Incidence of antidepressant discontinuation symptoms: a systematic review and meta-analysis

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Summary

Background Antidepressant discontinuation symptoms are becoming an increasingly important part of clinical practice, but the incidence of antidepressant discontinuation symptoms has not been quantified. An estimate of antidepressant discontinuation symptoms incidence could inform patients and clinicians in the discontinuation of treatment, and provide useful information to researchers in antidepressant treatments. We aimed to assess the incidence of antidepressant discontinuation symptoms in patients discontinuing both antidepressants and placebo in the published literature.

Methods We systematically searched Medline, EMBASE, and CENTRAL from database inception until Oct 13, 2022 for randomised controlled trials (RCTs), other controlled trials, and observational studies assessing the incidence of antidepressant discontinuation symptoms. To be included, studies must have investigated cessation or tapering of an established antidepressant drug (excluding antipsychotics, lithium, or thyroxine) or placebo in participants with any mental, behavioural, or neurodevelopmental disorder. We excluded studies in neonates, and those using antidepressants for physical conditions such as pain syndromes due to organic disease. After study selection, summary data extraction, and risk of bias evaluation, data were pooled in random-effects meta-analyses. The main outcome was the incidence of antidepressant discontinuation symptoms after discontinuation of antidepressants or placebo. We also analysed the incidence of severe discontinuation symptoms. Sensitivity and meta-regression analyses tested a selection of methodological variables.

Findings From 6095 articles screened, 79 studies (44 RCTs and 35 observational studies) covering 21 002 patients were selected (72% female, 28% male, mean age 45 years [range 19·6–64·5]). Data on ethnicity were not consistently reported. 16 532 patients discontinued from an antidepressant, and 4470 patients discontinued from placebo. Incidence of at least one antidepressant discontinuation symptom was 0·31 (95% CI 0·27–0·35) in 62 study groups after discontinuation of antidepressants, and 0·17 (0·14–0·21) in 22 study groups after discontinuation of placebo. Between antidepressant and placebo groups of included RCTs, the summary difference in incidence was 0·08 [0·04–0·12]. The incidence of severe antidepressant discontinuation symptoms after discontinuation of an antidepressant was 0·028 (0·014–0·057) compared with 0·006 (0·002–0·013) after discontinuation of placebo. Desvenlafaxine, venlafaxine, imipramine, and escitalopram were associated with higher frequencies of discontinuation symptoms, and imipramine, paroxetine, and either desvenlafaxine or venlafaxine were associated with a higher severity of symptoms. Heterogeneity of results was substantial.

Interpretation Considering non-specific effects, as evidenced in placebo groups, the incidence of antidepressant discontinuation symptoms is approximately 15%, affecting one in six to seven patients who discontinue their medication. Subgroup analyses and heterogeneity figures point to factors not accounted for by diagnosis, medication, or trial-related characteristics, and might indicate subjective factors on the part of investigators, patients, or both. Residual or re-emerging psychopathology needs to be considered when interpreting the results, but our findings can inform clinicians and patients about the probable extent of antidepressant discontinuation symptoms without causing undue alarm.

Funding None.

Introduction

The occurrence of adverse symptoms following the discontinuation of antidepressants is increasingly becoming a topic of research in psychiatry, and is also gaining attention in clinical practice, with patients, and in the general media.[1] The emergence of adverse symptoms was described as early as 1959,[2] but remained largely neglected until the late 1990s. Until very recently, guidelines have been criticised for referring to the duration of typical antidepressant discontinuation symptoms as 1–2 weeks, ignoring evidence of longer courses.[3,4] Experiences occurring after antidepressant discontinuation have been called withdrawal symptoms, phenomena, or events, or antidepressant discontinuation symptoms, syndromes, or symptomatology. In this Article, we refer to antidepressant discontinuation symptoms. Antidepressant

Research in context

Evidence before this study

Antidepressant discontinuation symptoms have been largely neglected in research and clinical practice, despite being identified in the 1950s, but have recently become a topic of debate in both the public and medical spheres. We comprehensively searched MEDLINE, Embase, and CENTRAL databases from inception until March 26, 2020, and again until Oct 13, 2022, without date, language, or publication type restrictions for systematic reviews or meta-analyses on antidepressant discontinuation symptoms from specific antidepressants or placebo. For the search entry we used generic and specific terms for antidepressants in combination with "withdraw*" or "discontinu*". The full search terms are shown in the appendix (pp 14–15). We found important summarising research and systematic reviews on several aspects of antidepressant discontinuation symptoms. In a previous attempt at quantification, in 2019, Davies and Read included work that is prone to selection and dissatisfaction bias, eg, online surveys. They estimated antidepressant discontinuation symptoms occur in most patients (56%), half of these classified as severe, but their findings have been discussed intensively on methodological grounds. Other previous attempts at summarising the available evidence refrained from quantification and comprehensive meta-analysis due to methodological difficulties. Today, as a result, no comprehensive systematic review and meta-analysis that aimed to quantify the incidence or severity of antidepressant discontinuation symptoms has been published. We found that the aspect of placebo and nocebo with regards to discontinuation symptoms has not been reviewed systematically. Such results are highly important both for informing our patients on suitable medication choices and clinical decision making as well as for antidepressant treatment research.

Added value of this study

To the best of our knowledge, this is the first meta-analytic assessment of the incidence of antidepressant discontinuation symptoms and of placebo effects. We found existing studies to be heterogeneous in both outcomes and methodologies. Overall, our findings indicate that approximately one in every three patients will have discontinuation symptoms after discontinuation of an antidepressant, and one in six patients will report discontinuation-like symptoms after discontinuation of placebo. Approximately 3% of patients will have severe antidepressant discontinuation symptoms. We found that certain antidepressants had a higher incidence and severity of reported antidepressant discontinuation symptoms.

