

Evidence on drug withdrawal reactions after medication discontinuation: An umbrella review

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Systematic Review

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Evidence on drug withdrawal reactions after medication discontinuation: An umbrella review

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Abstract

Physiological adverse drug withdrawal events, also known as adverse drug withdrawal reactions (ADWRs) are a potential harm from deprescribing. This overview of systematic reviews aimed to assess evidence on ADWRs related to medication discontinuation, specifically incidence and characteristics of these reactions. Nine databases were searched (inception-30/05/2025, PROSPERO: CRD420251071396). Two reviewers independently screened and data extracted, with quality assessment using AMSTAR-2. Where information on our primary outcomes (incidence and signs/symptoms of ADWRs) was not included in the review, we extracted this from individual studies. Data were extracted on incidence and signs/symptoms of ADWRs, approach to withdrawal, severity, time to onset and duration. Of 38 included systematic reviews, most (n=32) included mixed study designs (RCTs, non-RCTs, case reports/series). Methodological quality of the systematic reviews was mostly rated as critically low (n=18) or low (n=5) (due to incomplete reporting, absence of meta-analyses, inconsistent risk of bias assessments), with fewer rated moderate (n=5) or high quality (n=4). Twenty-one reviews focused on central nervous system (CNS) drugs (e.g., antidepressants, antipsychotics), thirteen reviews on non-CNS drugs (e.g., antihypertensives, proton pump inhibitors) with four on multiple drugs. Reported ADWR incidence varied widely across the individual studies included in these reviews, with the greatest variability for antidepressants (0.06-100%), opioids (0-100%), antihypertensives (2-100%) and antipsychotics (20-86%). The most common signs/symptoms of ADWRs for CNS drugs included dizziness, nausea and insomnia. This study reveals considerable variation in incidence and characteristics of ADWRs, including across reviews/studies of the same drugs. Standardised criteria for ADWR detection/reporting (distinguishing between physiological reactions and return of the condition being treated) would support future research.

Keywords: deprescribing, adverse drug withdrawal events, umbrella review, discontinuation, withdrawal.

1. Introduction

Adverse drug withdrawal events (ADWEs) are an important consideration when medications are being stopped and include physiologic reactions to drug withdrawal or the return of the condition for which the drug was prescribed [1, 2]. Physiological ADWEs, also known as adverse drug withdrawal reactions (ADWRs), are more likely to be experienced immediately after medication discontinuation and occur when prolonged medication use leads to changes in the regulation of end-organ receptors (such as up- or down-regulation), cellular adaptations, and other mechanisms that may be multifactorial or not fully understood [2, 3]. These alterations can result in receptor over-activation or under-activation when the medication is abruptly discontinued and may cause harmful physiological effects [1, 4]. There are various circumstances in which drug treatment may be stopped for a patient, including patient decision to stop (due to dissatisfaction with treatment, experiencing adverse effects or a desire to avoid long-

term use) [5], deprescribing (planned reduction or discontinuation of inappropriate medications to improve the patient's overall health and reduce polypharmacy) [1] and following serious adverse drug reactions (ADRs) [6]. ADWRs are an important consideration when medications are discontinued for any reason [1, 2, 7].

There is accumulating evidence demonstrating that several medication classes have a high risk of ADWRs [2-4, 8-12]. ADWRs are recognised as a significant clinical concern, particularly for drugs used for mental health conditions such as antipsychotics [9], antidepressants [10], and benzodiazepines [11], but also for treatments used in other conditions, including opioids [13] and corticosteroids [14]. ADWRs can range from mild to severe, and can have physical and psychological impact, and can also lead to mortality. The incidence and severity of ADWRs may be influenced by factors such as the type of drug, duration of use, dosage, pace of discontinuation/tapering, and individual physiological variations [3, 7, 8, 10, 15-17]. However, there is variability and a lack of consistency in how ADWRs and their characteristics are described and reported in the literature. Moreover, the existing evidence on the incidence of ADWRs is based on trials and systematic reviews that have used different methodologies and approaches to defining, measuring and reporting ADWRs. These differences, together with potential limitations of individual studies and reviews may limit the comparability and interpretation of the available evidence. In clinical practice, there is a lack of guidance on tapering approaches, how to monitor and avert ADWRs [2, 5, 18-20]. Moreover, there is limited systematic collection of ADWRs in the pharmacovigilance system as compared to ADRs [21-23].

Given the challenge of reducing medication harm, there is a growing need to extend the evidence base on the incidence and characteristics of ADWRs, to fully understand the potential risk of these events. Most systematic reviews have focused on withdrawal symptoms associated with a single drug [24-26] or specific drug classes [9, 18, 27, 28], resulting in fragmented evidence. An overview of these reviews would provide an understanding of where evidence on this topic exists and the commonalities and differences in ADWRs across different therapeutic areas. To the best of our knowledge, no overview of reviews on ADWRs has been conducted to-date. This could inform strategies for reducing medication-related harm, in line with the World Health Organisation's current Global Patient Safety Challenge of Medication Without Harm [29], by providing evidence to guide future research, clinical decision-making and development of guidelines.

Therefore, we aimed to conduct an overview of reviews to assess evidence on ADWRs related to medication discontinuation, including the incidence and characteristics of these reactions.

2. Methods

The protocol of this study was registered with PROSPERO (CRD420251071396) [30] and Open Science Framework (OSF) [31]. This study involved an overview of reviews (also referred to as an umbrella review), conducted in line with Cochrane Collaboration guidance on overviews of reviews

[32] and reported according to the Preferred Reporting Items for Overviews of Reviews (PRIOR) [33]. Details about PRIOR Checklist are provided in *supplementary file 1*. We made amendments to the protocol during the abstract and full-text screening stages by excluding reviews of iatrogenic withdrawal and critically ill patients with a narrow focus. Details are listed in *supplementary file 2*.

2.1. Eligibility criteria

The eligibility criteria for this overview were based on the PICOS (Population, Intervention, Comparison, Outcomes and Study) and applied to the selection of systematic reviews are presented in *table 1*. Detailed inclusion and exclusion criteria are provided in *supplementary file 2*.

Table 1: Description of PICOS eligibility criteria

PICOS	Description
Population	No restriction; however, reviews focused exclusively on critically ill patients were excluded during screening as a protocol amendment.
Intervention	Drug discontinuation (e.g. abrupt withdrawal, or tapering to complete withdrawal or by reducing the dose with the intention of withdrawal)
Comparator	Continuation of the relevant drug with or without a placebo, comparison of different discontinuation strategies (e.g. abrupt vs tapering), discontinuation of placebo, or no comparator.
Outcomes	The incidence of ADWR occurrence and characteristics of ADWRs were the primary outcomes, and reviews had to report either or both to be included. Reviews that focused on ADWEs in general (potentially combining ADWRs and those relating to the return of the condition) were included and, where possible, we extracted only the ADWR information. We excluded those that explicitly only focused on return of the condition/relapse.
Types of studies	Systematic reviews including RCTs, non-randomised studies, observational studies, case reports, or case series were included. Study designs excluded were scoping reviews, rapid reviews, qualitative studies or surveys, commentaries, letters, editorials, theses, conference abstracts, primary studies, animal studies, and studies of alcohol/nicotine/neonatal withdrawal, or iatrogenic withdrawal in critically ill or narrowly defined ICU populations.

RCT: Randomised control trial; ADWRs: Adverse drug withdrawal reactions; ICU: Intensive care unit

2.2. Search Strategy

The PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension) checklist was used in reporting the search strategy [34]. A search strategy was developed and run initially on PubMed (including Medline) and then extended to other databases, specifically Embase, CINAHL, PsycInfo, Scopus, Epistemonikos, Cochrane Database of Systematic Reviews, PROSPERO register, and the Database of Abstracts of Reviews of Effects using broad search criteria from inception to May 2025. The final updated search was conducted in all included databases on 30 May 2025. The search strategy contained a combination of keywords, synonyms and free text relating to drug withdrawal events and systematic reviews, and incorporated Boolean search operators, truncations,

medical subject headings [MeSH] and proximity operators. Moreover, known relevant studies and their abstracts were searched to identify any additional relevant keywords or terms, as described in *supplementary file 3*. A validated search filter was used to limit the results of the search to systematic reviews [35]. We piloted the search strategy across different databases to confirm its ability to identify known relevant reviews.

2.3. Study Selection process

Search results were combined and deduplicated using EndNote (version 21) and Covidence software, applying a validated deduplication protocol [36]. Titles/abstracts screening and then full-text review were conducted independently by two researchers (ZK, PC, JB, or FM), with disagreements resolved by consensus, or by a third reviewer. All eligible systematic reviews with overlapping evidence bases (where primary studies were represented in more than one review) were included to ensure as broad as possible scope of content. Overlap was assessed using a citation matrix and quantified by using corrected coverage area (CCA) index (as described in the statistical analysis) [37].

2.4. Data extraction

Two researchers independently performed data extraction in Excel (version 2108; Microsoft Redmond, Washington). Disagreements were resolved by consensus, or if needed, consultation with a third researcher. Data were extracted from included systematic reviews relating to our primary outcomes (incidence of ADWRs, and signs/symptoms of ADWRs). Additional extracted data included drug class or specific drug, approach to discontinuation, severity, timing (onset of symptoms upon withdrawal) and duration, any reasons or context for withdrawal and treatment and management of withdrawal symptoms. Further detailed about data extraction are provided in the *supplementary file 2*.

