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REVIEW

Rebound effect, discontinuation, and withdrawal syndromes associated with drugs used in psychiatric and neurological disorders

Aleksandra Wisłowska-Stanek[1] · Michał Jarkiewicz[2] · Dagmara Mirowska-Guzel[1]

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Abstract

Sudden cessation of the drug can cause withdrawal syndrome, discontinuation syndrome, or rebound effect. The common feature of these phenomena is a quick onset, usually limited duration depending on the drug's half-life and remission after restarting the therapy. They are characterized by varying clusters of somatic, autonomic, and psychiatric symptoms. Originally withdrawal syndrome was described for drugs with addictive properties such as barbiturates or benzodiazepines. On the other hand sudden abrupt of antidepressants or antipsychotics may cause discontinuation symptoms including movement or sensory disturbances, sleep disturbances, and hyperarousal but generally of less severity comparing to withdrawal syndrome. The aforementioned syndromes are physiologically based on the predominance of cellular counter-regulations as an effect of the sudden abrupt of a regularly taken medication. Classically the pathogenesis of withdrawal syndrome, based on physical dependence, results in life-threatening, long-lasting manifestations such as, seizures and delirium, different from the treated disease. In turn, these symptoms are not typical for discontinuation syndrome which is not considered as serious and usually spontaneously resolving. In turn, the rebound effect is clinically characterized by the relapse of the disease symptoms that are controlled by medication, but of greater severity than those before treatment.

In the current review, we describe withdrawal and discontinuation syndromes associated with selected drugs used in psychiatry and neurology, risk factors, and recommendations for diminishing syndrome occurrence. Knowledge of their pathogenesis and symptoms resulting from drug discontinuation may be helpful in syndrome management and expectantly reduces the risk of diagnostic and therapeutic errors.

Keywords withdrawal syndrome · discontinuation syndrome · rebound symptoms · psychiatric drugs · neurological drugs

Introduction

Chronic use of drugs changes the body homeostasis causing adaptations that alter downstream cell signaling [1–6]. Namely, long-term treatment with agonists decreases the receptors' amount and affinity that protects the cells against overstimulation [1–6], while chronic treatment with antagonists causes receptor up-regulation [7–8]. Consequently, sudden discontinuation of medication or dose reduction may produce withdrawal/discontinuation syndrome or rebound effect [9–20]. Their common features are limited persistence usually depending on the drug's half-life (typically 5 days to 3 weeks) and remission after restarting the therapy. It is worth stressing that discontinuation and withdrawal syndromes, similarly to rebound effect, are physiologically based on the principle of abrupt cessation of regularly taken medication that usually results in the temporary development of symptoms due to the predominance of cellular counter-regulations against the effect of a substance [21–24].

In clinical everyday practice the names: *withdrawal* and *discontinuation syndrome*, and also *rebound effect* are often used interchangeably, although the phenomena are suggested to differ (even though they overlap in some cases),

✉ Dagmara Mirowska-Guzel
dagmara.mirowska-guzel@wum.edu.pl

[1] Department of Experimental and Clinical Pharmacology, Centre for Preclinical Research and Technology (CEPT), Medical University of Warsaw, Banacha 1B, Warszawa 02-097, Poland

[2] Third Department of Psychiatry, Institute of Psychiatry and Neurology, Sobieskiego 9, Warszawa 02-957, Poland

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and their understanding evolves in time. Originally, the term *withdrawal syndrome* came from the withdrawal of substances with addictive properties such as ethanol, barbiturates, benzodiazepines, opioids, and others. It seems that in time any symptoms appearing after withdrawing the drug were called withdrawal syndrome, even though they were not connected with addiction itself. Proper understanding the nature of withdrawal/discontinuation syndrome is essential for adequate diagnosis and in consequence for effective management. Spreading the knowledge about the similarities and differences between aforementioned syndromes with an aim to provide a correct diagnosis is the first step in this process.