Implications of all the available evidence

A clinically relevant proportion of patients will have adverse symptoms after discontinuation of antidepressants. Non-specificity of symptoms and both patients' and doctors' expectations probably influence the incidence of antidepressant discontinuation symptoms. Subtracting non-specific effects, the frequency of antidepressant discontinuation symptoms can be expected to be in the range of approximately 15% (roughly one out of every six or seven patients can be expected to have antidepressant discontinuation symptoms that are specifically attributable to discontinuation). About one in 35 patients will have severe antidepressant discontinuation symptoms. Discontinuation symptoms are most frequently observed with desvenlafaxine or venlafaxine, and particular caution due to severe antidepressant discontinuation symptoms seems to be warranted when discontinuing imipramine, paroxetine, and desvenlafaxine or venlafaxine. This prevalence of antidepressant discontinuation symptoms could inform clinician guidance when discussing future treatment options with patients.

discontinuation syndromes instead depict a group of symptoms, and have been defined in various ways (eg four or more symptoms on the Discontinuation Emergent Signs and Symptoms Scale [DESS]). Antidepressant discontinuation syndromes are also sometimes referred to as ADS in the literature, but not in this Article. We also note that the term discontinuation symptoms after placebo sounds like a paradox. It is meant to cover all symptoms interpreted as discontinuation symptoms when stopping placebo.

Today, the existence of symptoms emerging after antidepressant discontinuation or dose-reduction is no longer questioned: recent national and transnational clinical practice guidelines recommend informing patients on the risks of abrupt antidepressant discontinuation and suggest tapering of antidepressive agents.[5–8] Antidepressant discontinuation symptoms can be highly variable and non-specific, with the most frequently reported symptoms being dizziness, headache, nausea, insomnia, and irritability. It has been reported that symptoms typically occur within a few days and are usually transient, but can last up to several weeks or months.[1,9–11]

What remains controversial is the incidence and severity of symptoms. Some reviewers estimated antidepressant discontinuation symptoms occurred in the majority of patients (56% [range 14–86%]), with almost half of cases classed as severe.[11,12] These previous attempts at assessment, however, have been questioned on methodological grounds, especially for including online surveys or other studies prone to selection and dissatisfaction bias.[13,14] Medical professionals continue to hold polarised positions on the incidence and severity of antidepressant discontinuation symptoms, and the debate continues in public media.[15]

Estimating the incidence of antidepressant discontinuation symptoms is complicated by methodological and clinical heterogeneity: there are several definitions and

assessment procedures, and it is plausible that different antidepressants carry different risks of discontinuation symptoms.[1,16] There is also no agreement on the duration of follow-up and frequency of examination necessary for detection of antidepressant discontinuation symptoms. Incidence figures might differ according to the method used, for example posing open questions or employing a structured instrument such as the DESS,[17] which lists more than 40 symptoms. Further difficulties arise from antidepressant discontinuation symptoms sometimes resembling symptoms caused by the return of the depression initially treated, and because given their frequently non-specific nature, they might also appear in the general population or in people taking placebo.

Consequently, many scholars have refrained from quantification,[11] and the incidence of antidepressant discontinuation symptoms and syndromes remains unclear. However, knowledge about the extent of the problem could inform both clinical decision making and research into new antidepressant treatment.

In this Article we aimed to examine the following questions pertaining to patients with psychiatric disorders whose antidepressant has been discontinued: first, what is the incidence of any discontinuation symptom? Second, what is the incidence of discontinuation symptoms among patients discontinuing placebo? And third, how frequent are severe discontinuation symptoms?

Methods

Search strategy and selection criteria

This is the first publication of a larger project on antidepressant discontinuation symptoms, and the pre-registered protocol is available online. We followed the recommendations from Cochrane's Handbook for Systematic Reviews of Interventions,[18] and PRISMA reporting guidelines for systematic reviews.[19]

For more on the **protocol** see https://osf.io/fupyh/wiki/home/?view_only=4e49157297ec40b28cfad465a869b819

A detailed description of the methods can be found in the appendix (pp 2–8). In brief, we searched PubMed, Embase, and CENTRAL from database inception to Oct 13, 2022, with no date, language, or publication type restrictions (ie, grey literature was not excluded). Our first search was conducted on March 26, 2020, with a secondary search on Oct 13, 2022, with additional searches in EudraCT and ClinicalTrials.gov. All included papers were published in languages spoken by the Authors. Exact search terms are shown in the appendix (pp 14–15). We selected studies using the population, intervention, comparison, outcome, and study type (PICOS) framework[20] with the following inclusion criteria. (P) Indication for antidepressant treatment: any mental, behavioural, or neurodevelopmental disorder, including sleep–wake disorders, and disorders associated with psychopathology such as premenstrual dysphoric disorder. We excluded studies on physical conditions such as pain syndromes due to organic disease and studies in neonatal patients. (I) An intervention group of discontinuation of antidepressant treatment, either open or masked via switching to placebo. We excluded studies where patients were treated with antipsychotics, lithium, or thyroxine. (C) With or without a control group of either discontinuation of a different antidepressant, or tapering of antidepressant treatment at a different rate, or discontinuation of placebo drug treatment (ie, patients who were initially treated with placebo and were withdrawn from their medication). (O) Assessment of the incidence of antidepressant discontinuation or withdrawal symptoms after discontinuation, excluding studies providing continuous outcome data only. (S) Controlled trials (randomised [RCTs] and non-randomised) and observational studies, including case-control-studies, and descriptive cross-sectional studies. We included observational studies because the number of antidepressants investigated in RCTs is small, and observational studies constitute a substantive part of the research.

See **Online** for appendix

The literature search, study selection, data extraction, and risk of bias (RoB) evaluation all were carried out independently by two reviewers (YS and US), and supervised by the senior authors (CB and JH). RoB was estimated through the Newcastle-Ottawa scale and with regard to the main outcome of our analyses ie, the incidence of antidepressant discontinuation symptoms (including verum and placebo groups in RCTs). Studies were rated as carrying a low or unknown RoB or a high RoB, and high RoB was assumed in studies with a maximum of six stars. Throughout, we solved discrepancies in assessment via discussions until a consensus was reached (US, YS, JH, and CB).

