JAMA Psychiatry | Original Investigation

Incidence and Nature of Antidepressant Discontinuation Symptoms
A Systematic Review and Meta-Analysis

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IMPORTANCE The incidence and nature of discontinuation symptoms following antidepressant cessation remain unclear.

OBJECTIVE To examine the presence of discontinuation symptoms using standardized scales (eg, Discontinuation-Emergent Signs and Symptoms [DESS]) and the incidence of individual discontinuation symptoms in individuals who stop taking antidepressants.

DATA SOURCES The databases Embase, PsycINFO, Ovid MEDLINE, and Cochrane Library were systematically searched from inception until November 7, 2023.

STUDY SELECTION Randomized clinical trials (RCTs) reporting discontinuation symptoms using a standardized scale or individual symptoms (eg, adverse events) following antidepressant cessation were included.

DATA EXTRACTION AND SYNTHESIS Data extracted were cross-checked by 2 reviewers. Additional unpublished data from 11 RCTs were included. A random-effects meta-analysis was conducted to calculate standardized mean difference between individuals who discontinued an antidepressant vs those who continued an antidepressant or discontinued placebo. A proportion and odds ratio (OR) meta-analysis was performed to assess incidence of individual discontinuation symptoms compared to placebo. Subgroup analyses were conducted to compare different antidepressants. Data analysis was conducted between September 2024 and December 2024.

MAIN OUTCOMES AND MEASURES The primary outcomes were incidence and nature of antidepressant discontinuation symptoms measured using standardized or unstandardized scales.

RESULTS A total of 50 studies were included, 49 of which were included in meta-analyses. The 50 studies included 17 828 participants in total, with 66.9% female participants and mean participant age of 44 years. Follow-up was between 1 day and 52 weeks. The DESS meta-analysis indicated increased discontinuation symptoms at 1 week in participants stopping antidepressants (standardized mean difference, 0.31; 95% CI, 0.23-0.39; number of studies [k] = 11; n = 3915 participants) compared to those taking placebo or continuing antidepressants. The effect size was equivalent to 1 more symptom on the DESS. Discontinuation of antidepressants was associated with increased odds of dizziness (OR, 5.52; 95% CI, 3.81-8.01), nausea (OR, 3.16; 95% CI, 2.01-4.96), vertigo (OR, 6.40; 95% CI, 1.20-34.19), and nervousness (OR, 3.15; 95% CI, 1.29-7.64) compared to placebo discontinuation. Dizziness was the most prevalent discontinuation symptom (risk difference, 6.24%). Discontinuation was not associated with depression symptoms, despite being measured in people with major depressive disorder (k = 5).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis indicated that the mean number of discontinuation symptoms at week 1 after stopping antidepressants was below the threshold for clinically significant discontinuation syndrome. Mood worsening was not associated with discontinuation; therefore, later presentation of depression after discontinuation is indicative of depression relapse.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2025.1362
Published online July 9, 2025.

Multimedia

Supplemental content

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The concept of antidepressant withdrawal syndrome was first introduced in the late 1950s.[1] While most international depression guidelines acknowledge and support tapering of antidepressants when discontinuing them,[2] there remains variability in specific guidance on duration and types of withdrawal symptoms among antidepressants.[3]

In the UK, guidelines from the National Institute for Health and Care Excellence state that for some people, antidepressant discontinuation symptoms can be mild and transient, but in other cases, symptoms can be more severe and last longer.[4] The American Psychiatric Association guidelines state that antidepressant discontinuation symptoms usually resolve within 1 to 2 weeks without treatment.[5]

There is also lack of consensus and clarity on the evidence relating to incidence and duration of antidepressant discontinuation symptoms. A meta-analysis by Henssler and colleagues[6] found the incidence of at least 1 discontinuation symptom was 31% after discontinuation of antidepressants and 17% after discontinuation of placebo. However, when directly comparing discontinuation of an antidepressant with placebo, the authors found a difference of 8%. Critiques of Henssler and colleagues' meta-analysis stated that it only analyzed categorical data and did not provide details about type of discontinuation symptoms experienced.[7] The authors acknowledged that assessment of discontinuation symptoms using a standardized continuous scale (eg, Discontinuation Emergent Signs and Symptoms scale [DESS][8]) may have been more informative compared to incidence rates alone. Determining the nature of discontinuation symptoms would enable clinicians and patients to identify them and distinguish them from relapse.

Zhang and colleagues[9] attempted to examine the incidence of individual symptoms but did not assess symptoms following placebo discontinuation and included a small number of randomized controlled trials (k = 14). These factors limit interpretation of their findings.

The primary aim of the current systematic review and meta-analysis was to examine discontinuation symptoms using the DESS by directly comparing scores between those who discontinued an antidepressant vs those who continued an antidepressant or discontinued placebo. A secondary aim was to directly assess incidence of specific discontinuation symptoms in those stopping antidepressants vs those stopping placebo.

Key Points

Question What are the incidence and nature of symptoms following discontinuation of antidepressants?

