The undersigned submits this petition to request the Commissioner of Food and Drugs to immediately require the addition of Boxed Warnings, Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information of Prescribing Information to the product label for all selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) products, including branded and generic formulations.

A. Actions Requested

Pursuant to 21 CFR 10.30, the undersigned requests that the FDA require the immediate revision of all SSRI and SNRI antidepressant product labels (included branded and generic formulations) to warn of serious and severe risks as follows:

1. Add a Boxed Warning to inform healthcare providers and patients about the risk of severe, protracted withdrawal symptoms, including symptoms that may persist for months or even years following cessation.
2. Add a Warning in the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information of Prescribing Information to inform healthcare providers and patients about the risk of severe, protracted withdrawal symptoms, including symptoms that may persist for months or even years following cessation.
3. Replace the term “discontinuation syndrome” with “withdrawal” in all Prescribing Information to better reflect the true nature and severity of withdrawal.
4. Add a Warning in the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information of Prescribing Information to inform that withdrawal-induced akathisia can occur upon discontinuation of SSRIs and SNRIs, and that it increases the risk of suicide.
5. Include a detailed description of withdrawal symptoms in the Warnings and Precautions and Adverse Reactions of Prescribing Information, covering the full spectrum of withdrawal effects.
6. Include a statement in the Warnings and Precautions section clarifying that withdrawal symptoms may be misinterpreted as a relapse of the underlying condition, leading to potential misdiagnosis and inappropriate treatment adjustments.
7. Provide evidence-based guidelines for tapering SSRIs and SNRIs in the Prescribing Information, including recommendations for gradual dosage reduction to minimize withdrawal risks, and emphasize that abrupt discontinuation or rapid tapering can increase the severity of withdrawal symptoms.

B. Statement of Grounds

It's well established that withdrawal from SSRI and SNRI antidepressants can lead to severe, long-lasting symptoms. The FDA's current prescribing information does not fulfill its responsibility under the Federal Food, Drug, and Cosmetic Act to provide accurate and complete labeling.

B.1 Mislabeling withdrawal

The pharmaceutical industry has long been criticized for intentionally misleading prescribers and consumers by using the term "discontinuation syndrome" instead of "withdrawal" to describe the symptoms of SSRI and SNRI antidepressant cessation [1-2]. By coining and popularizing the term "discontinuation syndrome," manufacturers aimed to downplay the severity of withdrawal symptoms and avoid associating SSRIs and SNRIs with drug dependence [1-2]. This linguistic choice effectively minimized the risks associated with stopping SSRIs and SNRIs, suggesting that the symptoms were brief and less serious [2]. However, evidence shows that SSRIs and SNRIs, like other psychotropic drugs, can lead to physical dependency, resulting in withdrawal symptoms that are similar to, and often indistinguishable from, those associated with substances like benzodiazepines [3-8]. In 2020, the FDA issued a Boxed Warning for benzodiazepines, acknowledging their potential for dependence and withdrawal [9]. Given that SSRI and SNRI withdrawal reactions can be identical to those of benzodiazepines, these medications warrant similar warnings about dependence and withdrawal. While SSRIs and SNRIs may not be psychologically addictive, they can cause physical dependency, which is thought to develop within about four weeks [10-14]. Withdrawal from these drugs can cause a range of debilitating symptoms, some of which persist for months or even years [2,5,10,15]. It is now well-established that, like benzodiazepines and other dependence-forming substances, SSRIs and SNRIs induce neurochemical changes in the brain, making the withdrawal process more complex and prolonged than previously acknowledged [4-8,11,15-18]. The continued mischaracterization of these symptoms as "discontinuation syndrome" has hindered proper treatment and management, exacerbating patients' suffering [2,19-20]. Given the overwhelming body of evidence regarding SSRI and SNRI dependence and withdrawal, the need for clearer, more accurate labeling and warnings is more urgent than ever.

