].

Given the evidence for the risk of rebound withdrawal with quetiapine, doses ≤150 mg/day of quetiapine as adjunctive therapy instead of monotherapy was recommended [157, 172]. When giving quetiapine as adjunctive or monotherapy for 2 months and more, attempts to decrease the dose with alternate dosing interval or with gradual decrease of quetiapine daily dose were recommended [9].

Lithium

The evidence for withdrawal after lithium decrease or discontinuation is weak and ambiguous. Early manic and depressive recurrences after lithium discontinuation may suggest rebound symptoms, but studies carried out with appropriate methodology failed to confirm it [173]. Anxiety, sleep problems, and irritability following lithium discontinuation were suggested as new withdrawal symptoms in one review [174] and in one study [175]. No data on persistent post-withdrawal disorders are available.

Other Mood Stabilizers

Food and Drug Administration approved anticonvulsants for the treatment of bipolar disorder in adults; they are carbamazepine, valproate, lamotrigine [176].

The literature on withdrawal after decrease or discontinuation of carbamazepine in psychiatric patients is limited. However, a preliminary study on carbamazepine-associated withdrawal reaction after microvascular decompression to treat trigeminal neuralgia showed the occurrence of new withdrawal symptoms (i.e., insomnia, dysphoria, hand fremitus, hallucination, severe headache), which were found dependent on the pre-operative dosage of carbamazepine and the changing rate of pre- and post-operative drug blood concentrations [177]. In addition, in patients with active epilepsy, the following new withdrawal symptoms were observed at decrease of carbamazepine (which was part of a programmed rationalization of therapy for each patient): anxiety, tension, agitation, irritability, lack of energy, impaired memory/concentration, depression, depersonalization, insomnia, anorexia, headache, muscle aches, twitching, tremor, shaking, dizziness, incoordination, paranoia, hyper-reflexia, gait ataxia, hypotension, tachycardia, faintness [178].

Also, the literature on withdrawal due to decrease or discontinuation of valproate or lamotrigine in psychiatric patients seems limited although some studies on epileptic patients are available. Duncan et al. [178] found the following new withdrawal symptoms at decrease of sodium valproate in patients with active epilepsy: anxiety, agitation, irritability, lack of energy, impaired memory/concentration, depression, depersonalization, insomnia, anorexia, tension, headache, muscle ache, twitching, nausea/vomiting, tremor, shaking, hyperreflexia, sweating, dizziness, photophobia, incoordination, faintness, tachycardia. However, in Duncan et al. [178] study, which was also mentioned for carbamazepine, new withdrawal symptoms occurred also in those who remained on stable therapy (the entire study was double-blind, with matching placebos replacing active drug in a stepwise fashion). Gelisse et al. [179] observed a case who presented anhedonia, tremor, slight tachycardia, and severe hands hyperhidrosis, which were considered new withdrawal reactions to lamotrigine discontinuation. In addition, 6 epileptic patients on stable-dose lamotrigine monotherapy presented end-of-dose new withdrawal symptoms (i.e., anxiety, emotional lability, irritability) [180].

No data are available on rebound symptoms and persistent post-withdrawal disorders.

Table 5. Withdrawal at decrease, discontinuation, or switch of psychotropic medications

Type of withdrawal according to Chouinard and Chouinard [10] (2015) diagnostic criteria	Drug classes	Molecules
New withdrawal symptoms	MAOIs	
	TCAs	
	Trazodone	
	Noradrenergic and specific serotonergic antidepressants	Mirtazapine
	Bupropion	
	Lithium	
	Food and Drug Administration-approved mood stabilizers for the treatment of bipolar disorder in adults	
New withdrawal symptoms rebound symptoms	Benzodiazepines	Alprazolam, triazolam
	Z-drugs	Eszopiclone
New withdrawal symptoms rebound symptoms persistent postwithdrawal disorders	SSRIs, SNRIs	Paroxetine, venlafaxine
	First-generation antipsychotics, second-generation antipsychotics	Quetiapine, clozapine
New withdrawal symptoms	Ketamine	Ketamine

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin noradrenaline reuptake inhibitors; MAOIs, monoamine oxidase inhibitors.

Considering that the phenomenon of withdrawal after discontinuation of anticonvulsants seems documented in the neurologic literature only, attention on this topic should be turned on by psychiatrists who use anticonvulsants as mood stabilizers.

Discussion

Psychotropic Medications in the Debate on Substance Use Disorders

Like all other pharmacological agents used in medicine, psychotropic medications discontinuation can induce withdrawal syndromes but not all psychotropic medications are the same between classes and within a class [13, 181]. A summary of the types of withdrawal at decrease, discontinuation, or switch of psychotropic medications is proposed in Table 5. Ketamine has a capacity to induce drug use disorders including psychological problems and tolerance. In addition, SSRIs, SNRIs, antipsychotics were consistently associated with persistent post-withdrawal disorders and increased severity of illness symptoms, including alterations of clinical course. Regarding specific molecules, alprazolam, lorazepam, triazolam, paroxetine, venlafaxine, clozapine, and quetiapine are more likely to induce withdrawal than other compounds of the same class.

