

BOOK REVIEW

Breaking free: Navigating antidepressant withdrawal

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Giovanni A Fava, *Discontinuing Antidepressant Medications*, Oxford University Press, January 2022, 192 pages, \$38.95 (paperback), ISBN: 97801928966

"It is an art of no little importance to administer medicines properly: but it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them."

-Phillipe Pinel

Antidepressant prescribing has increased substantially over the past few decades across all ages, as has the number of patients on these medications longterm [1-4]. This has raised valid concerns regarding polypharmacy and potentially inappropriate use of antidepressants in the absence of a psychiatric diagnosis [5,6]. In an effort to rationalise medication regimens, mitigate risks of polypharmacy, or for several other valid reasons — such as a previously useful drug no longer being needed — the decision may be made to discontinue the antidepressant. So, what happens when antidepressants are stopped?

According to a systematic review, antidepressants can lead to physical and psychological withdrawal symptoms upon dose reduction or discontinuation in approximately 56% of people; moreover, the symptoms are described as severe in 46% of patients experiencing withdrawal [7]. Furthermore, the duration of these withdrawal symptoms are variable, usually lasting for weeks, but may also be persistent and last for months to years [7]. A recent analysis comparing the risk of withdrawal among 15 antidepressants, using over 30 years of data captured in the World Health Organization's

Global Individual Case Safety Reports pharmacovigilance database, found that selective serotonin reuptake inhibitors (SSRIs) with a short half-life and serotonin and norepinephrine reuptake inhibitors (SNRIs) were associated with an increased risk of withdrawal symptom reports, with the highest risks being with paroxetine, venlafaxine, desvenlafaxine and duloxetine [8].

Despite the frequency and severity of antidepressant withdrawal, clinical practice guidelines (CPGs) do not provide adequate guidance on how to properly assess for and manage withdrawal symptoms. A systematic review of 21 CPGs for depression found that only 15 acknowledged that antidepressant withdrawal symptoms could occur [9]. None of the CPGs provided adequate guidance on mitigating antidepressant withdrawal, distinguishing it from relapse, or managing withdrawal [9]. In general, withdrawal symptoms were described as "mild, brief and self-limiting, and severe in a minority of cases" [9].

The inadequate guidance from CPGs is not surprising, given that prominent psychiatric organisations along with the pharmaceutical industry having long minimised and dismissed this as a problem [2]. These issues have concerned Dr Giovanni Fava, a critically-minded professor of psychiatry and, until recently, long-time editor of the journal *Psychotherapy and Psychosomatics*. His extensive work on harms related to long-term antidepressant use and withdrawal has culminated in his publication of the book *Discontinuing Antidepressant Medications* in 2022. Fava acknowledges the current gap that exists in mental healthcare where patients who experience antidepressant withdrawal symptoms receive inadequate management of their symptoms (unsurprisingly, given the scarcity of literature and lack of clear guidance on the topic), and subsequently seek external support for advice (support groups, online forums, associations) where medical expertise is lacking. The book consolidates the available scientific literature, from case reports to systematic reviews, in addition to several personal anecdotes from his own extensive clinical experience, to provide a comprehensive guide to the prevention, assessment and management of antidepressant withdrawal syndromes.

The first chapter of the book, "Gaining Insight to the Problem", discusses the introduction of SSRI antidepressants to the market and the subsequent emergence of withdrawal symptoms. The chapter provides important background related to the labelling of these withdrawal symptoms once

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they were noted in the 1990's and early 2000's. Fava highlights the swift involvement of the pharmaceutical industry in renaming the clinical presentation to "discontinuation syndromes" in an effort to separate the physical dependence associated with antidepressants from that of other psychotropic drugs such as benzodiazepines. The term "discontinuation syndrome" came into common use despite not having a scientific basis — publications funded by the pharmaceutical industry advocated for the use of "antidepressant discontinuation syndrome" rather than "withdrawal" in an effort to reassure patients concerned about addiction to their antidepressants [2]. However, as Fava highlights, the use of "discontinuation syndrome" in this context "minimizes the vulnerabilities induced by SSRIs and SNRIs".

The next chapter, "Clinical Manifestations of Withdrawal Following Discontinuation of Antidepressants," provides the findings from two systematic reviews led by Fava to characterise withdrawal symptoms from tapering/discontinuation of SSRIs [10], and SNRIs [11]. Similar to the more recent pharmacovigilance data analysis of 15 antidepressant medications described above [8], while the risk is never absent with antidepressants, drugs with shorter half-lives, such as paroxetine and venlafaxine, had higher rates of withdrawal symptoms, and gradual tapering did not eliminate the risk [10,11]. Fava lays out the wide array of withdrawal symptoms that can occur, including somatic symptoms of headache, dizziness, flu-like symptoms and nausea, and psychological symptoms such as agitation, anxiety, panic attacks, dysphoria, irritability, confusion and worsening mood. An exhaustive list of potential withdrawal symptoms organised by body system and associated diagnostic criteria are offered in this chapter and are useful assessment tools for the clinician. Fava goes on to discuss the rather convoluted concept of "behavioural toxicity", which can manifest in patients who are treated with antidepressants, such as by loss of clinical effect over time, paradoxical effects, induction of mania, or treatment resistance/refractoriness. A related concept, "iatrogenic comorbidity", encompasses behavioural toxicity and "refers to the unfavourable modifications in the course, characteristics, and responsiveness to treatment of an illness that may be related to previously administered therapies" during treatment or after discontinuation. Iatrogenic comorbidity helps to explain the prolonged cases of withdrawal syndromes when the drug is no longer in circulation.

