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Analysis

Selective serotonin reuptake inhibitor 'discontinuation syndrome' or withdrawal

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Summary

Attempts to define selective serotonin reuptake inhibitor (SSRI) withdrawal with the term 'discontinuation syndrome' are not supported by evidence. Acknowledging that SSRI use can result in dependence and withdrawal allows patients to be better informed around decisions related to these drugs, and helps inform strategies for safe tapering as appropriate.

Keywords

Antianxiety drugs; antidepressants; drug interactions and side-effects; drugs of dependence disorders; depressive disorders.

Declaration of interest

None.

Over the past two decades, the use of selective serotonin reuptake inhibitor (SSRI) antidepressants has increased markedly.[1–6] In addition to being prescribed more commonly, the increase in SSRI prescribing can be attributed, in part, to increase in long-term antidepressant use.[6,7] Symptoms associated with SSRI discontinuation are particularly salient around long-term use. In fact, such symptoms can contribute to prolonged use of antidepressants since patients can experience intolerable symptoms during attempts at cessation of an SSRI.[8–10]

A systematic review of symptoms associated with SSRI cessation concluded that, like benzodiazepines, barbiturates and other psychotropic drugs, SSRI cessation could result in withdrawal symptoms.[11] In addition, gradual tapering may not eliminate the risk of such withdrawal reactions.[11] An earlier similar study found that discontinuation symptoms with SSRIs were very similar to those from benzodiazepines.[12] According to a more recent systematic review, the incidence rates of symptoms associated with cessation of SSRI ranged from 27% to 86% across studies, with almost half of those having experienced such symptoms rating them at the highest level of the severity rating used, and symptom durations ranged from as little as a few days to years.[13]

Patients often express concerns that they will become dependent on their antidepressants.[14,15] A recent online survey sampling 1431 respondents from 38 countries found that 55.4% of patients taking antidepressants reported withdrawal effects (23.8% at the severe level), with 36.8% reporting addiction.[16] Similarly, in response to an online survey about experiences of 1829 people taking antidepressants, 55% reported 'withdrawal effects' and 27% reported 'some degree of addiction' to their prescribed antidepressant.[8] Of note, this study recruited participants via advertisements to complete an online survey, and so there may be a sampling bias. However, 82.8% of participants expressed that the drugs had reduced their depression, which indicates a sample not biased toward a negative perception of the drugs. Moreover, such studies involving direct surveying of patients serve to effectively include a reflection of patients' concerns, which appear to be quite prevalent and varied, in assessing symptoms following antidepressant cessation in addition to traditional research methodologies, which typically include randomised placebo-controlled trials utilising staggered dosage interruption and tapering to assess withdrawal (as per the studies included in the aforementioned systematic reviews).

Despite apparent patient concerns regarding symptoms following antidepressant cessation, clinicians often reassure patients that they will not become dependent or addicted to their antidepressants. A now former president of the American Psychiatric Association is quoted as saying: 'I don't think they're [antidepressants] difficult to go off … The vast majority of people aren't that sensitive'.[17] A pharmaceutical company spokesperson previously stated that symptoms associated with discontinuation of their SSRI drug were 'very rare… in only 2 out of every 1000 patients… Even then, the symptoms are mild and short lived'.[18] Moreover, the potential severity of symptoms associated with cessation of antidepressants has been deemphasised in the literature,[19–23] and in clinical practice guidelines, specifically those proposed by the National Institute for Health and Care Excellence, which has described symptoms following antidepressant cessation as 'usually mild and self-limiting over about 1 week,'[24] and the American Psychiatric Association, which claims that 'these symptoms typically resolve without specific treatment over 1–2 weeks. However, some patients do experience more protracted discontinuation syndromes, particularly those treated with paroxetine, and may require a slower downward titration regimen. Another strategy is to change to a brief course of fluoxetine, e.g., 10 mg for 1–2 weeks and then taper and discontinue the fluoxetine'.[25] In addition, one group of authors stated that, because of the 'usually mild and transient' nature of symptoms, 'many patients need only reassurance to help them cope with the adverse events'.[20] Such statements do not align with patients' experiences of severe withdrawal symptoms and difficulty during cessation of their medications. As an example, one participant of the aforementioned online survey study is quoted saying, 'The difficulty of getting off has been a tough road and taken me years of trying and is something that doctors could be more knowledgeable of and supportive with'.[8]

In the 1990s, the term 'antidepressant discontinuation syndrome' began to be used, distinct from 'withdrawal', to describe the symptoms experienced by patients attempting to discontinue their antidepressants. The validity of the term may depend on how it is defined. The following is a critical analysis of the history of the term antidepressant discontinuation syndrome, in an effort to evaluate the justification for its use and discuss implications for patients. To facilitate this analysis, a search of relevant literature regarding SSRI antidepressant cessation was followed by a detailed evaluation of potentially relevant articles to gather information regarding the use of the term discontinuation syndrome in relation to its counterpart, withdrawal, in the literature.

