

An Oppositional Tolerance Account for Potential Cognitive Deficits Caused by the Discontinuation of Antidepressant Drugs



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ABSTRACT

Depression is the leading cause of disability worldwide, making antidepressant drugs the most used psychiatric drugs in the USA. Withdrawal effects and rebound symptoms frequently occur after the reduction and/or discontinuation of these drugs. Although these phenomena have been investigated with respect to the clinical symptomatology, no studies have systematically investigated the effects of withdrawal/rebound on general cognition. We present a novel framework based on the idea of allostatic adaptation, which allows to predict how different antidepressants likely impair different cognitive processes as a result of withdrawal and rebound effects. This framework relies on the assumptions that the type of cognitive impairments evoked by an antidepressant is determined by the targeted neurotransmitter systems, while the severity of deficits depends on its half-life. Our model predicts that the severity of detrimental cognitive withdrawal and rebound effects increases with a shorter half-life of the discontinued antidepressant drug. It further proposes drug-specific effects: antidepressants mainly targeting serotonin should primarily impair aversive and emotional processing, those targeting norepinephrine should impair the processing of alerting signals, those targeting dopamine should impair motivational processes and reward processing, and those targeting acetylcholine should impair spatial learning and memory. We hope that this framework will motivate further research to better understand and explain cognitive changes as a consequence of antidepressant discontinuation.

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Introduction

Around 300 million people, or 4.4% of the global population, are estimated to be diagnosed with depression [1]. Depression is the leading cause of disability worldwide, with numbers continuously increasing, especially in lower-income countries [1], resulting in very high healthcare costs [2]. As a consequence of the recent COVID-19 pandemic, approximately 4 times as many individuals reported depressive symptoms in the US in June 2020, as compared to the previous year (24.3 vs. 6.5%) [3]. Other countries, such as Germany [4–6], China [7], and Iran [8] seem to follow the same trend.

To date, most national guidelines recommend pharmacotherapy for severely depressed individuals, and a recent meta-analysis has shown that a combination of psychotherapy and pharmacotherapy is most efficient for patients with moderate depression [9]. This, as well as the wide indication of “antidepressants” for other disorders (see below), makes antidepressant drugs the most used psychiatric drugs in the USA, with 12% of US adults reporting to take them [10]. This varies in Europe (average of 7.2%), ranging from 15.7% in Portugal to 2.7% in Greece [11]. In Germany, the use of antidepressants has slowly increased [12] from 3.3% in 2008 to 5.0% in 2017 (derived from federal statistical data available on <https://de.statista.com/infografik/16707/verordnungen-von-antidepressiva-in-deutschland/>). Further adding to this, antidepressants are also prescribed to treat other conditions like anxiety disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and bulimia [13]. In addition to the side effects of taking antidepressants, withdrawal effects (i. e., adverse reactions when ceasing to take a drug) and rebound symptoms (i. e., re-surfacing of depressive symptoms to a greater extent than before starting the medication) seem to frequently occur after their reduction and/or discontinuation [14]. As the brain tries to “compensate” the pharmacologic upregulation of neurotransmission by further physiological downregulation, these alterations drive patients even further away from a “baseline” point of optimal functioning [15].

It is crucial to correctly diagnose these phenomena because withdrawal and rebound symptoms can easily be mistaken for true relapse or recurrence of the original depression. While withdrawal symptoms are usually relatively short-lasting (typically a few hours to a few weeks until complete recovery), rebound symptoms may persist for much longer and last for several months [16]. In 1998, the antidepressant discontinuation syndrome (ADS) was defined to account for withdrawal effects [17]. Rosenbaum et al. [18] suggested the Discontinuation-Emergent Signs and Symptoms Checklist (DESS), which is an ADS symptom list comprising a total of 48 symptoms. Chouinard and Chouinard [16] further elaborated on this and suggested 3 different types of syndromes in a DSM-like type of classification: Type 1 (withdrawal: new symptoms with a peak of 26–96 hours after discontinuation, usually disappearing after a maximum of 6 weeks), Type 2 (rebound: the return of original symptoms, more intense, same peak and duration), and Type 3 (persistent withdrawal disorder: symptoms of new mental disorders, appearing after 24 hours to 6 weeks, may last for months, difficult to distinguish from a relapse) [16]. The likelihood of withdrawal symptoms increases with higher doses of antidepressants [14, 19–21] and with a shorter half-life of the respective drug