Common strategies used in practice to prevent or mitigate antidepressant withdrawal symptoms are based on pharmacokinetic principles. For example, given that drugs with a short elimination half-life, such as paroxetine and venlafaxine, are more likely to cause withdrawal symptoms, it seems intuitive to gradually taper the drug or switch to something with a long elimination half-life, such as fluoxetine, before tapering. Furthermore, a particularly compelling strategy based on clinical and serotonin transporter occupancy considerations is that of hyperbolic tapering, ie,

decreasing the dose by progressively smaller amounts, down to doses lower than minimally therapeutic doses [12]. However, Fava argues that pharmacokinetic principles alone cannot account for those who experience withdrawal symptoms long after the drug is cleared from the body, or who experience persistent postwithdrawal disorders associated with the return of their original illness with greater severity than prior to treatment or new-onset psychiatric disorders. Fava suggests a pharmacodynamic-based "oppositional model of tolerance" could be used to describe this phenomenon, where drug treatment over time may cause the body to enact processes that counter the effects of the drug. For example, these counter-processes could lead to a worsening depression at the beginning of antidepressant treatment or wearing off of clinical effects over time. In the context of withdrawal, once treatment is stopped, these counter-processes are no longer "balanced" by the antidepressant, leading to withdrawal symptoms and potential for persistent postwithdrawal disorder. Factors that influence the clinical course include previous antidepressant treatment (which includes the pharmacokinetic piece here), psychosocial and genetic factors, and therefore each patient is expected to have a unique experience.

Before explaining how he approaches antidepressant discontinuation, Fava reviews the complex decision to discontinue antidepressants. Importantly, the role of shared decision-making between the patient and the healthcare provider is discussed at length. Fava names this a "current gap in practice", which may contribute to patients discontinuing antidepressant treatment on their own, increasing their risk of withdrawal symptoms. It must be noted, though, that many patients and patient groups have developed resources for tapering off these medications [13]. At the same time, Fava points out the clinician's inability to appropriately weigh benefits and risks of treatment given the limitations of CPGs, which are based on studies largely looking at potential benefits for the patient, but tend to neglect the risk of adverse effects and likelihood of treatment response.

Despite this, there are several legitimate reasons why antidepressants are discontinued, and Fava reviews these in detail. This could include lack of tolerability, pregnancy/breastfeeding, paradoxical effects, a switch to a bipolar presentation, lack of or loss of efficacy, unclear indication, planned discontinuation, improved clinical condition or patient preference to discontinue. Fava also encourages the consideration when making this decision, of additional factors that are not well-described in clinical guidelines, such as the characteristics of the treatment setting, patient psychosocial factors, such as living conditions, patient and illness characteristics, and previous treatment course. As important as the reasons for discontinuing antidepressant therapy are, Fava also outlines the equally important reasons to delay discontinuation. This includes "allostatic overload", described as new stressful life circumstances in addition to chronic stress, medical or mood instability. The patient in

front of you is unique, whereas the guidelines provide information on an “average” patient. A holistic view of the situation is of key importance when collaborating with the patient on this decision.

Fava’s approach to assessment of antidepressant withdrawal is then reviewed in detail. Questions to assess for behavioural toxicity secondary to antidepressant medications and the presence of clinical manifestations of oppositional tolerance are clearly laid out. These tools help diagnose withdrawal symptoms and predict the development of a withdrawal syndrome when the antidepressant is discontinued. An important piece explored in detail is the differentiation between relapse and withdrawal symptoms. The clinical presentation of each may overlap and lead to confusion, and a common issue in practice is re-starting the antidepressant in fear of a depressive relapse when the picture is actually related to withdrawal symptoms. This could lead to continuing a medication that is already causing behavioural toxicity, or simply delaying the withdrawal symptoms to the next time discontinuation is attempted, neither of which are helpful.

With regard to managing antidepressant withdrawal, Fava points out the lack of randomised controlled trials to support commonly used strategies such as slow tapering, which Fava has not commonly had success with in his experience treating patients with severe and persistent withdrawal symptoms. Fava offers the reader the approach taken in his own unique and specialised clinic, which employs a psychiatrist (with psychotherapy background), an internist, and four psychotherapists, and offers several contact points with the patient, emphasising the importance of frequent contact and longitudinal psychiatric and medical assessments throughout the course of antidepressant discontinuation. Two types of treatment protocols are offered, consisting of different timelines of antidepressant tapering and discontinuation in combination with explanatory therapy, cognitive-behavioural therapy and well-being therapy. This includes extensive patient follow-up opportunities and a personalised approach to the patient that considers previous discontinuation experiences, the drug, duration of treatment, medical and psychiatric status, and patient preference. Similar to all other withdrawal management strategies currently adopted in practice, Fava’s approach has not been tested in a controlled trial.

