COMMENTARY

A key clinical consideration: antidepressant withdrawal or illness relapse?†

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SUMMARY

Distinguishing the symptoms of antidepressant withdrawal from those of relapse is a complex issue that has an impact on a significant number of clinicians and patients. This commentary expands on several important points made by Horowitz & Taylor in their examination of this critically under-researched area and illustrates the relationships between symptoms, and how their onset may provide insights into their aetiology.

KEYWORDS

Depressive disorders; antidepressants; bipolar affective disorders; drug interactions and side-effects; phenomenology.

We commend Horowitz & Taylor (Horowitz 2022) on their timely and informative article, which draws attention to the important topic of identifying antidepressant withdrawal and distinguishing this from relapse. We too have recently provided clinical advice on this matter as part of guidelines for the management of mood disorders (Malhi 2021) and therefore offer some additional insights.

At the outset, it is important to acknowledge, as noted by Horowitz & Taylor, that there is a paucity of research into the phenomenon of symptoms that occur when an antidepressant is withdrawn (termed antidepressant withdrawal) and that we are generally in agreement with their recommendations. However, we feel that some aspects warrant further elaboration and so we begin by expanding on a few points.

Differential risk of withdrawal symptoms: selective versus broad-spectrum antidepressants

The authors discuss in detail the study by Rosenbaum et al (1998) and note that antidepressants vary in terms of their propensity to cause withdrawal symptoms. This is most apparent for the selective serotonin reuptake inhibitor fluoxetine, which by virtue of its long half-life is inherently less likely to cause withdrawal. There are also several medications that appear to be more prone to causing withdrawal symptoms. In our experience, antidepressant agents that have a broader spectrum of neurotransmitter interaction, such as tricyclics and monoaminoxidase inhibitors ('broad-spectrum antidepressants'), are more likely to cause withdrawal symptoms. However, this is not always the case, as paroxetine and sertraline, which are more selective agents, have been shown to pose similar problems. Furthermore, broad-spectrum antidepressants allow for more flexible dosing, which can facilitate the minimisation of withdrawal symptoms. Additional variables that are likely to be in play and that need further examination are dosage and frequency of administration (for agents with marked differences in peak–trough plasma levels, an increase in the frequency of administration can reduce these fluctuations and the likelihood of inadvertent withdrawal effects that can occur with a sharp decrease in plasma levels), as withdrawal is partly a function of the extent to which antidepressants cause 'adaptations in the brain and body [that] can be thought of as resetting of the homeostatic set-point for neurotransmitters' (Horowitz 2022). Clearly determining differential risk of withdrawal symptoms for different antidepressants is an important area for future research as it will directly inform clinical practice.

Temporal aspects of withdrawal

The article also considers the temporal aspects of withdrawal. First, how long has an antidepressant been used? Preliminary research suggests that the longer an antidepressant is prescribed, the more difficult it will be to withdraw and the more likely this will cause symptoms. However, again, this is not always the case, and the first goal of antidepressant treatment is to achieve the complete remission of clinical symptoms. Nevertheless, in practice, the most usual outcome is a partial response, and to achieve the remission of depressive symptoms it is often necessary initially to increase the dose of the antidepressant being prescribed and to

trial augmentation. This is outlined in the 'medication, increase dose, augment, switch' (MIDAS) approach that is advocated by our recent guidelines (Malhi 2021, specifically Section 9, Table 13 and Recommendation Box 4), but inevitably this extends treatment duration. However, whether duration of treatment alone is a key factor in increasing the risk of withdrawal symptoms, or whether this is also dependent on the manner in which therapeutic benefit has been achieved, is yet to be determined. A second important risk factor that demands consideration is the patient's past experiences of withdrawal symptoms when doses of medication are missed. Clinically, the key consideration is that the duration of antidepressant treatment should not be curtailed purely because of this concern. Instead, the focus of management should be to achieve the complete remission of symptoms, and subsequent robust functional recovery, as quickly as possible and only once this has been attained should attention be turned to the gradual withdrawal of antidepressant treatments. This is especially important as the long-term benefits of antidepressants (i.e. in terms of prophylaxis and maintenance treatment) are largely unknown (Malhi 2021).