Findings This systematic review and meta-analysis of 49 randomized clinical trials found that on average, participants who stopped antidepressants experienced 1 more discontinuation symptom compared to those who discontinued placebo or continued antidepressants. The most common symptom in the first 2 weeks following antidepressant discontinuation was dizziness, and discontinuation of antidepressants was not associated with depressive symptoms.

Meaning Individuals who discontinued antidepressants experienced more symptoms compared to those discontinuing placebo or continuing an antidepressant, but the mean number of symptoms was below the cutoff for clinically important discontinuation syndrome.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[10] A protocol was preregistered on PROSPERO (CRD42023409477). Additional methodological details are presented in eAppendix 1 in Supplement 1.

Eligibility Criteria

Eligible studies were composed of randomized clinical trials (RCTs) (or open-label trials with a randomized double-blind discontinuation phase) that included adults and assessed discontinuation following treatment with any antidepressant. Eligible comparators were continuation of antidepressants, discontinuation of placebo, and prediscontinuation scores (within-participants designs). Discontinuation symptoms were measured either using standardized measures (eg, DESS[8]) or as reported adverse events (AEs).

Search Strategy

The electronic databases Embase, PsycINFO, Ovid MEDLINE, and the Cochrane Library were searched from inception to October 30, 2023 (PsycInfo), or November 7, 2023 (Embase, Ovid MEDLINE, and Cochrane). Reference lists of included studies and existing systematic reviews were searched by hand for potentially eligible studies. A search by hand was conducted on March 4, 2025, to identify potential studies published after the original search was conducted.

Study Selection

Rayyan open-source review management software[11] (Rayyan) was used to assist the study selection process. The study selection was conducted independently by 2 reviewers (M.K. and B.B.B.) blinded to each other's selections.

Data Extraction

Data were extracted by the first author (M.K.) and cross-checked by 2 coauthors (D.T. and B.B.B.). Discrepancies were resolved through discussion with the senior author (S.J.).

Statistical Analysis

To assess discontinuation symptoms, outcomes were analyzed separately depending on whether they assessed mean differences using a continuous scale (eg, DESS[8]) or incidence and odds ratio (OR) of individual symptoms. Statistical significance was set at $P < .05$ (2-tailed) for all meta-analyses. Meta-analysis was conducted using Stata version 18 (StataCorp).[12]

Symptoms Assessed Using a Continuous Scale

A random-effects meta-analysis was used to calculate the Hedges *g* standardized mean difference (SMD). A pooled ef-

fect size (ES) with 95% confidence intervals was computed to estimate differences in discontinuation symptoms for antidepressant discontinuation, with the comparator control group consisting of placebo (preferred when available) or antidepressant continuation. The I^2 statistic was used to assess heterogeneity, which was considered high if I^2 was greater than 50%.[13] Publication bias was examined by visually inspecting funnel plots and the Egger test. Trim-and-fill analysis was used to estimate the adjusted ES when the Egger test was significant.

The primary meta-analysis included studies that assessed DESS symptoms following abrupt or tapered discontinuation of antidepressants. Separate analyses were conducted to assess symptoms 1 and 2 weeks following discontinuation. Discontinuation symptoms at 3 weeks were only reported in 1 study[14] and were thus not analyzed. Subgroup analyses were conducted for individual antidepressants, tapering methods, and risk of bias. Meta-regression was performed using the restricted maximum likelihood method.

Incidence of Individual Symptoms

A random-effects meta-analysis was conducted to calculate the proportion, log OR, and risk difference (RD) of individual symptoms following discontinuation of an antidepressant vs placebo in placebo-controlled trials. This approach allowed direct comparison of symptoms in those who discontinued an antidepressant vs placebo and accounted for potential placebo or nocebo effects. ORs and 95% confidence intervals were exponentiated for ease of interpretation. Incident rates were transformed using the logit function. SMDs and 95% confidence intervals were back-transformed using the inverse-logit function. Similar symptoms were grouped into categories, as they were often reported as synonymous (eTable 1 in Supplement 1). Classification was theoretically driven, decided through consensus between 2 senior authors (J.F.H. and S.J.) prior to analysis.

