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Antidepressant discontinuation syndrome: a state-of-the-art clinical review

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Abstract:	Antidepressant drugs are prescribed to patients with depressive, anxiety disorders, and other conditions. Evidence about antidepressant discontinuation syndrome (ADS) and related outcomes is sparse, although potentially burdensome in some patients. The present state-of-the-art review aims to appraise the most current evidence about ADS critically. ADS has been documented for most antidepressant drugs, although most literature focuses on selective serotonin reuptake inhibitors prescribed for depression. While down-titration cannot exclude the chance of ADS, it is nonetheless warranted in the clinical setting, especially for short half-life and sedative compounds such as paroxetine. Integrative management with concurrent pharmacotherapy and psychotherapy may minimize the eventual unpleasant effects arising within the discontinuation process. In addition, patient-tailored interventions and education should be part of the discontinuation strategy. Future research must rely on broadly accepted definitions for ADS and related phenomena such as antidepressant withdrawal and shed further light on the underpinning neurobiology. Discriminating between ADS-related phenomena and relapse of depression is likewise warranted, along with a neuroscience-based nomenclature instead of a class one.

Highlights

- While exact incidence rates and duration are a matter of debate, antidepressant discontinuation syndrome (ADS) represents a quite frequent and burdensome outcome.
- ADS encompasses both physical and psychological symptoms not to be confused with relapse of depression.
- The management of ADS includes slow tapering of the antidepressant and supportive psychosocial care to enhance treatment adherence and doctor-patient relationship.
- Future studies should rely on validated operational criteria to inform the clinical practice.

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Antidepressant discontinuation syndrome: a state-of-the-art clinical review

"Antidepressant discontinuation"

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Abstract (167/250 words)

Antidepressant drugs are prescribed to patients with depressive, anxiety disorders, and other conditions. Evidence about antidepressant discontinuation syndrome (ADS) and related outcomes is sparse, although potentially burdensome in some patients. The present state-of-the-art review aims to appraise the most current evidence about ADS critically. ADS has been documented for most antidepressant drugs, although most literature focuses on selective serotonin reuptake inhibitors prescribed for depression. While down-titration cannot exclude the chance of ADS, it is nonetheless warranted in the clinical setting, especially for short half-life and sedative compounds such as paroxetine. Integrative management with concurrent pharmacotherapy and psychotherapy may minimize the eventual unpleasant effects arising within the discontinuation process. In addition, patient-tailored interventions and education should be part of the discontinuation strategy. Future research must rely on broadly accepted definitions for ADS and related phenomena such as antidepressant withdrawal and shed further light on the underpinning neurobiology. Discriminating between ADS-related phenomena and relapse of depression is likewise warranted, along with a neuroscience-based nomenclature instead of a class one.

Keywords: Antidepressant; discontinuation syndrome; withdrawal; review.

1. Introduction

Of the roughly 800 million people endorsing a mental disorder worldwide, depression and anxiety are among the most burdensome (Vos et al., 2020), driving the prescription of antidepressants. In addition, people with obsessive-compulsive disorder, insomnia, chronic pain, fibromyalgia, eating disorders, smoking cessation, migraine, and attention-deficit/hyperactivity disorders may receive antidepressant prescriptions (Cascade et al., 2007). However, estimates of antidepressants' utilization in the community need further assessment (Lunghi et al., 2022).

Common scenarios soliciting antidepressant discontinuation include i) remission of the condition requiring antidepressant pharmacotherapy; ii) unsatisfactory response despite "*adequate*" trialing (Quitkin et al., 1984); iii) loss of response (Fornaro et al., 2019); iv) severe treatment-emergent adverse reactions; v) change in the therapeutic schema due to the introduction of new drugs having relevant clinical interactions; and vi) changes in the insurance plan coverage (Zwiebel and Viguera, 2022). In addition, many patients abruptly discontinue their antidepressant medications early without the knowledge of the prescribing clinician for several reasons (Jaffray et al., 2014). Among other reasons, the fact that most antidepressants have a less favorable acceptability profile vs. placebo in the acute treatment of major depressive disorder (MDD), with odds of withdrawal ranging between odd ratio (OR)=1.64 and 4.44 and 95%C.I., excluding the null (Cipriani et al., 2018).

Antidepressant discontinuation may lead to systemic and neuropsychological symptoms of varying severity and duration, accounting for the so-called "*antidepressant discontinuation syndrome*" (ADS) (Figure n.1).

The burden associated with ADS may also mine the patient's trust in the doctor and overall treatment adherence (Jaffray et al., 2014), soliciting appropriate counseling, patient education, and doctor awareness.

The present review aims to appraise the most current evidence about ADS critically.

2. Methods

The present narrative review follows a "*state-of-the-art*" approach for selected topics (Table n.1), owing to the recommendations outlined elsewhere aiming to critically "*address more current matters in contrast to other combined retrospective and current approaches*" (Grant and Booth, 2009).

The search strategy ran on May 8th, 2022. adopted the following terms or their combination: "*antidepressant*," "*discontinuation*," "*withdrawal*," "*tapering*," "*dependence*," "*tolerance*," "*addiction*," "*acceptability*," "*tolerability*," and "*management*" for peer-reviewed records indexed in PubMed/MEDLINE database using MeSH (Medical Subjects Headings). No publication date or language restriction was applied. In addition, meta-analyses (MAs) and systematic reviews (SRs) of large-scale observational studies, randomized controlled trials (RCTs) providing a reliable quality assessment of the results were prioritized over single-drug packages and case-series/reports for preliminary emerging evidence not otherwise covered in the literature. Noteworthy, the putative mechanisms of action of the "*drugs used in the treatment of depression*" are broad to the extent that neuroscience, rather than a class-based, nomenclature approach, has been promoted by the European Neuropsychopharmacology Association through the present Journal (Zohar and Levy, 2022; Zohar et al., 2015). Yet, the present review adopts the classic monoamine-based nomenclature and "*ADS*" terminology to reflect the broadest evidence at synthesis, especially the most consolidated one.

3. Antidepressant discontinuation syndrome: conceptualization and current perspectives

Research interest in ADS and related phenomena holds high (Figure n.2).

The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders, text revision (DSM-5-TR) enlists ADS among the "*medication-induced movement disorders and other adverse effects of medication*" section G25.79, page n.818. The DSM-5-TR postulates that ADS "*may occur following treatment with all types of antidepressants" and that the "incidence depends on the dosage and half-life of the medication being taken and the rate at which the medication is tapered*." The DSM-5-TR also warrants further longitudinal studies on ADS and guidance for differential diagnosis (APA, 2022).

The guidance provided by the DSM-5-TR essentially stems from the reports concerning a "*self-limiting*" (usually resolving within 2-3 weeks) "*discontinuation syndrome*" following the serotonin reuptake inhibitors (SSRIs) originating in the late 1990s (Zajecka et al., 1997) (Schatzberg, 1997; Schatzberg et al., 1997).

Both the 2009 U.K. National Institute for Health and Care Excellence (NICE) (1.9.2.1 in CG90) (NICE, 2009) and the 2010 U.S. American Psychiatric Association (APA) depression guidelines for the treatment of MDD, third edition (APA, 2010) reflect such a view.

Yet, the amendment of the NICE guidelines for "*medicines associated with dependence or withdrawal symptoms*," published on April 20th, 2022, acknowledges that "*there is substantial variation in people's experience, with symptoms lasting much longer (sometimes months or more) and being more severe for some patients*" (NICE, 2022). This latter acknowledgment reflects the input from medical bodies and experts (Iacobucci, 2021; Mahase, 2019) to take into account the potential severity and duration of discontinuation-related phenomena and the risk of

misdiagnosis (Davies and Read, 2019; Fava et al., 2015) (Chouinard and Chouinard, 2015) (Cosci and Chouinard, 2020). Comparably, the Clinical Practice Guidelines for the Treatment of Depression Across Three Age Cohorts released by the APA in February 2019 still adopt the term "*discontinuation*" rather than "*withdrawal*," albeit acknowledging the chance for enduring effects following the cessation of the antidepressant exposure (APA, 2019).

Specifically, while a pivotal 2018 evidence-based, grounded SR from U.K.-based authors documented strikingly high incidence rates of antidepressant "*withdrawal*" (range 27-86%, weighted average of 56% of the exposed cases) (Davies and Read, 2019), expert prescribing psychiatrists based in the U.S. disputed the chance of frequent, long-lasting, highly disabling outcomes for the majority of the patients who stop their antidepressant medications (Pies R.W. and D.N., 2019). Please refer to Table n.2 for the core terminology relevant to the present review.