B.2 Misdiagnosing withdrawal

Withdrawal symptoms from SSRIs and SNRIs can present as a return of previously treated mental health symptoms or the emergence of entirely new psychological symptoms [2,10,20]. These symptoms may include heightened anxiety, depression, irritability, or suicidal thoughts, which can closely resemble the original condition for which the SSRI or SNRI were prescribed [2,10,20-21]. Unfortunately, many prescribers lack adequate education and training on the nature and severity of SSRI and SNRI withdrawal, leading to significant misdiagnosis [2,10,20,22]. In the absence of clear recognition of withdrawal symptoms, patients are often labeled as experiencing a relapse of their mental health condition [2,10,20,22]. In some cases, the patient may be diagnosed with entirely new conditions [23]. This occurs with both patients who have been treated with SSRIs and SNRIs for psychiatric and non-psychiatric conditions [23]. For those with previously diagnosed psychiatric conditions, this misinterpretation occurs because the withdrawal symptoms can present as more intense or severe versions of the mental health symptoms initially treated by the medication [22-23]. Furthermore, mental health diagnoses often carry a stigma that can undermine a patient's credibility, making them vulnerable to receiving additional and misinformed diagnoses [23-24]. As a result, patients may be prescribed additional medications or treated for conditions they do not actually have, prolonging their suffering and complicating their treatment regimen [2,10,22-23]. This lack of understanding is also why withdrawal symptoms are often underreported to prescribers [10,22]. Some patients may be unaware that what they are experiencing is withdrawal, not recognizing the symptoms as medication-related and therefore may not report them [22, 25]. Additionally, due to the lack of education among healthcare providers, patients may be dismissed when they attempt to discuss these symptoms [10,22-23,25]. Consequently, doctors are unaware of the underlying cause of the distress, and withdrawal symptoms go unrecognized [10,22-23,25]. This contributes to the cycle of misdiagnosis and unnecessary treatment adjustments [2,10,22-23,25]. The underreporting of withdrawal symptoms has serious consequences. It not only delays the correct diagnosis and management of withdrawal but also leads to unnecessary medical interventions and the addition of more medications, which could exacerbate the symptoms or result in further complications [10,22-23,25]. Moreover, patients often lose confidence in their healthcare providers, feeling misunderstood or dismissed when seeking help for what is, in fact, a medication-induced issue [10,22]. Addressing this knowledge gap among prescribers is essential to ensure that withdrawal symptoms are recognized and properly managed, and that patients are not incorrectly treated for non-existent mental health conditions.

B.3 Withdrawal severity and duration

A substantial body of research has historically characterized withdrawal symptoms from SSRIs and SNRIs as brief, mild, and self-limiting, often associating flu-like symptoms with "discontinuation syndrome" [26]. Contrary to this view, overwhelming evidence shows that for a significant number of patients, withdrawal symptoms can persist for months or even years [2,10,20,22,27]. The longest documented case of antidepressant withdrawal reported in recent literature spans 11 years (132 months) [10], while data from a peer support forum shows the mean duration to be 37 months, with the median at 26 months [2].

A 2023 study conducted by the National Institute on Drug Dependence in China reviewed the prevalence of antidepressant withdrawal symptoms and the factors that increase the likelihood of experiencing them [28]. The study revealed that 43% of participants reported withdrawal effects after discontinuing their antidepressant medication. It also found that the longer patients had been on antidepressants, the more likely they were to experience protracted and severe withdrawal symptoms [28]. This is especially concerning given that the majority of antidepressant users have taken the medication long-term, with one-fourth using it for 10 years or more, according to the most recent data [29].

The incidence of symptoms following SSRI discontinuation ranged from 27% to 86% across different studies [27]. Nearly half of those who experienced withdrawal symptoms rated their severity as the highest level, with symptom durations varying from just a few days to several years [27]. 80% of individuals experiencing antidepressant withdrawal reported moderate to severe impacts on their lives, including job loss [20]. 40% of participants had symptoms lasting more than two years, and 25% were unable to stop taking antidepressants due to the intolerability of withdrawal symptoms. While many patients experience an acute phase of withdrawal that may last weeks to months, the longer-lasting symptoms are also significantly distressing, impacting major aspects of life such as employment, family relationships, divorce, and social participation [10,20].