Results

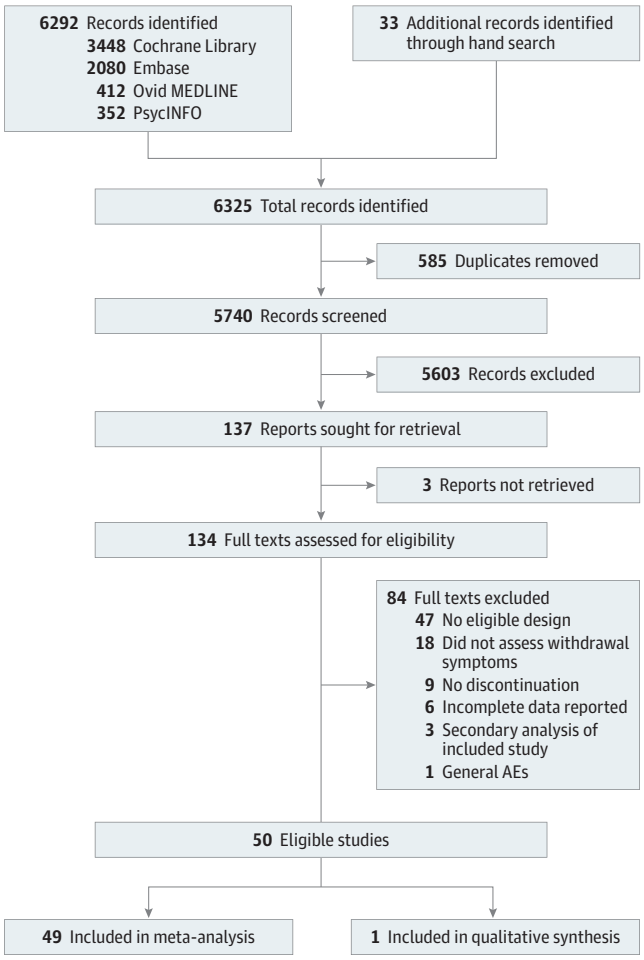
Search Results

The search resulted in 6292 records, in addition to 33 studies identified through hand searches. Full texts of 134 studies were screened for inclusion, 50 of which were included in the systematic review (**Figure 1**). Of those, 19 used a continuous scale to assess discontinuation symptoms and 45 reported individual symptoms following discontinuation. Missing data from 11 studies were obtained either directly from the authors or through a formal data request through Vivli (Vivli.org).

Study Characteristics

The 50 studies included 17 828 participants in total, with 66.9% female participants and mean participant age of 44 years. The following diagnoses were studied: major depressive disorder (MDD) (k = 28), generalized anxiety disorder (k = 9), panic disorder (k = 4), fibromyalgia (k = 2), premenstrual dysphoric disorder (k = 2), posttraumatic stress disorder, generalized social anxiety disorder (k = 1), and compulsive-shopping disorder (k = 1). Two studies included women with (post)menopause.

Figure 1. PRISMA Flowchart



AE indicates adverse event.

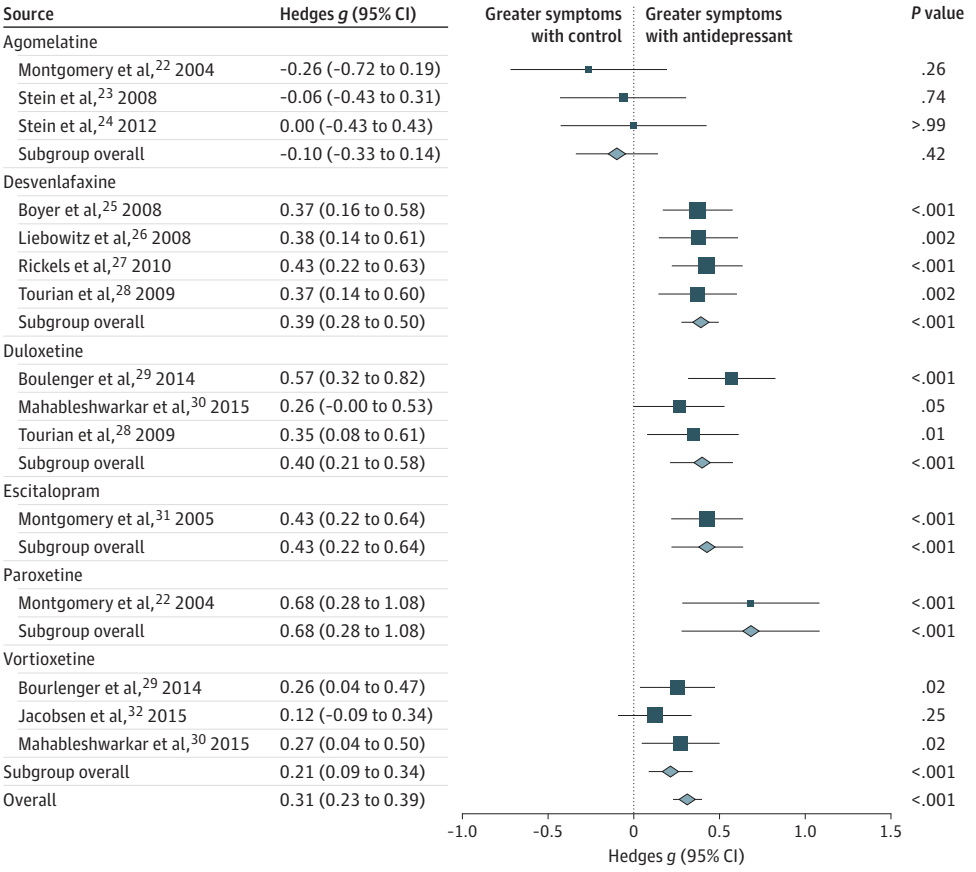
Meta-Analyses

Symptoms Assessed Using a Continuous Scale

A total of 18 studies assessed discontinuation symptoms using a continuous scale and were included in the continuous outcomes meta-analysis (n = 5237; antidepressant discontinuation: n = 3307). Of those RCTs, most (k = 15) used the original DESS,[8] whereas 1 used a modified DESS and 2 used the Physician Withdrawal Checklist questionnaire[15] or the Michelson SSRI Withdrawal Symptoms scale.[16] One study that used the modified DESS[17] is presented in the qualitative synthesis.