4. Antidepressant discontinuation syndrome: a critical appraisal of the evidence and essential neurobiology towards optimal clinical management

Antidepressant discontinuation reactions follow a characteristic pattern, although rare outcomes have likewise been reported. This is the case of extrapyramidal syndromes, states mimicking (hypo-)mania (Haddad and Anderson, 2007; Narayan and Haddad, 2011), sensation perceived as electrical flashes that occur inside the brain decreasing the antidepressant levels - "brain zaps" (Papp and Onton, 2018), and other effects prone to be misdiagnosed as relapse of depression (Chouinard and Chouinard, 2015; Warner et al., 2006). In addition, neurocognitive symptoms are often neglected (Popovic et al., 2015).

The clinical experience suggests gradual discontinuation of the antidepressant drugs (Jha et al., 2018; Pies R.W. and D.N., 2019). This latter approach is in line with the results from positron emission tomography studies of serotonin transporter (SERT) occupancy by the SSRIs, supporting the practice of a hyperbolical dose reduction of the antidepressant rather than a linear one to reduce ADS-related phenomena (Horowitz and Taylor, 2019).

Specifically, the SERT occupancy of the SSRIs would vary across different doses (Meyer et al., 2004). For example, the SSRI citalopram steadily administered at 60mg/day would result in 87.8% SERT occupancy, 40mg/day would result in 85.9%, 20mg/day in 80.5%, 9.1mg/day in 70%, 5.4mg/day in 60%, 2.3mg/day in 40%, 1.5mg/day in 30%, 0.8mg/day in 20%, and 0.37mg/day in 10%, using the Michaelis-Menten equation of best fit for doses produced by a combination of tablets and liquid formulations, approximated (Meyer et al., 2004). This means that tapering off should be particularly gradual, especially upon reaching low doses of the SSRI, following a hyperbolic decrease rather than a fixed decrement (Horowitz and Taylor, 2022).

While existing evidence-based recommendations essentially rely on RCTs hardly reflect the real-world setting, consistent with the clinical practice, rational pharmacotherapy involving temporary augmentation strategies with benzodiazepines, anticholinergic, antihistamine, beta-blockers, or the non-selective α-2 agonist clonidine should be considered (Naguy, 2016), particularly in the case of abrupt discontinuation poorly responsive to the prompt reintroduction of the discontinued antidepressant. This is particularly true for antidepressants with "*sedative*" pharmacodynamic profiles: e.g., anticholinergic or antihistamine supplementation should be recommended for the most sedative tricyclic antidepressants – TCAs or, to a lesser extent, for the SSRIs paroxetine and citalopram, respectively.

Tapering of the antidepressant drugs also relies on pharmacokinetic considerations: the antidepressant discontinuation syndrome is most frequently seen with paroxetine (the shortest half-life SSRI compound) and less commonly seen with fluoxetine (the longest half-life drug among the SSRIs, accounting also for its active metabolite norfluoxetine) (Jha et al., 2018).

Gradual tapering of the antidepressant is warranted for people who have already proved to be vulnerable to antidepressant discontinuation symptoms, depressed patients presenting hints of sub-threshold bipolarity, panic disorder (Baldessarini et al., 2010), or those subjects who already experienced jitteriness/anxiety syndrome upon commencing an antidepressant drug (Jeon et al., 2022).

Patients with MDD who already achieved remission would have lower odds of relapse in case of slow tapering over six months compared to abruptly discontinued controls (Lejoyeux and Adès, 1997). Gradual vs. rapid antidepressant discontinuation was corroborated by more recent evidence (Baldessarini et al., 2010). However, it is noteworthy that a recent large-scale

quantitative Cochrane review, including 33 studies encompassing 4,995 adults with depression, suggested very low certainty of evidence that abrupt discontinuation without psychological support may inflate the risk of relapse according to 13 documenting studies (hazard ratio [HR]=2.09, 95%C.I.=1.59-2.74, based on 1,373 participants from ten studies). Also, insufficient evidence exists about the effect of abrupt discontinuation of the antidepressant on adverse events (OR=1.11, 95%C.I.=0.62-1.99; n=1,012 participants, N=7 studies; I^2= 37%) compared to the continuation of the antidepressant, without specific assessment of withdrawal symptoms, according to the same piece of evidence, concluding that effects of abrupt discontinuation on withdrawal symptoms (number of studies=1) is very uncertain. However, none of the studies included a successful discontinuation rate as a primary endpoint (Van Leeuwen et al., 2021). In addition, it has been suggested that withdrawal reactions with the antidepressant drugs could occur both with abrupt and gradual discontinuation of the SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), with no significant advantage of the latter strategy (Fava et al., 2015) (Chouinard and Chouinard, 2015) (Fava et al., 2018). Moreover, it has been claimed that gradual tapering of the antidepressants may inflate the risk for misdiagnosis of relapse of depression instead of ADS (Fava and Cosci, 2019). However, underscoring the benefits of gradual vs. abrupt discontinuation of the antidepressant contrasts with the clinical experience of many clinicians, and caution in the interpretation of general guidance is particularly warranted in the lack of conclusive evidence suggesting performing the opposite.

Indeed, this is a long-lasting matter of debate: expert consensus statements for the prevention and the clinical management of antidepressant discontinuation originated decades ago (Andersen and Kristiansen, 1959).

Statements and recommendations have been updated over the past years resulting in clinically-oriented guidance (Jha et al., 2018). Yet, only a bounce of evidence systematically appraised the role of antidepressants other than the SSRIs in recent years (Fava et al., 2018; Lejoyeux and Adès, 1997), essentially due to publication bias, though even the non-SSRI antidepressant may induce antidepressant discontinuation symptoms or related phenomena such as rebound, tolerance/treatment-emergent loss of efficacy, and discontinuation-induced refractoriness (Cattaneo et al., 2020; Grady and Stahl, 2012) (Fornaro et al., 2019).

4.1 Neurobiological and pharmacological considerations matter towards the understanding of ADS and related phenomena.

Specific non-SSRI drugs may, in theory, feature a better acceptability profile for discontinuation symptoms, namely agomelatine (Harvey and Slabbert, 2014) or the "*anxiolytic*" azapirone antidepressants such as buspirone, gepirone, tandospirone, or vilazodone, and the multi-modal agent vortioxetine, essentially in the virtue of their post-synaptic 5-HT2A-receptor sparing activity (either of them), particularly in the presence of eventual presynaptic 5-HT1A auto-receptor stimulatory activity (Celada et al., 2004; Hosenbocus and Chahal, 2011). In contrast, enduring post-synaptic 5-HT2A receptor stimulation by SSRIs and similar antidepressants would lead to the downregulation of such receptors. Therefore, subsequent abrupt discontinuation of the 5-HT2A agonist antidepressant, such as an SSRI drug, would result in sudden compensatory up-regulation of the already down-regulated 5-HT2A receptors.

Moreover, a sudden "*hypodopaminergic state*" may theoretically underline both the neurobiology of antidepressant discontinuation and that of related phenomena as mania emerging following abrupt discontinuation of serotonergic drugs (Narayan and Haddad, 2011),

recommending prompt reintroduction of the causative agent to allow for subsequent prudent down titration whenever possible (Jha et al., 2018; Wilson and Lader, 2015).

Receptor reserve ("spare receptors") are also crucial for the understanding of the putative neurobiology of ADS and the differential vulnerability profile people may have towards the same antidepressant drug, especially serotonergic ones, beyond diagnostic target, mean dose, and length of exposure considerations. Specifically, receptor reserve refers to the condition in a tissue whereby the agonist must activate only a tiny fraction of the existing receptor population to produce the maximal system response. The magnitude of the reserve depends upon the sensitivity of the tissue and the efficacy of the agonist. Spare receptors are responsible for tissue-specific actions of the agonist (e.g., a 5-HT2A agonist like an SSRI drug) because the presence of spare receptors increases the potency of an agonist. Individual neurobiological differences, namely tissues with a high proportion of spare receptors highly responsive to agonists even at lower concentrations, even if they contain the same receptor subtypes, may theoretically account also for the onset and the severity of some of the side effects associated with the serotonergic drug (Stahl, 1998).

Besides, the multitude of symptom domains seen during ADS nonetheless suggests that neurotransmitter systems affected by the SSRIs, and virtually other antidepressants, extend beyond the serotonergic one to encompass glutamatergic modulation – which is affected by the administration of N-methyl-D-aspartate receptor antagonist (Harvey et al., 2003), and dopamine neurotransmission as well as the hypothalamic-pituitary-adrenal axis (Renoir, 2013) (Harvey et al., 2003) (Jha et al., 2018) (Blier and Tremblay, 2006).

Additional insights about the putative neurobiology underlying ADS and related phenomena stem from preclinical studies suggesting the relevance of N-methyl-aspartate receptor activity or the inhibition of the nitric oxide-cyclic guanosine monophosphatase pathway, as well as increasing central nervous system (CNS) levels of gamma-aminobutyric acid, suggesting complex multi-receptor interplay beyond the core serotonergic up-regulation issues (Hung et al., 2011; Roca et al., 2013). In particular, reliable preclinical ADS models are warranted since animal models may help generate important translational insights into the human ADS condition, prevention, and therapy (Zabegalov et al., 2018).