Discontinuation and withdrawal syndromes are clusters of somatic, autonomic, and psychiatric symptoms observed for a limited period of time after a drug is stopped or its dosage is reduced. The symptoms of withdrawal/discontinuation are usually opposite to the action of the substance. According to the strict pharmacologic definition, withdrawal syndrome is experienced in people with physical dependence and manifests with more profound symptoms, in some cases seizures or delirium than discontinuation syndrome [9, 21–22]. Symptom severity depends on the addiction potential of the drug, the duration of therapy, and the drug's pharmacokinetics [18–29]. Discontinuation and withdrawal syndromes have a predictable onset, which depends on the pharmacokinetic properties of the specific drug, and a specific duration (usually 5 days to 3 weeks) depending on the half-life of the drug [30]. In most cases, discontinuation syndrome is transient and mild, but about 3% of patients experience severe symptoms associated with a deterioration of the patient's condition and sometimes even the need for hospitalization [20, 28]. Moreover, some data suggest that discontinuation effects evoked by selected groups of drugs like, for example, benzodiazepines, antidepressants, and antipsychotics, can occasionally last longer than 6 months and fluctuate. These are called protracted withdrawal symptoms and occur especially after high-dose use [31].

A rebound effect is usually described clinically as the emergence or re-emergence of symptoms that were controlled while taking the medication but reappear when the medication is discontinued or reduced in dosage. Very often rebound effect is considered an adverse event of the drug [32]. In the literature rebound effect is referred to as disease exacerbation, disease reactivation, or recurring disease activity. It has been broadly reported after drugs used in multiple sclerosis [33], but may occur following treatment with any drug, including anticoagulants, anticonvulsants, antipsychotics, benzodiazepines, clonidine, corticosteroids, opiates, propranolol, antidepressants, and others. The full manifestation of this phenomenon appears depending on the drug's half-life. In aim to minimize this effect, it is recommended to discontinue a drug gradually [9–12].

Originally *withdrawal syndrome* was described for substances acting on the central nervous system (CNS) such as alcohol and heroin, but also for GABA mimetics such as barbiturates or benzodiazepines [34] and is manifested most often by neurological/psychiatric symptoms. In turn, the term *discontinuation syndrome* developed in connection with the introduction of novel drugs such as selective serotonin reuptake inhibitors without known addictive potential [35] to distinguish their nature from classically addictive drugs.

The current review focuses on withdrawal/discontinuation syndrome and the rebound effect of selected medications used in psychiatry and neurology. We present a variety of drugs and symptoms appearing after drug cessation, their etiopathogenesis as well as the strategies for avoiding them. Knowledge of the specific nature of symptoms connected to drug discontinuation, and their correct interpretation has special meaning as it may reduce the risk of diagnostic and therapeutic errors and provides rationale for accurate pharmacotherapy.

Withdrawal syndromes for drugs used in psychiatry and neurology

Some drugs widely used in psychiatry and neurology, although very effective are well known to cause withdrawal syndrome after sudden stop [34, 36–39]. These are mainly GABA mimetics (such as barbiturates, benzodiazepines, and Z-drugs) but also clomethiazole, gabapentinoids, esketamine, and cannabinoids. Constant widespread use of these drugs gives the reason for recalling their addictive nature and repeated warnings about the risk associated with careless usage.

GABA mimetics: barbiturates, benzodiazepines,Z-drugs, clomethiazole

Barbiturates, benzodiazepines (BZDs), and Z-drugs (zolpidem, zopiclone, and zaleplon) stimulate inhibitory gamma-aminobutyric acid type A (GABA-A) receptors [36–38]. They exert an inhibitory effect on the central nervous system. Barbiturates due to their narrow therapeutic index and high addiction potential are nowadays used very rarely in anesthesiology and resistant epilepsy [39]. Benzodiazepines are registered for the treatment of anxiety, and resistant epilepsy, while Z-drugs are used in the treatment of insomnia [40].