The pattern of symptoms

The reason for briefly reviewing the factors that predispose to a withdrawal syndrome, such as the type of antidepressant, the duration of the treatment prior to commencement of withdrawal and the speed of withdrawal, is that although all these aspects are useful indicators of the likelihood of withdrawal symptoms, they remain both individually and even collectively insufficient to determine the risk definitively. Further, they do not specifically help determine the source of symptoms that may occur – in terms of whether they are a consequence of antidepressant withdrawal or relapse of the underlying illness. Therefore, Horowitz & Taylor emphasise the importance of discerning the nature and pattern of any symptoms that may occur on the withdrawal of an antidepressant. They point out that some symptoms are almost unique to the withdrawal syndrome and go as far as describing some of them as pathognomonic.

While we are cautious about describing any symptoms as pathognomonic, we regard this approach of symptom pattern recognition as useful, especially as it is in keeping with our rubric for the diagnosis of depression – for which we have proposed the 'activity, cognition and emotion' (ACE) model (Malhi 2018), which assumes a dimensional perspective and is intended for use alongside DSM and ICD classifications. The ACE model may assist in disentangling withdrawal symptoms from relapse, by comparing the known symptoms experienced during a mood episode across these three domains with those experienced when treatment is removed. We value, for example, the examination of cognition in addition to emotions; indeed, when distinguishing withdrawal from relapse, the latter offer little in the way of discriminative power. Hence, in practice, it is the somatic (physical) symptoms along with unusual neurocognitive symptoms that are perhaps most helpful. In our guidelines, these are summed up neatly as FINISH (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances and hyperarousal) (Berber 1998). But clinically, it may be that these more distinctive symptoms do not emerge, and instead it is mood and cognitive symptoms that appear most prominently. In this case, as discussed by Horowitz & Taylor, the pattern of symptoms comes into play, and although it is of some use, they acknowledge the limitations of trying to identify symptom pattern changes in clinical settings.

It is important to note that clinical symptoms often fluctuate, and so here again, both identifying a pattern and then distinguishing this in real-world practice remains a significant challenge, especially as the two sets of symptoms (withdrawal versus relapse) are not always mutually exclusive. In addition, to detect these symptoms clinically and map their respective patterns it is necessary for clinicians to be attuned to their detection in the first place and know what to look for.

We illustrate this challenge in Fig. 1, which also highlights some of the key features of withdrawal. Given the lack of research in this field, it is quite likely that in many instances when antidepressants are withdrawn, both withdrawal symptoms and symptoms related to a recurrence of the illness intermingle and co-occur.

Horowitz & Taylor also correctly point out that even the rating scales used in clinical trials are ill-suited to distinguishing these two sets of symptoms, and they therefore advocate the use of the Discontinuation-Emergent Signs and Symptoms (DESS) checklist (Rosenbaum 1998). However, it should be noted that this is a rather large scale that essentially lists all manner of symptoms and therefore perhaps a more concise scale that targets specifically those symptoms that have the greatest discriminative value is needed.

The role of psychological symptoms

An intriguing consideration that Horowitz & Taylor only touch on briefly is the potential misinterpretation of psychosomatic symptoms of withdrawal as relapse of depression. This is important and worthy of brief discussion, as the cessation of medication is often instituted by patients themselves or