Similarly, treatment-resistant depression is also highly relevant to a better understanding of ADS-related phenomena and for developing novel antidepressant drugs (Caraci et al., 2018). Interestingly, the novel antidepressant agent esketamine treatment-resistant depression did not result in drug-specific withdrawal symptoms after stopping 1-year of intermittent treatment with its nasal spray formulation in a representative Phase-III trial (Kato et al., 2021), potentially representing an avenue for a better understanding of the ADS phenomena for drugs other than 5-HT2 post-synaptic serotonergic agonists, such as the SSRIs.

4.2 Towards a better management of antidepressant discontinuation phenomena

Additional "*backward*" insights are likewise warranted for the older agents, such as the TCAs or monoamine oxidase inhibitors (MAOIs) antidepressants (Lejoyeux and Adès, 1997). The substantial lack of evidence about the chance of ADS for agents older than the SSRIs (Harvey and Slabbert, 2014) may appear parodical, especially considering that antidepressant discontinuation events were first reported shortly after their release to the market (Davies and Read, 2019) and that the 1983 definition of discontinuation syndrome of antidepressants having

"*predictable onset, duration, and offset of action containing psychological and bodily symptoms not previously complained by the patient*" well anticipated the SSRI blockbuster, as reviewed elsewhere (Mahase, 2019). Yet, it must be remarked that, albeit highly effective for the management of depression, the TCAs and the MAOIs have been replaced mainly by the SSRIs drugs, which better tolerability and safety profiles, overall, are not necessarily bound to better efficacy profiles over the more established agents, even when it comes to ADS propensity (Hengartner et al., 2020; Tomlinson et al., 2019) (Lejoyeux and Adès, 1997) (Haddad, 1997) (Van den Eynde et al., 2022). Additional guidance about the prevention and the management of antidepressant discontinuation should also cover particular scenarios (e.g., "*drug holiday*" for sexual side effects may lead to ADS in vulnerable patients prescribed paroxetine), populations such as pediatric patients suffering from MDD (Berber, 1998), especially considering the caveats concerning the use of the antidepressant among children and adolescents overall (Davies and Read, 2019; Hosenbocus and Chahal, 2011), as well as depressed women in the peripartum period. In addition, abrupt discontinuation of the antidepressants should be avoided in pregnant women with the previously treated affective disorder (Mahase, 2019). Also, case-specific considerations apply to MDD patients endorsing psychiatric or medical comorbidities as well as those exposed to complex polypharmacy (Hengartner et al., 2020; Tomlinson et al., 2019), being elder, or those requiring psychotherapeutic intervention to enhance adequate treatment adherence to minimize the chance of ADS (Berber, 1998), invariably excluded by most RCTs the "*guidelines*" would be then paved on.

While forthcoming treatment guidelines need to appraise the antidepressant discontinuation phenomenon, the most pertinent evidence is anecdotal, using inconsistent operational definitions. Unless further systematically grading the observational evidence, too, we reinforce the issue that

most "*high-yield evidence*" relies on randomized controlled trials, barely fitting real-world clinical scenarios (Davies and Read, 2019; Mahase, 2019).

5. Discussion

Psychiatrists understand patients' frustration when they discontinue an antidepressant, either spontaneously or after being directed to, particularly in the case of treatment-emergent side effects and unsatisfactory response, and how difficult it can be to engage them in treatment (Stein, 2022).

Stopping antidepressants is a crucial phase of the treatment plan (Fava and Cosci, 2019; Framer, 2021). This applies virtually to any antidepressant drug, regardless of the pharmacological "*class*" they belong to and the diagnostic target they are prescribed for.

5.1 *Limitations of the study*

The present state-of-the-art review followed a narrative approach. As such, "*the method is time-bound and may distort the overall picture of the development in ADS, failing to rely on a strict systematic appraisal of the quality of the reviewed evidence*" (Grant and Booth, 2009). In addition, the literature search is based on a single database.

5.2 Conclusions and implications for the clinical practice and future research

The terms "*discontinuation*" and "*withdrawal*" should not be used interchangeably. However, the present review relies on "*discontinuation*" rather than "*withdrawal*" as it still reflects the largest body of evidence on the matter, in terms quite like the 2018 evidence-based view of Jha and colleagues (Jha et al., 2018). Specifically, ADS has been proposed to differ from other CNS withdrawal syndromes (Nielsen et al., 2012), contrasting other postulates (Fava et al., 2015) (Chouinard and Chouinard, 2015). Moreover, while ADS may underscore the risks associated with antidepressant discontinuation compared to "*withdrawal*" (Chouinard and Chouinard,

2015), the chance of genuine addiction phenomena to the antidepressants has been traditionally ruled out (Lichtigfeld and Gillman, 1998) (Coupland et al., 1996), and tolerance and tachyphylaxis phenomena associated with the SSRIs seem infrequent compared to substances such as alcohol or barbiturates, or illicit drugs (Targum, 2014). However, recent evidence calls for caution in prescribing those SSRIs reported to be associated with dependence phenomena (Chiappini et al., 2022).

Despite the controversies surrounding the safety of antidepressants, ADS and related phenomena have significant clinical implications, especially considering that many clinicians may be pushed to prescribe medications due to regulatory or insurance issues. Yet, most prescribing clinicians virtually receive no education on how and when to discontinue the antidepressants.

Future research needs to review the historical definitions for ADS and withdrawal, further testing the criteria proposed for putative SSRIs and SNRIs withdrawal, rebound, and persistent post-withdrawal reactions (Chouinard and Chouinard, 2015). In addition, ADS phenomena may occur even with antidepressants other than SSRIs. Most importantly, SSRIs encompass drugs with significant pharmacokinetic and pharmacodynamic profiles.

Discriminating ADS/withdrawal from relapse of depression owing to operationalized criteria (Chouinard and Chouinard, 2015) is likewise crucial, as misdiagnosis is common in clinical practice (Horowitz and Taylor, 2022).

Specifically, unlike ADS symptoms, those associated with relapse of depression usually take more than a few days to onset and tend to disappear following the introduction of the antidepressant (Warner et al., 2006; Zajecka et al., 1997). Discriminating between ADS and relapse of depression should improve the internal validity of the relapse prevention trial,

especially considering that existing recommendations for long-term antidepressant treatment are based almost entirely on such discontinuation trials. In these relapse prevention trials, participants with remitted depression are randomized to receive an antidepressant. Then, abruptly discontinued and replaced by an "*inert*" placebo or continued the active treatment (Krol et al., 2020). The drug-placebo difference in relapse rates at the end of the maintenance phase is granted as a prophylactic drug effect. However, substantial withdrawal confounding in discontinuation trials often renders the findings of the trial uninterpretable (Hengartner, 2020), and the ultimate call for a quick resume of the discontinued drug to be continued for an indefinite length of time may be likewise biased.

Again, re-appraisal of evidence-based operational definitions (Chouinard and Chouinard, 2015; Haddad, 1998) of ADS and related phenomena is also warranted, ranking the evidence according to validated assessment tools (Cosci et al., 2018; Rosenbaum et al., 1998), balancing real-world clinical data from long-term prospective observational studies against RCTs (Rosenbaum et al., 1998; Tint et al., 2008).

Besides, management of comorbidities associated with MDD (Hung et al., 2011) and cognitive-behavioral therapy (Van Leeuwen et al., 2021) (Fava and Belaise, 2018) (Maund et al., 2019) (Bockting et al., 2018) are crucial whenever planning to stop antidepressant medications (Malhi et al., 2021). Self-care behavior, particularly mindfulness, relaxation, and supportive relationships, explains up to 20-30% of the variance in predicting successful discontinuation of the antidepressants after controlling for baseline sociodemographic, clinical, and medication-related factors (Lincoln et al., 2021). Yet, the patients are rarely proactively involved in the antidepressant-discontinuation process. They should be rather educated to reduce the risk for abrupt discontinuation (Jha, 2019), especially those with prominent anxious features or

ascertained history of poor treatment adherence (Karter, 2020) (Solmi et al., 2020), promoting patient-tailored interventions to enhance treatment adherence (Gabriel and Sharma, 2017). Up to 48% of the patients exposed to antidepressants did not have their drug reviewed at least every three months, and 65% had never discussed with the prescriber whether or how to come off, according to an online survey of 752 users in the U.K. (Read et al., 2019). Online surveys are prone to selection bias, as people are more likely to respond to a survey if they have experienced a problem than if they have not. However, it must be remarked that the most rigorous review currently available about the incidence rate of antidepressant "*withdrawal*" documented overlapping weighted averages independent of the study design of the reviewed material: three online surveys resulted in 57.1% (1,790/3,137) vs. five naturalistic studies yielding 52.5% (127/242) and six RCTs leading to 50.7% (341/673) (Davies and Read, 2019), thus remarking the need to acknowledge further the patient reports in appraising the ADS-related phenomena.