Chronic use of these substances produces tolerance in about 15–50% of patients, and abrupt cessation or a dose reduction can cause severe withdrawal syndrome [24,

41–46]. Especially vulnerable to barbiturates, BZD, and Z-drugs withdrawal syndrome are the elderly, children, and patients with substance use disorders and psychiatric disorders [1]. Studies suggest that withdrawal syndrome develops in nearly half of patients who use a BZD daily for more than a year [47]. Thus, it is important to not exceed 4 weeks of pharmacotherapy and to gradually decrease the dose [1, 9]. The BZD withdrawal symptoms are insomnia, anxiety, irritability, dysphoria, increased tension, panic attacks, hand tremor, sweating, difficulty concentrating, nausea, tachycardia, visual changes, headache, muscular spasms, and pain [9, 12, 48–50] (Table 1). BZD withdrawal syndrome can be complicated with seizures and psychotic reactions [12, 51]. Withdrawal phenomena appear to be more severe following short-acting BZD (alprazolam, oxazepam, lorazepam, and temazepam), typically occur within 48 h, while symptoms of withdrawal from long-acting BZD (e.g., diazepam) appear after 5 days, with peak severity after about 9 days [9, 12, 52]. The symptoms are transient, and usually last till 3 weeks [9].

The pharmacological mechanisms underlying BZD withdrawal are complex and not clear. They reflect neuronal hyperexcitability associated with chronic stimulation of GABA-A receptors and follow underactivity of inhibitory gamma-aminobutyric acid (GABA) functions and increased excitatory neurotransmission activity [1, 4]. Upregulation of N-methyl D-aspartic acid (NMDA) and metabotropic

Table 1 Withdrawal symptoms observed after decrease or cessation the treatment of abused drugs used in the psychiatric and neurologic disorders

Type of symptoms	Benzodiazepines	Z-drugs	Esketamine	Medical marijuana
General	sweating fatigue weakness flu-like symptoms headache	sweating fatigue weakness	headache weakness	sweating headache fatigue flu-like symptoms
Cardiovascular	tachycardia hypertension	tachycardia hypertension	-	-
Gastrointestinal	nausea vomiting diarrhea abdominal pain	nausea	nausea vomiting loss of appetite abdominal cramps	nausea vomiting loss of appetite abdominal cramps
Sensory	tinnitus blurred vision visual changes	-	-	-
Neuromuscular	paresthesia myoclonus tremor coordination problems myalgia ataxia muscular spasm fasciculation	-	myalgia	-
Neurological	seizures	seizures	-	-
Cognitive	confusion amnesia decreased concentration lethargy	-	-	-
Affective	nervousness anxiety agitation depression irritability panic derealization depersonalization	nervousness anxiety dysphoric mood irritability derealization	nervousness dysphoric mood anxiety irritation	dysphoria agitation depression irritation
Psychotic	hallucination delirium paranoia psychosis	delirium	-	-
Behavioral	restlessness aggressive behavior	-	-	restlessness aggressive behavior
Sleep associated	insomniac nightmares	insomnia nightmares	-	insomnia
References	[9, 48–50]	[9, 55]	[70–71]	[60–61]

glutamate receptors in the cerebrocortical areas is also observed [4].

Withdrawal syndrome associated with Z-drugs is similar to that of BZD [40–54]. It develops 1–2 days after stopping the medication and is associated with a high risk of seizures and delirium. Other symptoms are nausea, nightmares, and insomnia [9, 55]. The safe prescribing of Z-drugs significantly reduces the risk of dependence and consequent withdrawal syndrome. Treatment duration preferably does not exceed 4 weeks; alternatively, these drugs can be used intermittently, 3–4 times a week up to 15 times a month [56]. Z-drugs withdrawal syndrome etiopathogenesis reflects neuronal hyperexcitability associated with chronic stimulation of GABA-A receptors and follows the underactivity of inhibitory GABA functions and increased excitatory neurotransmission [39, 51].

To avoid withdrawal syndrome in patients addicted to BZD or Z-drug, professional, under-control detoxification is recommended. It is based on long-acting BDZ, most commonly diazepam, with a gradual tapering [49]. Adjunctive therapies include beta-blockers (for controlling autonomic arousal), and anticonvulsants to decrease the risk of seizures [42]. There is also evidence suggesting that concomitant behavioral-cognitive therapy reduces the risk of anxiety and insomnia in BZD users [9].

Barbiturate withdrawal syndrome includes insomnia, anxiety, or delirium, and sometimes also delusions and hallucinations with intensity higher than benzodiazepines. The body temperature rises and muscle tremors, and epileptic seizures [57].

