Psychotherapy and Psychosomatics

Editorial

Psychother Psychosom 2023;92:148–151
DOI: 10.1159/000530692

Received: April 6, 2023
Accepted: April 6, 2023
Published online: May 24, 2023

Discontinuation of Antidepressant Medications: A Significant Healthcare Problem Insufficiently Addressed by the NICE Guidelines

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In 2008, Chouinard and Chouinard [1] published an editorial in *Psychotherapy and Psychosomatics* applying the basic pharmacological concepts of withdrawal to symptoms associated with psychiatric drug discontinuation and described the same phenomena reported in basic pharmacology and medicine, which include new symptoms, rebound, supersensitivity, and drug-induced iatrogenic disorders. The same authors provided detailed diagnostic criteria for the pharmacological withdrawal syndromes produced by dose decrease and switch or discontinuation of selective serotonin reuptake inhibitors and criteria to discriminate between new withdrawal symptoms, relapse, rebound, and persistent syndromes [2]. Psychotropic drug withdrawal symptoms were further elaborated in an article on antidepressant withdrawal [2] and on antipsychotic withdrawal [3]. These diagnostic criteria were then applied to a review of the literature on withdrawal symptoms of psychotropic drugs [4]. Furthermore, Fava et al. published systematic reviews on withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation [5] and serotonin-noradrenaline reuptake inhibitor discontinuation [6]. Epidemiological studies, whether retrospective or prospective, cannot establish a cause-and-effect relationship of the pharmacological concept of withdrawal developed in basic and animal pharmacology and in medicine but are important to confirm its presence in the treatment of patients. These pharmacological concepts are summarized here as follows:

- New withdrawal symptoms: rapid appearance of at least two new symptoms (unspecific or specific for the psychotropic medication class) within 36–96 h after dose reduction, discontinuation, or switch; transient (less than 6 weeks); reversible, with complete recovery; new symptoms, which were not experienced before the beginning of the treatment. This concept of new symptoms originated from discontinuation withdrawal of barbiturates and morphine-like drugs and included three major new symptoms: death, seizure, and psychosis [2].
- Rebound symptoms: rapid return of original symptoms, within 36–96 h after dose reduction, discontinuation, or switch, at a greater intensity than before treatment; transient (less than 6 weeks); reversible, with complete recovery [2]. Rebound is a key concept in medicine and was reported recently with antiviral drugs given in the treatment of SARS-CoV-2, and rapidly, data from basic pharmacology were obtained [7].

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- Persistent post-withdrawal disorders: rapid appearance, between 24 h and 6 weeks after decrease, discontinuation, or switch, of original symptoms at a greater intensity than before treatment and/or rapid appearance of new withdrawal symptoms or a new psychiatric disorder, which can be unspecific or specific for the psychotropic medication class; persistent (>6 weeks); potentially irreversible [2].

Psychotherapy and Psychosomatics publications cited above [1–6] lead to reconsideration of withdrawal of antidepressants: the term discontinuation syndrome was replaced by withdrawal syndrome, based on similarities with other psychiatric medications withdrawal, in particular, benzodiazepines for rebound and antipsychotics for persistent post-withdrawal disorders [8]. However, conclusions of the abovementioned studies and pharmacological concepts of withdrawal inherent to any drug have been ignored by most guidelines on antidepressants [9]. In contrast, in 2019, the Royal College of Psychiatrists [10] took into consideration this issue via a position statement on antidepressants and depression which called for a "greater recognition of the potential in some people for severe and long-lasting withdrawal symptoms on and after stopping antidepressants in NICE guidelines and patient information" [10].

In 2022, the National Institute for Health and Care Excellence (NICE) guidelines included the above recommendation for large spectra of psychotropic medications [11]. Withdrawal symptoms were described in the NICE guidelines under the rubric of "Identifying and managing withdrawal symptoms" and were characterized by (a) a rapid or early onset after a dose reduction or discontinuation of the drug; (b) symptoms of the underlying illness that the person reports as qualitatively different or more intense than before; (c) new symptoms never experienced by the person before. These descriptions are similar to the diagnostic criteria we proposed for withdrawal syndromes due to dose reduction, drug discontinuation, or switch of psychotropic medications [2, 3].

Unfortunately, the 2022 NICE guidelines did not focus on the pharmacological concepts of withdrawal used in medicine and now, in psychiatry including antidepressants [1, 3]. This concept allows a clear distinction between reversible, transient manifestations, which pertain to new symptoms and rebound symptoms, and persistent, potentially irreversible post-withdrawal disorders [1–4, 12]. This distinction is clinically important as these transient and persistent manifestations may have different clinical courses (e.g., impact on a person's functioning) and treatment strategies [13, 14]. Management of withdrawal syndromes may thus be adapted to the spectrum of treatment-induced withdrawal symptomatology [15] and severity (less severe for reversible symptoms; transient manifestations and more severe for persistent, potentially irreversible symptoms).