Data analysis

The primary outcome was the incidence of symptoms after antidepressant discontinuation or placebo discontinuation (ie, the number of patients having any discontinuation symptom in relation to the total number of patients discontinuing). The key secondary outcome was the event rate of severe discontinuation symptoms, again following trial authors' definitions of antidepressant discontinuation symptoms, but additionally classifying discontinuation symptoms leading to study withdrawal as severe. We analysed data separately per antidepressant or placebo discontinuation study group, with antidepressant groups of individual trials treated as separate observational studies. If required, we combined groups of different antidepressants within one RCT to avoid multiple entries of a given trial in one meta-analysis (ie, if a trial had one group discontinuing placebo, one group discontinuing one antidepressant, and one group discontinuing a different antidepressant, the two antidepressants would be grouped, and those data analysed separately to placebo). We did not include drug-continuation groups within antidepressant studies, as assessments of antidepressant discontinuation symptoms could be confounded by side-effects of antidepressant treatment. We also did not include studies presenting continuous data only, eg, DESS

scores, because for clinical purposes we considered categorical data particularly instructive.

All pooled event rates, incidences with 95% CIs, were calculated using random-effects meta-analyses (DerSimonian and Laird inverse variance method), as effect sizes were sampled from a wide variety of studies with different populations and protocols. Event rates of included studies were transformed using the logit function. Statistical significance was set at an α of 0·05 (two sided) for the primary outcome. For the sensitivity analysis, we re-calculated all meta-analyses using the arcsine transformation, and only report these results if they are different from the original analysis. Statistical heterogeneity is expressed as I^2 as well as τ^2, and prediction intervals were calculated where possible. The likelihood of publication bias with regard to the primary outcome, incidence of antidepressant discontinuation symptoms, was assessed via funnel plots. Egger's test was used to assess funnel plot asymmetry. A limit meta-analysis[21] and a Thompson-Sharp test were conducted if Egger's test was significant ($p<0·1$). The robustness of results was also tested by a leave-one-out meta-analysis.

The pre-specified sensitivity analysis included studies with low risk of bias. We also conducted pre-specified subgroup analyses alongside univariable meta-regressions to investigate the potential effects of specific antidepressants, the presence of tapering regimens, the length and dosing of antidepressant treatment, the duration of observation periods, whether or not structured instruments were used to assess symptoms, and diagnosis as an indication for antidepressant treatment on the incidence of antidepressant discontinuation symptoms. We conducted a post hoc subgroup analysis for the presence or absence of trial funding from a pharmaceutical company. Post hoc, we analysed the risk difference of antidepressant discontinuation symptoms between groups that discontinued antidepressants and the corresponding groups who discontinued placebo, using one risk difference from each RCT. Analyses were conducted according to the Cochrane Handbook and using Comprehensive Meta-Analysis Version 4, Professional Version (Biostat, Engelwood, NJ USA), and the R packages meta and metasens[22]. All changes to the protocol are designated as post hoc. We did not include anyone with lived experience of discontinuing antidepressants in the design or conduct of the study.

Role of the funding source

There was no funding source for this study.

Results

Our database and hand searches retrieved 6095 unique articles after duplicates were removed. After screening the titles and abstracts, the full texts of 366 articles were assessed. After 260 articles were excluded, 76 publications including 79 studies were included and constitute the final sample for quantitative synthesis (figure 1).

In total, 100 separate study groups included 21 002 patients, with 16 532 patients discontinuing from antidepressants (77 groups, of which 27 groups were double blind and two were single blind), and 4470 patients discontinuing from placebo. The mean age was 45 years (range 19·6–64·5), and 72% of participants were female and 28% of participants were male (not all studies provided exact numbers). Data on ethnicity were not consistently reported. Publication dates ranged from 1961 to 2019. Articles were published in English (72 studies), Italian (two studies), and French (two studies). 44 (56%) of included studies were RCTs and 35 (44%) were observational studies. 32 (41%) of the 79 studies had a NOS score of 7 or higher, so were classified as of low risk of bias. 38 studies (50%) of 76 applied some degree of tapering (see appendix pp 18–42 for study details). In the 76 included publications, the following diagnoses were reported in decreasing frequency: 49 (64%) for mood disorders (43 [57%] major depressive disorder, two [3%] bipolar