Clomethiazole is a sedative and hypnotic that is used in treating and preventing symptoms of acute alcohol withdrawal. Several case reports imply clomethiazole's addictive properties [58–59].

Gabapentinoids

Gabapentinoids are GABA analogue medications (pregabalin and gabapentin). Both are used for seizure control and diabetic and postherpetic neuropathic pain, while pregabalin is also used to treat generalized anxiety disorder [60]. Gabapentinoids are known to have a low risk of dependence [61–62]. The symptoms of gabapentinoid withdrawal are anxiety, agitation, dysphoria, irritability, depersonalization, gait instability, vertigo, dizziness, fatigue, tremor, insomnia, myalgia, flu-like symptoms, abdominal discomfort, nausea, palpitations, tachycardia and an increased risk of delirium and confusion [63]. The abrupt discontinuation of gabapentinoids can cause upregulation of the frontolimbic circuit mediated by calcium channels [63–64].

Esketamine

Esketamine together with an oral antidepressant is registered as a nasal spray as a therapy for treatment-resistant depression, especially in cases of co-occurring suicidal behavior [65–68]. Esketamine potentially produces psychological dependence and induces pharmacological tolerance [9]. Esketamine withdrawal symptoms are dysphoric mood, anxiety, agitation, irritability, insomnia, derealization, loss of appetite, headaches, and weakness (Table 2) [69–70]. They typically begin within 24 h of discontinuation and last approximately 3 days, although in some cases they may persist for 2 weeks [17].

Cannabinoids

Medical marijuana is used for spasticity in patients with multiple sclerosis, as adjunctive therapy for drug-resistant epilepsy, and for pain and emesis [71–73]. The typical symptoms of withdrawal are cannabinoid craving, dysphoria, agitation, aggressive behavior, anxiety, depression, decreased appetite, insomnia, sweating, nausea, vomiting, abdominal cramps, tremor, and increased temperature (Table 1) [63, 59–60, 73]. The incidence of withdrawal syndrome in patients who take medical marijuana is about 50–60% [68–69]. Symptom onset occurs 24–48 h after cessation and peaks at days 2–6, with some symptoms lasting up to 3 weeks [70]. Most are of moderate severity [68–71]. The neurobiological etiopathogenesis of cannabinoid withdrawal is probably associated with CB_1 receptor down-regulation [71–77].

Discontinuation syndrome for drugs used in psychiatry and neurology

In the treatment of psychiatric and neurologic conditions many drugs without known addiction properties are used. After being withdrawn they may cause a set of symptoms which are proposed to be called discontinuation syndrome. It is most commonly described after cessation or tapering of antidepressants and antipsychotic drugs [11, 17, 21].

Antidepressants

Antidepressant discontinuation syndrome occurs in 20–78% of patients [9, 11–14]. Symptoms can vary in form and intensity depending on the profile of a drug [21]. Symptoms are heterogeneous and can include gastrointestinal distress, sleep disturbances, neurological symptoms, and relapse of depression or anxiety [11, 12, 13, 14, 21, 78–79]. In most cases, antidepressant discontinuation syndrome is mild or

Table 2 Discontinuation symptoms observed after decrease or cessation the treatment of drugs used in the psychiatric and neurologic disorders

Type of symptoms	Antidepressants	Antipsychotics	Dopamine agonists	Drugs used in multiple sclerosis
General	sweating fatigue weakness flu-like symptoms headache chills	sweating fatigue flu-like symptoms headache chills hypothermia	sweating fatigue	-
Cardiovascular	tachycardia dizziness hypertension arrhythmia	tachycardia dizziness chest pain hypertension risk of myocardial infarction	hypotension	-
Gastrointestinal	nausea vomiting anorexia diarrhea abdominal pain	nausea vomiting anorexia diarrhea abdominal pain salivation	nausea	-
Sensory	electric shock sensation tinnitus blurred vision visual changes brain zaps hypesthesia	electric shock sensation brain zaps	-	-
Neuromuscular	paresthesia myoclonus tremor coordination problems stiffness myalgia ataxia neuromuscular spasm jerkiness cramps	paresthesia tremor coordination problems stiffness myalgia hyperreflexia	-	spasticity tremor
Neurological	-	akathisia parkinsonism	-	seizures
Cognitive	amnesia decreased concentration lethargy attention difficulties slurred speech	confusion amnesia disorientation attention difficulties	-	attention deficits
Affective	nervousness anxiety agitation depression irritability panic derealization depersonalization mood swings hypomania/euphoria fear tension	nervousness anxiety dysphoric mood irritability	nervousness panic attack agitation depression	irritation
Psychotic	-	catatonia	-	
Behavioral	restlessness aggressive behavior impulsivity	restlessness aggressive behavior	-	restlessness
Sleep associated	insomnia nightmares hypersomnia	insomnia	-	insomnia
References	[11–14, 21, 78–79]	[9, 95–96]	[103]	[106–108]