Finally, while independent forums and registries run by patients and their families need to be accounted for in the update process of treatment guidelines of the antidepressants, also concerning the ADS and potential withdrawal phenomena (Tomlinson et al., 2019), alarming messages should be avoided by promoting doctor and patient education programs since the already much stigmatized (Fornaro et al., 2009) antidepressants represent a core armamentarium of modern pharmacotherapy for a variety of conditions beyond MDD. In addition, population-based registries able to capture all the clinically relevant information, such as those run by Scandinavian countries, should also be promoted to systematically account for ADS and related outcomes (Hengartner et al., 2020; Tomlinson et al., 2019).

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Table 1: Main themes relevant for the present review.

Antidepressant discontinuation syndrome
Essential evidence
Essential neurobiology
Implications for an optimal management

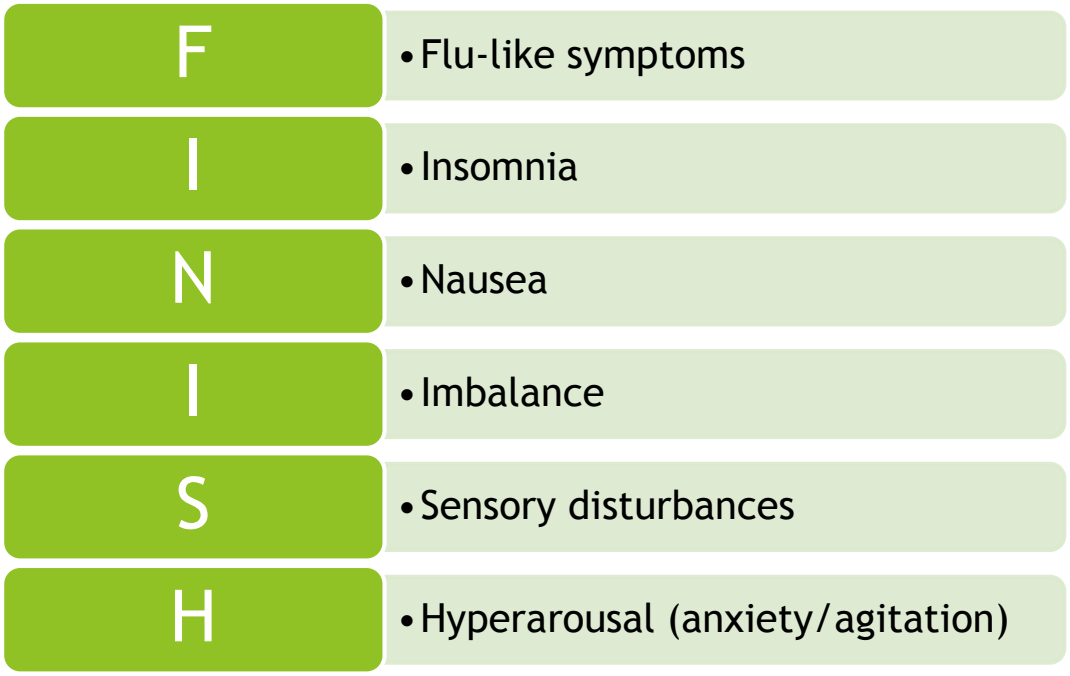
Note: The themes outlined in the table were a-priori defined but could be expanded throughout the review process.

Table 2: Core concepts relevant to antidepressant discontinuation syndrome.

Withdrawal: "*physiological reactions when a drug or medicine that has been taken repeatedly is removed*." (Tomlinson et al., 2019) (Henssler et al., 2019). Note: withdrawal typically leads to re-emerging the initial symptoms associated with new ones.
Tolerance: "*neuroadaptation arising from repeatedly taking some drugs and medicines, in which higher-dose are required to achieve the effect*." (Tomlinson et al., 2019).
Dependence: "*an adaptation to repeated exposure to some drugs or medicines usually characterized by tolerance and withdrawal*." (Tomlinson et al., 2019)
Relapse (of depression): *"return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission, but before recovery*." (Frank et al., 1991).
Recurrence (of depression): "*the appearance of a new episode of major depressive disorder and, thus, can occur only during a recovery*." (Frank et al., 1991). Note: recurring symptoms are the same characteristic of the index episode.
Rebound: "*the emergence or re-emergence of symptoms that were either absent or controlled while taking a medication, but appear when that same medication is discontinued, or reduced in dosage*." (Henssler et al., 2019). Note: it typically occurs after abrupt withdrawal of benzodiazepines, especially short-life compounds. It is usually short-lasting but intense in terms of the severity of symptoms.
Jitteriness: "*early worsening of anxiety, agitation and irritability commencing antidepressants*." (Sinclair et al., 2009).

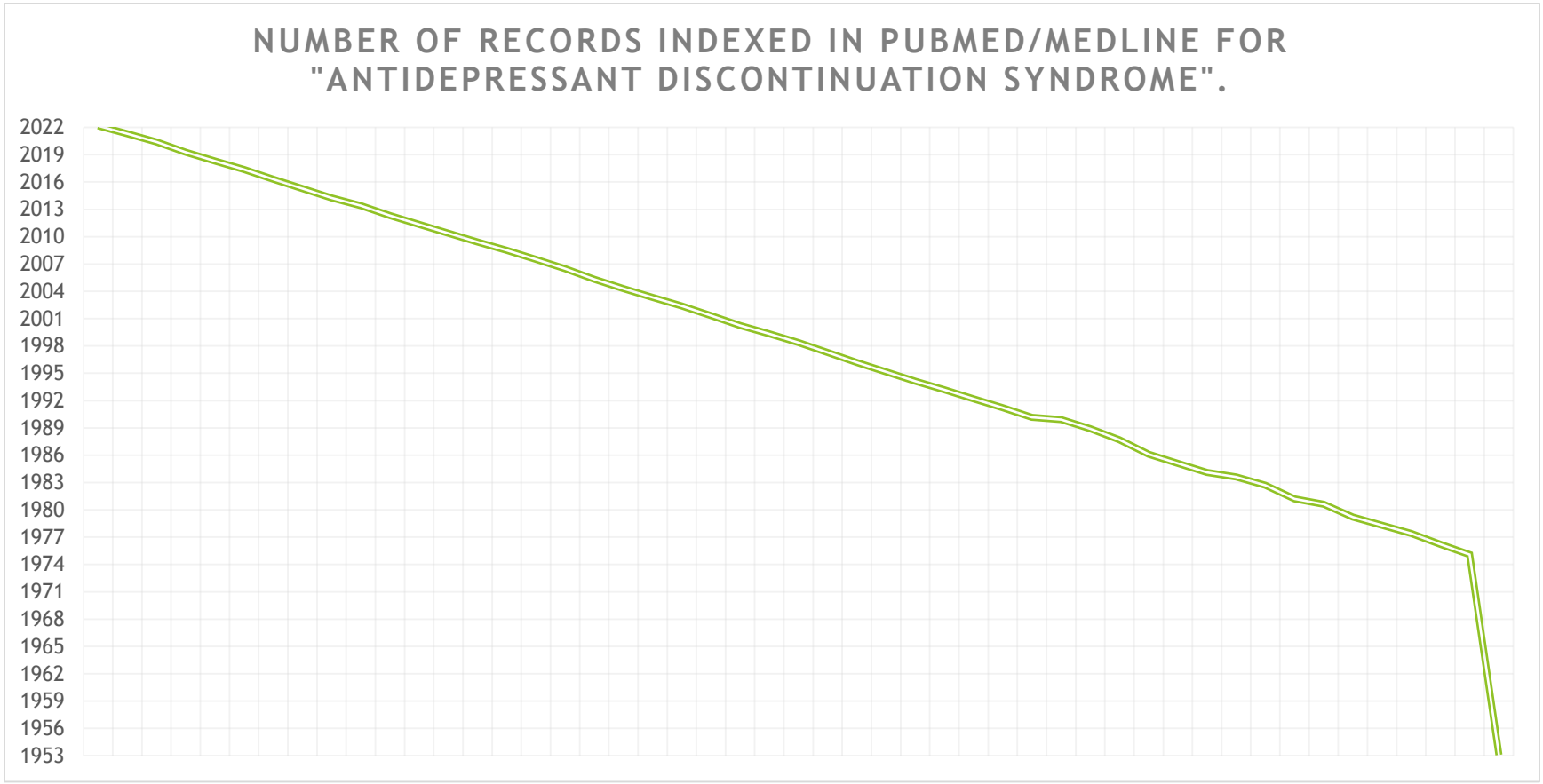
Note: See the detailed operational criteria for withdrawal and rebound phenomena following the interruption of antidepressants proposed elsewhere (Chouinard and Chouinard, 2015).

Figure 1: An adapted classical mnemonic for antidepressant discontinuation reactions (Berber, 1998).