Where information on our primary outcomes (incidence and signs/symptoms of ADWRs) was not included in the review, we extracted this from individual studies. As case reports/series do not allow incidence to be estimated, we only extracted missing information on ADWR signs/symptoms from individual case reports/series. If discrepant data was identified across systematic reviews including the same studies, two reviewers independently cross checked the data with the primary studies to manage this during data extraction.

2.5. Quality assessment of reviews

Risk of bias was assessed for included systematic reviews using AMSTAR-2 (A Measurement Tool to Assess systematic Reviews), a validated 16-item scale [38]. The overall quality grading (high, moderate, low or critically low) of a systematic review is assigned by a combination of ratings. Given systematic reviews including case reports/case series could only provide limited evidence relating to our primary outcomes, AMSTAR-2 was applied only to systematic reviews also containing other study designs. Item

scores for each included systematic review were presented in a tabular form to compare the rigour and reporting. Detailed description about AMSTAR-2 is presented in the *supplementary file 4*.

2.6. Synthesis

A narrative synthesis of results was conducted due to anticipated heterogeneity across included reviews. This focused on (a) incidence of ADWRs reported across reviews, across drug classes, across types of withdrawal (i.e., abrupt stopping, dose reduction), and across populations, (b) nature of ADWRs that occurred, including signs/symptoms, duration and timing, and (c) details of the withdrawal approaches, any co-delivered interventions and comparator groups. A citation matrix was developed to highlight the extent of primary study overlap within the included systematic reviews. The mathematical formula of CCA is $N - r/rc - r$ where N is the number of included publications in evidence synthesis (the sum of the ticked box in the citation matrix); r is the number of rows (number of indexed publication) and c is the number column (number of systematic review). The possible values of CCA ranged from 0-100% (0-5 indicate slight overlap; 6-10: moderate; 11-15: high and >15: very high).

3. Results

3.1. Description of review selection

A total of 9,244 articles were initially identified, with 102 potentially relevant full-texts assessed. Of these, 64 reviews did not meet eligibility criteria (see *supplementary file 5* for excluded studies with reasons for exclusion). Therefore, 38 systematic reviews fulfilled the inclusion criteria and were included in this overview of reviews. The overall study selection process is also illustrated in *Figure 1*.

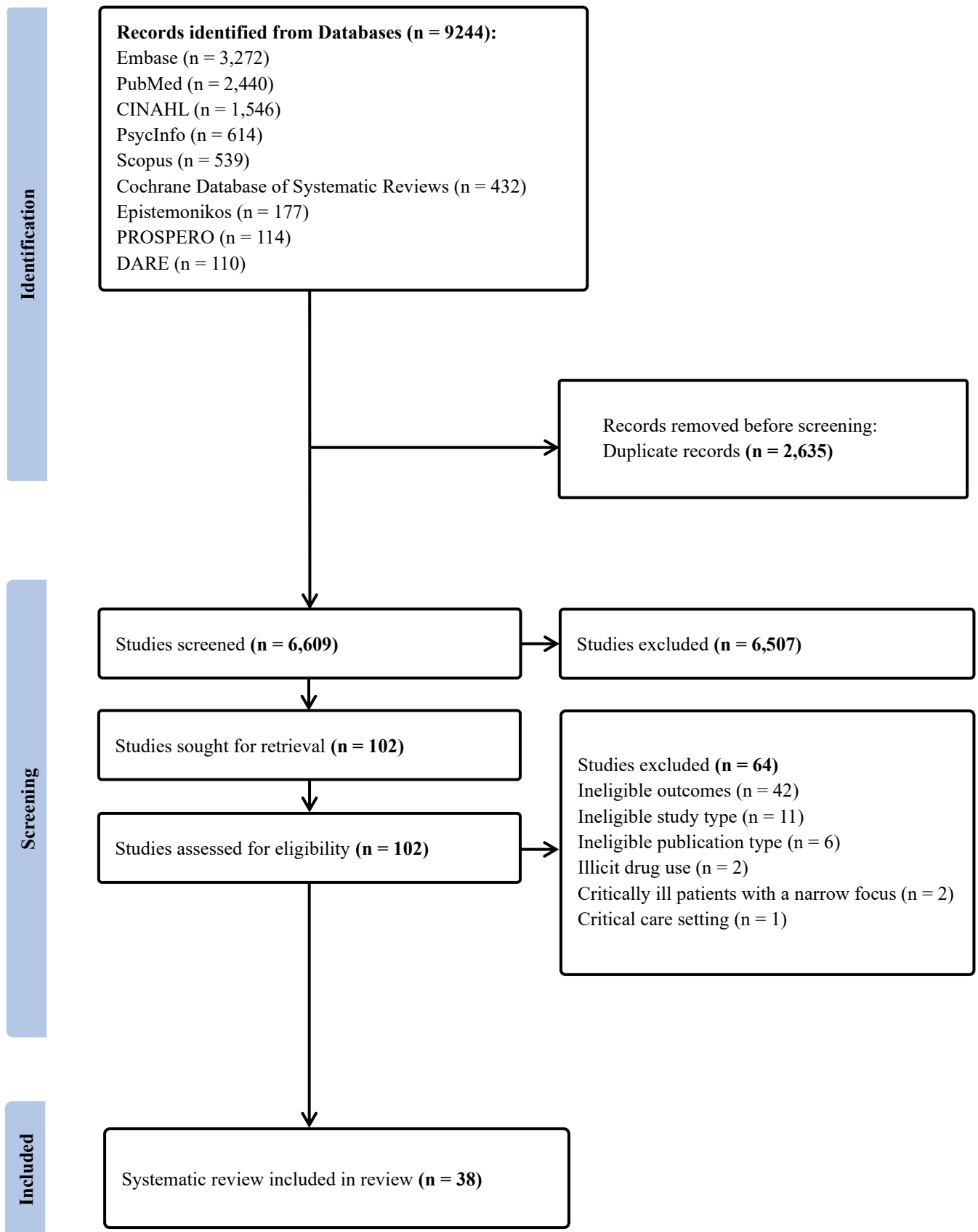


Figure 1: PRISMA Flow Diagram

3.2. Review characteristics

The included systematic reviews were published from 2004-2025, with 60% (n=23) published in the last 7 years (2019-2025). Most reviews (n=37) were written in English, only one review was in German language [39]. A total of 21 reviews focused on central nervous system (CNS) drugs including antidepressants (n=10 reviews) [10, 28, 40-47], antipsychotics (n=4) [9, 24, 25, 48], opioids (n=2) [49, 50], lithium (n=2) [39, 51] z-drugs [52], benzodiazepines and z-drugs [53] and cholinesterase inhibitor or memantine [54]. Thirteen reviews examined non-CNS drugs, including antihypertensives (n=4 reviews) [18, 55-57], heart failure medication (n=2) [58, 59], proton pump inhibitors (PPIs: n=2) [60, 61], corticosteroids (n=2) [62, 63], atropine [64], baclofen [65], and tyrosine kinase inhibitors [66]. Finally, four reviews included multiple drugs classes [20, 67-69]. The characteristics of all reviews are summarised in *supplementary files 6, 7 and 8*.

The age group eligibility criteria of the included reviews varied. Most reviews focused on adults (n=17), followed by older adults (n=7) and paediatric populations (n=2). Most reviews (n=34) included mixed study designs (interventional/RCTs, observational studies, case reports/series), while four included only case reports/series [25, 47, 48, 65]. However, in two mixed study designs reviews only the included case reports/series met our eligibility criteria [50, 62]. Overall, the included reviews evaluated interventions involving the complete discontinuation or dose reduction of medications, with or without replacement by placebo, across both CNS and non-CNS drug classes. These interventions were most frequently compared with continuation of the same medicines, usual care, or placebo; however, a comparator was not included or specified in 13 reviews [10, 24, 25, 39, 46-50, 62, 63, 65, 66].

A total of 730 eligible primary studies were included across 38 reviews. These included 245 case reports or case series followed by RCTs (n=183), other interventional (non-RCTs) studies (n=49) and observational studies (n=164) (*supplementary files 6 and 7*). The results showed slight overlap in eligible primary studies (CCA=0.31%) among the included reviews. Reviews focusing on the same medication class also demonstrated slight overlap, with antidepressants (2.71%), antipsychotics (1.45%), antihypertensive and heart failure medications (1.05%), and multiple drug classes (4.44%). The details about CCA (overall and overlap for reviews focusing on the same class) are provided in *supplementary file 9*.

Methodological quality of reviews

Of the total 38 reviews, AMSTAR-2 was applied to the 32 that included at least one RCT, interventional or observational study such that the findings could inform the primary outcome of incidence and reviews were rated as critically low (n=18) or low (n=5), with fewer rated moderate (n=5) or high quality (n=4). The remaining 6 reviews included only case reports/series and were not assessed using AMSTAR-2. The most commonly identified methodological limitations were the absence of registered review protocols, lack of quantitative synthesis or meta-analysis, incomplete or inconsistent assessment of risk

of bias, and limited exploration of heterogeneity. Additional concerns included inadequate reporting of study selection procedures, failure to assess publication bias, and lack of reporting on the sources of funding for the included studies. The complete details are available in *supplementary file 4*.