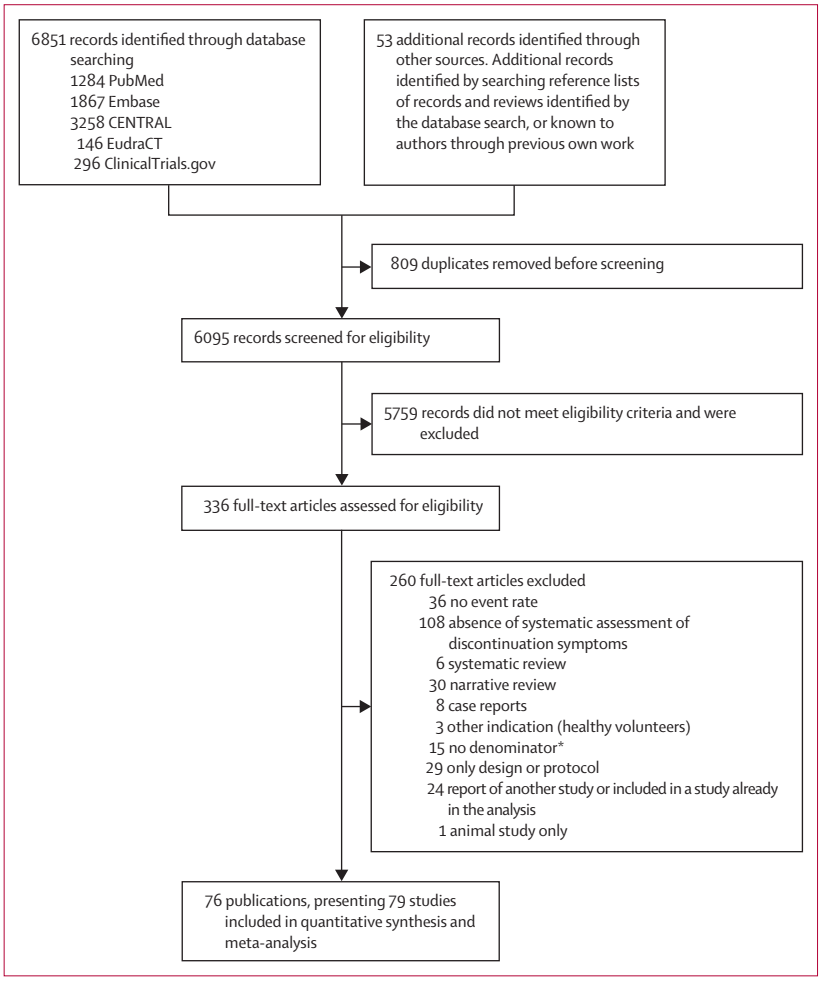

Figure 1: **PRISMA flowchart**

*Articles reporting cases of antidepressant discontinuation symptoms, but where total number of patients discontinuing from antidepressant was not reported, eg, case series.

disorder, one [1%] dysthymic disorder); 21 (28%) for anxiety disorders (nine [12%] panic disorder, seven [9%] generalised anxiety disorder, and two [3%] social anxiety disorders), three (4%) on fibromyalgia, three (4%) on premenstrual dysphoric disorder, two (3%) on anorexia nervosa, and one study (1%) each on OCD, post-menopausal vasomotor symptoms, sleep-wake-disorders, impulse-control disorders, and psychotic disorders. Mean duration of antidepressant therapy before discontinuation ranged from 1 to 156 weeks. Duration of observation of discontinuation symptoms ranged from 1·5 to 196 days.

The event rate of any antidepressant discontinuation symptoms among the 62 study groups that provided results was 0·31 (95% CI 0·27 to 0·35), with a prediction interval of 0·11 to 0·62 (table 1). Among the 25 low RoB studies, the incidence estimate was 0·29 (95% CI 0·24 to 0·35) versus 0·33 (0·27 to 0·39) for the 37 studies with high RoB. With regards to our pre-specified subgroup analyses, applying structured instruments to identify discontinuation symptoms (event rate 0·40 [0·34 to 0·46]) versus studies without instruments (0·27 [0·23 to 0·33]) had a group difference of 0·13 (0·05 to 0·21, p<0·001 when the Q-test had one degree of freedom). Among 37 RCTs, there was an event rate of 0·28 (0·24 to 0·33) versus 0·37 (0·30 to 0·45) in 25 non-RCT studies, with a group difference of 0·09 (0·02 to 0·16, p=0·032). For the 20 studies applying taper,

	Number of studies*	Event rate (95% CI)	I^2	τ^2	Prediction interval	Group mean difference (95% CI), p†
Any antidepressant symptom						
All studies	62	0·31 (0·27 to 0·35)	94·1%	0·416	0·11 to 0·62	NA
RoB	..	..	..	..	..	0·04 (–0·04 to 0·12), 0·386
Low	25	0·29 (0·24 to 0·35)	95·6%	0·406	0·10 to 0·61	..
High	37	0·33 (0·27 to 0·39)	92·5%	0·492	0·10 to 0·67	..
RCT as study design	..	..	..	..	..	0·09 (0·02 to 0·16), 0·032
Yes	37	0·28 (0·24 to 0·33)	95·3%	0·456	0·09 to 0·61	..
No	25	0·37 (0·30 to 0·45)	90·2%	0·408	0·13 to 0·70	..
Use of assessment instrument	..	..	..	..	..	0·13 (0·05 to 0·21), 0·001
Yes	18	0·40 (0·34 to 0·46)	91·2%	0·201	0·20 to 0·64	..
No	44	0·27 (0·23 to 0·33)	94·5%	0·561	0·08 to 0·64	..
Pharmaceutical company funding	..	..	..	..	..	0·02 (–0·06 to 0·10), 0·656
Yes	45	0·30 (0·26 to 0·35)	95·4%	0·413	0·10 to 0·62	..
No	9	0·28 (0·21 to 0·37)	52·0%	0·162	0·12 to 0·53	..
Unclear funding or possible COI	8	0·42 (0·23 to 0·63)	84·8%	1·130	0·04 to 0·92	NA
Tapering	..	..	..	..	..	0·01 (–0·09 to 0·11), 0·502
With taper	20	0·30 (0·24 to 0·37)	95·3%	0·394	0·10 to 0·62	..
Without taper	28	0·29 (0·22 to 0·37)	93·9%	0·728	0·06 to 0·71	..
Placebo discontinuation (any symptom)						
All studies (all RCT)	22	0·17 (0·14 to 0·21)	90·0%	0·316	0·06 to 0·41	NA
RoB	..	..	..	..	..	0·09 (0·02 to 0·16), 0·028
Low	14	0·20 (0·16 to 0·26)	91·9%	0·311	0·07 to 0·47	..
High	8	0·11 (0·07 to 0·18)	81·4%	0·387	0·02 to 0·40	..
Use of assessment instrument	..	..	..	..	..	0·17 (0·11 to 0·23), <0·001
Yes	6	0·30 (0·25 to 0·36)	80·6%	0·088	0·15 to 0·51	..
No	16	0·13 (0·10 to 0·17)	85·8%	0·300	0·04 to 0·34	..
Severe symptoms after antidepressant discontinuation						
All studies	19	0·028 (0·014 to 0·057)	84·1%	1·928	0·001 to 0·377	NA
Imipramine	4	0·123 (0·015 to 0·557)	84·6%	4·082	0·000 to 1·000	NA
Paroxetine	4	0·053 (0·025 to 0·107)	45·4%	0·274	0·003 to 0·481	NA
Desvenlafaxine or venlafaxine	3	0·056 (0·002 to 0·678)	94·6%	9·374	0·000 to 1·000	NA
Duloxetine	3	0·020 (0·008 to 0·047)	50·4%	0·312	0·000 to 0·995	NA
Fluoxetine	3	0·018 (0·006 to 0·050)	0%	0·000	NA	NA
Severe symptoms after placebo discontinuation						
All studies	6	0·006 (0·002 to 0·013)	0%	0·000	NA	NA

COI=conflict of interest. df=degrees of freedom. NA=not applicable. RCT=randomised controlled trial. RoB=risk of bias. *Depending on study design and outcomes reported, studies might be included in only some of the analyses, resulting in varying samples in between analyses. †All p-values result from Q-tests with df=1.