The main continuous meta-analysis included 11 studies that used the original or modified DESS scale (n = 3915; discontinued an antidepressant: n = 2217) and as a comparator used placebo or antidepressant continuation. Two studies were only included in the subgroup analyses, as 1 assessed symptoms following taper only,[18] while the other assessed symptoms 1 to 3 days following discontinuation.[19] One study[20] was excluded from the DESS meta-analysis because it appeared to assess the symptoms occurring over 2 weeks following discontinuation, rather than a specific time point.

Figure 2. Symptoms Assessed Using the Discontinuation-Emergent Signs and Symptoms (DESS) 1 Week Following Discontinuation



Cessation of an antidepressant moderately increased discontinuation symptoms 1 week following placebo substitution (SMD, 0.31; 95% CI, 0.23-0.39; 95% prediction intervals [PI], 0.08-0.54; I^2 = 36%; k = 11). A similar SMD was found after removing agomelatine from the analysis (SMD, 0.35; 95% CI, 0.28-0.42; 95% PI, 0.25-0.45; I^2 = 5%; k = 9). Heterogeneity decreased after including only studies in MDD (I^2 = 25%; SMD, 0.33; k = 8). The SMD was back-transformed to the DESS scale by multiplying it by the pooled standard deviation (3.49).[21] This showed a mean increase of 1.08 (95% CI, 0.80-1.36) points (ie, symptoms) on the DESS for the discontinuation group compared to those who continued antidepressants or were treated with placebo. The Egger regression test yielded a *P* value of .051. There was no publication bias when only assessing studies in MDD (*P* = .53). The SMD did not change after removing 1 study rated at high risk of bias (0.31; 95% CI, 0.21-0.41; I^2 = 50%).

The overall SMD at 2 weeks following discontinuation was statistically significant (0.13; 95% CI, 0.05-0.21; 95% PI, 0.03-0.23; I^2 = 0%; k = 8). Only 1 of the included studies had a statistically significant ES (eFigure 3B in Supplement 1). There was no evidence of publication bias (*P* = .052). Removing 1 trial rated as being at high risk of bias did not change the SMD (0.13; 95% CI, 0.04-0.22; I^2 = 0%).

Meta-regression indicated no association between antidepressant treatment duration and discontinuation symptoms at week 1 (slope, −0.014; 95% CI, −0.04 to 0.00) or week 2 (slope, 0.007; 95% CI, −0.04 to 0.05).

Subgroup analysis by individual antidepressant at week 1 indicated significant discontinuation symptoms following the cessation of desvenlafaxine (SMD, 0.39; 95% CI, 0.28-0.50; I^2 = 0%; k = 4), duloxetine (SMD, 0.40; 95% CI, 0.21-0.58; I^2 = 32%; k = 3), and vortioxetine (SMD, 0.21; 95% CI, 0.09-0.34; I^2 = 0%; k = 3) (**Figure 2**).[22-32] Converting the SMD to the original scale indicated 1.61 more symptoms in the duloxetine group, 1.37 in desvenlafaxine, and 0.56 in vortioxetine. Escitalopram and paroxetine were only assessed in 1 study. Subgroup analysis at week 2 scores indicated a small SMD for vortioxetine (0.15; 95% CI, 0.03-0.28; I^2 = 0%; k = 3) but not desvenlafaxine (SMD, 0.079; 95% CI, −0.07 to 0.23; k = 3).

Abrupt discontinuation of antidepressants resulted in statistically significant discontinuation symptoms at week 1 (SMD, 0.28; 95% CI, 0.16-0.39; 95% PI, −0.09 to 0.64; I^2 = 55%; k = 11). A similar SMD was found when removing from the analysis 1 study that assessed symptoms 1 to 3 days following discontinuation (SMD, 0.28; 95% CI, 0.15-0.41; I^2 = 59%). Subgroup analysis indicated discontinuation symptoms following the abrupt cessation of desvenlafaxine (SMD, 0.46; 95% CI, 0.31-0.61; I^2 = 0%) and vortioxetine (SMD, 0.21; 95% CI, 0.09-0.34; I^2 = 0%). There was a small SMD at 2 weeks following abrupt discontinuation (SMD, 0.13; 95% CI, 0.05-0.21; I^2 = 0%),

Table 1. Incidence of Individual Symptoms in the First 2 Weeks Following Discontinuation in Placebo-Controlled Studies[a]