Among the included systematic reviews, 35 (92.1%) reported the incidence rates or signs and symptoms of ADWRs across different drug classes. Incidence and signs/symptoms were the most commonly reported characteristics, whereas severity, onset/duration, tapering and management were inconsistently documented (**Figure 2**). Moreover, we extracted information on our primary outcomes from the individual studies that were not reported in three reviews (7.9%) [53, 56, 69] (*supplementary file 8*).

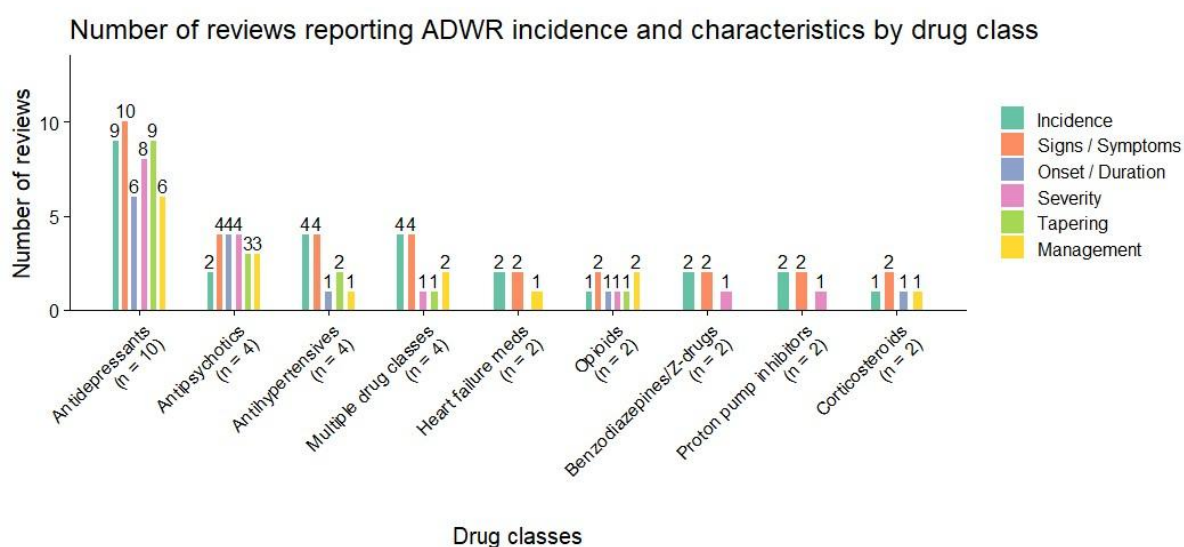


Figure 2: Number of reviews reporting incidence and characteristics of ADWRs by drug class

**Drug classes with at least two reviews are shown. Six reviews each focusing on single drugs/drug class (e.g., lithium [n=2], tyrosine kinase inhibitors [n=1], baclofen [n=1], atropine [n=1], and cholinesterase inhibitors or memantine [n=1]) are not shown in the figure.*

3.3. Incidence and characteristics of ADWRs across CNS and non-CNS drug reviews

3.2.1. CNS reviews

3.2.1.1. Antidepressants

Among CNS-drug reviews, ten examined ADWRs across various antidepressants. Of these, one review focused on selective serotonin reuptake inhibitors (SSRIs) alone [40], another on serotonin-noradrenaline reuptake inhibitors (SNRIs) [41], and one on tranylcypromine (monoamine oxidase inhibitor or MAOI) [47] and seven reviews [10, 28, 42-46] examined both SSRIs and SNRIs. Information on incidence rates was extracted from 9 reviews and was not applicable for one review (case reports) [47]. Most reviews quantified the occurrence of ADWRs as percentage of participants experiencing an ADWR. However, two reviews used the Discontinuation-Emergent Signs and

Symptoms scale (DESS) [40, 44] and one employed DESS along with the "Penn State Worry Questionnaire (PSWQ: to assess the frequency and severity of worry symptoms)" and the "Fear of Negative Evaluation Scale (FNES) to determine a withdrawal symptom score [43]. Further details are listed in **table 2 and supplementary file 8**.

Overall antidepressant withdrawal reaction incidence were reported in three reviews [10, 28, 45]. Henssler et al. [28] and Zhang et al. [45] reported pooled incidence estimates of 31% and 42.9% respectively, whereas Davies et al. [10] reported incidence rates ranging from 27% to 86% across individual studies (weighted average 56%). Henssler et al. also reported that the incidence of at least one discontinuation symptom was higher following antidepressant discontinuation than placebo discontinuation (31%, 95%CI 27-35% vs 17%, 95%CI 14-21%, respectively) [28]. Similarly, among RCTs included by Zhang et al, the incidence was 44.4% (95%CI 34.5-54.4%) following antidepressant discontinuation compared with 16.6% (95%CI 8.2-25.0%) among patients who continued treatment [45]. Severe discontinuation symptoms were also reported in one review with a synthesised incidence of 2.8% of patients following antidepressant discontinuation compared with 0.6% of patients in the placebo discontinuation group [28]. Drug-class incidence rates were reported in some reviews for SSRIs (DESS score 0.2-7.8; 20-86% of participants) [40, 44, 45], SNRIs (29.7%) and tricyclic antidepressants (TCAs) (59.7%) [45]. Reported individual-drug ADWR incidence varied widely (0.06-100%), and across SSRIs included: paroxetine 5-100% [10, 28, 40, 42, 44-46], fluvoxamine 0.40-86% [10, 28, 40, 45, 46], citalopram 19-70% [10, 28, 40, 44-46], escitalopram: 8-56% [10, 28, 40, 44-46], sertraline 0.9-60% [10, 28, 40, 45, 46] and fluoxetine 0.06-77% [10, 28, 40, 45, 46]. Among SNRIs, incidence of ADWRs ranged from 23-78% (venlafaxine), 5.3-55% (desvenlafaxine), 6-55% (duloxetine), 11.7-30% (milnacipran) and 9-10% (levomilnacipran) [10, 28, 41-46]. Imipramine (44-100%) [28, 46] was the TCA with highest reported incidence of ADWRs, followed by amitriptyline (80%) [44] and clomipramine (31-83%) [46]. Moreover, among atypical antidepressants, nefazodone, vortioxetine and bupropion reported ADWR incidence rates of 21% [28], 3% and 1.4% [46], respectively (**table 2, supplementary file 8**).

The nature of ADWRs included somatic, cognitive, affective, behavioural, and neurological symptoms. Common somatic and neurological effects included dizziness, headache, nausea, fatigue, impaired balance, paraesthesia, tremor, brain zaps, and sleep disturbances [10, 28, 40-46]. Psychological and affective symptoms included irritability, anxiety, mood swings, and depression. Gastrointestinal symptoms (diarrhoea, abdominal pain, vomiting), autonomic signs (tachycardia, sweating, flushing), sexual dysfunction, and vivid dreams or nightmares were also reported [40, 41, 47].

Studies varied in the terms used to describe ADWRs, including discontinuation symptoms/syndrome [10, 28, 40-42], discontinuation-emergent signs and symptoms (DESS) [43, 44], antidepressant

discontinuation syndrome [44], antidepressant withdrawal symptoms/syndrome [45], discontinuation/withdrawal-emergent adverse events [46], discontinuation-emergent adverse events [42] and withdrawal phenomena/discontinuation phenomena [47]. Moreover, three reviews clearly distinguished between ADWRs or relapse [42, 45, 47]; however, one reported mixed ADWEs [28] and others noted no clear distinction but acknowledged this as a challenge [10, 40, 41, 43, 44, 46] (table 1, *supplementary file 8*).

Antidepressants were discontinued either abruptly or via tapering. Tapering strategies varied greatly for different antidepressants such as SSRIs including paroxetine (reduced to 10 mg/day over 1-4 weeks) [28, 40, 42, 46], sertraline (50 mg reductions every 10-20 days over 8 weeks, 25 mg/day less for 2 weeks or 25% weekly for 4 weeks) [28, 40, 46], fluvoxamine (150-100-50 mg/day over 3 days) [40], escitalopram (15-10-5 mg over 9 months, 5 mg/day for 3 weeks, 20 to 10mg 1 week) [28, 40, 46]. Similarly, SNRIs including desvenlafaxine (25 mg/day for 1 week, depending on dose) [28, 42, 43, 46], levomilnacipran (tapered to 40 to 20 mg/day over 1 week) [28, 46], duloxetine (tapered over 1-3 weeks) [45, 46] and venlafaxine (tapered over 3-15 days) [28, 46]. However, detailed tapering schedules were not consistently reported across the included studies. Details of tapering strategies are listed in *supplementary files 7 and 8*.

Severity of ADWRs ranged from mild to very severe, with symptom onset within 1 day to 6 weeks of discontinuation and duration extending from a few days to several months, and in one review reported >3 years [10]. Management strategies involved restarting the same antidepressant or switching to another SSRI/SNRI, along with symptomatic treatments such as benzodiazepines, antipsychotics, antihistamines, antimuscarinics, or gamma-aminobutyric acid (GABA) modulators [40-42, 44, 46, 47] (*supplementary files 7 and 8*).