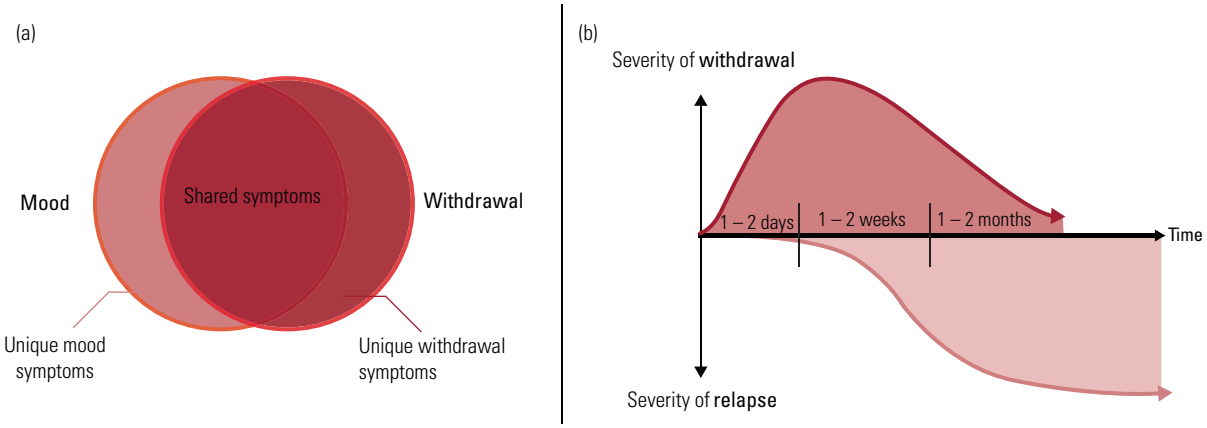

FIG 1 The overlap and temporal relationship between symptoms of withdrawal and relapse. (a) Symptoms that reflect relapse into a mood disorder episode and those that occur because of withdrawal: many typical symptoms of a mood disorder overlap with those of the withdrawal syndrome, making it difficult to distinguish these syndromes based on symptom profile alone. (b) The temporal relationship between withdrawal and relapse symptoms: withdrawal symptoms typically follow a '1 to 2' rule, usually appearing 1–2 days after the commencement of withdrawal, reaching peak severity at 1–2 weeks and eventually remitting within 1–2 months; the symptoms of relapse have a slower onset and, once established, they remain undiminished. Thus, the temporal onset of symptoms may assist in determining the process through which the symptoms have emerged. However, it is important to note that the co-occurrence of withdrawal and mood symptoms is also possible, and perhaps common.

requested by them once they are reasonably well. This may be because, having recovered from their primary illness, the side-effects of treatment are now more evident. In addition, patients often do not want to feel that they 'have to take something to remain well'. This is an understandable desire, and given that the prophylactic benefits of long-term antidepressant therapy remain unclear, it is a request that most clinicians will agree to. However, the conclusion of pharmacotherapy is also a time when it is natural to experience some anxiety and apprehension, as it is only when treatment is finally stopped that it is possible to know for sure whether full recovery has been achieved. Therefore, the emergence of withdrawal symptoms at this time, which are likely to be construed as a relapse, is particularly damaging. Psychoeducation that forewarns of this possibility is likely to be of benefit, as it will reassure patients that if symptoms emerge, it does not necessarily mean they are experiencing a relapse.

The importance of awareness

We agree with much of what Horowitz & Taylor have detailed, and in addition highlight those aspects of the clinical picture that are perhaps most useful in differentiating withdrawal and relapse. We agree with the general advice of withdrawing antidepressants gradually and, ideally, during a period when there are no additional stressors on the patient, while simultaneously taking heed of the duration for which they have been prescribed and also noting the particular class of agent. However, fundamentally both the patient and the clinician need to be aware of the likelihood of withdrawal symptoms. A reasonable working estimate is that approximately one-third of patients stopping antidepressant treatment will experience withdrawal symptoms; symptoms can be mild and negligible but on occasion severe, and they must be sought out specifically.

Knowledge of this is even more important presently because of the introduction of newer agents that have a much faster onset of action with potential side-effects that overlap with those of antidepressant withdrawal. Esketamine, for example, an enantiomer of ketamine, is indicated for use alongside antidepressants and has been found to have a rapid onset of action possibly because of its action on glutamatergic neurotransmission. The acute effects of the medication can be confused with those of depression, especially as the effect of the medication wears off. As is the case with antidepressants, the withdrawal symptoms of esketamine can also be difficult to disentangle from symptoms of an underlying mood disorder, such as loss of appetite, fatigue, anxiety, irritability, insomnia and depressed mood. These new or worsening symptoms that may occur on cessation of esketamine are experienced by approximately 20% of patients, and thus awareness of this possibility is essential for both clinicians and patients (Wajs 2020).

Conclusions

Horowitz & Taylor have drawn attention to a critically under-researched area that affects a significant proportion of patients with mood disorders. Importantly, they provide a useful summary

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of the typical symptoms of withdrawal from antidepressants and note that there are differences in the underlying processes that drive symptoms of withdrawal and relapse. They also note that the symptoms themselves and their timing may also assist clinicians in disentangling the two. In this commentary, we have extended these points and have attempted to illustrate possible relationships between the experience of withdrawal and relapse symptoms, and how their onset may provide further insights into the aetiology of these potentially overlapping sets of symptoms.

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