Table 1: **Primary outcome and secondary outcomes across subgroup analyses**

the event rate was 0·30 (95% CI 0·24 to 0·37) versus 0·29 (0·22 to 0·37) for the 28 abrupt discontinuation studies, and the group difference was 0·01 (–0·09 to 0·11), p=0·502. Our post hoc funding subgroup analysis showed an event rate of 0·30 (0·26–0·35) for the 45 studies funded by a pharmaceutical company versus 0·28 (0·21–0·37) for the nine non-pharma-funded trials.

Meta-regression did not indicate significant associations of incidence with duration of antidepressant treatment, diagnosis (depressive *vs* anxiety disorder), RoB as a continuous variable, year of publication, or length of observation (table 2). Stratified by length of observation, 1–3 days gave an event rate of 0·54 (95% CI 0·24–0·81); 5–10 days 0·24 (0·16–0·35); 14–16 days 0·32 (0·25–0·39); 20–25 days 0·35 (0·28–0·44); 28 days 0·37 (0·26–0·51); 42–56 days 0·36 (0·30–0·44); and 63–84 days 0·40 (0·18, 0·67).

Among antidepressants with evidence from two or more studies available, those associated with the highest incidences of any discontinuation symptom were imipramine (0·44 [95% CI 0·25–0·66]), and either desvenlafaxine or venlafaxine (0·40 [0·35–0·45]), as opposed to the lowest rates of any discontinuation symptom with fluoxetine (0·15 [0·01–0·80]) and sertraline (0·18 [0·08–0·35]; table 3).

In the 22 placebo-controlled antidepressant RCTs, incidence of antidepressant discontinuation symptoms was 0·17 (95% CI 0·14–0·21) under placebo, with a prediction interval of 0·06–0·41 (table 1, figure 2). Among the 14 studies on placebo discontinuation with low RoB, incidence of antidepressant discontinuation symptoms in placebo groups was 0·20 (95% CI 0·16–0·26) versus 0·11 (0·07–0·18) for the eight studies with high RoB. Among six studies applying a structured instrument to assess antidepressant discontinuation symptoms (eg, DESS), incidence was 0·30 (0·25–0·36) versus 0·13 (0·10–0·17) in the 16 studies without an instrument (group difference p<0·001). Meta-regression revealed no association of incidence with length of observation. Stratified by duration of observation, 1 to 3 days had no data; 5 to 7 days had an incidence of 0·16 (0·08–0·29); 14 days 0·17 (0·13–0·22); 20 to 25 days 0·28 (0·20–0·36); and 30 days 0·07 (0·04–0·11), although there was only one study with a 30 day observation period. There was no indication of an association between incidence and year of publication or length of placebo treatment.

For our post hoc subgroup analyses, we calculated the incidence of antidepressant discontinuation symptoms in antidepressant groups of placebo-controlled RCTs. In 20 RCTs the event rate was 0·24 (0·18–0·30). The risk difference between both groups was 0·079 (0·039–0·119), with a prediction interval of –0·094 to 0·251.

19 studies reported figures for severe antidepressant discontinuation symptoms, with an incidence of 0·028 (95% CI 0·014–0·057) and a prediction interval between 0·001 and 0·377. After discontinuation of placebo treatment, the incidence of severe antidepressant discontinuation symptoms was 0·006 (0·002–0·013) in the six studies with available data. The highest rates were observed after discontinuation of imipramine (0·123 [0·015–0·577]), paroxetine (0·053 [0·025–0·107]) and either venlafaxine or desvenlafaxine (0·056 [0·002–0·678]; table 1).

I^2 and τ^2 statistics indicated substantial heterogeneity in most of our analyses, reflected in wide prediction intervals (table 1, 3). Subgroup and sensitivity analyses allowed for partial attribution of heterogeneity to moderating factors (eg, application of structured assessment instruments, study methodology, and study rigour; table 1). Leave-one-out analyses did not indicate that single studies substantially influenced calculations (pooled antidepressant discontinuation symptom event rates ranged from 0·304 [0·27–0·34] to 0·320 [0·28–0·36]).

For publication bias, our funnel plot of 62 studies included in the estimate of the incidence of any antidepressant discontinuation symptoms indicated substantial heterogeneity but no clear asymmetry. Egger's test was significant (p=0·01), however, neither the limit meta-analysis (0·31 [0·27–0·36]) nor the

	Slope	Degrees of freedom	Two-sided p-value	R^2
Any antidepressant symptom				
Length of observation	–0·0036	1	0·38	0·00
Therapy duration	0·0056	1	0·13	0·00
Diagnosis (depression *vs* anxiety)	–0·0807	1	0·72	0·00
RoB as continuous variable	–0·0727	1	0·18	0·00
Year of publication	–0·0148	1	0·11	0·00
Placebo discontinuation				
Length of observation	0·0057	1	0·79	0·00