3.2.1.2. Antipsychotics

ADWRs related to antipsychotic medications were evaluated in four reviews. One review [9] investigated typical antipsychotics (i.e. phenothiazine, thioxanthene, chlorpromazine) and three examined atypical antipsychotics specifically clozapine [24, 48] and quetiapine [25]. Information on incidence rates was available in two reviews [9, 24]. Brandt et al. (2020) [9] reported an overall weighted mean ADWR occurrence of 53% (range 25-86%) in discontinuation groups versus 10-12.5% in control groups (continuation), with sensitivity analysis across three studies showing similar results of 49% versus 11% in discontinuation versus control respectively. Yee et al. (2023) [24] found psychotic symptom in 29% and non-psychotic symptoms in 20% after clozapine discontinuation. Incidence data were not applicable for the other two reviews (case reports/series) [25, 48].

The nature of ADWRs included autonomic, neurological, and psychiatric symptoms. Terms used to describe these reactions were varied across reviews. Three reviews clearly differentiated ADWRs and relapse [24, 25, 48]. Both withdrawal methods (abrupt and tapering) were reported for antipsychotics. Tapering regimens for quetiapine [25] and clozapine [24, 48] were highly variable and incompletely described. The severity of symptoms was mild to severe with onset within hours to 4 weeks. Management of these symptoms often involved restarting the same drug, with adjuncts (e.g., sodium valproate, benzodiazepines derivatives etc.). The complete details are provided in **table 2, supplementary files 7 and 8**.

3.2.1.3. Opioids

Two reviews evaluated ADWRs associated with opioids [49, 50]. The studies examined a range of opioid medications including morphine, hydrocodone, oxycodone, methadone, codeine, tramadol, and buprenorphine. One review [49] documented a varied range of ADWRs incidence (0-100%) across studies, depending on population and opioid type, while another [50] consisted of case reports and incidence rates were not applicable. Frank et al. (2017) reported withdrawal symptoms including sweating, restlessness, muscle aches, nausea, vomiting, diarrhoea and mild or worsening pain after discontinuation of opioids [49]. Lozano-López et al. (2021) reported more atypical or severe neuropsychiatric withdrawal symptoms, including as hallucinations, delusions, psychosis, affective symptoms, suicidal ideation, depersonalization and sleep disturbance [50]. Both reviews referred to these reactions as opioid withdrawal or discontinuation symptoms, and neither provided a clear distinction between ADWRs and relapse phenomena (**table 2, supplementary file 8**). Additionally, opioids were tapered (including a 1-week inpatient taper, tapering over 2–7 days, or gradual tapering) or abruptly stopped, often with co-delivered multidisciplinary pain management programs (cognitive behavioural therapy/CBT, pharmacologic, inpatient pain rehabilitation) [49, 50]. Symptoms ranged from mild to worsening pain [49], onset 36 hours to 2 weeks [50], and management strategies included methadone, buprenorphine, clonidine, benzodiazepines, ketamine, analgesics, or oxycodone [49, 50] (**table 2, supplementary files 7 and 8**).

3.2.1.4. Other CNS drugs

Reviews of ADWRs reported mixed results on incidence following benzodiazepine discontinuation (40% versus 25% in the continuation group in one study, with four studies finding no increased incidence) and increased incidence following Z-drug discontinuation (25-38% for zopiclone and 38% for zolpidem compared with 24% in the continuation group) [52, 53]. For lithium, pooled incidence was 7.2% in the discontinuation versus 6.2% in the continuation group, with individual study estimates ranging from 0-25% [39, 51]. Detailed findings are presented in **table 2, supplementary files 7 and 8**.

Table 2: incidence and characteristics ADWRs in CNS-drug reviews (n=21)

Author (year), quality rating AMSTAR 2	Drug(s) targeted	Overall incidence rate	Drug class incidence rate	Individual incidence rate	Nature ADWRs (signs/symptoms)	Terms used for ADWRs	Distinction between ADWRs or relapse
Antidepressants (n=10)							
Gahr M et al (2013) ^[47]	Tranlycypromine	Not applicable/case reports	Not applicable	Not applicable	Delirium, agitation, abdominal cramps, diarrhoea, headaches, hypersomnia, nausea, nocturnal myoclonus, restlessness, sialorrhea, vomitus, seizures	Withdrawal phenomena/ discontinuation phenomena (WP/DP)	Clear distinction
Fava GA et al (2015) ^[40] , *	SSRIs (paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram)	Not reported	DESS* Scores: SSRIs 0.2-7.8 (paroxetine 2.2-7.8, sertraline 5.7, escitalopram 2.4-3.2), fluoxetine 0.20). <i>Incidence of discontinuation Symptoms (%)</i> : 45%-86% (taper 46-52% and abrupt 86%)	Paroxetine 5.1-100%; fluvoxamine 0.4-86%; citalopram 45-70%; escitalopram 17-27%; sertraline 0.9-59.1%; fluoxetine 0.06-73.3%	Somatic, sleep, cognitive, sexual, affective and behavioural symptoms	Discontinuation symptoms	No clear distinction, acknowledged as a challenge
Fava GA et al. (2018) ^[41] , *	SNRIs (venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran)	Not reported	Not reported	Venlafaxine: 23-78%; desvenlafaxine: 17.2-55%; duloxetine: 6-55%; milnacipran: 13-30%; levomilnacipran: 9-10%	Headache, fatigue, malaise, pain, blurred vision, dizziness, tachycardia, nausea, vomiting, abdominal pain, electric shock sensations, tremor, ataxia, seizures, sweating, flushing, confusion, anxiety, irritability, mood swings, depression, visual hallucinations, insomnia, vivid dreams, nightmares, impulsivity, aggression	Discontinuation symptoms	No clear distinction, acknowledged as a challenge
Davies J et al (2019) ^[10] , *	Antidepressants: SSRIs, SNRIs, TCAs, MAOIs	^a RCTs: 50.7%, observational studies: 52.5%, Surveys: 57.1%, ^b Combined incidence rate in all studies: 27% to 86% (weighted average 56%)	Not reported	Paroxetine 35-100%, fluvoxamine 36-86%, fluoxetine 9-77%, citalopram 36-70%, venlafaxine 36-71%, sertraline 58-60%, escitalopram 27-56%	General, sensory, neuromuscular, GI, sleep, cognitive, psychiatric, autonomic, sexual, behavioural	Discontinuation symptoms	No clear distinction, acknowledged as a challenge

Henssler J et al (2019) ^[44] , *	Antidepressants	Not reported	SSRIs: 20-45%	Citalopram/escitalopram abrupt 20% vs 10%; paroxetine >30%; desvenlafaxine taper/abrupt 4.1-5.3 DESS*; milnacipran 16.3%; amitriptyline 80%	Dizziness, fatigue, nausea, impaired balance, sleep disturbance, irritability, brain zaps, emotional lability, hallucinations	Antidepressant discontinuation syndrome (ADS)/discontinuation-emergent signs and symptoms (DESS)	No clear distinction, acknowledged as a challenge
Maund E et al (2019) ^[42] , **	Antidepressants: SNRI (desvenlafaxine), SSRI (paroxetine)	Not reported	Not reported	Posttherapy emergent adverse events: desvenlafaxine: 1-week taper 39% vs abrupt 51% (risk ratio 0.76); discontinuation syndrome: desvenlafaxine: 1-week taper 22% vs abrupt 21% (risk ratio 1.02); paroxetine gradual taper 5% vs abrupt 34% (risk ratio 0.14)	Dizziness, light-headedness, headache, nausea, paraesthesia, loss of balance, irritability, agitation, and insomnia.	Discontinuation-emergent adverse events and discontinuation syndrome/symptoms	Clear distinction
Van Leeuwen E et al (2021) ^[43] , ****	Antidepressants	Not reported	Not reported	Desvenlafaxine: DESS* increase ≥ 4 : Abrupt 5.3 vs control 4.1; Taper 4.8 vs control 4.1. Antidepressant (SSRI, SNRI, TCA) Penn State Worry Questionnaire (PSWQ) (frequency and severity of symptoms of worrying): mean score discontinuation 42 vs control 39.3. Fear of Negative Evaluation Scale (FNES): discontinuation 10.3 vs control 8.4	Dizziness, headache, nausea, anxiety, irritability, fatigue, insomnia, flu-like, electric shocks	Discontinuation-emergent signs and symptoms (DESS)	No clear distinction, acknowledged as a challenge
Henssler J et al (2024) ^[28] , ***	Antidepressants	<i>Antidepressant discontinuation symptom:</i> Discontinuation 0.31 (0.27-0.35) = 31% (62 studies), <i>placebo discontinuation</i> 0.17 (0.14-0.21) = 17% (22 studies), <i>Severe discontinuation symptoms</i> 0.028 (0.014-0.057) = 2.8% (19 studies), placebo	Not reported	<i>Antidepressant discontinuation symptom:</i> Imipramine 44%, desvenlafaxine/venlafaxine 40%, escitalopram 39%, fluvoxamine 38%, paroxetine 32%, duloxetine 32%, nefazodone 21%, levomilnacipran/milnacipran 19%, citalopram 19%, sertraline 18%, fluoxetine 15%. <i>Severe discontinuation symptoms:</i> Imipramine	Dizziness, headache, nausea, insomnia, irritability, vivid dreams, electric shocks, rapid mood-swings	Discontinuation symptoms	Mixed