Note: The symptoms of antidepressant discontinuation syndrome may vary in severity, duration, series, and trajectories.

Figure 2: Publication trend for "*antidepressant discontinuation syndrome*." No filter was applied. Results, n=1,049. A similar trend applies to "*antidepressant withdrawal*" (not shown).



Note: The term "*antidepressant discontinuation syndrome*" appeared sporadically in the literature before the late 1990s, virtually underscoring the research interest in the phenomenon in the previous decades; 2022 could cover only the first quarter of the year (the most current access date, May 8th, 2022).

Main-text=3,812 words
Abstract=167 words
Tables=2
Figures=2
References=95

Antidepressant discontinuation syndrome: a state-of-the-art clinical review

"Antidepressant discontinuation"

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#**Joint co-first**

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Abstract (167/250 words)

Antidepressant drugs are prescribed to patients with depressive, anxiety disorders, and other conditions. Evidence about antidepressant discontinuation syndrome (ADS) and related outcomes is sparse, although potentially burdensome in some patients. The present state-of-the-art review aims to appraise the most current evidence about ADS critically. ADS has been documented for most antidepressant drugs, although most literature focuses on selective serotonin reuptake inhibitors prescribed for depression. While down-titration cannot exclude the chance of ADS, it is nonetheless warranted in the clinical setting, especially for short half-life and sedative compounds such as paroxetine. Integrative management with concurrent pharmacotherapy and psychotherapy may minimize the eventual unpleasant effects arising within the discontinuation process. In addition, patient-tailored interventions and education should be part of the discontinuation strategy. Future research must rely on broadly accepted definitions for ADS and related phenomena such as antidepressant withdrawal and shed further light on the underpinning neurobiology. Discriminating between ADS-related phenomena and relapse of depression is likewise warranted, along with a neuroscience-based nomenclature instead of a class one.

Keywords: Antidepressant; discontinuation syndrome; withdrawal; review.

1. Introduction

Of the roughly 800 million people endorsing a mental disorder worldwide, depression and anxiety are among the most burdensome (Vos et al., 2020), driving the prescription of antidepressants. In addition, people with obsessive-compulsive disorder, insomnia, chronic pain, fibromyalgia, eating disorders, smoking cessation, migraine, and attention-deficit/hyperactivity disorders may receive antidepressant prescriptions (Cascade et al., 2007). However, estimates of antidepressants' utilization in the community need further assessment (Lunghi et al., 2022).

Common scenarios soliciting antidepressant discontinuation include i) remission of the condition requiring antidepressant pharmacotherapy; ii) unsatisfactory response despite "*adequate*" trialing (Quitkin et al., 1984); iii) loss of response (Fornaro et al., 2019); iv) severe treatment-emergent adverse reactions; v) change in the therapeutic schema due to the introduction of new drugs having relevant clinical interactions; and vi) changes in the insurance plan coverage (Zwiebel and Viguera, 2022). In addition, many patients abruptly discontinue their antidepressant medications early without the knowledge of the prescribing clinician for several reasons (Jaffray et al., 2014). Among other reasons, the fact that most antidepressants have a less favorable acceptability profile vs. placebo in the acute treatment of major depressive disorder (MDD), with odds of withdrawal ranging between odd ratio (OR)=1.64 and 4.44 and 95%C.I., excluding the null (Cipriani et al., 2018).

Antidepressant discontinuation may lead to systemic and neuropsychological symptoms of varying severity and duration, accounting for the so-called "*antidepressant discontinuation syndrome*" (ADS) (Figure n.1).

The burden associated with ADS may also mine the patient's trust in the doctor and overall treatment adherence (Jaffray et al., 2014), soliciting appropriate counseling, patient education, and doctor awareness.

The present review aims to appraise the most current evidence about ADS critically.

2. Methods

The present narrative review follows a "*state-of-the-art*" approach for selected topics (Table n.1), owing to the recommendations outlined elsewhere aiming to critically "*address more current matters in contrast to other combined retrospective and current approaches*" (Grant and Booth, 2009).

The search strategy ran on May 8th, 2022. adopted the following terms or their combination: "*antidepressant*," "*discontinuation*," "*withdrawal*," "*tapering*," "*dependence*," "*tolerance*," "*addiction*," "*acceptability*," "*tolerability*," and "*management*" for peer-reviewed records indexed in PubMed/MEDLINE database using MeSH (Medical Subjects Headings). No publication date or language restriction was applied. In addition, meta-analyses (MAs) and systematic reviews (SRs) of large-scale observational studies, randomized controlled trials (RCTs) providing a reliable quality assessment of the results were prioritized over single-drug packages and case-series/reports for preliminary emerging evidence not otherwise covered in the literature. Noteworthy, the putative mechanisms of action of the "*drugs used in the treatment of depression*" are broad to the extent that neuroscience, rather than a class-based, nomenclature approach, has been promoted by the European Neuropsychopharmacology Association through the present Journal (Zohar and Levy, 2022; Zohar et al., 2015). Yet, the present review adopts the classic monoamine-based nomenclature and "*ADS*" terminology to reflect the broadest evidence at synthesis, especially the most consolidated one.

3. Antidepressant discontinuation syndrome: conceptualization and current perspectives

Research interest in ADS and related phenomena holds high (Figure n.2).

The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders, text revision (DSM-5-TR) enlists ADS among the "*medication-induced movement disorders and other adverse effects of medication*" section G25.79, page n.818. The DSM-5-TR postulates that ADS "*may occur following treatment with all types of antidepressants" and that the "incidence depends on the dosage and half-life of the medication being taken and the rate at which the medication is tapered*." The DSM-5-TR also warrants further longitudinal studies on ADS and guidance for differential diagnosis (APA, 2022).

The guidance provided by the DSM-5-TR essentially stems from the reports concerning a "*self-limiting*" (usually resolving within 2-3 weeks) "*discontinuation syndrome*" following the serotonin reuptake inhibitors (SSRIs) originating in the late 1990s (Zajecka et al., 1997) (Schatzberg, 1997; Schatzberg et al., 1997).

Both the 2009 U.K. National Institute for Health and Care Excellence (NICE) (1.9.2.1 in CG90) (NICE, 2009) and the 2010 U.S. American Psychiatric Association (APA) depression guidelines for the treatment of MDD, third edition (APA, 2010) reflect such a view.

Yet, the amendment of the NICE guidelines for "*medicines associated with dependence or withdrawal symptoms*," published on April 20th, 2022, acknowledges that "*there is substantial variation in people's experience, with symptoms lasting much longer (sometimes months or more) and being more severe for some patients*" (NICE, 2022). This latter acknowledgment reflects the input from medical bodies and experts (Iacobucci, 2021; Mahase, 2019) to take into account the potential severity and duration of discontinuation-related phenomena and the risk of

misdiagnosis (Davies and Read, 2019; Fava et al., 2015) (Chouinard and Chouinard, 2015) (Cosci and Chouinard, 2020). Comparably, the Clinical Practice Guidelines for the Treatment of Depression Across Three Age Cohorts released by the APA in February 2019 still adopt the term "*discontinuation*" rather than "*withdrawal*," albeit acknowledging the chance for enduring effects following the cessation of the antidepressant exposure (APA, 2019).

Specifically, while a pivotal 2018 evidence-based, grounded SR from U.K.-based authors documented strikingly high incidence rates of antidepressant "*withdrawal*" (range 27-86%, weighted average of 56% of the exposed cases) (Davies and Read, 2019), expert prescribing psychiatrists based in the U.S. disputed the chance of frequent, long-lasting, highly disabling outcomes for the majority of the patients who stop their antidepressant medications (Pies R.W. and D.N., 2019). Please refer to Table n.2 for the core terminology relevant to the present review.

4. Antidepressant discontinuation syndrome: a critical appraisal of the evidence and essential neurobiology towards optimal clinical management

Antidepressant discontinuation reactions follow a characteristic pattern, although rare outcomes have likewise been reported. This is the case of extrapyramidal syndromes, states mimicking (hypo-)mania (Haddad and Anderson, 2007; Narayan and Haddad, 2011), sensation perceived as electrical flashes that occur inside the brain decreasing the antidepressant levels - "brain zaps" (Papp and Onton, 2018), and other effects prone to be misdiagnosed as relapse of depression (Chouinard and Chouinard, 2015; Warner et al., 2006). In addition, neurocognitive symptoms are often neglected (Popovic et al., 2015).

The clinical experience suggests gradual discontinuation of the antidepressant drugs (Jha et al., 2018; Pies R.W. and D.N., 2019). This latter approach is in line with the results from positron emission tomography studies of serotonin transporter (SERT) occupancy by the SSRIs, supporting the practice of a hyperbolical dose reduction of the antidepressant rather than a linear one to reduce ADS-related phenomena (Horowitz and Taylor, 2019).