SSRI and SNRI withdrawal can present in a variety of ways, including affective, somatic, sleep-related, cognitive, and neurological symptoms. Many symptoms resemble dysautonomia, such as tachycardia, orthostatic hypotension, exercise intolerance, blurred vision, and difficulty regulating temperature. Common psychiatric symptoms induced by withdrawal include panic, anxiety, and depression [2,20,25].

Though it is most commonly linked to antipsychotics, emerging evidence and patient reports show that akathisia can also occur during the withdrawal process from all psychoactive medications, including SSRIs and SNRIs [19,20,30,31,32]. Patients often describe akathisia as extreme agitation and restlessness, accompanied by feelings of

terror, and the overwhelming compulsion to move. The emergence of withdrawal-induced akathisia is a critical yet often overlooked issue. Akathisia can cause profound psychological distress and is strongly associated with suicide [19,30].

This evidence reinforces that antidepressant withdrawal can be not only prolonged and debilitating but also dangerous. While akathisia is not universally experienced, its occurrence in even a subset of patients underscores the urgent need for heightened awareness and a proactive approach to managing withdrawal-induced akathisia. This necessitates the FDA updating prescribing information to include this critical risk.

B.4 Mechanistic insights

It's a common misconception that withdrawal symptoms last only as long as it takes for a drug to be eliminated from the body. In reality, the duration and severity of withdrawal are more closely linked to the brain's process of re-establishing its pre-drug equilibrium, which varies between individuals, rather than being solely determined by the drug's half-life [32]. Furthermore, research suggests that long-term use of SSRIs and SNRIs may cause lasting changes in serotonergic pathways, such as receptor density and sensitivity, contributing to severe and prolonged withdrawal symptoms long after discontinuation [5,32,33].

PET imaging reveals a hyperbolic relationship between the dose of serotonergic medications and SERT receptor occupancy [32,34]. As the dose increases, the number of serotonin transporters blocked rises rapidly at first. However, after a certain point, further increases in dose lead to smaller increases in receptor occupancy, eventually reaching a plateau where nearly all available receptors are occupied, and higher doses have little additional effect [34]. This relationship also applies when tapering: patients may experience larger reductions in SSRI or SNRI doses without significant withdrawal symptoms as the receptors are already saturated [32-34]. Once the dose reduction surpasses this saturation point, the receptors are increasingly affected, which is why tapering should follow a hyperbolic pattern [32-34].

Research suggests that prolonged use of SSRI and SNRI antidepressants can lead to functional changes in the brain that may take months or even years to fully recover from—far longer than the time it takes for the medication to leave the system. This slow process of restoring receptor density and sensitivity can leave the brain in a dysregulated state, emphasizing the importance of hyperbolic tapering, as the brain needs the opportunity to readapt gradually [32-34]. Current guidelines lack evidence-based tapering strategies for

prescribers, and linear reduction schedules are commonly used when discontinuing SSRIs and SNRIs [35]. As demonstrated by the evidence, this approach is not optimal, as receptor occupancy follows a hyperbolic pattern [32,34].

B.5 Conclusion

The evidence is clear that withdrawal from SSRIs and SNRIs can lead to severe, prolonged symptoms for a substantial cohort of patients that are not adequately reflected in the current FDA-approved prescribing information. The undersigned respectfully requests that the Commissioner of Food and Drugs take immediate action to revise the prescribing information for all selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including both branded and generic formulations. The current labeling fails to meet the requirements of the Federal Food, Drug, and Cosmetic Act by not providing accurate, complete, and non-misleading information regarding the nature and duration of SSRI and SNRI withdrawal symptoms.

A growing body of research, coupled with patient testimony, demonstrates that withdrawal symptoms from these medications can persist far longer than what's suggested by SSRI and SNRI prescribing information. This failure to reflect the true extent of withdrawal leads to misdiagnosis, inappropriate treatment changes, and unnecessary suffering for patients.