		0-006 (0-002-0-013) = 0.6% (6 studies)		12.3%, desvenlafaxine/venlafaxine 5.6%, paroxetine 5.3%, duloxetine 2%, fluoxetine 1.8%.			
Zhang MM et al (2025) ^[45] , *	Antidepressants	^a Discontinuation group 42.9% (29 studies), ^c RCTs: discontinuation group 44.4% (11 studies) vs continuation 16.6% (6 studies)	SNRIs 29.7%, SSRIs 45.6%, TCAs 59.7%	Citalopram 62.6%, sertraline 55.9%, venlafaxine 52.9%, escitalopram 46.9%, paroxetine 45.5%, fluoxetine 40%, desvenlafaxine 31%, fluvoxamine 13.4%, milnacipran 11.7%	Brain zaps, anger or irritability, dizziness, insomnia or trouble sleeping, headache, sweating, nightmares or increased dreaming, worsened mood or depression, anxiety or panic, confusion or impaired concentration, agitation, and nausea	discontinuation of antidepressants/antidepressant withdrawal symptoms or syndrome (AWSs)	Clear distinction
Stimpfl JN et al (2025) ^[46] , *	Antidepressants (SSRIs, SNRIs, TCA and atypical antidepressants)	Not reported	Not reported	SSRIs: Citalopram: ADWEs were more frequent in the discontinuation group; escitalopram: New adverse events in discontinuation 8% vs continuation 7%; paroxetine: discontinuation-related adverse events 47.2% vs 32.5%; fluoxetine 10-15% vs 0-5%; sertraline 11-56%; fluvoxamine 86%. SNRIs: venlafaxine: discontinuation group 27-33% vs placebo 15%; duloxetine 19% vs 15%; desvenlafaxine 5.3-21.6% vs 0-4.9%; levomilnacipran 10% vs 10%; Atypical: bupropion: 1.44%; vortioxetine: discontinuation symptoms 3%. TCAs: imipramine: 100%; clomipramine: 31-83%	Dizziness, headaches, fatigue, paraesthesia, brain zaps, palpitations, GI symptoms, emotional/behavioral, sleep disturbances, diarrhea, myalgia, hyperhidrosis	Discontinuation/withdrawal-emergent adverse events	No clear distinction, acknowledged as a challenge

Antipsychotics (n=4)							
Brandt L et al (2020) ^[9] , ***	Antipsychotics (Derivates of phenothiazine, thioxanthene, butyrophenone, or piperazinyl, chlorpromazine and/or reserpine: thioridazine)	Quantitative analysis based on all studies: *Weighted mean 53% (discontinuation); Sensitivity analysis (3 studies) weighted mean: discontinuation group 0.49 vs control 0.11	Not reported	Discontinuation 25-86% vs control 10-12.5%	Nausea, vomiting, sweating, restlessness, headache, insomnia, hyperkinesia, diarrhea, tachycardia, anxiety, abdominal pain and dry mucous membranes.	Withdrawal symptoms	No clear distinction, acknowledged as a challenge
Monahan K et al (2021) ^[25]	Quetiapine	Not applicable/case reports	Not applicable	Not applicable	Mood disturbance, irritability, agitation, nausea, palpitations, tachycardia, dizziness, insomnia, dyskinesia, headache or fatigue and appetite disturbance.	Discontinuation symptoms	Clear distinction
Yee B et al (2023) ^[24] , *	Clozapine	Not reported	Not reported	Psychotic symptoms after discontinuation: 29% and non-psychotic 20%	Cholinergic rebound, extrapyramidal symptoms, catatonia, psychotic symptoms	Discontinuation symptoms	Clear distinction
Bickerton L & Kuriakose JL (2024) ^[48]	Clozapine	Not applicable/case reports	Not applicable	Not applicable	Cholinergic rebound: diaphoresis, nausea, vomiting, dyskinesia, dystonia, urinary/fecal incontinence, insomnia; non-cholinergic: agitation, hallucinations, anxiety, disorganized thought, delusions, and affective instability.	Cholinergic rebound syndrome	Clear distinction
Opioids (n=2)							
Frank JW et al (2017) ^[49] , *	Opioids (morphine, hydrocodone, oxycodone, methadone, codeine, tramadol)	0-100%	Not reported	Not reported	Opioid withdrawal symptoms, mild pain, worsening pain	Opioid withdrawal/discontinuation symptoms	No clear distinction and no acknowledgement
Lozano-López MT et al (2021) ^[50]	Opioids (methadone, buprenorphine, tramadol, oxycodone, morphine)	Not applicable/case reports	Not applicable	Not applicable	Hallucinations (visual, auditory, olfactory/kinesthetic), delusions (persecutory, paranoid, mystical), formal thought disorder, disorganized thinking, psychosis, affective symptoms (hypomania, depression, anxiety), suicidal thoughts, sleep disturbance, unusual withdrawal phenomena (e.g., depersonalization, Lilliputian hallucinations)	Withdrawal symptoms	No clear distinction and no acknowledgement
Benzodiazepines or Z-drugs (n=2)							

Dündar Y et al (2004) ^[52] , *	Z-drugs (zolpidem, zopiclone)	Not reported	Not reported	Zopiclone: 25-38%; zolpidem 38% vs 24% (discontinuation vs continuation)	Sleep complaints, anxiety, seizures, restlessness, tremor, facial flushing, nightmares, sweating, low mood, palpitation, tachycardia, rebound insomnia, craving	Withdrawal symptoms	No clear distinction and no acknowledgement
Reeve E et al (2017) ^[53] , *	Benzodiazepines or Z-drugs	Not reported	Not reported	Placebo discontinuation 40% (4/10) vs lormetazepam continuation 25% (1/4) (1 study)	Worsened sleep (possibly rebound insomnia)	Withdrawal symptoms	No clear distinction and no acknowledgement
Lithium (n=2)							
de Vries C et al (2013) ^[51] , *	Lithium	Not reported	Not applicable	Lithium less effective after discontinuation vs lithium less effective after reintroduction: 80% (104/130) vs 71.5% (93/130) and 45% (13/28) vs 32.9% (9/27)	Discontinuation-induced refractoriness	Discontinuation-induced refractoriness	Clear distinction
Gutwinski S et al (2021) ^[39] , *	Lithium	Not reported	Not applicable	Individual studies: 0-25%	Anxiety, irritability, sleep disturbance, nausea, dizziness, restless behaviour, euphoria, manic symptoms	Lithium withdrawal symptoms	Clear distinction
Cholinesterase inhibitors (n=1)							
Parsons C et al (2019) ^[54] , **	Cholinesterase inhibitors or memantine	Neuropsychiatric symptoms (Short term up to 2 months): *SMD -0.48 (-0.82 to -0.13); medium term (3 to 11 months): SMD -0.27 (-0.47 to -0.08); long term (12 months or longer): Little to no change in neuropsychiatric status *MD -0.87 (-8.42 to 6.68) Neuropsychiatric Inventory (NPI) points	Not reported	Not reported	Neuropsychiatric symptoms	Neuropsychiatric symptoms	No clear distinction and no acknowledgement

^a Incidence rate in the control group was not reported in the review; ^b Combined incidence rate in both RCTs and observational (face-to-face and online studies); ^c Incidence rate only in RCTs; AMSTAR 2 quality rating: *=Critically Low; **=Low; ***=Moderate; ****=High. No asterisk indicates that AMSTAR 2 was not applicable (reviews including only case reports/series); DESS: Discontinuation-Emergent Signs and Symptoms Scale; MD: Mean difference; OR: Odds ratio; RCT: Randomized controlled trial; SMD: Standardized mean difference; Clear distinction: Confirmed distinction and only include ADWRs; Mixed: some included studies distinguish and only include ADWRs, while other do not have explicit distinction

3.2.2. Non-CNS drug reviews

3.2.2.1. Antihypertensive and heart failure medications

ADWRs associated with antihypertensive medications were evaluated in four reviews. Three studies [18, 55, 56] investigated multiple classes of antihypertensives, including beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, diuretics, and centrally acting agents, while one review [57] focused specifically on diuretics. Jongstra et al. (2016) reported increases in systolic and diastolic blood pressure (BP) at 7 days and over 16 weeks after discontinuation [55]. Van der Wardt et al. (2017) reported ADWRs incidence rate for clonidine (31-100%), oxprenolol/nitrendipine (26-74%), metoprolol (25%) and tiamenidine (10%) [56]. Reeve et al. (2020) observed ankle oedema in 51.2% of the loop or thiazide-type diuretics discontinuation groups versus 29.1% in continuation groups, along with slight increases in potassium level [18]. Van Poelgeest et al. (2025) reported increases in BP (2-10%), ankle/peripheral oedema (6-15%), and furosemide-specific ADWRs ranging from 15.8-55% [57]. Only one review clearly distinguished ADWRs from relapse [18], whereas the other reviews made no clear distinction or acknowledgement. The details are available in *table 3, supplementary file 8*.