Specifically, the SERT occupancy of the SSRIs would vary across different doses (Meyer et al., 2004). For example, the SSRI citalopram steadily administered at 60mg/day would result in 87.8% SERT occupancy, 40mg/day would result in 85.9%, 20mg/day in 80.5%, 9.1mg/day in 70%, 5.4mg/day in 60%, 2.3mg/day in 40%, 1.5mg/day in 30%, 0.8mg/day in 20%, and 0.37mg/day in 10%, using the Michaelis-Menten equation of best fit for doses produced by a combination of tablets and liquid formulations, approximated (Meyer et al., 2004). This means that tapering off should be particularly gradual, especially upon reaching low doses of the SSRI, following a hyperbolic decrease rather than a fixed decrement (Horowitz and Taylor, 2022).

While existing evidence-based recommendations essentially rely on RCTs hardly reflect the real-world setting, consistent with the clinical practice, rational pharmacotherapy involving temporary augmentation strategies with benzodiazepines, anticholinergic, antihistamine, beta-blockers, or the non-selective α-2 agonist clonidine should be considered (Naguy, 2016), particularly in the case of abrupt discontinuation poorly responsive to the prompt reintroduction of the discontinued antidepressant. This is particularly true for antidepressants with "*sedative*" pharmacodynamic profiles: e.g., anticholinergic or antihistamine supplementation should be recommended for the most sedative tricyclic antidepressants – TCAs or, to a lesser extent, for the SSRIs paroxetine and citalopram, respectively.

Tapering of the antidepressant drugs also relies on pharmacokinetic considerations: the antidepressant discontinuation syndrome is most frequently seen with paroxetine (the shortest half-life SSRI compound) and less commonly seen with fluoxetine (the longest half-life drug among the SSRIs, accounting also for its active metabolite norfluoxetine) (Jha et al., 2018).

Gradual tapering of the antidepressant is warranted for people who have already proved to be vulnerable to antidepressant discontinuation symptoms, depressed patients presenting hints of sub-threshold bipolarity, panic disorder (Baldessarini et al., 2010), or those subjects who already experienced jitteriness/anxiety syndrome upon commencing an antidepressant drug (Jeon et al., 2022).

Patients with MDD who already achieved remission would have lower odds of relapse in case of slow tapering over six months compared to abruptly discontinued controls (Lejoyeux and Adès, 1997). Gradual vs. rapid antidepressant discontinuation was corroborated by more recent evidence (Baldessarini et al., 2010). However, it is noteworthy that a recent large-scale

quantitative Cochrane review, including 33 studies encompassing 4,995 adults with depression, suggested very low certainty of evidence that abrupt discontinuation without psychological support may inflate the risk of relapse according to 13 documenting studies (hazard ratio [HR]=2.09, 95%C.I.=1.59-2.74, based on 1,373 participants from ten studies). Also, insufficient evidence exists about the effect of abrupt discontinuation of the antidepressant on adverse events (OR=1.11, 95%C.I.=0.62-1.99; n=1,012 participants, N=7 studies; I^2= 37%) compared to the continuation of the antidepressant, without specific assessment of withdrawal symptoms, according to the same piece of evidence, concluding that effects of abrupt discontinuation on withdrawal symptoms (number of studies=1) is very uncertain. However, none of the studies included a successful discontinuation rate as a primary endpoint (Van Leeuwen et al., 2021). In addition, it has been suggested that withdrawal reactions with the antidepressant drugs could occur both with abrupt and gradual discontinuation of the SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), with no significant advantage of the latter strategy (Fava et al., 2015) (Chouinard and Chouinard, 2015) (Fava et al., 2018). Moreover, it has been claimed that gradual tapering of the antidepressants may inflate the risk for misdiagnosis of relapse of depression instead of ADS (Fava and Cosci, 2019). However, underscoring the benefits of gradual vs. abrupt discontinuation of the antidepressant contrasts with the clinical experience of many clinicians, and caution in the interpretation of general guidance is particularly warranted in the lack of conclusive evidence suggesting performing the opposite.

Indeed, this is a long-lasting matter of debate: expert consensus statements for the prevention and the clinical management of antidepressant discontinuation originated decades ago (Andersen and Kristiansen, 1959).

Statements and recommendations have been updated over the past years resulting in clinically-oriented guidance (Jha et al., 2018). Yet, only a bounce of evidence systematically appraised the role of antidepressants other than the SSRIs in recent years (Fava et al., 2018; Lejoyeux and Adès, 1997), essentially due to publication bias, though even the non-SSRI antidepressant may induce antidepressant discontinuation symptoms or related phenomena such as rebound, tolerance/treatment-emergent loss of efficacy, and discontinuation-induced refractoriness (Cattaneo et al., 2020; Grady and Stahl, 2012) (Fornaro et al., 2019).

4.1 Neurobiological and pharmacological considerations matter towards the understanding of ADS and related phenomena.

Specific non-SSRI drugs may, in theory, feature a better acceptability profile for discontinuation symptoms, namely agomelatine (Harvey and Slabbert, 2014) or the "*anxiolytic*" azapirone antidepressants such as buspirone, gepirone, tandospirone, or vilazodone, and the multi-modal agent vortioxetine, essentially in the virtue of their post-synaptic 5-HT2A-receptor sparing activity (either of them), particularly in the presence of eventual presynaptic 5-HT1A auto-receptor stimulatory activity (Celada et al., 2004; Hosenbocus and Chahal, 2011). In contrast, enduring post-synaptic 5-HT2A receptor stimulation by SSRIs and similar antidepressants would lead to the downregulation of such receptors. Therefore, subsequent abrupt discontinuation of the 5-HT2A agonist antidepressant, such as an SSRI drug, would result in sudden compensatory up-regulation of the already down-regulated 5-HT2A receptors.

Moreover, a sudden "*hypodopaminergic state*" may theoretically underline both the neurobiology of antidepressant discontinuation and that of related phenomena as mania emerging following abrupt discontinuation of serotonergic drugs (Narayan and Haddad, 2011),

recommending prompt reintroduction of the causative agent to allow for subsequent prudent down titration whenever possible (Jha et al., 2018; Wilson and Lader, 2015).

Receptor reserve ("spare receptors") are also crucial for the understanding of the putative neurobiology of ADS and the differential vulnerability profile people may have towards the same antidepressant drug, especially serotonergic ones, beyond diagnostic target, mean dose, and length of exposure considerations. Specifically, receptor reserve refers to the condition in a tissue whereby the agonist must activate only a tiny fraction of the existing receptor population to produce the maximal system response. The magnitude of the reserve depends upon the sensitivity of the tissue and the efficacy of the agonist. Spare receptors are responsible for tissue-specific actions of the agonist (e.g., a 5-HT2A agonist like an SSRI drug) because the presence of spare receptors increases the potency of an agonist. Individual neurobiological differences, namely tissues with a high proportion of spare receptors highly responsive to agonists even at lower concentrations, even if they contain the same receptor subtypes, may theoretically account also for the onset and the severity of some of the side effects associated with the serotonergic drug (Stahl, 1998).

Besides, the multitude of symptom domains seen during ADS nonetheless suggests that neurotransmitter systems affected by the SSRIs, and virtually other antidepressants, extend beyond the serotonergic one to encompass glutamatergic modulation – which is affected by the administration of N-methyl-D-aspartate receptor antagonist (Harvey et al., 2003), and dopamine neurotransmission as well as the hypothalamic-pituitary-adrenal axis (Renoir, 2013) (Harvey et al., 2003) (Jha et al., 2018) (Blier and Tremblay, 2006).

Additional insights about the putative neurobiology underlying ADS and related phenomena stem from preclinical studies suggesting the relevance of N-methyl-aspartate receptor activity or the inhibition of the nitric oxide-cyclic guanosine monophosphatase pathway, as well as increasing central nervous system (CNS) levels of gamma-aminobutyric acid, suggesting complex multi-receptor interplay beyond the core serotonergic up-regulation issues (Hung et al., 2011; Roca et al., 2013). In particular, reliable preclinical ADS models are warranted since animal models may help generate important translational insights into the human ADS condition, prevention, and therapy (Zabegalov et al., 2018).

Similarly, treatment-resistant depression is also highly relevant to a better understanding of ADS-related phenomena and for developing novel antidepressant drugs (Caraci et al., 2018). Interestingly, the novel antidepressant agent esketamine treatment-resistant depression did not result in drug-specific withdrawal symptoms after stopping 1-year of intermittent treatment with its nasal spray formulation in a representative Phase-III trial (Kato et al., 2021), potentially representing an avenue for a better understanding of the ADS phenomena for drugs other than 5-HT2 post-synaptic serotonergic agonists, such as the SSRIs.