[14, 18, 22]. Relapse data in discontinuation studies and animal data measuring neurotransmission [23] further suggest that the stronger the effect of the drug on monoaminergic neurotransmission, the higher the likelihood of relapse. While antidepressant tapering (i. e., gradually reducing the dose) does not necessarily prevent withdrawal and rebound phenomena, it may reduce their severity [24, 25]. The frequency of withdrawal symptoms is difficult to estimate (numbers range between 10 and 70% [22]), as there is currently no agreement on the diagnostic instruments used to measure occurrence and severity. However, the group of Giovanni Fava has recently suggested a diagnostic interview for withdrawal syndromes [26]. Although the incidence of withdrawal symptoms is debated, discontinuation of antidepressants is a frequent phenomenon, which should be reflected in the frequency of withdrawal symptoms, in particular as most patients discontinue without medical supervision: After 1 month of treatment, around one-quarter of patients have already discontinued their antidepressants, and after 6 months, the number rises to nearly two-thirds [27–29].

Many initial prescribers, in particular non-psychiatrists, do not seem to be sufficiently aware of possible withdrawal symptoms. As a consequence many, if not most, patients are not informed about this possible consequence of discontinuation when starting their antidepressant medication [30, 31]¹. This is particularly relevant as antidepressants seem to be no more effective than placebos when prescribed for less severe cases of depression [32]. The most recent discussions of the withdrawal syndromes have focused on their existence, incidence, diagnostics, or management. The clinical picture of withdrawal symptoms for selective serotonin reuptake inhibitors (SSRIs) has been nicely described with the acronym FINISH (Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal) [14, 16, 22]. Yet, most of these publications mainly focus on the serotonergic system. In this article, we chose to take a different approach by focusing on cognitive symptoms during and after withdrawal and by considering the potential functional role of different involved neurotransmitters. Importantly, such cognitive (dys)functions might also be of considerable clinical importance even though their prevalence is commonly underestimated in depression. In a recent survey, over 90% of patients suffering from depression stated to experience cognitive problems in their daily living activities. Yet, only 50% of those patients had ever been asked about cognitive dysfunction by a healthcare professional [33]. So far, only a single study [34] has investigated the effects of the abrupt and brief discontinuation of SSRI antidepressant treatment on cognitive function. It observed that both depressive symptoms and self-reported failures in perception, memory, and motor function increased during discontinuation and were most severe in patients taking paroxetine (as compared to those patients taking fluoxetine, sertraline, or citalopram). While all of the antidepressant medications investigated in this study were SSRIs, it is noteworthy that the SSRI with the shortest half-life accounted for the most severe worsening of both depressive and cognitive complaints during discontinuation. Despite the current

1 Read [30] reported that in a recent online survey of 867 people from 31 countries who used antidepressants, only “six people (0.7%) recalled being told anything about withdrawal, dependence or addiction by the initial prescriber.”