moderate, but in 3–5% it is severe and associated with deterioration of the patient's mental condition and significant impairment of functioning [31]. The most serious symptoms are disturbances of consciousness, including delirium. They have been most commonly described after monoamine oxidase inhibitors (MAO-I), e.g., tranylcypromine and tricyclic antidepressants (TCA) discontinuation, but there are case reports considering fluoxetine, mirtazapine, and venlafaxine [21, 80–85]. There are rare occurrences of mania upon discontinuation of TCA, MAO-I, trazodone, mirtazapine, and paroxetine in patients with bipolar disorder [86]. The onset of symptoms is usually within a few days of stopping treatment (depending on the half-life of the antidepressant) or occasionally during taper or after missed doses of drugs with short half-lives. Higher doses of drugs with short half-lives, like paroxetine, duloxetine, and venlafaxine are associated with a greater risk of discontinuation syndrome [9, 16, 27, 87–88], while the lowest risk is associated with agomelatine and vortioxetine [21].

Symptoms of the discontinuation associated with selective serotonin reuptake inhibitors (SSRI), serotonin and epinephrine reuptake inhibitors (SNRI), and bupropion are described by the acronym FINISH: flu-like syndrome, insomnia, vivid dreams, nausea, abdominal pain, sensory disturbances (electric shock sensation), hyperarousal (anxiety, agitation, impulsive behavior, depressed mood) (Table 2) [17, 21, 60, 78–79]. Some authors report that the most common symptom is dizziness exacerbated by head movement and therefore likely to be vestibular in origin [89]. The onset of SSRI discontinuation syndrome occurs 36 h to 10 days after dose decrease or stopping, and its symptoms are usually reversible and last from a few hours to 6 weeks [9]. SSRI discontinuation syndrome is associated with a temporary deficiency of synaptic serotonin [19, 90]. It is compounded by the fact that downregulated receptors will remain in their relatively hypoactive state for days to weeks [19].

Discontinuation symptoms are described for TCA and noradrenergic and specific serotonergic antidepressants (NaSSA) (e.g. mirtazapine, mianserin). These include gastrointestinal distress, insomnia, nightmares, akathisia or parkinsonism, hypomania or mania for TCA [9, 91], and panic, anxiety, restlessness, irritability, hypomania, insomnia, dizziness, paresthesia, nausea, vomiting for NaSSA [88].

There is a higher risk of any antidepressant discontinuation syndrome in men, adolescents, and those treated for longer than 2 years [77].

The Cochrane database suggests that the gradual discontinuation of antidepressants together with psychotherapy decreases the risk of discontinuation syndrome [89]. To avoid consequences of sudden stop of the drug the dose should be gradually reduced over 4 weeks [92–94].