Symptom	Studies, No.	Incidence (95% CI), %		Antidepressant vs placebo comparison			
				Odds ratio		Risk difference	
		Antidepressant discontinuation	Placebo discontinuation	Odds ratio (95% CI)	I^2, %	Risk difference (95% CI), %	I^2, %
Dizziness or light-headedness	15	7.50 (4.83 to 11.47)	1.82 (1.25 to 2.65)	5.52 (3.81 to 8.01)[b]	0	6.24 (3.70 to 8.79)[b]	91
Nausea	14	4.11 (2.50 to 6.70)	1.49 (0.83 to 2.68)	3.16 (2.01 to 4.96)[b]	22	2.90 (1.53 to 4.27)[b]	83
Vertigo	3	2.72 (1.73 to 4.25)	0.40 (0.08 to 1.95)	6.40 (1.20 to 34.19)[b]	0	2.31 (1.01 to 3.60)[b]	45
Headache	11	4.70 (3.39 to 6.48)	3.43 (2.12 to 5.55)	1.40 (0.98 to 1.99)	23	1.49 (0.39 to 2.59)[b]	34
Nervousness or irritability	6	3.02 (1.10 to 8.02)	0.85 (0.27 to 2.64)	3.15 (1.29 to 7.64)[b]	0	1.30 (0.47 to 2.12)[b]	19
Diarrhea or gastroenteritis	7	3.06 (1.61 to 5.74)	1.66 (0.70 to 3.91)	1.56 (0.87 to 2.79)	0	0.97 (0.05 to 1.90)[b]	0
Vivid dreams or nightmares	4	2.86 (0.95 to 8.29)	1.12 (0.32 to 3.86)	3.00 (0.74 to 12.08)	45	2.44 (−1.41 to 6.29)	94
Vomiting	7	1.86 (0.97 to 3.56)	1.02 (0.58 to 1.76)	2.07 (0.99 to 4.32)	0	1.16 (−0.04 to 2.36)	72
Loss of appetite	2	1.63 (0.08 to 26.64)	1.51 (0.24 to 8.78)	2.10 (0.54 to 8.14)	0	1.07 (−1.72 to 3.87)	44
Tremor	3	0.76 (0.09 to 6.11)	0.57 (0.14 to 2.27)	1.02 (0.09 to 11.40)	37	0.60 (−1.52 to 2.72)	53
Paresthesia or feeling abnormal	4	1.25 (0.28 to 5.30)	0.88 (0.24 to 3.20)	1.37 (0.24 to 7.79)	52	0.53 (−1.05 to 2.10)	54
Depression or mood worsening	5	1.29 (0.52 to 3.16)	1.45 (0.57 to 3.59)	1.03 (0.24 to 4.40)	52	0.39 (−1.31 to 2.09)	77
Dry mouth	3	0.41 (0.13 to 1.27)	0.73 (0.21 to 2.50)	0.68 (0.12 to 3.64)	0	0.19 (−0.34 to 0.72)	0
Palpitations or tachycardia	2	0.21 (0.03 to 1.44)	0.74 (0.15 to 3.59)	0.24 (0.02 to 2.97)	0	−0.01 (−0.15 to 0.14)	NA[c]
Pain	3	1.71 (1.01 to 2.87)	2.27 (1.14 to 4.47)	0.70 (0.28 to 1.77)	0	−0.69 (−2.35 to 0.09)	0
Upper respiratory tract infection	4	3.22 (2.45 to 4.22)	4.32 (1.69 to 10.60)	0.77 (0.34 to 1.75)	0	−0.70 (−3.96 to 2.57)	65
Insomnia	9	2.67 (1.50 to 4.68)	1.63 (0.71 to 3.69)	1.62 (0.99 to 2.63)	0	NA[d]	NA[c]
Fatigue or increased sleep	5	1.63 (0.56 to 4.61)	1.68 (0.77 to 3.63)	0.85 (0.31 to 2.33)	0	NA[d]	NA[c]

Abbreviation: NA, not available.

[a] Symptoms assessed in ≥2 studies that involved discontinuation of both an antidepressant and placebo.

[b] Statistically significant comparison.

[c] Heterogeneity could not be be computed.

[d] Random-effects model could not be computed.

which was significant for vortioxetine (SMD, 0.15; 95% CI, 0.03-0.28; I^2 = 0%) but not desvenlafaxine (SMD, 0.079; 95% CI, −0.07 to 0.23).

Incidence of Individual Symptoms

Individual symptoms were assessed in 45 studies (n = 10 612) (1 study of which was a pooled analysis of 8 RCTs), in which 7520 participants discontinued an antidepressant and 3092 discontinued placebo.

In the main analysis, we explored incidence of individual symptoms in placebo-controlled trials (k = 16) in which participants discontinued an antidepressant (n = 4357) or placebo (n = 2801). One RCT was not included in this meta-analysis, as it did not report individual symptoms in placebo,[33] but is presented in eTable 4B in Supplement 1. Studies assessed individual symptoms within 2 weeks after discontinuation. Findings are presented in **Table 1** and **Table 2** and in eAppendix 4 in Supplement 1. The Egger test indicated absence of publication bias for all symptoms except respiratory infection. Findings for respiratory infection did not change after accounting for publication bias using trim-and-fill analysis (OR, 0.69; 95% CI, 0.39-1.21).

Additional analysis assessing the incidence of symptoms in all eligible studies (k = 45) that used different comparators (antidepressant continuation, placebo discontinuation, within-participants design) is presented in eAppendix 4 in Supplement 1.