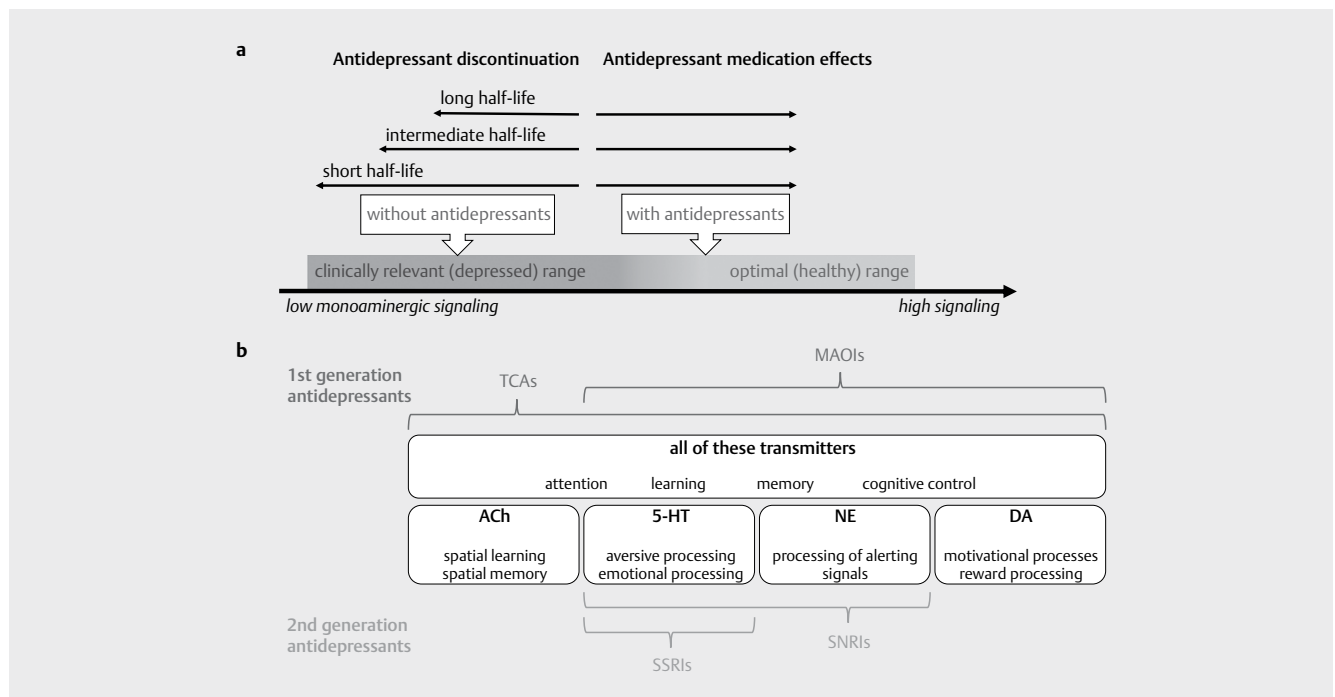
lack of further studies on this topic, identifying and targeting cognitive dysfunctions caused by the discontinuation of antidepressants is crucial given that biases in cognitive processes such as attention and memory may not only be associated with depressive symptoms, but they have actually been shown to predict patients' vulnerability for the first onset and recurrence of depression [35]. Likewise, the decision to invest effort has been shown to be linked to prospective relapse risk after antidepressant discontinuation [36], thus further highlighting the importance of cognitive markers (like effort-related decision-making) in predicting relapse risk. In sum, we deem it of utmost importance to shed more light on potential cognitive deficits caused by the discontinuation of antidepressants, as targeting such potential deficits might reduce or delay relapse rates and enhance the productivity of patients in working environments [37, 38].

In the following, we will outline different types of antidepressants and their effects on different families of neurotransmitter transporters, the potential allostatic mechanisms underlying withdrawal and rebound effects, and how the different neurotransmitter systems targeted by antidepressants affect cognitive processes. We argue that as a consequence of withdrawal and rebound effects, cognitive deficits are likely to develop depending on a) the type of antidepressants and the neurotransmitters affected by them and b) the half-life of the antidepressants used. Taking into account both of these factors, we propose a novel framework, which is based on the idea of allostatic adaptation and allows to predict how the different antidepressants are likely to impair cog-

nitive processes as a result of withdrawal and rebound effects (► Fig. 1).

Antidepressants affect different neurotransmitter systems: A very short overview

The first generation of antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) was introduced in the 1950s and served as evidence to formulate the monoamine hypothesis of depression [39], which suggests that a lack of monoamines and/or monoaminergic signaling fosters depression. In the 1980s, the second generation of antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin-noradrenaline reuptake inhibitors [SNRIs]) hit the market and revolutionized the pharmacological therapy for depression [39]. Due to their improved tolerability and safety profile, the second generation has largely replaced the use of the first generation of antidepressants in treatment [40]. However, it should not go unmentioned that there are also other, more recently developed multimodal antidepressants such as vortioxetine, which increases both serotonergic and acetylcholinergic signaling and is receiving increasing attention as an add-on therapy in patients with SSRI-resistant depression, and might also benefit cognition [41]. Aside from the monoamine hypothesis, alterations in glutamate receptors, neuronal plasticity, GABAergic transmission, stress/hypothalamic pituitary adrenal (HPA)-axis, and neuroinflammation have also been suggested to contribute to depressive symptoms and thus provide potential alternative targets for pharmacological intervention [42]. While