While Fava acknowledges the many possible ways of tapering and discontinuing an antidepressant, he offers that a common strategy employed in his clinic is a rapid antidepressant taper (consisting of dose reduction every two weeks) and the introduction of clonazepam, which is titrated upward in dose as antidepressant withdrawal symptoms increase (again, a disclaimer is provided that this approach has not been tested in a controlled trial). The choice of clonazepam over other benzodiazepines was driven by the “anti-anxiety properties, paucity of side effects, facility to titrate, paucity of significant drug interactions, mood-modulating effects, value in conjunction with or after antidepressants, and low likelihood

for dependence compared to other [benzodiazepines].” It is highlighted that “the clinical manifestations in discontinuing antidepressant medications appear to be much worse than with benzodiazepines.” While it is acknowledged that the author’s work is within the context of severe antidepressant withdrawal, the safety of benzodiazepine withdrawal should also be considered. While there is much overlap in reported withdrawal symptoms for both of these drug classes [14], there is a risk of life-threatening seizures that are not present in SSRI withdrawal. Finally, in this chapter, an important consideration brought up by Fava is the management of drug interactions upon discontinuation of the antidepressant. It is recommended that the clinician “consult manuals and resources”. The clinician is also strongly encouraged to collaborate with the patient’s pharmacist, a medication expert who is not only trained to manage drug interactions, but who often has the most accurate picture of the patient’s current medications.

The next three chapters describe the three “psychotherapeutic modules” employed in Fava’s approach to management of antidepressant withdrawal symptoms. The first is “explanatory therapy”, where the clinician provides the patient with accurate information, clarification, principles of selective perception, reassurance, and repetition of the above every 1 to 2 weeks for up to 24 sessions. The goal of this module is to enhance the patient’s endurance throughout the withdrawal symptoms. The second module is cognitive-behavioural therapy, which can be done before or after the explanatory therapy and tapering off of the antidepressant. The approach is largely focused on exposures kept in a detailed journal, with sessions for an observer to interpret the exposures and provide an approach to cognitive restructuring. The third module is “well-being therapy”, where the patient keeps track of well-being (rather than distress) and is provided with homework to perform activities that elicit well-being and optimal experiences, improving the patient’s ability to identify well-being and restructure interfering thoughts or behaviours through cognitive behavioural techniques. All of these modules are quite flexible, but place particular emphasis on frequent patient contact for longitudinal assessment.

After a discussion of methods to discontinue antidepressants, Fava reviews prevention as well, with the focus being on reducing antidepressant prescriptions. Ensuring use of antidepressants only when indicated is important, as in the case of major depressive disorder. However, in cases of anxiety disorders, Fava recommends using antidepressants sparingly and alternatively offering psychotherapeutic approaches (due to the large evidence base) or benzodiazepines. While the case is made that both benzodiazepines and antidepressants are associated with physical dependence and withdrawal, and that benzodiazepines are unlikely to be associated with switching to a mania/hypomania or refractoriness/

resistance, readers may understandably be confused given that the risk of substance use disorders associated with benzodiazepines (and not antidepressants) may outweigh potential benefits.

Fava closes the guide by offering his view on the approach to psychiatric care, the current use of scientific literature in practice, and the importance of scepticism and critical thinking in the interpretation of evidence. Overall, the book provides a detailed look into Dr Fava's research, clinical experience, and the service offered to his patients with severe and prolonged antidepressant withdrawal symptoms. The programme offered is comprehensive and intensive, with dozens of contact points with the specialised team over time, providing patients with excellent support for what can be an extremely challenging time in their lives. The model is idealistic and may not be feasible in all practice settings, and lack of access for patients (either due to scarce availability of providers with the resources to provide such a service, or lack of public psychotherapy funding) can be barriers.

Fava's pioneering work in the area of discontinuing antidepressants, culminating in this book, has been a great service to the many patients, and their clinicians, experiencing severe difficulties in stopping SSRI medication. Importantly, it raises awareness around the issue of antidepressant withdrawal, which remains lacking among clinicians and patients. However, there is a fine balance between ensuring that clinicians and patients take the risks of SSRI withdrawal seriously, and not contributing to patients and clinicians feeling daunted by the prospect of stopping their antidepressant. Indeed, the majority of patients who taper and discontinue their antidepressant do not experience severe symptoms, and more clinicians should consider and pursue deprescribing. More fundamentally, we should question the pathologising of distress, and reconsider the widespread use of antidepressants [15]. For those patients who do end up on antidepressants and experience severe or protracted withdrawal when discontinuing them, this book is a novel and important tool available for clinicians to consult.

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