Table 5 content should be evaluated under the light of the timing of release on the market of the different classes of drugs. Additional research reports may come for Z-drugs, the more recent zaleplon was approved only in 1999. The literature on SNRIs may increase since they were released 13 years later SSRIs. Additional evidence is also expected for new antidepressants. Interestingly, although esketamine was approved only on March 05, 2019 by the FDA as medication for treatment-resistant depression, the literature on ketamine already shows new withdrawal symptoms and neurotoxicity, which may indicate future evidence of persistent post-withdrawal disorders. Finally, knowledge on FDA-approved mood stabilizers for the treatment of bipolar disorder in adults is limited to the neurologic field.

In this framework, it seems important to clarify whether the clinical phenomenon of withdrawal can equate psy-

chotropic medications (especially SSRIs, SNRIs, and antipsychotics) to substances.

It has been suggested that the presence of withdrawal symptoms is not enough to establish a diagnosis of substance-induced disorder. Moreover, the DSM-5 [182] suggested that the criterion of withdrawal is not considered to be met for individuals taking psychotropic medications under medical supervision [183]. One direct implication is that clinicians have been forced to use antidepressants, or even antipsychotics, in anxiety disorders because benzodiazepines were claimed to be addictive; and mental health professionals receive poor academic teaching and training regarding these agents [184]. For instance, Batelaan et al. [185] recommendation for chronic antidepressant treatment of anxiety disorders, instead of benzodiazepines, seems to be misleading based on the results of the present overview of the literature and on the observation that benzodiazepines are at least as effective as antidepressants for treatment of anxiety disorders [186]. The International Task Force on Benzodiazepines suggested that benzodiazepines have not been adequately compared to other psychotropic medications in various indications, and their risks and side effects have been overemphasized [187].

The debate on abuse, dependence, and addiction of psychotropic medications seems endless and apparently unresolved. What is needed is a better understanding of withdrawal syndromes and pharmacological dependence, which is already evident for instance for ketamine, and engage in evidence-based, open-minded discussions about these important classes of medication.

Psychotropic Medications in the Debate on Tolerance

In 1968–1969, DiMascio et al. [188–190] described the pharmacological 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 well-being. Examples of such tolerance phenomena are switching from unipolar to bipolar course [24, 45] and increased chronicity of affective disorders [191] with antidepressants, supersensitivity psychosis with antipsychotic medications [9]. Paradoxical reactions may occur, such as increased agitation, excitement, insomnia, and talkativeness with benzodiazepines [192]; restlessness and agitation with antidepressants. Tolerance may also entail subtle manifestations such as cognitive impairment associated with psychotropic drugs [193, 194], apathy related to the use of antidepressants [195], and depression [196] related to the use of antipsychotics. Withdrawal symptoms which may follow discontinuation of psychotropic drugs, and in particular persistent post-withdrawal disorders, as well as their associated clinical manifestations, such as modifications of the illness course and refractoriness to treatment, are also a tolerance manifestation [24].

Tolerance thus manifests as adverse drug reactions (ADR), which are undesired effects of a medication that increases toxicity or decreases desired therapeutic effect or both [197] and which can occur right after the therapy or even during therapy [198]. When ADR related to tolerance are misinterpreted or simply ignored, a cascade iatrogenesis – a serial development of multiple medical complications that can be set in motion by a seemingly innocuous first event [28, 199] – may result together with iatrogenic comorbidity, that is, the unfavorable modifications in the course, characteristics, and responsiveness to a treatment of an illness related to treatments previously administered [5, 24, 200–202].

The oppositional model of tolerance offers a unitary view for the clinical phenomena described [201, 203]. According to this, 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. These processes may also propel the illness to a more malignant and treatment-unresponsive course, as with bipolar depression [24, 45], apathy [195], or paradoxical reactions. When drug treatment ends, oppositional processes may encounter no more resistance, resulting in the appearance of withdrawal manifestations, hypomania, and resistance to treatment if it is reinstituted. In the long run, antidepressants may increase chronicity, vulnerability to depressive disorders, and comorbidity [26, 204]. The model is complex and multifactorial and is influenced by the duration of and prior exposure to drug treatment as well as by psychosocial and genetic factors [201].

Clinical Implications

A solid clinical competence in recognizing withdrawal phenomena, and later formulating the correct diagnosis, is needed. Apparently recognizing withdrawal syndromes is highly challenging for clinicians, since they may not fit with the diagnostic criteria described by the DSM-5 [182] and the ICD-11 [205] and they may include physical manifestations which do not subsume under the rubric of codified organic illnesses. Current diagnostic methods in psychiatry, both DSM-5 [182] and ICD-11 [205], are inadequate to assess psychotropic medication withdrawal

because they do not take into account the issue of iatrogenic comorbidity [28] and they refer to drug-free patients, although most of the psychiatric cases seen at first visit in psychiatry and in clinical psychology are already under a psychotropic medication [28]. As a result, patients experiencing anguish and mental pain [206–208] of withdrawal syndromes have not received appropriate medical attention [27].