4.2 Towards a better management of antidepressant discontinuation phenomena

Additional "*backward*" insights are likewise warranted for the older agents, such as the TCAs or monoamine oxidase inhibitors (MAOIs) antidepressants (Lejoyeux and Adès, 1997). The substantial lack of evidence about the chance of ADS for agents older than the SSRIs (Harvey and Slabbert, 2014) may appear parodical, especially considering that antidepressant discontinuation events were first reported shortly after their release to the market (Davies and Read, 2019) and that the 1983 definition of discontinuation syndrome of antidepressants having

"*predictable onset, duration, and offset of action containing psychological and bodily symptoms not previously complained by the patient*" well anticipated the SSRI blockbuster, as reviewed elsewhere (Mahase, 2019). Yet, it must be remarked that, albeit highly effective for the management of depression, the TCAs and the MAOIs have been replaced mainly by the SSRIs drugs, which better tolerability and safety profiles, overall, are not necessarily bound to better efficacy profiles over the more established agents, even when it comes to ADS propensity (Hengartner et al., 2020; Tomlinson et al., 2019) (Lejoyeux and Adès, 1997) (Haddad, 1997) (Van den Eynde et al., 2022). Additional guidance about the prevention and the management of antidepressant discontinuation should also cover particular scenarios (e.g., "*drug holiday*" for sexual side effects may lead to ADS in vulnerable patients prescribed paroxetine), populations such as pediatric patients suffering from MDD (Berber, 1998), especially considering the caveats concerning the use of the antidepressant among children and adolescents overall (Davies and Read, 2019; Hosenbocus and Chahal, 2011), as well as depressed women in the peripartum period. In addition, abrupt discontinuation of the antidepressants should be avoided in pregnant women with the previously treated affective disorder (Mahase, 2019). Also, case-specific considerations apply to MDD patients endorsing psychiatric or medical comorbidities as well as those exposed to complex polypharmacy (Hengartner et al., 2020; Tomlinson et al., 2019), being elder, or those requiring psychotherapeutic intervention to enhance adequate treatment adherence to minimize the chance of ADS (Berber, 1998), invariably excluded by most RCTs the "*guidelines*" would be then paved on.

While forthcoming treatment guidelines need to appraise the antidepressant discontinuation phenomenon, the most pertinent evidence is anecdotal, using inconsistent operational definitions. Unless further systematically grading the observational evidence, too, we reinforce the issue that

most "*high-yield evidence*" relies on randomized controlled trials, barely fitting real-world clinical scenarios (Davies and Read, 2019; Mahase, 2019).

5. Discussion

Psychiatrists understand patients' frustration when they discontinue an antidepressant, either spontaneously or after being directed to, particularly in the case of treatment-emergent side effects and unsatisfactory response, and how difficult it can be to engage them in treatment (Stein, 2022).

Stopping antidepressants is a crucial phase of the treatment plan (Fava and Cosci, 2019; Framer, 2021). This applies virtually to any antidepressant drug, regardless of the pharmacological "*class*" they belong to and the diagnostic target they are prescribed for.

5.1 *Limitations of the study*

The present state-of-the-art review followed a narrative approach. As such, "*the method is time-bound and may distort the overall picture of the development in ADS, failing to rely on a strict systematic appraisal of the quality of the reviewed evidence*" (Grant and Booth, 2009). In addition, the literature search is based on a single database.

5.2 Conclusions and implications for the clinical practice and future research

The terms "*discontinuation*" and "*withdrawal*" should not be used interchangeably. However, the present review relies on "*discontinuation*" rather than "*withdrawal*" as it still reflects the largest body of evidence on the matter, in terms quite like the 2018 evidence-based view of Jha and colleagues (Jha et al., 2018). Specifically, ADS has been proposed to differ from other CNS withdrawal syndromes (Nielsen et al., 2012), contrasting other postulates (Fava et al., 2015) (Chouinard and Chouinard, 2015). Moreover, while ADS may underscore the risks associated with antidepressant discontinuation compared to "*withdrawal*" (Chouinard and Chouinard,

2015), the chance of genuine addiction phenomena to the antidepressants has been traditionally ruled out (Lichtigfeld and Gillman, 1998) (Coupland et al., 1996), and tolerance and tachyphylaxis phenomena associated with the SSRIs seem infrequent compared to substances such as alcohol or barbiturates, or illicit drugs (Targum, 2014). However, recent evidence calls for caution in prescribing those SSRIs reported to be associated with dependence phenomena (Chiappini et al., 2022).

Despite the controversies surrounding the safety of antidepressants, ADS and related phenomena have significant clinical implications, especially considering that many clinicians may be pushed to prescribe medications due to regulatory or insurance issues. Yet, most prescribing clinicians virtually receive no education on how and when to discontinue the antidepressants.

Future research needs to review the historical definitions for ADS and withdrawal, further testing the criteria proposed for putative SSRIs and SNRIs withdrawal, rebound, and persistent post-withdrawal reactions (Chouinard and Chouinard, 2015). In addition, ADS phenomena may occur even with antidepressants other than SSRIs. Most importantly, SSRIs encompass drugs with significant pharmacokinetic and pharmacodynamic profiles.

Discriminating ADS/withdrawal from relapse of depression owing to operationalized criteria (Chouinard and Chouinard, 2015) is likewise crucial, as misdiagnosis is common in clinical practice (Horowitz and Taylor, 2022).

Specifically, unlike ADS symptoms, those associated with relapse of depression usually take more than a few days to onset and tend to disappear following the introduction of the antidepressant (Warner et al., 2006; Zajecka et al., 1997). Discriminating between ADS and relapse of depression should improve the internal validity of the relapse prevention trial,

especially considering that existing recommendations for long-term antidepressant treatment are based almost entirely on such discontinuation trials. In these relapse prevention trials, participants with remitted depression are randomized to receive an antidepressant. Then, abruptly discontinued and replaced by an "*inert*" placebo or continued the active treatment (Krol et al., 2020). The drug-placebo difference in relapse rates at the end of the maintenance phase is granted as a prophylactic drug effect. However, substantial withdrawal confounding in discontinuation trials often renders the findings of the trial uninterpretable (Hengartner, 2020), and the ultimate call for a quick resume of the discontinued drug to be continued for an indefinite length of time may be likewise biased.

Again, re-appraisal of evidence-based operational definitions (Chouinard and Chouinard, 2015; Haddad, 1998) of ADS and related phenomena is also warranted, ranking the evidence according to validated assessment tools (Cosci et al., 2018; Rosenbaum et al., 1998), balancing real-world clinical data from long-term prospective observational studies against RCTs (Rosenbaum et al., 1998; Tint et al., 2008).

Besides, management of comorbidities associated with MDD (Hung et al., 2011) and cognitive-behavioral therapy (Van Leeuwen et al., 2021) (Fava and Belaise, 2018) (Maund et al., 2019) (Bockting et al., 2018) are crucial whenever planning to stop antidepressant medications (Malhi et al., 2021). Self-care behavior, particularly mindfulness, relaxation, and supportive relationships, explains up to 20-30% of the variance in predicting successful discontinuation of the antidepressants after controlling for baseline sociodemographic, clinical, and medication-related factors (Lincoln et al., 2021). Yet, the patients are rarely proactively involved in the antidepressant-discontinuation process. They should be rather educated to reduce the risk for abrupt discontinuation (Jha, 2019), especially those with prominent anxious features or

ascertained history of poor treatment adherence (Karter, 2020) (Solmi et al., 2020), promoting patient-tailored interventions to enhance treatment adherence (Gabriel and Sharma, 2017). Up to 48% of the patients exposed to antidepressants did not have their drug reviewed at least every three months, and 65% had never discussed with the prescriber whether or how to come off, according to an online survey of 752 users in the U.K. (Read et al., 2019). Online surveys are prone to selection bias, as people are more likely to respond to a survey if they have experienced a problem than if they have not. However, it must be remarked that the most rigorous review currently available about the incidence rate of antidepressant "*withdrawal*" documented overlapping weighted averages independent of the study design of the reviewed material: three online surveys resulted in 57.1% (1,790/3,137) vs. five naturalistic studies yielding 52.5% (127/242) and six RCTs leading to 50.7% (341/673) (Davies and Read, 2019), thus remarking the need to acknowledge further the patient reports in appraising the ADS-related phenomena.

Finally, while independent forums and registries run by patients and their families need to be accounted for in the update process of treatment guidelines of the antidepressants, also concerning the ADS and potential withdrawal phenomena (Tomlinson et al., 2019), alarming messages should be avoided by promoting doctor and patient education programs since the already much stigmatized (Fornaro et al., 2009) antidepressants represent a core armamentarium of modern pharmacotherapy for a variety of conditions beyond MDD. In addition, population-based registries able to capture all the clinically relevant information, such as those run by Scandinavian countries, should also be promoted to systematically account for ADS and related outcomes (Hengartner et al., 2020; Tomlinson et al., 2019).

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Table 1: Main themes relevant for the present review.