► **Fig. 1 a.** Illustration of the suggested shift in monoaminergic signaling underlying withdrawal and rebound effects. Please note that antidepressants with a short half-life are expected to cause more severe dysregulation (i. e., deficient monoaminergic signaling) and thus more severe cognitive deficits upon their discontinuation. **b.** Illustration of the antidepressant drug types and the different neurotransmitters that they affect. The first generation of antidepressants (TCAs and MAOIs) affects a broad spectrum of neurotransmitters, whereas the second generation of antidepressants (SSRIs and SNRIs) has a more selective effect. The targeted neurotransmitters also determine the range of cognitive deficits that are likely to develop as a result of withdrawal and rebound effects triggered by drug discontinuation.

the research on glutamate receptors and other hypotheses is promising, alternative treatments like ketamine administration are still in too early stages to be considered a validated and established approach in the treatment of depression as of yet [42]. As most patients are therefore still prescribed primarily monoaminergic antidepressants, we will mainly focus on this class of antidepressants in this article. Moreover, even if the mechanism of effects on mood might be related to other processes than monoaminergic neurotransmission, discontinuation of standard antidepressants will nevertheless cause monoaminergically-mediated withdrawal effects, as their effects on those neurotransmitters are strong and undisputed. Over the next section, we will briefly sketch the essential pharmacodynamics of the first and second generation of antidepressants, as well as vortioxetine, to establish an understanding of their shared and different pharmacological properties (► **Fig. 1b**).

First-generation antidepressants

TCAs

Tricyclic antidepressants block serotonin and norepinephrine transporters, thus increasing the synaptic levels of serotonin (5-HT) and norepinephrine (NE). They further act as potent antihistamines and anticholinergics, showing a high affinity for antagonizing the α adrenoreceptor and the H1 and H2 histamine receptors, as well as the muscarinic acetylcholine (ACh) receptors [43].

MAOI

Monoamine oxidase inhibitors inhibit the activity of 1 or both monoamine oxidase enzymes (MAO-A and MAO-B). As these enzymes are responsible for metabolizing monoaminergic neurotransmitters like dopamine (DA), NE, and 5-HT, MAOIs increase the availability of those neurotransmitters in the brain [43].

Second-generation antidepressants

SSRIs

SSRIs increase the extracellular level of 5-HT by limiting its reabsorption (reuptake) into the presynaptic cell. This makes more 5-HT available to bind to the postsynaptic receptor [44].

SNRIs

SNRIs bind to 5-HT and NE transporters, thus increasing the extracellular levels of 5-HT and NE [45].

Newly developed multimodal antidepressants

Newly developed multimodal antidepressants, such as vortioxetine, target both 5-HT_{1A} receptors and the serotonin transporter (SERT) [42], and among other effects, facilitate the release of ACh [46].

In sum, the first and second generation of antidepressants share similar mechanisms of action on monoamines, but while the former impact a broad spectrum of neurotransmitters, the latter have more selective/specific effects on only 1 or 2 tightly interrelated neurotransmitter systems [47].

Mechanisms of Action of Withdrawal and Rebound Effects

In this section, we discuss the potential mechanisms of action underlying withdrawal and rebound effects (► **Fig. 1a**). In this context, 2 interesting hypotheses have been proposed: the allostatic adaptation account [48] and the oppositional tolerance model [49]. Both are based on the assumption that monoamines underlie homeostatic control, but they differ in their assumptions on whether or not this control can be maintained during depression and/or the intake and discontinuation of monoaminergic medication [23].

All pharmacologically active compounds produce neuroadaptation (i. e., physiological changes that serve to maintain homeostasis and take place as a result of using drugs) [50]. As a consequence of this neuroadaptation, a new homeostatic point is set, so when the drugs are abruptly discontinued, this induces disruption of the homeostasis [48]. This disruption is thought to cause withdrawal and rebound effects, and the deeper the drug-induced disruption of the homeostasis, the stronger the withdrawal and rebound effects will be [48]. For antidepressants, at least 4 weeks of drug intake appear to be required for withdrawal and rebound effects to occur after discontinuation, suggesting that this is long enough for antidepressants to change allostatic adaptation [51]. Such disrupted homeostasis can lead to a hyper-responsive serotonergic system [14]. Indeed, several antidepressants do not only block the 5-HT and NE transporters but also cause a decrease (and not a counter-regulatory increase) in these transporters when taken long-term [52–54].

In contrast to this [23], adaptationist hypotheses such as the oppositional tolerance account [49] suggest that homeostatic mechanisms are properly functioning in most depressive patients but that oppositional tolerance arises with protracted antidepressant use, where oppositional forces trigger monoamine levels to alter/perturb their equilibrium levels when medication use is discontinued. As depressive symptoms are modulated by monoamines, this overshoot triggers a potential re-emergence of depressive symptoms, which is proportional to the perturbational effect of the protracted antidepressant use.