In addition to the limitations of the current nosography, the standard clinical interview nowadays include data on type, dose, duration, and efficacy of treatments received while a crucial point in collecting data about previous treatments would be investigating the occurrence of ADR related to tolerance [28]. Once such data have been obtained, the clinician is asked to place them within the context of psychiatric and medical morbidity. Thus, when the psychiatrist approaches patients' complaints, he should consider different and interconnected pathways which include biological, psychological, and social factors of iatrogenic nature whose consequences may be considered potentially counter-therapeutic [209].

Research Implications

New withdrawal symptoms, rebound symptoms, and persistent post-withdrawal disorders which occur after decrease, switch, or discontinuation of psychotropic medications are very likely to affect the findings of randomized controlled trials [210, 211].

Randomized controlled trials tend to deliberately incorporate in their design a drug discontinuation procedure in order to reach conclusions about drugs' effectiveness in preventing relapse or recurrence of mental disorder [210]. In particular, in relapse prevention randomized controlled trials, researchers place participants on a drug, divide them into responders and non-responders, and responders are randomized to remain on the drug or discontinue it. If at the end of this randomized discontinuation phase, outcome measures favor the drug-maintained group, investigators conclude that the drug is effective [211]. It follows that withdrawal after discontinuation of the previous treatment may confound trial outcomes [211] both increasing the impact of randomization to the new drug and misleadingly increasing ratings of adverse effects [212]. Such designs also risk exaggerating contrasts in morbidity between subjects continuing a treatment proven as effective versus being withdrawn to another treatment or an inactive placebo [211, 213]. As a consequence, the results of such trials may be confounded by the failure to account for drug withdrawal symptoms [211], they are likely to provide inadequate and confounded evidence of potential long-term or prophylactic benefits [214, 215], and their scientific soundness seems compromised [212].

Withdrawal must be considered and assessed when clinical trials are run; this will allow the possibility to reproduce, in research, conditions which are a true proxy of those occurring in the clinic realm.

Conclusions

Withdrawal after psychotropic medication discontinuation represents a major challenge in research and clinical practice, there are still major difficulties in distinguishing symptoms of the disease and those induced by the treatment and the information available from randomized controlled trials is questionable, scanty, and inadequate [216, 217]. There is also reluctance toward accepting that psychoactive drugs can cause withdrawal, which is paradoxical and potentially dangerous. The paradox is related to the fact that DSM-5 describes withdrawal (p. 484) [182] and the essential feature for substance withdrawal (p. 486) [182], but although these criteria nicely fit into the new withdrawal symptoms described for psychotropic medications, they are not commonly used for this purpose. There is danger in that patients presenting withdrawal syndromes are at risk of being misdiagnosed, mistreated, and entering the cascade iatrogenesis, which is the front door for chronicity. This is true also in clinical practice in children and adolescents in which withdrawal syndromes can occur, much more caution is needed, and there is almost no literature [202].

Clinicians and researchers should accept that subjects in trials and real-life patients are no more drug-naïve, or even drug-free, the rule is being under polypharmacy [218, 219]. Unfortunately, this is simply not addressed by the literature although commonly encountered in clinical reality. There are important issues that need to be explored, and we have tools such as the Discontinuation-Emergent Signs and Symptoms [111] and the Diagnostic clinical Interview for Drug Withdrawal 1 – New Symptoms of SSRI and SNRI [220] which can help. The most urgent are neurobiological studies to shed some light on why certain patients develop withdrawal syndromes and others do not; longitudinal studies exploring the occurrence, clinical features, and neurobiological correlates of persistent post-withdrawal disorders are warranted as well as well-designed randomized controlled trials with

appropriately titrated doses of medication comparing different strategies of psychotropic medication discontinuation, comparing different methods of managing withdrawal syndromes (including adjunctive psychotherapeutic strategies), and considering the possibility that withdrawal syndromes may be confounded with relapses in long-term drug/placebo continuations studies [201]. Clinical pharmachopsychology [221, 222], the discipline applying clinimetric methods to the assessment of psychotropic effects of medications, may provide additional sources of information.

Disclosure Statement

The copyright of the DID-W1, The Diagnostic clinical Interview for Drug Withdrawal 1 – New Symptoms of SSRI and SNRI, was deposited by the University of Florence, Florence, Italy, at the request of F.C. and based on a copyright management agreement with G.C.

Author Contributions

Both authors run the literature search. F.C. wrote the drafts of the papers. G.C. revised all the drafts and added materials, texts, references.

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