Discussion

Discontinuation of antidepressants was associated with an increase in DESS discontinuation symptoms compared to placebo. This increase was equivalent to 1 additional symptom on the DESS after 1 week in those who discontinued an antidepressant vs those who continued an antidepressant or discontinued placebo. Antidepressant discontinuation was associated with greater odds of dizziness, nausea, vertigo, and nervousness. The most frequent symptom in the first 2 weeks following antidepressant cessation was dizziness (RD, 6.24%), followed by nausea (RD, 2.90%). The incidence of individual discontinuation symptoms in the first 2 weeks varied by antidepressant: (des)venlafaxine was associated with the most symptoms, with no evidence that vortioxetine was associated with more individual discontinuation symptoms than placebo. The incidence of discontinuation symptoms in the antidepressant group was considerably lower in the meta-analysis of trials directly comparing discontinuation of antidepressants with placebo.

Table 2. Incidence of Individual Symptoms in the First 2 Weeks Following Discontinuation by Antidepressant After Taking Into Account Placebo[a]

Symptom	Incidence, %[b]				
	Desvenlafaxine	Duloxetine	Paroxetine	Venlafaxine	Vortioxetine
Dizziness or light-headedness	9.4[c]	5.1[c]	2.9[d]	17.5[e]	−0.7[e]
Nausea	6.5[c]	2.2[f]	0.6[e]	7.6[e]	−0.2[e]
Vertigo	2.1[e]	NA[g]	NA[g]	NA[g]	NA[g]
Nervousness or irritability	10.9[e]	1.3[e]	NA[g]	NA[g]	0[e]
Vivid dreams or nightmares	7.8[e]	0.8[e]	NA[g]	NA[g]	−0.3[e]
Diarrhea or gastroenteritis	6.4[e]	0.6[d]	NA[g]	NA[g]	−0.3[e]
Headache	3.1[c]	0.7[f]	0.8[e]	NA[g]	−0.6[e]
Insomnia	4.7[d]	0.2[d]	−1.1[e]	NA[g]	0[e]
Vomiting	NA[g]	0.4[d]	NA[g]	NA[g]	−0.2[e]
Mood worsening or depression	0.8[d]	NA[g]	NA[g]	NA[g]	−1.1[e]
Fatigue or sleepiness	2.8[e]	NA[g]	NA[g]	NA[g]	−1.1[e]
Paresthesia or feeling abnormal	NA[g]	0.9[e]	NA[g]	NA[g]	−0.7[e]
Dry mouth	NA[g]	NA[g]	NA[g]	NA[g]	−0.3[e]
Pain	NA[g]	NA[g]	NA[g]	NA[g]	−0.9[e]
Upper respiratory tract infection	−0.6[e]	−1.6[e]	NA[g]	NA[g]	−1.1[e]

Abbreviation: NA, not applicable.

[a] Placebo-control studies involving discontinuation of an antidepressant and placebo.

[b] Estimated incidence after subtracting with the incidence following placebo discontinuation on the assumption of the intervention and placebo rates being additive.

[c] Incidence assessed in 5 studies.

[d] Incidence assessed in 3 studies.

[e] Incidence assessed in 2 studies.

[f] Incidence assessed in 4 studies.

[g] Incidence assessed in <2 studies.

On the DESS, 4 or more symptoms has been used as the cutoff point for clinically significant discontinuation syndrome.[8,34] The mean score on the DESS at 1 week was below this cutoff for duloxetine, desvenlafaxine, and vortioxetine. Although discontinuation symptoms may be long lasting in some individuals,[4,35] it is generally acknowledged that symptoms peak at 1 to 2 weeks following discontinuation (except for fluoxetine).[5,34,36] Therefore, our estimate (range) of 1.08 points (0.80-1.36) is likely to represent the peak of DESS scores.

Abrupt discontinuation of desvenlafaxine was not associated with notably greater symptoms (SMD, 0.46) than tapered discontinuation (SMD, 0.36). Two meta-analyses reported a similar event rate of symptoms following taper and abrupt discontinuation.[6,9] However, most studies used a 1-week taper, which may explain high general rates in this group. There remains limited evidence on the usefulness of longer tapering methods, such as hyperbolic.[3,37] While intuitively appealing, the theoretical evidence put forward (eg, molecular imaging studies of serotonin transporter) does not explain individual variation or high incidence of discontinuation symptoms with drugs like paroxetine, in addition to other concerns.[38] Recent evidence suggests that abrupt discontinuation of antidepressants may be associated with greater depression relapse rate compared to taper.[39] Length of antidepressant treatment was not associated with discontinuation symptoms, consistent with previous meta-analyses.[6,9] Nevertheless, treatment duration in the included studies was likely shorter than in real-world settings, which could have influenced our findings.

Dizziness was the most common symptom across all antidepressants, affecting around 6% of those discontinuing an antidepressant after accounting for placebo effects. The greater incidence of dizziness in the discontinuation group may be related to the effects of serotonin on the vestibular system.[40] Antidepressant discontinuation was not associated with greater depressive symptoms in the first 2 weeks compared to placebo, despite being measured in studies specifically examining MDD. This suggests discontinuation symptoms are unlikely to be mistaken for mood relapse in these individuals and that later presentation of depression symptoms is more likely to represent depression relapse. On the other hand, symptoms of nervousness or anxiety were more prevalent, which suggests discontinuation may be misdiagnosed as reemergent anxiety. It could also be that anxiety may reemerge more rapidly than depression following discontinuation.