Therefore, the undersigned urges the FDA to update the prescribing information, incorporating a Boxed Warning, detailed descriptions of withdrawal symptoms, guidance on proper tapering, and recommendations for healthcare providers to recognize withdrawal symptoms and avoid misdiagnosis. These changes are critical to ensuring that patients are fully informed and that healthcare providers are equipped to properly manage SSRI and SNRI tapering.

C. Environmental Impact

This petition qualifies for categorical exclusion under 21 CFR 25.30. The proposed labeling changes do not have any significant impact on the human environment.

D. Economic Impact

An economic impact analysis can be provided upon request in accordance with 21 CFR 10.30(b).

E. Certification

The undersigned certifies that, to the best of their knowledge and belief, this petition contains all the information and views upon which the petitioner relies, including representative data both favorable and unfavorable to the arguments presented. The petitioner is prepared to supply additional data or clarification as may be requested by the FDA.

Morgan Stewart
Founder, Antidepressant Coalition for Education
Email: ace@antidepressantinfo.org
Mailing Address:
P.O. Box 140073
Garden City, Idaho 83714

May 7th, 2025

References

1. Massabki I, Abi-Jaoude E. Selective serotonin reuptake inhibitor 'discontinuation syndrome' or withdrawal. *The British Journal of Psychiatry*. 2021;218(3):168-171. doi:10.1192/bjp.2019.269
2. Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020;10. doi:10.1177/2045125320980573
3. Fava GA, Cosci F. Understanding and Managing Withdrawal Syndromes After Discontinuation of Antidepressant Drugs. *The Journal of Clinical Psychiatry*. 2019;80(6). doi:https://doi.org/10.4088/jcp.19com12794
4. Nielsen, M., Hansen, E.H. and Gøtzsche, P.C. (2012), What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors. Addiction, 107: 900-908. https://doi.org/10.1111/j.1360-0443.2011.03686.x

5. Lerner A, Klein M. Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development. Brain Commun 2019; 1: fcz025.
6. Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. Psychother Psychosom 2020; 89: 283–306.
7. Baldessarini RJ, Tondo L. Effects of treatment discontinuation in clinical psychopharmacology. Psychother Psychosom 2019; 88: 65–70.
8. Marsden J, White M, Annand F, et al. Medicines associated with dependence or withdrawal: a mixed-methods public health review and national database study in England. Lancet Psychiatry 2019; 6: 935–950.
9. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. *FDA*. Published online October 2, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class
10. Framer A. What I have learnt from helping thousands of people taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. 2021;11. doi:10.1177/2045125321991274
11. Taylor DM, Horowitz M. *The Maudsley Deprescribing Guidelines in Psychiatry: Antidepressants, Benzodiazepines, Gabapentinoids and Z-Drugs*. Maudsley Prescribing Guide; 2024:16–17.
12. Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: a review of the clinical evidence and the possible mechanisms involved. *Front Pharmacol*. Epub ahead of print 16 April 2013.
13. Hyman SE and Nestler EJ. Initiation and adaptation: a paradigm for understanding psychotropic drug action. *American Journal of Psychiatry*. 1996; 153: 151–162.
14. O'Brien C. Addiction and dependence in DSM-V. *Addict Abingdon Engl*. Epub ahead of print 6 October 2010.
15. Fava GA. The Clinical Meaning of Withdrawal with Antidepressant Drugs. *Psychotherapy and Psychosomatics*. 2024;93(4):224-229. doi:https://doi.org/10.1159/000540033
16. Ma Y. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. *Molecular Psychiatry*. 2014;20(3):311-319. doi:https://doi.org/10.1038/mp.2014.24
17. Fava Giovanni A, Belaise C. Discontinuing Antidepressant Drugs: Lesson from a Failed Trial and Extensive Clinical Experience. *Psychotherapy and Psychosomatics*. 2018;87(5):257-267. doi:https://doi.org/10.1159/000492693