Commonly reported ADWRs symptoms included autonomic, cardiovascular, and general symptoms. Reported symptoms included change in systolic/diastolic BP, heart rate changes, ankle/peripheral/facial oedema, rebound hypertension, orthostatic hypotension, headache, palpitations, dizziness, nausea, vomiting, sweating, malaise, and diarrhoea [56, 57] (*table 3, supplementary file 8*).

Heart failure medications (ACE inhibitors/ARBs, beta-blockers, diuretics, vasodilators, digoxin, aspirin, and HMG-CoA reductase inhibitors) were also investigated in two reviews [58, 59]. Hopper et al. (2014) documented a significant rise in heart rate after digoxin discontinuation (mean difference 6.57 beats/min), and captopril discontinuation was associated with increased RAAS activation, angiotensin II, aldosterone, plasma/urinary cortisol, heart rate, and arterial blood pressure. Diuretics showed a 29% incidence of ADWRs. Reported symptoms included pulmonary oedema, shortness of breath, ankle swelling, weight gain, increased heart rate, and elevated blood pressure [58]. Whereas, Duong et al. (2025) reported ADWRs for beta-blockers (3.2-44.3%), diuretics (7-30%), ACEIs/ARBs (16.8-19%), and digoxin (1-22%), with symptoms including ventricular arrhythmia, atrial fibrillation, acute coronary syndrome, syncope, oedema, hypertension, dyspnea, orthopnea, and tachycardia [59] (*table 3, supplementary file 8*).

Withdrawal strategies for antihypertensive and heart-failure drugs varied and were as performed either abruptly or by tapering [18, 55-57, 59]. Tapering schedules included gradual dose reductions over 1-6 weeks (1-week dose-halving then stop; discontinuation over 6 weeks) [55, 57]. Onset of reaction was reported in one review, ranging from 7 days to 16 weeks [55]. Two reviews reported the reintroduction

of the same medication (particularly diuretics) for the management of withdrawal symptoms [57, 58]. Further details are presented in *supplementary files 7 and 8*.

3.2.2.2. Proton pump inhibitors (PPIs)

Two reviews investigated ADWRs associated with PPI discontinuation. One review reported ADWRs incidence of 20-68% following abrupt PPI withdrawal [61], while another observed 5% incidence of ADWRs (mild esophagitis) in the esomeprazole discontinuation group compared with 0% in the continuation group [60]. Rossi et al. (2024) reported symptoms after the discontinuation of PPIs such as gastroesophageal reflux disease (GERD) symptoms, heartburn, acid regurgitation, and dyspepsia [61] and Boghossian et al. (2017) noted mild esophagitis [60]. None of the reviews clearly described a distinction between ADWRs or relapse. Both on-demand tapering and abrupt withdrawal methods were reported for PPIs [60, 61]. The symptoms were mild in nature [60], and no severe adverse events were reported (see *table 3, supplementary files 7 and 8*).

3.2.2.3. Corticosteroids

Among two corticosteroid reviews, incidence and characteristic of ADWRs varied by route and type of corticosteroid. Incidence data was reported in one review [63] and was not applicable in another review (case reports) [62]. Broersen et al. (2015) reported an 18.8% incidence of adrenal insufficiency following corticosteroid discontinuation with rates varied by route of administration and highest for intra-articular (52.20%), oral (48.7%), and multiple routes (42.7%) [63]. Hajar et al. (2015) reported cutaneous reactions after topical corticosteroid discontinuation, including erythema, papules/nodules, pustules, swelling/oedema, scaling, burning/stinging, pruritus, pain, and hyperesthesia [62]. Moreover, withdrawal reaction for topical corticosteroids occurred within 24 hours to 21 days and was managed by complete discontinuation/avoidance of topical corticosteroids or reinitiation of low-potency corticosteroids with adjunctive therapies, such as antibiotics, antihistamines, cold compresses, and psychological support [62] (*table 3, supplementary files 7 and 8*).

3.2.2.4. Others non-CNS drugs

Three studies examined ADWRs associated with discontinuation of Tyrosine kinase inhibitors (TKIs) [66], baclofen with [65] and atropine [64]. Further details are listed in the *table 3, supplementary files 7 and 8*.

3.2.3. Multiple drug classes

Four reviews examined ADWRs following discontinuation of multiple drug classes [20, 67-69]. Incidence varied across studies and drug classes, with higher rates reported for antipsychotics (15-72%)

and diuretics (9-20%), followed by benzodiazepines (0-42%), antihypertensives (0-10%), statins (6.9%), and levothyroxine (5%) [20, 67-69]. These reviews also provided additional drug-specific or contextual findings. Iyer et al. reported ADWRs after antihypertensive, nitrate and antipsychotics discontinuation [69]. Hickman et al. reported cardiovascular events in 6.9% of participants in the statin discontinuation group compared with 5.7% in the continuation group , but made no clear distinction or acknowledgement regarding ADWRs and relapse [68] and Page et al. provided broader estimates across multiple drug classes, including levothyroxine, diuretics and antipsychotics, categorising outcomes as physiological ADWEs [67]. Lee et al. (2025) reported overall ADWEs across multiple drug classes, including benzodiazepine [20]. This review provided no clear distinction between ADWRs and relapse but, acknowledged this as a challenge. Across these reviews, tapering strategies were inconsistently reported and varied by drug class, while severity, duration and management were least consistently reported (*table 3, supplementary files 7 and 8*).

Table 3: Incidence and characteristics ADWRs in non-CNS drug reviews (n=17) and multiple drug classes reviews (n=4)

Author (year)	Drug(s) targeted	Overall incidence rate	Drug class incidence rate	Individual incidence rate	Nature ADWRs (signs/symptoms)	Terms used for ADWRs	Distinction between ADWRs or relapse
Antihypertensive (n=4)							
Jongstra S et al (2016) ^[55] , ****	Antihypertensives (any previously prescribed)	Change in BP (discontinuation group): systolic and diastolic (at 7 days) +9.5 and +5.1 mmHg; Over 16 weeks: +7.4 and +2.6 mmHg;	Not reported	Not reported	Change in systolic/diastolic BP	Not clearly explained (change in BP was regarded as ADWR)	No clear distinction and no acknowledgement
van der Wardt V et al (2017) ^[56] , *	Antihypertensives (Angiotensin-II-receptor blockers, Renin inhibitors, Angiotensin converting enzyme inhibitors, centrally acting drugs, diuretics, calcium antagonists, vasodilators and N-amidino-2- acetamide hydrochloride)	Not reported	Beta-blockers: Discontinuation group: Increase HR from 69±5 to 74±7 beats/min and increase BP 159/106± 16/7 mm Hg; diuretic: decrease HR from 79±6 to 75±8 and increase BP 165/104± 17/7	Clonidine: 31.2-100%; oxprenolol/nitrendipine: 26-74%; metoprolol: 25%; tiamenidine: 10%	Increased HR and BP, orthostatic hypotension, rebound hypertension, headache, general malaise, joint pain, palpitations, sweating, ankle oedema, restlessness, nausea, vomiting	Withdrawal symptoms	No clear distinction and no acknowledgement
Reeve E et al (2020) ^[18] , ****	Antihypertensives (loop or thiazide-type diuretics)	No studies directly reported ADWRs, an increase in ankle oedema (discontinuation 51.2% vs continuation 29.1%) was observed in one study, while another study reported overall reductions. Slight potassium increases were noted in 3 studies after withdrawal.	Not reported	Loop or thiazide-type diuretics (ankle oedema): 51.2%; changes (mainly an increase) in potassium in the discontinuation group	Ankle oedema, potassium changes	Ankle oedema was regarded as ADWR	Clear distinction
van Poelgeest E et al (2025) ^[57] , ***	Diuretics	Not reported	BP increase: 2-10%; ankle oedema: 6-15%; peripheral oedema 10%	Furosemide: 15.8-55%	Increased BP, ankle/ peripheral/ facial/ limb oedema, dizziness, hypotension symptoms, dyspnea, diarrhea	General adverse diuretic withdrawal events	No clear distinction and no acknowledgement
Heart failure medications (n=2)							
Hopper I et al (2014) ^[58] , *	Heart failure medications (ACEI, ARBs, beta-blockers, diuretics, vasodilators, aspirin, digoxin, HMG-CoA reductase inhibitors)	Not reported	Digoxin: discontinuation group: a significant rise in heart rate MD 6.57 (3.74 - 9.41) beats/min; ACEI (captopril): Increase in RAAS, angiotensin II, aldosterone, plasma/urinary cortisol excretion, heart rate and arterial BP; Diuretics: 29%	Not reported	Pulmonary oedema, shortness of breath, ankle swelling, weight gain, increased HR and arterial BP	General withdrawal term	No clear distinction and no acknowledgement
Duong MH et al (2025) ^[59] , **	Heart failure medications (antihypertensives, digitalis glycosides)	Not reported	Beta-blockers: 3.2-44.3%; diuretics: 7-30%; ACEI/ARB: 16.8-19%; digoxin: 1-22%	Not reported	Ventricular arrhythmia, atrial fibrillation, acute coronary syndrome, syncope, oedema,	General ADWEs	No clear distinction and no acknowledgement