A lower incidence of symptoms was found when directly comparing antidepressant discontinuation with placebo, which highlights the need for placebo control when assessing discontinuation symptoms. This discrepancy may be attributed to nonpharmacological processes, such as nocebo effects, due to the commonality of symptoms.[41-43] However, this does not suggest that symptoms experienced are not real. Consistent with this, Henssler and colleagues[6] found a 7% lower incidence when directly comparing placebo with antidepressant discontinuation. The lack of placebo control likely also explains the higher incidence of symptoms reported in a recent meta-analysis.[9]

Antidepressant discontinuation was not associated with fatigue, paresthesia, tremor, or pain. Findings showed a very small RD for headache (1.5%) and diarrhea (0.97%), although the OR was not significant. The antidepressants associated with the highest incidence of individual discontinuation symptoms were venlafaxine and desvenlafaxine, consistent with previous studies and its rapid clearance.[6,36,44] The most commonly experienced symptom following discontinuation of desvenlafaxine and venlafaxine was dizziness, which affected 9.4% and 17.5% of participants, respectively.

The DESS meta-analysis at week 2 indicated a very small SMD (0.13), likely to be attributed to low power, as the individual SMD of only 1 of the 8 studies was statistically significant. The ANTLER trial,[17] which had the longest follow-up, reported discontinuation symptoms occurring 4 to 8 weeks after

discontinuation. Nevertheless, the increased DESS scores at this follow-up duration are more likely to reflect mood relapse rather than discontinuation symptoms, since the DESS also captures depressive symptoms. Consistent with this, the depression relapse rate following antidepressant discontinuation was greater at 6 months (34.8%) compared to the first month.[39] Depression relapse is also seen within weeks of stopping maintenance electroconvulsive therapy, which has no known withdrawal syndrome.[45]

Strengths and Limitations

A strength of the current meta-analysis is the inclusion of unpublished data from 11 RCTs, the inclusion of placebo control, and examination of both standardized and nonstandardized measures to assess discontinuation symptoms, which has not been addressed before, to our knowledge.

However, this meta-analysis has limitations. Due to the small number of studies, some analyses might have been underpowered, while in others, the confidence intervals (eg, for vivid dreams and vomiting) and PIs were wide, indicating low precision. Assessing symptoms using a nonstructured instrument may result in smaller ESs, as reported in another meta-analysis.[6] The classification of the symptoms was theoretical, and different symptoms may highly correlate with each other. In some studies, it was unclear whether the grouped symptoms were reported by different individuals, which may have inflated the overall incidence. Some of the discontinuation symptoms assessed, such as irritability, may also be indicative of depression, although for this analysis we considered depression symptoms to be the core symptoms used in current classification systems. It remains challenging to distinguish symptoms of relapse from withdrawal.

Regarding limitations of the included studies, some commonly used antidepressants (eg, fluoxetine) were underrepresented in the analyses. No studies were found on newly US Food and Drug Administration-approved antidepressants (eg, gepirone, dextromethorphan-bupropion). Theoretically, gepirone (a 5-HT1A partial agonist) is less likely to cause discontinuation symptoms, as it does not directly affect synaptic serotonin. Similarly, dextromethorphan-bupropion, with weak serotonin and norepinephrine reuptake inhibitor (SNRI) effects, is less likely to cause discontinuation symptoms compared to selective serotonin reuptake inhibitors (SSRIs). Future trials should examine discontinuation symptoms following antidepressant treatment with these novel compounds. Studies included predominantly White participants and were conducted in Europe and the US, which limits the generalizability of findings. Some RCTs only reported AEs occurring in more than 10% of the sample. Consequently, some of the most severe but less common discontinuation symptoms would not have been reported. Studies often reported only symptoms statistically different to placebo, which may have inflated incidence in the antidepressant group. The DESS has not been validated as a continuous measure, although most studies treat it as a continuous scale.[17] The majority of trials that used the DESS only followed up participants for up to 2 weeks, and therefore potential long-term discontinuation symptoms could not be assessed. Participants in most studies were taking the antidepressant for a relative short period, although 6 studies had a treatment period ranging from 36 weeks to 4.5 years.

Implications

The proposed high incidence of discontinuation symptoms from RCTs and surveys has had significant effects on policy and attitudes toward antidepressant use.[46,47] The current meta-analysis questions that prevailing idea and suggests that placebo-controlled RCTs are a better estimate of the true incidence of discontinuation symptoms. We identified the short length of treatment and follow-up in most RCTs, highlighting the need for more real-world studies, such as the ANTLER trial.[17]

The lack of evidence of prolonged withdrawal symptoms could reflect shorter duration of antidepressant use, although our findings do cast a degree of doubt on the need for routine use of longer-term tapering regimens apart from any theoretical concerns.[3,37] Acknowledgment of the burden of discontinuation effects is crucial; nevertheless, it is important that professional practice[43] and media narratives[41] surrounding discontinuation effects are proportionate. Undue emphasis on discontinuation effects may increase the likelihood of real and debilitating symptoms, which arise (or are maintained) via processes distinct from pharmacological mechanisms (eg, nocebo effects).[42,43] Our finding that, in people with MDD, depression relapse was uncommon suggests that when depression symptoms present after discontinuation, it is more indicative of depression relapse. This is an important reminder of the risks of depression relapse on antidepressant discontinuation and the need for careful monitoring after antidepressant cessation. Furthermore, judicious decision-making should take place in initial prescription of antidepressants, and their indication should be made clear.