Antidepressant discontinuation syndrome
Essential evidence
Essential neurobiology
Implications for an optimal management

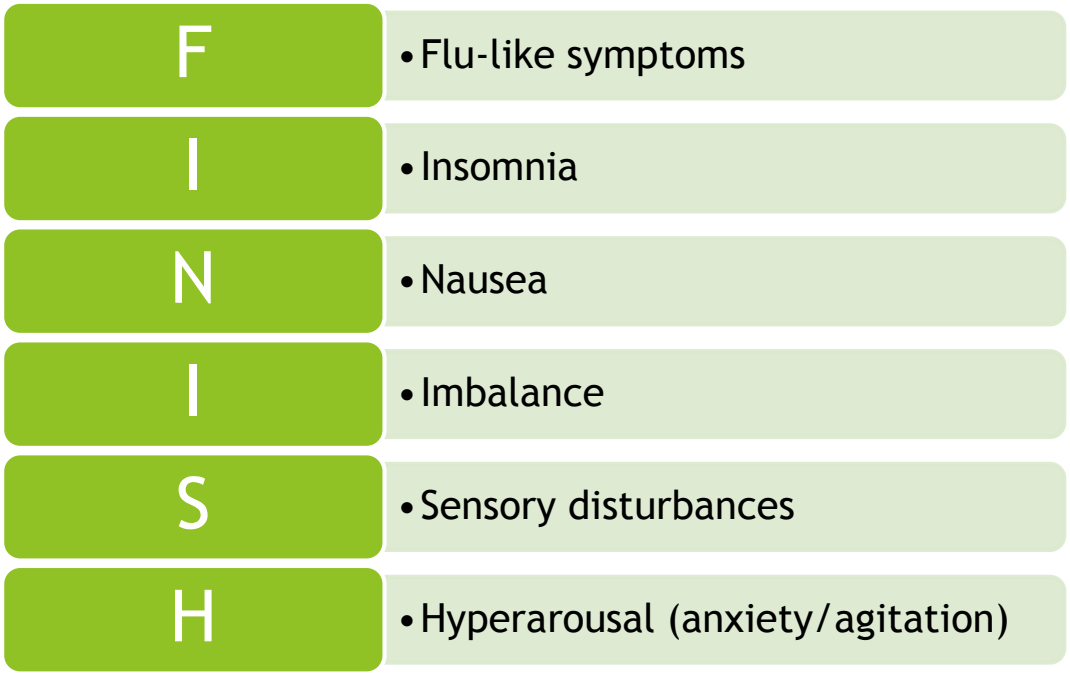
Note: The themes outlined in the table were a-priori defined but could be expanded throughout the review process.

Table 2: Core concepts relevant to antidepressant discontinuation syndrome.

Withdrawal: "*physiological reactions when a drug or medicine that has been taken repeatedly is removed*." (Tomlinson et al., 2019) (Henssler et al., 2019). Note: withdrawal typically leads to re-emerging the initial symptoms associated with new ones.
Tolerance: "*neuroadaptation arising from repeatedly taking some drugs and medicines, in which higher-dose are required to achieve the effect*." (Tomlinson et al., 2019).
Dependence: "*an adaptation to repeated exposure to some drugs or medicines usually characterized by tolerance and withdrawal*." (Tomlinson et al., 2019)
Relapse (of depression): *"return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission, but before recovery*." (Frank et al., 1991).
Recurrence (of depression): "*the appearance of a new episode of major depressive disorder and, thus, can occur only during a recovery*." (Frank et al., 1991). Note: recurring symptoms are the same characteristic of the index episode.
Rebound: "*the emergence or re-emergence of symptoms that were either absent or controlled while taking a medication, but appear when that same medication is discontinued, or reduced in dosage*." (Henssler et al., 2019). Note: it typically occurs after abrupt withdrawal of benzodiazepines, especially short-life compounds. It is usually short-lasting but intense in terms of the severity of symptoms.
Jitteriness: "*early worsening of anxiety, agitation and irritability commencing antidepressants*." (Sinclair et al., 2009).

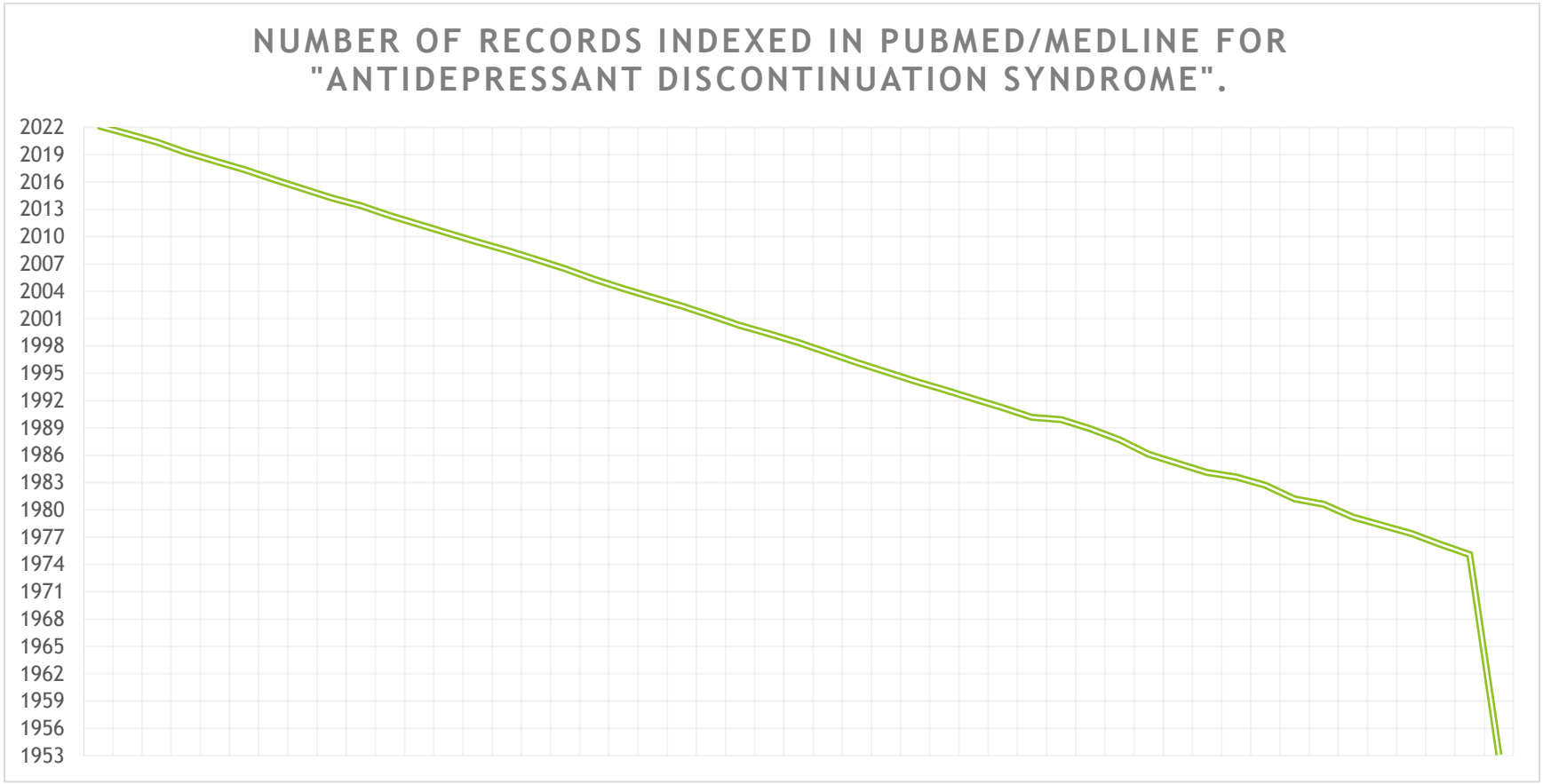
Note: See the detailed operational criteria for withdrawal and rebound phenomena following the interruption of antidepressants proposed elsewhere (Chouinard and Chouinard, 2015).

Figure 1: An adapted classical mnemonic for antidepressant discontinuation reactions (Berber, 1998).



Note: The symptoms of antidepressant discontinuation syndrome may vary in severity, duration, series, and trajectories.

Figure 2: Publication trend for "*antidepressant discontinuation syndrome*." No filter was applied. Results, n=1,049. A similar trend applies to "*antidepressant withdrawal*" (not shown).



Note: The term "*antidepressant discontinuation syndrome*" appeared sporadically in the literature before the late 1990s, virtually underscoring the research interest in the phenomenon in the previous decades; 2022 could cover only the first quarter of the year (the most current access date, May 8th, 2022).

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Contributors

CIC conceived the report; MF drafted the main-text and its attachments; EV, CIC, FVR, DDB and GM assisted in proof reading and editing. All authors contributed to the study and approved the final version of the manuscript.

Conflicts of interest

EV has received grants and served as consultant, advisor, or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Aimentia, Angelini, Biogen, Boehringer -Ingelheim, Casen-Recordati, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Janssen, Lundbeck, Organon, Otsuka, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris.

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