18. Iacobucci G. NICE updates antidepressant guidelines to reflect severity and length of withdrawal symptoms. *BMJ* 2019; 367: l6103.
19. For Clinicians – Akathisia Alliance. Akathisiaalliance.org. Published 2015. Accessed March 4, 2025. https://akathisiaalliance.org/for-clinicians/
20. Moncrieff J, Read J, Horowitz MA. The nature and impact of antidepressant withdrawal symptoms and proposal of the Discriminatory Antidepressant Withdrawal Symptoms Scale (DAWSS). *Journal of Affective Disorders Reports*. 2024;16:100765. doi:https://doi.org/10.1016/j.jadr.2024.100765
21. Shapiro B, Kramer E, Khoury D, Preda A. Establishing Core Symptoms of Acute Serotonin Reuptake Inhibitor Withdrawal: Results from an International Survey of Online Peer-Support Communities. Pharmacopsychiatry. 2023 Jul;56(4):133-140. doi: 10.1055/a-2078-4593. Epub 2023 May 30. PMID: 37253382.
22. Horowitz MA, Taylor D. Distinguishing relapse from antidepressant withdrawal: clinical practice and antidepressant discontinuation studies. *BJPsych Advances*. 2022;28(5):297-311. doi:10.1192/bja.2021.62
23. Guy A, Brown M, Lewis S, et al. The 'patient voice': patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. *Ther Adv Psychopharmacol* 2020; 10: 204512532096718.
24. Shefer G, Henderson C, Howard LM, Murray J, Thornicroft G. Diagnostic Overshadowing and Other Challenges Involved in the Diagnostic Process of Patients with Mental Illness Who Present in Emergency Departments with Physical Symptoms – A Qualitative Study. Dekel S, ed. *PLoS ONE*. 2014;9(11):e111682. doi:https://doi.org/10.1371/journal.pone.0111682
25. Haddad PM, Anderson IM. Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment. 2007;13(6):447-457. doi:10.1192/apt.bp.105.001966
26. Gabriel M, Sharma V. Antidepressant discontinuation syndrome. CMAJ. 2017 May 29;189(21):E747. doi: 10.1503/cmaj.160991. PMID: 28554948; PMCID: PMC5449237.
27. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: are guidelines evidence-based? *Addict Behav* 2019; 97: 111–121.
28. Zhang MM, Tan X, Zheng YB, Zeng N, Li Z, Horowitz MA, Feng XZ, Wang K, Li ZY, Zhu WL, Zhou X, Xie P, Zhang X, Wang Y, Shi J, Bao YP, Lu L, Li SX. Incidence and risk factors of antidepressant withdrawal symptoms: a meta-analysis and systematic

review. Mol Psychiatry. 2024 Oct 11. doi: 10.1038/s41380-024-02782-4. Epub ahead of print. PMID: 39394455.
29. Pratt LA, Brody DJ, Gu Q. Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. Centers for Disease Control and Prevention. Published August 2017. Accessed March 10, 2025. https://www.cdc.gov/nchs/products/databriefs/db283.htm
30. Akathisia Alliance for Education and Research. Akathisia Alliance. https://akathisiaalliance.org/
31. Henssler J, Heinz A, Brandt L, Bschor T. Antidepressant withdrawal and rebound phenomena. *Deutsches Aerzteblatt Online*. 2019;116(20). doi:https://doi.org/10.3238/arztebl.2019.0355
32. Taylor DM, Horowitz M. *The Maudsley Deprescribing Guidelines in Psychiatry: Antidepressants, Benzodiazepines, Gabapentinoids and Z-Drugs*. Maudsley Prescribing Guide; 2024:28–33.
33. Gray NA, Milak MS, DeLorenzo C, et al. Antidepressant Treatment Reduces Serotonin-1A Autoreceptor Binding in Major Depressive Disorder. *Biological Psychiatry*. 2013;74(1):26-31. doi:https://doi.org/10.1016/j.biopsych.2012.11.012
34. Sørensen A, Ruhé HG, Munkholm K. The relationship between dose and serotonin transporter occupancy of antidepressants—a systematic review. *Molecular Psychiatry*. Published online September 21, 2021. doi:https://doi.org/10.1038/s41380-021-01285-
35. Sørensen A, Juhl Jørgensen K, Munkholm K. Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review. *Therapeutic Advances in Psychopharmacology*. 2022;12:20451253211067656. doi:https://doi.org/10.1177/20451253211067656