Conclusions

In conclusion, data from RCTs suggest that on average, those who discontinue antidepressants experience 1 more discontinuation symptom compared to placebo or continuation of antidepressants, which is below the threshold for clinically important discontinuation syndrome. Mood change was not seen in antidepressant discontinuation. While acknowledging that discontinuation symptoms exist, results of this systematic review and meta-analysis suggest that the rates are lower than those reported in prior reviews. The need for prolonged tapering regimens is open to question, with concerns previously noted, in addition to possible nocebo effects. This, therefore, requires careful examination through methodologically rigorous, placebo-controlled RCTs in real-world settings.

ARTICLE INFORMATION

Accepted for Publication: April 8, 2025.

Published Online: July 9, 2025. doi:10.1001/jamapsychiatry.2025.1362

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Conflict of Interest Disclosures: Mr Kalfas reported personal fees from Neurocentrx Pharma outside the submitted work; employment by King's College London; and funding by the UK National Institute for Health Research (NIHR) Biomedical Research Centre. Dr Butler reported serving as a Wellcome Trust Doctoral Clinical Research Fellow (227515/Z/23/Z); royalty fees from Taylor & Francis; teaching fees from Infomed; and work as a medic on clinical trials sponsored by pharmaceutical companies, including Janssen, outside the submitted work. Dr McCutcheon reported personal fees from Boehringer Ingelheim, Janssen, Lundbeck, Newron, and Viatris outside the submitted work and codirecting a company that designs digital resources to support treatment of mental ill health. Dr Strawbridge reported personal fees from Janssen outside the submitted work. Dr Haddad reported honoraria for authorship of articles on antidepressant discontinuation symptoms published in journal supplements sponsored by Eli Lilly in 1997, 2000, and 2006. Dr Howes reported research funding from and/or participation in advisory or speaker meetings organized by AbbVie, Alkermes, Angelini, Autifony Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb (Karuna), Delix Therapeutics, Eli Lilly, Elysium, Global Medical Education, Invicro, Janssen, Karuna Therapeutics, Lundbeck, Merck, Neumora Therapeutics, Neurocrine Biosciences, Ono Pharmaceutical, Ontrack Therapeutics/Pangea Bio, Otsuka Pharmaceutical, Recordati, Roche, Rovi, Sosei Heptares (now Nxera Pharma), Sunovion Pharmaceuticals, Teva Pharmaceuticals, and Viatris/Mylan; previous part-time employment by Lundbeck; and holding a patent for the use of dopaminergic imaging. Dr Nutt reported lecture fees from Janssen, Lundbeck, and Takeda; materials for research from Compass Pathways and the Usona Institute; and personal fees from Awakn Life Sciences outside the submitted work. Dr Baldwin reported editors fees from Elsevier and Wiley; grants to his institution from Idorsia, the NIHR Health Technology Assessment, and the NIHR Applied Research Collaborations outside the submitted work; and serving as Medical Patron of Anxiety UK, a mutual aid organization. Dr Pariante reported grants from the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London during the conduct of the study; consultant or speaker fees from GH Research, Lundbeck, and Värde Partners; grants from Compass Pathways outside the submitted work; and funding by a Wellcome Trust strategy award to the Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) Consortium (2015-2023; 104025/Z/14/Z), which was also funded by GlaxoSmithKline, Janssen, Lundbeck, and Pfizer. Dr Lewis reported grants to University College London (UCL) from the NIHR during the conduct of the study; grants to UCL from the NIHR and the Wellcome Trust; and travel fees from the European College of Neuropsychopharmacology (ECNP) in 2023 outside the submitted work. Dr Hayes reported consultancy fees from juli health, Swiss Re, and the Wellcome Trust outside the submitted work and a pending patent with juli health. Dr Jauhar reported speaker fees from Boehringer Ingelheim, the Dubai Masterclass conference, Janssen, Lundbeck, and Recordati; serving as a nonpaid member of the UK National Institute for Health and Care Excellence (NICE) Health Technology Appraisal committee; serving as a committee member and on the funding panel for the Wellcome Trust; and advisory board fees from Boehringer Ingelheim and LB Pharmaceuticals outside the submitted work. No other disclosures were reported.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We would like to thank Siegfried Kasper, MD; Prof Glyn Lewis, PhD; and Prof Louise Marston, PhD, for sharing study data.

Additional Information: This publication used data from data contributors Lundbeck, Takeda, Lilly, and Pfizer that has been made available through Vivli Inc. Vivli has not contributed to or approved and Vivli, Eli Lilly, Lundbeck, Takeda, Lilly, and Pfizer are not in any way responsible for the contents of this publication. Only data from 9 of the 49 studies analyzed were provided by the sponsors through Vivli Inc.

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