Antipsychotics

Long-term administration of antipsychotics upregulates dopaminergic type 2 receptors and results in their hypersensitivity [17]. Discontinuation of antipsychotics can cause rebound symptoms, including illusions, hallucinations, and catatonia [9, 95], more commonly in treatment-resistant schizophrenic patients [13]. Furthermore, depending on the receptor's profile of action, different patterns of symptoms might be observed, such as adrenergic discontinuation syndrome (headache, anxiety, agitation, increased blood pressure, risk of myocardial infarction, palpitations, chest pain); muscarinic cholinergic discontinuation syndrome (agitation, insomnia, anxiety, depression, dizziness, lightheadedness, tachycardia; nausea, vomiting, salivation, diarrhea, abdominal cr tremor, parkinsonism, restlessness, myalgia, rigidity, myosis; paresthesia; confusion, disorientation, hypothermia, sweating); histaminic discontinuation syndrome (irritability, insomnia, agitation, loss of appetite, nausea, incoordination, increased inducible seizure, amnesia) or serotonin discontinuation syndrome (flu-like symptoms, dizziness, tachycardia; diarrhea, abdominal pain; restlessness, myalgia, rigidity, hyperreflexia, inducible clonus, paresthesia, electric shock sensations, zaps, confusion, amnesia, coma, premature ejaculation) (Table 2) [9, 95–96]. Current data suggest that the antipsychotics that are rapidly eliminated or rapidly dissociate from D_2 receptors (clozapine, quetiapine) generate greater risks of discontinuation, including even rebound when the dose, is switched, or discontinued [9]. A drug that requires special caution is clozapine, because rarely it can cause catatonia or neuroleptic malignant syndrome (with negativism, stupor, mutism, fever, hyperhidrosis, and elevated creatine kinase levels) [9, 97]. The discontinuation syndrome in the form of relapse of the disease is also observed after stopping long-acting injection antipsychotic formulations. In this case, the relapse is usually postponed and less severe compared to standard therapy [98].

Medical stimulants used in the treatment of attention deficit hyperactivity disorder (ADHD)

Medical stimulants are the first choice pharmacotherapy for ADHD, recommended in patients who have not responded to behavioral intervention [99]. In ADHD pharmacotherapy methylphenidate, modafinil, and amphetamine derivatives are used [99]. Amphetamine derivatives have addiction potential so their discontinuation could be associated with withdrawal syndrome with main symptoms such as depression and insomnia [100].

Methylphenidate discontinuation can cause depression or relapse of ADHD and, very rarely, movement disorders

such as dystonia [101]. In turn, a randomized clinical trial on children aged 6 to 17 revealed that abrupt discontinuation of modafinil was not associated with symptoms of withdrawal or ADHD rebound [102].

Dopamine agonists

Dopamine agonists are used in the treatment of parkinson's disease and restless leg syndrome [103–104]. The discontinuation or tapering of dopamine agonists causes so-called dopamine agonist withdrawal syndrome (DAWS) [103–104] although these drugs have no known addiction potential/properties [103]. It affects up to 19% of patients who undergo a dopamine agonist taper [103–104]. The discontinuation symptoms include panic attacks, depression, diaphoresis, agitation, fatigue, pain, drug cravings, nausea, and orthostatic hypotension (Table 2) [103]. To avoid DAWS, doses of dopamine agonists should be decreased gradually. Identified risk factors for DAWS include impulse-control behavioral disorders and sudden stopping of high dopamine agonist dosage [103]. Some data suggest that deep brain stimulation may also be a risk factor [102–105].

Discontinuation syndrome of drugs used in multiple sclerosis – rebound effect

In neurology rebound effect gained special attention within last years when new, very efficient disease modifying drugs were introduced to multiple sclerosis (MS) therapy. Shortly after introducing natalizumab and later fingolimod to MS treatment case reports of severe disease reactivation after drug cessation were described [106–108]. Rebound effect in MS is defined as a severe disease reactivation after drug withdrawal with symptoms exceeding pre-treatment baseline inflammatory activity. About 12% of patients treated with natalizumab may experience a rebound effect within 12 months after discontinuation [107]. The data also suggest that more than 26% of patients are at risk of having a relapse within 6 months after fingolimod discontinuation [107]. In some cases, the decline is very severe [108]. Based on current knowledge, the recommended protocol is to gradually discontinue the immunomodulatory drugs and replace them with other treatment affecting the immune system [108].