History

To our knowledge, the term discontinuation syndrome, with respect to cessation of an SSRI, was first used in a single article published in

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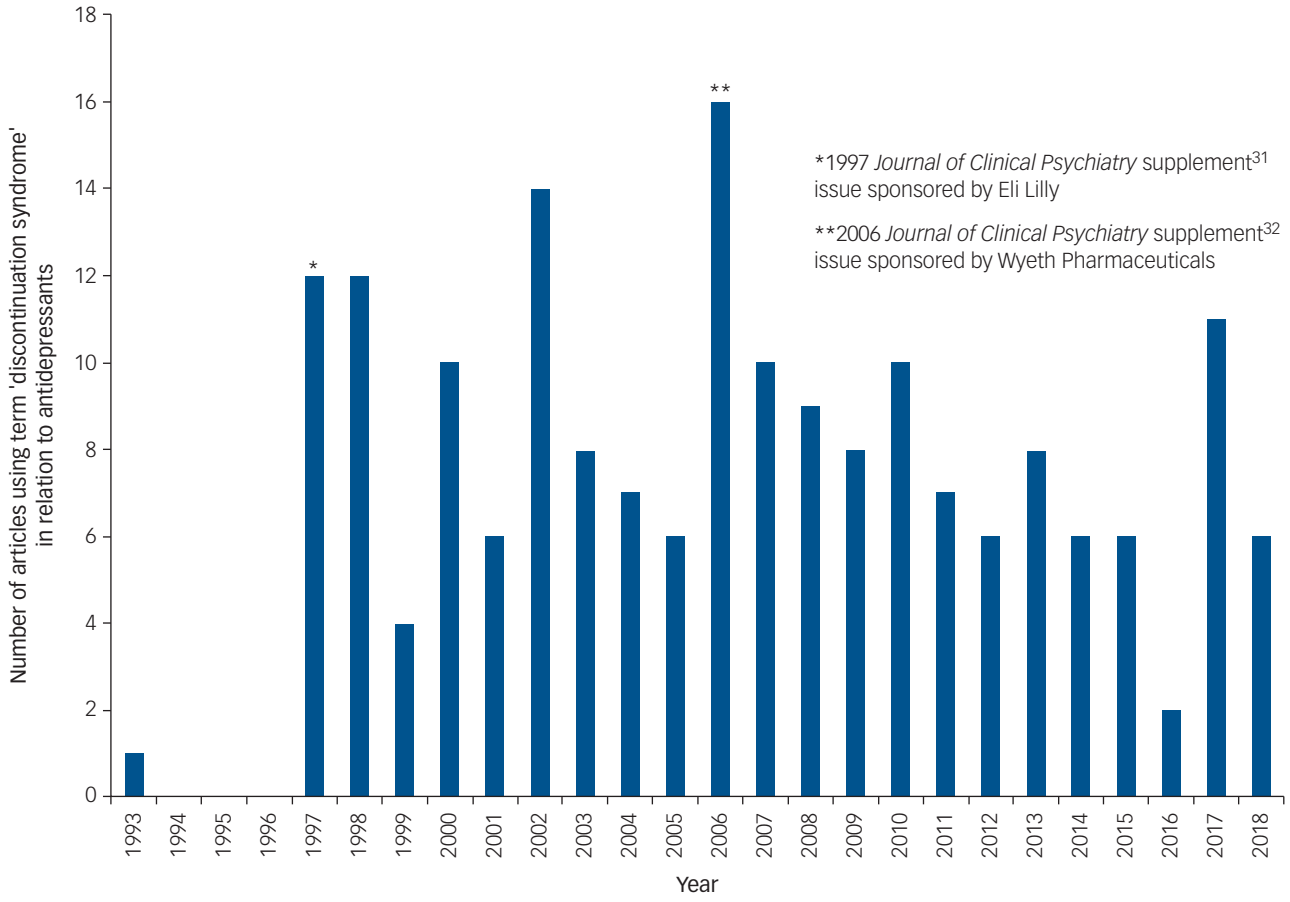

Fig. 1 Number of publications per year from 1993 to 2018 that mention the term 'discontinuation syndrome' in relation to SSRI antidepressants. Articles retrieved from Medline, EMBASE and PsychInfo, using the search terms 'antidepressant' AND 'discontinuation syndrome'. The search retrieved 183 publications once duplicates and irrelevant results (i.e. results not related to SSRI cessation) were removed.

SSRI, selective serotonin reuptake inhibitor.