					hypertension, dyspnoea, orthopnoea, tachycardia		
Proton pump inhibitors (n=2)							
Boghossian TA et al (2017) ^[60] , ****	Proton pump inhibitors	Not reported	Not reported	Esomeprazole: Discontinuation group 5% vs continuation 0%	Mild esophagitis	Not clearly explained (mild esophagitis was regarded as ADWR which may be potentially rebound in nature)	No clear distinction and no acknowledgement
Rossi A et al (2024) ^[61] , **	Proton pump inhibitors	Not reported	Symptom recurrence: 20-68%	Not reported	GERD symptoms, heartburn, acid regurgitation, dyspepsia	Not clearly explained (GERD symptoms, heartburn, acid regurgitation, dyspepsia may be potentially rebound in nature)	No clear distinction and no acknowledgement
Corticosteroids (n=2)							
Broersen LH et al (2015) ^[63] , *	Corticosteroids	18.8% (adrenal insufficiency)	Not reported	Routes: Intra-articular 52.2%, oral 48.7%, multiple 42.7%, inhaled 7.8%, topical 4.7%, intranasal 4.2%	Symptoms of adrenal insufficiency	Adrenal insufficiency	No clear distinction and no acknowledgement
Hajar T et al (2015) ^[62]	Topical corticosteroids	Not applicable/case reports	Not applicable	Not applicable	Erythema, papules/nodules, pustules, swelling/oedema, dryness, telangiectasia, peeling, scaling, burning/stinging, heat/sun exacerbation, pruritus, pain, hot flashes, hyperesthesia	Topical corticosteroid withdrawal	Clear distinction
Others (Tyrosine Kinase Inhibitors, baclofen and atropine)							
Chen KK et al (2019) ^[66] , *	Tyrosine Kinase Inhibitors (TKIs)	Not applicable	TKI-WS weighted mean: 27%	Imatinib/Nilotinib/Dasatinib: 30.7; nilotinib alone: 14.1-48%; imatinib alone: 14.7-30%.	Musculoskeletal pain, pruritus	TKI withdrawal syndrome (TKI-WS)	Clear distinction
Phu PJJ et al (2023) ^[65]	Baclofen	Not applicable/case reports	Not applicable	Not applicable	Hallucinations (visual/auditory), delusions, confusion, paranoia, agitation, abnormal movements	Baclofen withdrawal psychosis	Clear distinction
Lee SH et al (2024) ^[64] , ***	Atropine	Not reported	Not reported	Rebound SE weight mean difference (WMD) after discontinuation = 6-month 0.926 diopters per year (D/y) vs 12-month 0.268 D/y; rebound AL WMD= 6-month 0.328 millimeters per year (mm/y) vs 12-month 0.121 mm/y; photophobia:	Rebound myopia (SE/AL), photophobia, blurred near vision	Rebound myopia, photophobia, blurred near vision may be considered ADWRs	Clear distinction

				discontinuation group 76.2% vs continuation 60.9%; blurred near vision: 25.3% vs 22.2%.			
Multiple drugs classes (n=4)							
Iyer S et al (2008) ^[69] , *	Antihypertensives, diuretics, psychotropic medications, digoxin, nitrates	Not reported	Antipsychotics: 26.7%; thiazide/diuretics: discontinuation group 26.7-50% vs continuation 25%; BP mean increase of 13.5 mmHg systolic and 4.6 mmHg diastolic compared to the continuation; nitrate: 10% vs 2.5%	Not reported	Antipsychotics: worsening nocturnal symptoms, poor sleep; thiazide/diuretics: ankle oedema, increased BP, sudden cardiovascular events, agitation, recurrent angina; carbamazepine: increased agitation and aggression; nitrate: recurrent/rebound angina pectoris	Withdrawal syndromes	No clear distinction and no acknowledgement
Page AT et al (2016) ^[67] , **	Antihypertensives, diuretics, levothyroxine, antipsychotics, carbamazepine, glucosamine, corticosteroids, benzodiazepines, antidepressants, dopamine agonists, diabetic therapy, lithium	Not reported	Antipsychotics: 15-72%; diuretics: 9-20%; antihypertensives: 0-10%; levothyroxine: 5%	Not reported	Antihypertensives: Increased BP; diuretics: peripheral oedema, BP, asthma; levothyroxine: agitation, restlessness; antipsychotics: nausea, vomiting, diarrhoea, vertigo, dyskinesia, altered appetite, insomnia, anxiety, hallucinations, sleep problems, restlessness; carbamazepine: aggression and agitation	Adverse drug withdrawal events	No clear distinction and no acknowledgement
Hickman E et al (2023) ^[68] , ***	Antihypertensives, statins, anti-diabetics, aspirin, digoxin, diuretics, combination of multiple medications	Not reported	Statins: discontinuation 6.9% vs continuation 5.7%; increased BP from 128 ± 19.5 to 143 ± 25.5 mmHg; diuretic: increased BP to 180/110 mmHg (two consecutive readings); digoxin: drop in left ventricular ejection fraction (LV) rate (60 to 50%).	Not reported	Statins: cardiovascular events, antihypertensive/diuretics: increased systolic BP, hypertension, digoxin: drop in LV ejection fraction, tachycardia, dyspnoea.	Not clearly explained (hypertension, atrial fibrillation, tachycardia etc. may be considered ADWRs)	No clear distinction and no acknowledgement
Lee JJ et al (2025) ^[20] , *	Non-specific drug classes, antithrombotic, antipsychotic, lipid-lowering agent, calcium, analgesic, antiresorptive, nutritional supplement, gastric acid suppression therapy, medication for constipation, sedative hypnotics, first-generation antihistamines, glyburides, and NSAIDs	0-1.25 ADWEs per patient; 1.02 ADWEs per 100 person-months discontinuation group compared to control group	Benzodiazepines: 0-42%, Not reported for other drug classes	Not reported	General symptoms, cardiovascular, respiratory, metabolic, mental health, GI, sedative-hypnotic, benzodiazepine related withdrawal symptoms	Recognised as ADWEs.	No clear distinction, acknowledged as a challenge

AL: Axial length; AMSTAR 2 quality rating: *=Critically Low; **=Low; ***=Moderate; ****=High. No asterisk indicates that AMSTAR 2 was not applicable (reviews including only case reports/series); BP: Blood pressure; HR: Heart rate; SE: Spherical equivalent; Clear distinction: Confirmed distinction and only include ADWRs

4. Discussion and Perspective

Our knowledge of ADWRs and when and how often they occur is limited [2]. This study reveals considerable variation in the incidence and characteristics of ADWRs, including across reviews/studies of the same drugs. This variability may partly reflect differences in data sources and method used to identify, measure, and report withdrawal reactions across studies. In the included reviews, ADWR assessment methods varied considerably, with some studies using systematic assessment tools or predefined withdrawal symptom scales, while others relied on spontaneously reported adverse events, retrospective data collection, or case reports. Studies using active and systematic assessment are more likely to identify mild or transient withdrawal symptoms, whereas studies relying on passive reporting may capture mainly symptoms that are spontaneously reported by patients or recognised by clinicians and may miss minor symptoms, potentially leading to underestimation of ADWR incidence and overestimation of severity.

Most reviews focused on CNS drugs, mainly antidepressants and antipsychotics, while opioids, benzodiazepines/z-drugs, and cholinesterase inhibitors are less frequently studied. This pattern was also reflected in the underlying primary-study evidence, with antidepressant reviews including more individual studies than reviews of other drug classes. Moreover, non-CNS drugs reviews mostly included antihypertensives and heart failure medication, while PPIs, corticosteroids, atropine, baclofen and tyrosine kinase inhibitors were less frequently examined. This limited focus highlights gaps in the existing evidence base on ADWRs related to both CNS and non-CNS drugs, with no evidence synthesis identified for some drug classes frequently considered to cause ADWRs, such as gabapentinoids. The lack of synthesised evidence in this area highlights a clear research need, either to collate existing information or to generate new evidence to address this gap to better inform clinical decision-making and support safer deprescribing practices.

Overall, the findings demonstrate that ADWRs are widely reported across CNS medications. However, the incidence and characteristics of these symptoms varied significantly across reviews and drug classes. Most of the included reviews focused on antidepressants and antipsychotics, reflecting discontinuation phenomena in psychotropic drugs. Psychotropic medications (i.e., antidepressants, antipsychotics, benzodiazepines, opioids, and lithium) may cause clinically relevant ADWRs [70, 71]. Opioids may lead to ADWRs due to decrease in opioid receptor activity with physical and psychological symptoms [49, 50, 72]. Benzodiazepines can also be associated with ADWRs due to the development of physiological dependence [11, 20, 53, 73]. Less extensive evidence exists regarding ADWRs associated with non-CNS drugs. In this overview, antihypertensive showed highest incidence of ADWRs, followed by PPIs and corticosteroids. PPIs also have a risk of ADWRs, as abrupt discontinuation may induce gastric acid hypersecretion above pre-treatment levels due to persistent hypergastrinemia [74, 75]. Moreover, corticosteroid ADWRs occur primarily due to suppression of the

hypothalamic-pituitary-adrenal axis during long-term corticosteroid therapy [76, 77]. These findings highlight that ADWRs are not limited to CNS drugs and careful tapering and monitoring should also be considered during discontinuation of non-CNS drugs with physiological adaptations. Further research is needed to systematically examine ADWRs and establish best tapering schedules to guide clinical practice and develop evidence-based strategies for optimal deprescribing.