Baclofen

Baclofen is a GABA-B receptor (gamma-aminobutyric acid type B receptor) agonist used in the treatment of muscle spasticity [109]. Chronic use of baclofen can result in neuroadaptation changes similar to those of alcohol or BZDs, which can result in similar withdrawal symptoms such as confusion, agitation, seizures and delirium seizures, psychotic manic or paranoid states, dyskinesia, fever, and worsening spasticity. The baclofen cases neuroadaptive changes not defined as addiction. Consequently, it cessation should be considered more as discontinuation than withdrawal syndrome. The abrupt cessation of oral baclofen can in result in otherwise unexplained fever or extrapyramidal syndrome with dysautonomia [109].

Antiepileptic drugs (according ILAE – international league against epilepsy recommendation are called antiseizures) [109]

Antiepileptic drugs can be discontinued in patients who have been seizure-free for at least two years or those who have undergone successful surgical treatment [110–112]. The risk of seizure recurrence depends on the epilepsy type and risk factors (long duration of epilepsy before remission, short seizure-free interval before antiepileptic drug stop, older age at onset of epilepsy in patients aged > 25 years, history of febrile seizures, more than 10 seizures before remission, epileptiform abnormality on EEG (electroencephalogram) [111–113]. Approximately 30–50% of patients will experience a relapse of seizures. If seizures recur, the majority of patients regain seizure control when treatment is resumed. However up to 20% do not achieve immediate remission [113]. Most relapses occur during the first year after discontinuation [114].

The antiepileptic drugs that most commonly cause withdrawal syndromes are those with addiction potential, like GABA mimetics (BZD, barbiturates) and gabapentoids (pregabalin, and gabapentin). Syndromes are seen in patients with both active and inactive epilepsy whilst the drug is being withdrawn or decreased. Felbamate and vigabatrin cause seizures related to their withdrawal [115]. Discontinuation syndrome caused by non-addictive antiepileptic drugs such as lamotrigine has rarely been described and manifests as anhedonia, tremor, and a slight tachycardia that spontaneously disappears after a few days [116].

Conclusions

Some drugs and substances acting on the CNS are well known to produce addiction and withdrawal syndrome that after their stopping. Independently, other drugs, even without addictive potential/properties may cause neuroadaptive changes that requires gradual diminishing of dose when intended to stop. Patients should be informed about the risk of these symptoms to decrease the probability of sudden discontinuation or reducing in dosage of the drugs. There are still major difficulties in distinguishing symptoms of the disease progression itself and discontinuation or withdrawal

syndrome in psychiatric and neurologic disorders. To avoid or diminish the symptoms of withdrawal or discontinuation syndrome it is important to educate patients about the addiction potential of certain drug classes. In case of discontinuation, it is crucial to take into account the risk of rebound effect and to presume the possible need for its management.

Randomized clinical trials are needed to evaluate the risk of withdrawal, discontinuation or rebound symptoms or assess the effectiveness of restarted treatment. Furthermore, general and specific guidelines are needed to mitigate these syndromes between each other after stopping or decreasing the dose of drugs used in neurological and psychiatric diseases. Knowledge of the specific nature of symptoms connected to drug discontinuation, and their correct interpretation may reduce the risk of diagnostic and therapeutic errors.

Taking into account increasing usage of drugs acting on the CNS such as e.g., antidepressants, cannabinoids or stimulants in ADHD and still vast usage of others such as BZD or Z-drugs, knowledge about the syndromes associated with drug cessation or dose reducing is of critical importance. Moreover, precise understanding of pathological basis that differentiate aforementioned syndromes is essential for careful and proper nomenclature. Education in this area is crucial to adequately predict the occurrence of these syndromes and effects and to undertake appropriate actions in aim to minimize their risk.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
BZD	Benzodiazepine(s)
CB_1	Cannabinoid type 1
DAWS	Dopamine agonist withdrawal syndrome
GABA	Gamma–aminobutyric acid
GABA	A receptor–gamma–aminobutyric acid type A receptor
GABA	B receptor–gamma–aminobutyric acid type B receptor
ILAE	International League Against Epilepsy
MAOIs	Monoamine oxidase inhibitors
MS	Multiple sclerosis
NaSSA	Noradrenergic and specific serotonergic antidepressant
NMDA	N–methyl D–aspartic acid
SSRI	Selective serotonin reuptake inhibitors
SNRI	Serotonin and noradrenaline reuptake inhibitors
TCA	Tricyclic antidepressants

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