1993.[26] However, it appears next only in 1997, with the publication of a supplement issue in the *Journal of Clinical Psychiatry*.[19–22,27–31] This supplement issue was based on a closed symposium titled 'SSRI Discontinuation Events'; both the symposium and the supplement were sponsored by Eli Lilly.[31] Immediately after this supplement, the term became more frequently used in the literature (Fig. 1). The *Journal of Clinical Psychiatry* published another supplement issue in 2006 that was based on a 2004 meeting funded by Wyeth Pharmaceuticals.[32] In this supplement, authors advocated for replacing the term withdrawal with antidepressant discontinuation syndrome in the literature as the former was regarded as 'particularly confusing to patients, many of whom are already concerned about becoming addicted to antidepressants'.[23] According to one of the articles, 'the distinctions between discontinuation symptoms and drug withdrawal are clear. Thus, the use of proper terminology when discussing this phenomenon with patients will help to alleviate concerns and stop the spread of common misperceptions'.[23]

Defining antidepressant discontinuation syndrome

As the term antidepressant discontinuation syndrome came into use, there were various attempts to define it and distinguish it from withdrawal. In an article from the *Journal of Clinical Psychiatry* 1997 supplement, Schatzberg described five 'hallmark features' of discontinuation syndrome as proposed by a panel of experts: 'It is not attributable to other causes; It is emergent upon abrupt discontinuation, frequent nonadherence (missed doses), and, less often, after dose reduction; It is generally mild and short-lived but can be distressing; It can be reversed by the reintroduction of the original medication or one that is pharmacologically similar; It is minimized by a slow taper or by using a drug that has an extended half-life'.[21] There are several limitations in this description of discontinuation syndrome. First, none of the above criteria serve to distinguish discontinuation syndrome from withdrawal syndrome. Second, there is much evidence that adverse effects following antidepressant cessation are often neither 'mild' nor 'short lived'.[11–13,33] From a systematic literature review on withdrawal symptoms following discontinuation of SSRIs and benzodiazepines, Nielsen *et al* concluded that adverse effects following SSRI cessation include potentially debilitating symptoms that resemble those associated with benzodiazepines.[12] In a more recent systematic review, the authors found that symptoms following discontinuation of antidepressants occur at a weighted average rate of 56%, and are described as severe in 46% of patients experiencing them.[13] Lastly, although the severity of withdrawal symptoms can presumably be 'minimized by a slow taper or by using a drug that has an extended half-life',[21] they may still be a significant challenge despite such strategies.[11,34]

In 1998, Rosenbaum *et al* developed the Discontinuation Emergent Signs and Symptoms checklist, entailing 43 items to assess for discontinuation syndrome.[35] Two years later, Black *et al* proposed a new set of diagnostic criteria for antidepressant discontinuation syndrome after examining 46 case reports published from

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1986 to 1997 inclusive.[36] These criteria include two or more of the following symptoms developing within 1–7 days of discontinuation or reduction in dose of an SSRI after at least 1 month's use: dizziness, light-headedness, vertigo or feeling faint; shock-like sensations or paraesthesia; anxiety; diarrhoea; fatigue; gait instability; headache; insomnia; irritability; nausea or emesis; tremor and visual disturbances.[36] However, in the case of antidepressants with a longer half-life, such as fluoxetine, such symptoms may not be present within 7 days of discontinuation. The *Journal of Clinical Psychiatry* 2006 supplement included an article describing an alternative system, characterising SSRI discontinuation syndrome 'according to the following syndromic features: neurosensory (e.g., vertigo, paresthesias, shock-like reactions, myalgia, other neuralgia); neuromotor (e.g., tremor, myoclonus, ataxia, visual changes); gastrointestinal (e.g., nausea, vomiting, diarrhea, anorexia); neuropsychiatric (e.g., anxiety, depressed mood, intensification of suicidal ideation, irritability, impulsiveness); vasomotor (e.g., diaphoresis, flushing); and other neurologic (e.g., insomnia, vivid dreaming, asthenia/fatigue, chills)'.[23] None of these various proposed criteria justify the distinction between discontinuation syndrome and withdrawal. Instead, the symptoms described are typical of patients experiencing withdrawal and indicate the various ways in which patients can become dependent upon their SSRIs, thus making it difficult to reduce their use of antidepressants.