The 2022 NICE guidelines on psychotropic medication prescription [11] also referred to the use of clinical judgement to determine the need for further investigation and ruling out new pathology. In addition to clinical judgement [16, 17], we recommend the use of the Diagnostic clinical Interview for Drug Withdrawal 1 [18] and the Discontinuation-Emergent Signs and Symptoms [19] for assessment of withdrawal. These two instruments were developed to differentiate withdrawal symptoms from relapse. To help further the differential diagnosis, the literature we contributed to can guide clinicians [2, 4] as both relapse and recurrence have clinical features which differ from withdrawal syndromes. First, relapse and recurrence tend to be associated with a gradual onset of the original symptoms and illness, while drug discontinuation (which includes dose decrease, switch, and drug cessation) tends to produce acute, abrupt withdrawal symptoms. Second, symptom severity in relapse is similar to that before drug treatment, while drug withdrawal produces greater severity of symptoms [2, 4]. Furthermore, withdrawal from psychotropic medications can be associated with drug tolerance such as reduced therapeutic effects, need to increase the dosage, treatment resistance when the medication is reintroduced, and gradual drug treatment resistance [14, 20]. The most important aspect is to consider the length of antidepressant intake. Short-term intake is less than 4 months, long-term intake is at least 2 years, and chronic intake is more than 4 years. Generally, persistent withdrawal symptoms are seen after 2 years of continuous drug treatment. The physician should know about them, so when they occur, they could be identified and recognized.

The NICE guidelines on psychotropic medication prescription [11] suggested to review and document recommendations when continuing a medication, including potential harms of continuing and reasons for continuing without dose reduction. Alternative approaches are needed to address treatment-related comorbidity [15, 21]. Such vulnerabilities may manifest themselves during treatment administration and/or after its discontinuation and may be persistent rather than limited to a short phase during treatment. The human clinical studies needed to demonstrate that these withdrawal syndromes will never be done. The best we could do is to describe them so that they could be recognized and identified when they do occur and hope that drug agencies will eventually require inserting withdrawal studies in basic pharmacology,

animal pharmacology, and human studies before approving a drug. In medicine, researchers are more reactive to antiviral drug withdrawal effects after treatment cessation, and a recent example was when virological rebound of COVID-19 was reported following the discontinuation of nirmatrelvir-ritovir [7]. Immediately, researchers and clinicians looked for rebound in ongoing treatment patients and ongoing studies. The best we could hope for is that clinicians and researchers report cases of withdrawal symptoms and syndromes and that antidepressant guidelines request the addition by the drug agencies of basic withdrawal pharmacological studies in the monography.

The NICE guidelines on psychotropic medication prescription [11] tend to use the term "withdrawal" interchangeably to refer to both withdrawal symptoms at reduction or discontinuation of a psychotropic medication and to drug discontinuation, which is discussed. The lack of a distinction between tapering and discontinuation on one side and withdrawal on the other may imply that the problem is limited to the period of tapering or at discontinuation of the psychotropic medication. The literature suggests that the problem related to drug discontinuation can persist overtime [2–4, 12].

Overall, 2022 NICE guidelines [11] neglect the literature on basic pharmacological concepts of withdrawal [1–3] and its application to all studies published on psychotropic drug withdrawal [4], which is of great interest for psychiatrists and clinical psychologists because it depicts what challenges their everyday practice: the differential diagnosis between withdrawal and relapse; how to recognize and subtype withdrawal; how to manage withdrawal. In addition, the NICE guidelines do not mention that withdrawal symptomatology may be associated with loss of treatment efficacy despite adequate adherence to the antidepressant treatment and lack of response to a previously effective antidepressant treatment when it was restarted, which is part of treatment resistance [21]. These clinical manifestations can deeply influence the individual trajectories of development of a mental disorder, representing the trigger to move to a different, and more severe or chronic, stage of the same illness [22]. In brief, clinicians must manage what is not mentioned in guidelines; most importantly when a drug is started, clinicians should know what may happen at dose decrease and drug discontinuation.

Organization for Economic Cooperation and Development datasets observed that the average antidepressant consumption across 18 European countries was 30.5 defined daily dose per 1,000 people per day in 2000 rising to 75.3 defined daily dose in 2020, a 147 per cent increase [23]. Since 1 out of 2 patients is unable to discontinue the antidepressant medication due to withdrawal symptoms [24], this problem is sufficiently serious to be considered in guidelines. The NICE guidelines are a first step to fill in this gap but do it insufficiently. We hope that guidelines should be more convincing to influence drug agencies to act on drug monography of psychotropic drugs including antidepressants by insertion of information on withdrawal contained in basic laboratory and human pharmacology studies. Rebound COVID-19 with cessation of antiviral drugs is another example of the importance of this clinical phenomenon.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for preparing the present manuscript.

Author Contributions

Fiammetta Cosci, Virginie-Anne Chouinard, and Guy Chouinard equally contributed to this study.

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