RoB=risk of bias

Table 2: **Meta-regression across subgroup analyses**

	Number of studies	Event rate (95 CI%)	I^2	τ^2	Prediction interval
Imipramine	2	0·44 (0·25–0·66)	79·6%	0·32	NA
Desvenlafaxine and venlafaxine	15	0·40 (0·35–0·45)	92·3%	0·13	0·22–0·61
Escitalopram	6	0·39 (0·26–0·53)	93·7%	0·45	0·08–0·83
Fluvoxamine	3	0·38 (0·08–0·81)	88·2%	2·48	0·00–1·00
Paroxetine	10	0·32 (0·25–0·39)	71·9%	0·17	0·14–0·56
Duloxetine	7	0·32 (0·22–0·44)	95·7%	0·47	0·07–0·76
Nefazodone	2	0·21 (0·16–0·28)	0%	0	NA
Levomilnacipran and milnacipran	8	0·19 (0·09–0·33)	96·4%	1·23	0·01–0·80
Citalopram	2	0·19 (0·05–0·48)	0%	0	NA
Sertraline	5	0·18 (0·08–0·35)	82·3%	0·82	0·01–0·85
Fluoxetine	2	0·15 (0·01–0·80)	80·5%	4·37	NA

NA=not applicable. *Antidepressants required at least two studies for inclusion.

Table 3: **Outcomes of specific antidepressants***

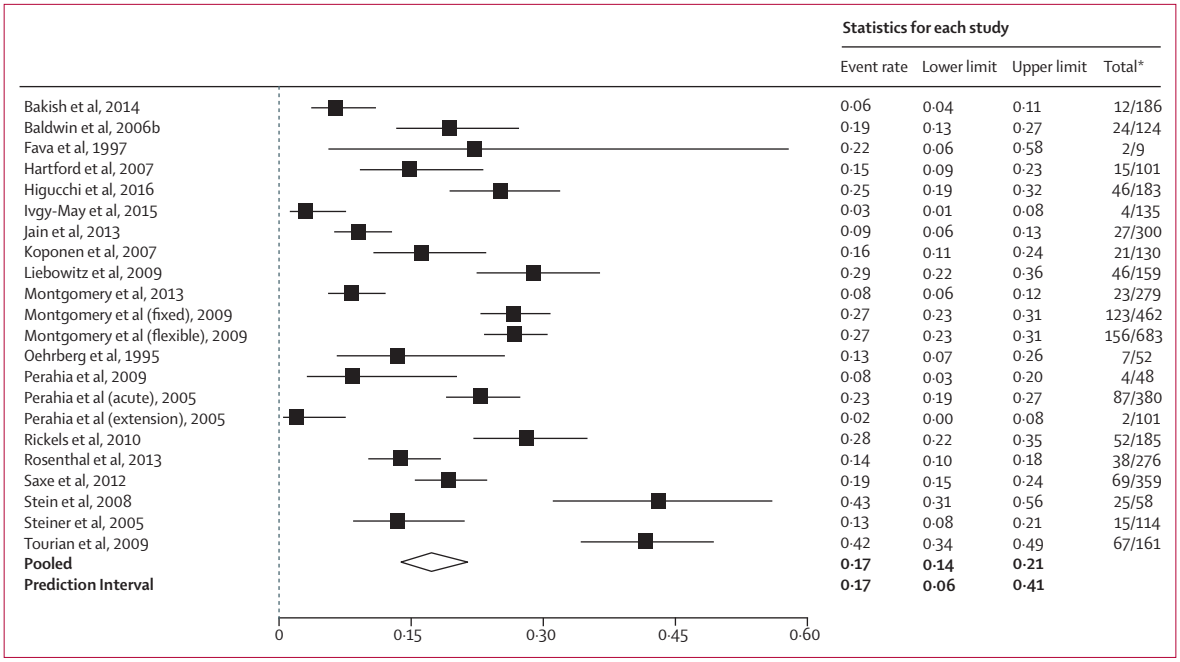

Figure 2: **Event rate of discontinuation symptoms after placebo withdrawal**
For a full list of the studies cited, see appendix (pp 16–17). *n/N, where n is the number of patients with at least one symptom, and N is total number of patients receiving placebo in the study.

Thompson-Sharp test (p=0·64) indicated publication bias. The funnel plot of the analysis of the 22 placebo discontinuation studies for the incidence of any symptom indicated missing small studies to the right of the mean (appendix p 14). Egger's test was significant (p<0·01). This result was supported by limit meta-analysis (0·22 [0·17–0·29]) and Thompson-Sharp test (p<0·01). Pooled event rates did not change substantially using the arcsine transformation for the incidence of any antidepressant discontinuation symptoms and placebo discontinuation. However, pooled event rates were smaller for severe antidepressant discontinuation symptoms (0·021 [0·010–0·036]).

Discontinuation syndromes (as opposed to symptoms) are not included as a main outcome in this study because definitions vary widely, restricting the comparability of studies. For a broader picture, we examined 15 studies in a supplementary post hoc analysis, finding a similar incidence (0·29 [0·18–0·45], τ^2 1·666 *vs* 0·31 [0·27–0·35], τ^2 0·416).

Discussion

Our study yielded four main results. First, across all studies and antidepressants, we found that approximately every third patient discontinuing antidepressants will have antidepressant discontinuation symptoms of any kind (event rate 0·31). Second, even in studies of people receiving a placebo, discontinuation symptoms (which could be called discontinuation-like symptoms) occurred in approximately one in six patients (event rate 0·17). Third, severe discontinuation symptoms occurred in around one in 30 patients discontinuing antidepressants (event rate 0·03). Fourth, the incidence of antidepressant discontinuation symptoms is modified by specific antidepressants, the use of instruments for detecting antidepressant discontinuation symptoms, and by study rigour, but substantial statistical heterogeneity remains.