Distinguishing discontinuation syndrome from withdrawal

A common argument for the use of the term discontinuation syndrome is that it must be distinguished from withdrawal since it is claimed that antidepressants, such as SSRIs, do not cause dependence. One author has argued that substance dependence is distinct from antidepressant discontinuation in the DSM-IV since the diagnostic criteria for substance dependence, including a loss of control, excessive time using the drug or development of tolerance toward the drug 'rarely occur in patients taking antidepressants'.[37] However, the DSM-IV – and, for that matter, the DSM-5 – includes further criteria for dependence that are inconsistent with this argument. The substance dependence criteria also include withdrawal, as manifested by either the characteristic withdrawal syndrome (outlined elsewhere in the DSM-IV), or the same substance being taken to relieve or avoid withdrawal symptoms. By this definition, antidepressants can be considered to cause dependence since patients do experience characteristic withdrawal symptoms upon discontinuation, and may continue to take their antidepressants to avoid withdrawal symptoms.[9,10] Furthermore, it must be stressed that, although SSRI cessation may not involve addictive behaviours such as excessive time using the drug (as often associated with opiate or alcohol dependence), the evidence for significant symptoms associated with cessation of SSRI drugs is consistent with dependence.

There have been several studies refuting the use of the term discontinuation syndrome in place of withdrawal, in relation to SSRIs. A recent article by Baldessarini and Tondo described reactions following reduction of antidepressants, particularly SSRIs, as being similar to the 'withdrawal-like syndromes [that] occur with most sedatives and antianxiety agents, as well as opioids, alcohol, and other psychoactive agents'.[38] Furthermore, after evaluating the literature on benzodiazepines and SSRIs, Nielsen *et al*[12] found that 37 out of 42 withdrawal symptoms were described for both benzodiazepines and SSRIs, thus indicating that the withdrawal reactions of SSRIs are comparable with those of benzodiazepines. They concluded that it 'makes no sense' to describe only benzodiazepines as being associated with dependence. Using these findings alongside other studies included in a systematic review, Fava *et al*[11] concluded that using the term withdrawal syndrome to refer to the symptoms caused by benzodiazepine, antipsychotics and tricyclic antidepressants while using the term discontinuation syndrome for those pertaining to SSRIs has 'minimized the potential vulnerabilities induced by SSRI and has provided the ground for misleading indications'. Similarly, the authors of a recent systematic review on the topic argue against use of the term discontinuation syndrome: it can be misleading since relevant symptoms can occur without discontinuing the drug (e.g. with dose reduction), and, 'the term "syndrome" subtly medicalises withdrawal by associating it with a disorder endogenous to the person than with a non-dysfunctional reaction to the cessation of a drug'.[13] In addition to these arguments in the literature, several medical organisations, including the Royal College of Psychiatrists[39] and British Medical Association,[40] have released statements in which the term discontinuation syndrome to describe symptoms following SSRI cessation has been abandoned in favour of the term withdrawal. The Royal College of Psychiatrists' recent statement on antidepressants and depression has 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',[39] a contention that is well supported in the literature.[41]

Discussion

From a critical review of the term discontinuation syndrome in the literature, it is clear that the use of the term in place of withdrawal is not justified. As seen in Fig. 1, the use of the term in the literature grew markedly after pharmaceutical company–sponsored conferences in 1997 and 2006. The term discontinuation syndrome, compared with its counterpart withdrawal, does not entail similar negative connotation and, as a result, may serve to reduce patients' fears of dependence.[37] Several authors have expressed concerns that if patients worry about developing dependence or addiction to antidepressants, they may decide to not pursue such treatments.[20,33,37] Such arguments are inconsistent with principles of autonomy and informed consent. An aforementioned survey of 1829 individuals taking antidepressants found that only 1% recalled having been informed about withdrawal effects when they were prescribed the drug.[33] The use of the term withdrawal better enables patients to make appropriately informed decisions.

In addition, the recognition that SSRI use can result in dependence and withdrawal underlines the importance of effective discontinuation management strategies. Although some patients manage to discontinue their SSRI antidepressants without difficulty, SSRI withdrawal symptoms are common and can be severe, and it should not simply be assumed that the patient is having a relapse. Prescribing a medication with a longer half-life is often insufficient to address withdrawal symptoms, especially since the course of resolution of such symptoms is often much longer than the half-life of a drug such as fluoxetine. Tapering of these drugs likely needs to be more conservative than what is usually done for many patients.

It is also worthwhile to note that, although the analysis has focused on symptoms following cessation of SSRI antidepressants, withdrawal occurs with other antidepressants as well, including serotonin–noradrenaline reuptake inhibitor medications[38] and other psychotropic drugs.[42]

In conclusion, the term discontinuation syndrome, which appears to have been established and publicised with the support of the pharmaceutical industries to minimise patient concerns regarding use of SSRI medications, is misleading and should be abandoned in favour of the more appropriate term SSRI withdrawal. Overt acknowledgement that SSRI use can result in dependence and withdrawal

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allows patients to be truly informed in their decisions, and helps inform strategies for safe tapering of these widely prescribed drugs.

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I.M. conducted the literature search, analysis and writing. E.A.-J. was responsible for conception, literature search, analysis and writing, and is the guarantor.

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