In this overview of reviews, methods used to assess incidence of ADWRs were varied across reviews. Measurement approaches included validated instruments such as the discontinuation-emergent signs and symptoms (DESS) scale, open-ended questions and a range of reporting metrics (e.g., percentages, weighted means, odds ratios, standardised mean differences, and mean differences). A recent systematic review similarly reported that fewer than 10% of deprescribing trials measured ADWEs and that six different reporting criteria were used, reflecting a lack of standardisation in outcome measurement [20]. In the included studies, the incidence of ADWRs for individual drugs was more commonly reported than drug-class incidence, which limited comparison of ADWRs between studies and drug classes. Moreover, only two reviews provided combined and separate incidence rate of ADWRs by study design. Additionally, an appropriate control or placebo group is important, where feasible, to help determine whether reported symptoms are attributable to treatment discontinuation. This is particularly relevant because some studies reported no difference in ADWRs between participants who discontinued the active treatment and those who discontinued placebo. The included reviews comprised different study designs, including RCTs, observational studies, case reports and case series, with RCTs accounting for 183 (25%) of the included studies. However, information on incidence in control groups is inconsistently reported across reviews and studies, limiting assessment of whether reported symptoms are attributable to treatment discontinuation. Therefore, future reviews should also explicitly consider study design and the availability of an appropriate control or placebo group in their inclusion criteria, perform stratified analyses, and report findings separately for different study designs and control-group status to enhance interpretability.

The nature of the withdrawal reaction signs and symptoms varied across drug classes. The most common signs/symptoms ADWRs of CNS drugs were dizziness, nausea, insomnia, agitation, and anxiety. However, a major methodological challenge identified across the included systematic reviews was the limited ability to clearly differentiate ADWRs from relapse of the underlying condition. Only 13 reviews provided a clear distinction between ADWRs and relapse, whereas 24 reviews did not clearly distinguish between these terms (i.e., no clear distinction and no acknowledgement=16; no clear distinction, acknowledged as a challenge=8). The difficulty in distinguishing ADWRs from relapse also appeared to vary according to medication class. This challenge was particularly evident for antidepressants, where discontinuation symptoms may overlap with recurrence of depression or anxiety symptoms. Similar difficulties were observed with antipsychotics, where withdrawal symptoms may overlap with early relapse, and with benzodiazepines or Z-drugs, where symptoms such as insomnia

may represent either withdrawal-related rebound insomnia or recurrence of the underlying sleep disorder. A clear distinction between ADWRs and relapse is important for conceptual accuracy and methodological rigour in future studies. This challenge was also reflected during study selection, as 42 reviews were excluded because they specifically focused on relapse, return of the underlying condition, treatment outcomes, or the effectiveness of discontinuation strategies rather than physiological ADWRs. Symptoms that cannot be clearly classified as either ADWRs or relapse, particularly those unrelated to the original treated condition, could be reported separately. This approach will enable more accurate estimation of ADWR incidence, improve understanding of the symptom profile, and support evidence-based deprescribing and clinical management decisions.

Most reviews reported the discontinuation strategies as abrupt, tapered, or mixed, and only 9 (23.7%) provided detailed tapering schedules. However, there were very few comparisons of ADWR incidence between tapering/discontinuation strategies or between discontinuation and continuation approaches. In the current overview, across the included systematic reviews, no consistent evidence was provided that tapering significantly reduces the incidence of ADWRs compared with abrupt discontinuation [10, 28, 43, 45]. Some narrative syntheses suggest that gradual discontinuation may be associated with fewer withdrawal symptoms compared with abrupt cessation [24, 40, 41, 78] however, the available evidence varies considerably across drug classes. Robust evidence on the comparative benefits of different tapering approaches and their effects on ADWR incidence remains lacking [28]. Moreover, for some medicines, such as antidepressants and benzodiazepine receptor agonists, conducting randomised trials comparing abrupt discontinuation with tapering may not be ethically appropriate because of the established risk of clinically significant withdrawal symptoms.

Another important finding across both CNS and non-CNS drug reviews was heterogeneity in tapering strategies. Considerable variation was observed in tapering duration and schedules across and within drug classes and even for the same drug (e.g., SSRIs including paroxetine or escitalopram were reduced over days, weeks, or months) across different reviews [24, 40, 41, 78]. However, evidence and expert opinion suggests that ADWRs can be prevented or minimised through strategies including tapering and monitoring (e.g. through a symptom action plan) [2, 79-83]. International guidelines recommend educating patients on the risks of abrupt discontinuation and recommend gradual tapering of medications [84-86]. Given the lack of explicit, actionable recommendation on deprescribing in many guidelines [87], there is a need for more evidence-based guidance on appropriate discontinuation strategies to minimise ADWR risk.

4.1. Strengths and limitations

To our knowledge, this is the first overview of reviews examining ADWRs. A key strength of this overview is its rigorous methodology, including comprehensive searches across nine databases with all stages performed independently in duplicate by two reviewers. We included all available systematic

reviews without language restrictions to ensure a comprehensive synthesis and minimise the risk of omitting relevant evidence.

However, there are some limitations associated with this overview of reviews. Firstly, we were unable to combine data to perform quantitative statistical analysis due to the variability across study designs and heterogeneity in reported outcomes. Secondly, the variation in age-related eligibility criteria across the included reviews was another limitation. The included reviews evaluated different populations, including adults, older adults and paediatric populations, which may have contributed to heterogeneity in the reported incidence, clinical presentation, and characteristics of ADWRs. Differences in age-related factors, such as multimorbidity, polypharmacy, pharmacokinetic and pharmacodynamic changes, and patterns of medication use, may influence the risk and manifestation of ADWRs. Therefore, the findings may not be generalisable across all age groups, and future research should consider applying clear age definitions or conducting age-stratified analyses to better understand variations in ADWR risk. Finally, the lack of consistent terminology for ADWRs was a significant barrier to our overview. There were also limitations in the evidence reported by the included reviews. Fifteen of the 38 reviews in this overview included case reports either alone or in combination with other study types. These reports do not capture the incidence of ADWRs and generally describe isolated or unusual cases. The quality of most of the included reviews based on AMSTAR-2 was rated as critically low or low (n=23), and only nine reviews had a moderate or high quality. Future reviews should particularly focus on prospective protocol registration, independent duplicate study selection and data extraction, comprehensive risk-of-bias assessment, and transparent reporting.

4.2. Implications for research, practice and policy

This overview of reviews has identified several key gaps in the current evidence on ADWRs that should be priorities for future research. Existing systematic reviews have primarily focused on antidepressants (SSRIs and SNRIs) and cardiovascular medications (antihypertensives), while ADWRs of other drug classes (i.e., gabapentinoids, antidiabetics) remain unexplored; therefore, more research is needed to assess the occurrence of ADWRs among other drug classes and to identify factors associated with an increased risk of clinically significant ADWRs.

Some reviews did not provide sufficient details regarding the distinction between ADWRs and relapse, while others reported outcomes (incidence or sign/symptoms) using heterogeneous terminology and assessment methods. This variability limits comparability across and within reviews and contributes to uncertainty when interpreting the frequency and clinical characteristics of ADWRs. Future studies should focus on the development and adoption of standardised definitions, assessment tools and reporting frameworks to improve the consistency, transparency, and comparability of ADWR evidence.

Moreover, as adequately powered randomised controlled trials across all drug classes and populations are likely not feasible, other approaches may be needed to generate evidence to supplement RCTs,

including pharmacovigilance data [88, 89]. However, pharmacovigilance data are subject to limitations such as under-reporting, reporting bias and difficulties in distinguishing ADWRs from relapse. Despite these significant evidence gaps, the available evidence provides guidance on the need to taper in these drug classes and the importance of monitoring for relevant withdrawal symptoms. Overall, this emphasises the need for individualised care when deprescribing.

5. Conclusion

This overview has identified thirty-eight systematic reviews and synthesised the existing evidence on ADWRs following the discontinuation of a range of drugs. It reveals considerable variation in the incidence, sign/symptoms and reporting of ADWRs, including across reviews/studies of the same drugs. Additionally, other aspects including definitions of ADWRs, tapering strategies, the reporting of outcomes (severity, onset, and duration), and the description of management strategies were also varied and often limited across reviews. Standardised criteria for detection and reporting (including clear distinction between ADWRs and return of the condition being treated) would support future research.

Declarations of interest

ER has received royalties for co-authoring a chapter on deprescribing in UpToDate. The other authors declare no competing interests.

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Availability of data and other materials

Supplementary file 1: PRIOR Checklist

Supplementary file 2: Details of inclusion-exclusion criteria and data extraction

Supplementary file 3: Search strategy

Supplementary file 4: AMSTAR 2 results

Supplementary file 5: Reviews excluded at full text screening (with reasons)

Supplementary file 6: Characteristics of included reviews

Supplementary file 7: Additional characteristics of reviews

Supplementary file 8: Detailed extracted data and explanatory text

Supplementary file 9: Corrected coverage area (CCA) index results

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