With regard to the substantive heterogeneity in this study, the degree of between-study heterogeneity is not unexpected, as heterogeneity is usually larger in single arm meta-analyses than in meta-analyses comparing two groups under the same study conditions.[23] Part of the heterogeneity plausibly reflects the variability of clinical characteristics and methodological approaches. However, the use of established instruments in placebo discontinuation studies also resulted in higher antidepressant discontinuation symptoms event rates, indicating the risk of false positive signals. Other characteristics, thought to be possible confounders a priori, did not contribute to explaining the heterogeneity. Contrary to our expectations, the length of the observation period was not a significant factor in observed incidences of antidepressant discontinuation symptoms. However, our results when the first 3 days after discontinuation were left out of the analysis suggest length of the observation period might have an effect. Still, it is plausible that if the length of observation period has no effect, this contradicts previous criticism regarding the risk of underestimation in antidepressant discontinuation symptom studies with shorter observation periods. It is plausible that antidepressant half-life affects not only severity of antidepressant discontinuation symptoms, but also their

time of appearance, as was shown in the case of fluoxetine with its particularly long half-life.[24] A confounder in both placebo and verum arms is the possible overlap of symptoms that could indicate residual or recurring depression rather than a discontinuation symptom in the narrow sense. An attempt to distinguish one from the other was made in 30 studies (appendix pp 37–42). Prospective differentiation is difficult, but a best possible approach could be based on the time of onset (within days *vs* within weeks or months) and by considering specific symptoms that are atypical of the underlying disease (eg, vivid dreams, electric shock-like sensations, rapid mood-swings, and windows of affective symptoms within a day *vs* persistent mood alterations).

The idea for the present study and its design directly arose from our clinical practice and the experiences with discontinuation of antidepressants that our patients brought to us. A limitation of the study is that no people with lived experience were formally involved in the conceptualisation and realisation of the study itself.

We did not find a difference between studies that applied tapering of the drug and studies with abrupt cessation of the drug. The substantial heterogeneity in study designs (eg, duration of taper) and specific antidepressants used preclude firm conclusions; for example, all trials on venlafaxine and desvenlafaxine were among the studies that applied tapering. In using a variable at the study level, it is important to consider ecological inference fallacy when interpreting results. However, the tapering regimen was identical for the whole study population in many studies, and only some applied individual taper regimens, yet our results stem from indirect comparisons. Results should also be viewed with caution as there is a limited power to detect patterns when heterogeneity is high. Within some individual studies, frequency and severity of antidepressant discontinuation symptoms appeared to be reduced through protracted tapering of the antidepressant (eg, Kramer and colleagues),[25] but a lack of robust evidence from larger randomised trials on the comparative benefits of different dose reduction regimens remains a limitation. Tapering of antidepressants is recommended in most guidelines, and there is research suggesting that prolonged and hyperbolic tapering of antidepressants will substantially reduce (although not completely exclude) withdrawal effects and increase the likelihood of successful discontinuation of antidepressants.[26,27] Hyperbolic tapering has also been criticised,[28,29] and as only a portion of patients will have discontinuation symptoms, and because its pragmatic feasibility is limited, hyperbolic tapering might not be indicated in every patient discontinuing antidepressants. If antidepressant discontinuation symptoms occurs, then patients do need appropriate treatment to ameliorate their symptoms, which could be through application of hyperbolic tapering.[26,30]

We previously proposed a very basic hierarchy of antidepressants concerning their risk of antidepressant discontinuation symptoms,[1] which has since been expanded by Horowitz and colleagues.[31] Individual differences among antidepressive agents were not the main topic of the present review, and substantial heterogeneity in study designs must be taken into account and renders a direct comparison between drugs difficult. Although our main analysis included 62 studies, only seven antidepressants have been investigated in three or more reports. Imipramine and desvenlafaxine or venlafaxine have relatively high incidences of antidepressant discontinuation symptoms, and sertraline and fluoxetine have relatively low incidences. With the exception of desvenlafaxine or venlafaxine, the confidence and prediction intervals are wide, pointing to the preliminary nature of substance-specific results. Another limitation is that we found no studies on several widely used antidepressants, for example, mirtazapine, bupropion, or amitriptyline.

Our findings suggest that imipramine, paroxetine, and desvenlafaxine and venlafaxine are associated with a higher risk of severe antidepressant discontinuation symptoms compared with other antidepressants, although we only found small differences between individual antidepressive agents, possibly a manifestation of relevant non-pharmacological effects. The heterogeneity in our study could point to considerable subjectivity among researchers and patients, and wide prediction intervals suggest that single studies might arrive at results that are markedly different from the summary estimates in this study.

As with any meta-analysis, we might have missed potentially suitable studies. Narrow confidence intervals and our sensitivity analyses (leave-one-out, publication bias) support the robustness of our analyses. Studies varied in inclusion criteria, and whether assessment of discontinuation was the primary or secondary objective of the study, possibly resulting in selection bias. Study design and methodology therefore were the subject of various subgroup and sensitivity analyses, suggesting lower rates of antidepressant discontinuation symptoms in studies with higher methodological rigour.

Categorical results do not have the granularity of continuous outcomes, but much of the literature refers to the presence or absence of antidepressant discontinuation symptoms.

We re-calculated analyses without studies with high risk of selection bias, addressed specific substances, and took into consideration pharmaceutical company funding, study quality, and key methodological characteristics, eg, follow-up time and duration of treatment, as confounders. We therefore hope that we have arrived at a valid estimate of the incidence of antidepressant discontinuation symptoms. We assessed the incidence of antidepressant discontinuation symptoms or antidepressant discontinuation-like symptoms in

placebo groups, a control group largely neglected in earlier scholarly work on the topic (with an exception in the work of Horowitz and colleagues).[31] We therefore believe the numbers presented here allow for a more comprehensive view of the problems associated with antidepressant discontinuation.