Notably, a meta-analysis of antidepressant discontinuation studies supports the notion that the relapse risk after antidepressant discontinuation is positively associated with the drug's enhancing effects on monoamine concentrations in the brain [23]. Based on this, Andrews et al. [23] deemed it more likely that withdrawal and rebound effects are the result of oppositional tolerance [49].

Antidepressant types are likely to determine which cognitive processes will be impaired by withdrawal and rebound effects

In this section, we outline the link between the neurotransmitters modulated by antidepressants (i. e., 5-HT, NE, DA, ACh) and specific cognitive deficits that may be produced by withdrawal and rebound effects (see ► **Fig. 1b**).

The monoamines most consistently linked to depression are 5-HT and the catecholamines NE and DA. Monoamines coordinate many important biological processes like sleep, circadian rhythm, body temperature, appetite, pain, and motor activity, but they also regulate higher brain functions like cognitive processes [55]. The

high density of monoaminergic and cholinergic projections in the midbrain nuclei, hippocampus, substantia nigra, and prefrontal cortex [56, 57] highlights their anatomical and neurochemical affiliation with brain regions most commonly linked to cognitive processes. Pharmacological challenges, patients, and animal studies have consistently demonstrated that these neurotransmitters have overlapping and interactive effects in driving attention, memory, and learning. Importantly, all of these cognitive functions are known to be dysfunctional in neuropsychiatric and neurodegenerative diseases, in which these neurotransmitters are affected (e. g., schizophrenia, Parkinson's, and Alzheimer's disease) [58–62]. Even though there is a large functional overlap between monoamines [60, 62] and ACh [58], these neurotransmitter systems are differently affected by different antidepressant drug types and seem to partly subserve different cognitive functions (► **Fig. 1b**). DA, NE, and 5-HT are important for cognitive control (i. e., the way we control our thoughts and goal-directed behavior, including core executive functions) [63–71].

5-HT is also likely involved in processing aversive and emotional information, even if that effect might not be uniquely restricted to this neurotransmitter system [60]. Enhancing 5-HT levels boosts the processing of positive emotional information both in healthy controls and patients with severe depression, indicating that enhancing a positive bias might be the prerequisite for patients being able to start the cognitive restructuring of their symptoms [72].

NE seems to be particularly relevant for the processing of attentional control [73] and to have a crucial role in the maintenance of attentional biases [74]. The NE system has further been suggested to underlie impairments in disengaging attention from mood-congruent material, which is typical of depressive patients [75].

DA has a predominant, but not exclusive, effect on motivational control and reward learning (i. e., how we process rewards to choose the most adaptive response to the environment) [76]. Notably, reward processing appears to be dysfunctional in depression, and this has been linked to abnormal phasic striatal dopamine signaling, which is crucial for reinforcement learning and for an optimal allocation of effort to obtain rewards [77].

ACh seems to have a major, but not exclusive, role in spatial learning and spatial memory [58, 78]. ACh has been linked to deficits typical of depressive patients in how information about the external environmental space is acquired, stored, organized, and used [79].

Lastly, the excitatory neurotransmitter glutamate plays a major role in learning and neuronal plasticity [42, 80], while the inhibitory neurotransmitter GABA plays a major role in response selection and the regulation of cognition, emotion, and memory [42, 81–83]. Patients with depression have been shown to suffer from impaired neuroplasticity due to changes in glutamatergic signaling [42, 80, 84] as well as reduced CNS levels of GABA [42, 85].

So far, we found no studies that systematically investigated the effects of withdrawal/rebound on general cognition. Regarding the potential specific cognitive deficits produced by the discontinuation of the different antidepressant types, we expect SSRIs, by their selective effect on 5-HT, to mainly induce impairments in the processing of aversive and emotional information (besides attention, learning, memory, and cognitive control). As a consequence of their selective effect on both 5-HT and NE, SNRIs are likely to cause similar changes as SSRIs, but with deficits extending to the processing

of alerting signals, as this function depends on NE. Regarding the first generation of antidepressants, MAOIs should exert deficits comparable to SNRIs, but they should additionally encompass motivational and reward processing. Further, we hypothesize TCAs to broaden their impairments even further than MAOIs and also affect spatial learning and spatial memory when discontinued. Lastly, newly developed multimodal antidepressants, such as vortioxetine, are known to exert procognitive effects via ACh [86], and, consequently, should negatively affect spatial learning and spatial memory when discontinued.

In sum, we suggest that due to the differences in the functional neurotransmitter systems targeted by different antidepressants, it should be possible to determine which cognitive processes will be most likely impaired by withdrawal and rebound effects.

The severity of the cognitive deficits triggered by withdrawal and rebound effects are likely to depend on the half-life of the antidepressants

In this section, we argue that similar to what is known about the clinical symptoms and irrespective of the antidepressant types / the targeted neurotransmitter systems, the severity of the cognitive deficits caused by withdrawal and rebound effects are likely to depend on the half-life (i. e., plasma elimination time) of the antidepressants. For clinical symptoms of SSRI discontinuation, it is well-known that paroxetine (which has a very short half-life) is much more likely to induce withdrawal symptoms than drugs like fluoxetine (which has a very long half-life) [17, 87]. Matching this hypothesis, it has indeed been reported that the abrupt interruption of paroxetine intake caused significantly more cognitive deficits than the interruption of fluoxetine intake, and the deficits were reportedly only reversed after the reinstatement of the treatment [34]. The onset of withdrawal and rebound symptoms are likely to happen around 3 – 5 half-lives after discontinuation [88], and the shorter the half-life of the antidepressants, the more severe the withdrawal and rebound symptoms are expected to be [14]. Based on the idea that the affected neurotransmitter systems will not only be relevant for specific clinical symptoms but also for cognitive withdrawal effects, we propose a correlation: The more severe the clinical withdrawal and rebound symptoms, the stronger the expected cognitive impairments will be (► **Fig. 1a**). In the case of longer half-life, such as for the SSRI drug fluoxetine (better known as Prozac) [17, 87] and the SNRI drug milnacipran (commercialized under the name Savella and MilnaNeurax), we hypothesize mild withdrawal and rebound symptoms [89], which should translate into subtle cognitive deficits. Many of the most used antidepressants show intermediate half-lives, such as the SSRI drug citalopram (better known as Celexa), sertraline (sold under the brand name Zoloft), and the SNRI drug duloxetine (known as Cymbalta). Given their intermediate half-life, we expect them to display moderate withdrawal and rebound symptoms [20, 90, 91], which should on average trigger more cognitive impairments than drugs with a long half-life. In contrast, antidepressants with a short half-life like MAOIs [92] and TCAs [93], the SNRI drug venlafaxine (commercialized as Effexor) [25, 94], and the SSRI drug paroxetine (better known as Paxil and Seroxat) [95], should be associated with strong withdrawal and rebound symptoms, which are most likely to produce severe

cognitive impairments, as compared to substances with a longer half-life.

In sum, we expect the half-life of antidepressants to predict the severity of the cognitive impairments triggered by withdrawal and rebound effects: the shorter the half-life, the more severe the cognitive deficits. It is for empirical research to determine whether this is true and if there are also long-term cognitive deficits like they have been described for clinical symptoms.

Conclusions

Worldwide, antidepressant drugs are the most prescribed and sold psychiatric drugs, which are used to not only treat depression, but also anxiety, OCD, and PTSD. Considering that antidepressants are also commonly prescribed for milder symptoms, even though their use in minor depression has been shown to yield no advantage over placebos in alleviating clinical symptoms [32, 96], it is crucial to question whether the negative effects (withdrawal and rebound effects) are outweighing the limited potential positive effects in mild cases. Keeping in mind that intact cognitive functioning is a reliable predictor known to prevent relapses, we present a comprehensive novel framework based on the idea of allostatic adaptation, which details how withdrawal and rebound effects might potentially cause cognitive deficits. The framework proposes that the type of cognitive impairment is likely to be determined by the neurotransmitter systems targeted by the specific antidepressants and that the severity of the deficits will depend on the half-life of the antidepressants used. Given that the field of withdrawal and rebound effects produced by antidepressants is still under-investigated, we hope that this framework will motivate new research to better understand and explain cognitive changes as a consequence of antidepressant discontinuation, as well as their contribution to relapses of depression. Therefore, prospective cohort studies that take different antidepressant types into account should also provide evidence for causal relationships between antidepressant discontinuation and cognitive deficits, as well as their role in relapses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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