The publication bias analysis suggests that the incidence rate for any antidepressant discontinuation synptom is robust. However, adjusting for small study effects increased incidence of antidepressant discontinuation symptoms in placebo groups. Considering the placebo results, approximately half of antidepressant discontinuation symptoms could be attributable to expectation or non-specific symptoms. Assuming that patients in RCTs are usually not unmasked before outcome assessments are finished, many allocated to a placebo group might expect to be discontinuing from verum and thus would be susceptible to nocebo effects. The incidence of antidepressant discontinuation symptoms (or antidepressant discontinuation-like symptoms) remains stable throughout sensitivity and low RoB analyses, and when antidepressant and placebo groups in RCTs are contrasted directly the difference narrows to about 8%. We caution that the range of antidepressants examined in the RCTs included in the present meta-analysis is smaller than in the entire sample of studies, and might produce statistically robust but clinically underrepresentative findings. However, when restricting analyses to those antidepressants captured in RCTs, incidences of antidepressant discontinuation symptoms are still lower in RCTs than in observational trials (0·28 [0·24–0·33] *vs* 0·37 [0·28–0·46]). Considering all available data, we conservatively estimate that one out of six to seven patients has truly pharmacologically caused antidepressant discontinuation symptoms. This might still be an over-estimate, as it is difficult to factor in residual or re-emerging symptoms of depression or anxiety.

The numbers presented here are meant to inform clinicians and patients about the probable extent of antidepressant discontinuation symptoms without causing undue alarm. Our results confirmed that for a proportion of patients discontinuation symptoms will be severe, and will potentially lead to disengaging from practitioners or to reinstating antidepressant use. The substantial rate of antidepressant discontinuation symptoms reported by patients on placebo suggests the role of nocebo effects in the development of antidepressant discontinuation symptoms. This is not to say all antidepressant discontinuation symptoms are caused by patient expectations; in practice, all patients discontinuing antidepressants need to be counselled and monitored, and patients who report antidepressant discontinuation symptoms must be helped, in particular those who develop severe antidepressant discontinuation symptoms.

A relevant proportion of patients will have symptoms after discontinuation of antidepressants. Non-specificity of symptoms, the expectations of patients (and possibly doctors), as well as recurring psychopathology, might all influence incidence to an extent, a possibility supported by the significant variability in study results. Subtracting non-specific effects, we estimate the frequency of antidepressant discontinuation symptoms to be in the range of approximately 15%, thus affecting about one in six to seven patients. Evidence that about one in 35 patients suffers from severe antidepressant discontinuation symptoms must be considered preliminary at present, but caution towards severe antidepressant discontinuation symptoms seems to be warranted when discontinuing imipramine, paroxetine, or desvenlafaxine and venlafaxine.

Contributors

JH and CB conceptualised the study and its design. YS and US conducted the literature search, screened the articles, and did the quality assessments, supervised by JH and CB. YS and US reviewed all full texts for inclusion and collected the data independently, supervised by CB. JH read full texts of included studies and collected data independently. JH, YS, and CB analysed the data. TB and GS gave expert input to data analysis and conducted additional analyses. JH drafted the paper, supervised by CB; all authors revised the paper and approved the final version. All authors had full access to all the data in the study. JH and CB verified all data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

The authors declare no competing interests.

Data sharing

All extracted data are available in the Article and in the appendix online. Study screening data and outcome data for included studies will be shared upon reasonable request after the overarching project has finished.

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References

1 Henssler J, Heinz A, Brandt L, Bschor T. Antidepressant withdrawal and rebound phenomena. *Dtsch Arztebl Int* 2019; **116:** 355–61.
2 Andersen H, Kristiansen ES. Tofranil-treatment of endogenous depressions. *Acta Psychiatr Scand* 1959; **34:** 387–97.
3 Sørensen A, Juhl Jørgensen K, Munkholm K. Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review. *Ther Adv Psychopharmacol* 2022; **12:** 20451253211067656.
4 Davies J, Read J, Hengartner MP, et al. Clinical guidelines on antidepressant withdrawal urgently need updating. *BMJ* 2019; **365:** l2238.
5 National Institute for Health and Care Excellence. Depression in adults: treatment and management. 2022. https://www.nice.org.uk/guidance/ng222 (accessed Aug 25, 2023).
6 Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder-update 2015. *World J Biol Psychiatry* 2015; **16:** 76–95.
7 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf (accessed Aug 26, 2023).
8 Nationale Versorgungs Leitlinien. NVL unipolare depression, version 3.1. 2022. https://www.leitlinien.de/themen/depression (accessed May 19, 2024).

9 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015; **84:** 72–81.

10 Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal symptoms after serotonin-noradrenaline reuptake inhibitor discontinuation: systematic review. *Psychother Psychosom* 2018; **87:** 195–203.

11 Horowitz MA, Framer A, Hengartner MP, Sørensen A, Taylor D. Estimating risk of antidepressant withdrawal from a review of published data. *CNS Drugs* 2023; **37:** 143–57.

12 Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: are guidelines evidence-based? *Addict Behav* 2019; **97:** 111–21.

13 Jauhar S, Hayes J. The war on antidepressants: what we can, and can't conclude, from the systematic review of antidepressant withdrawal effects by Davies and Read. *Addict Behav* 2019; **97:** 122–25.

14 Jauhar S, Hayes J. Corrigendum to the war on antidepressants: what we can, and can't conclude, from the systematic review of antidepressant withdrawal effects by Davies and Read. *Addict Behav* 2019; **97:** 126.

15 Aviv R. The challenge of going off psychiatric drugs. The New Yorker, April 1, 2019. https://www.newyorker.com/magazine/2019/04/08/the-challenge-of-going-off-psychiatric-drugs (accessed May 19, 2024).

16 Sørensen A, Ruhé HG, Munkholm K. The relationship between dose and serotonin transporter occupancy of antidepressants – a systematic review. *Mol Psychiatry* 2022; **27:** 192–201.

17 Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry* 1998; **44:** 77–87.

18 Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). *Cochrane Handbook for systematic reviews of interventions* version 6.4 (updated August 2023). Cochrane, 2023. www.training.cochrane.org/handbook (accessed May 19, 2024).

19 Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.

20 Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014; **14:** 579.

21 Rücker G, Schwarzer G, Carpenter JR, Binder H, Schumacher M. Treatment-effect estimates adjusted for small-study effects via a limit meta-analysis. *Biostatistics* 2011; **12:** 122–42.

22 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019; **22:** 153–60.

23 Schwarzer G, Rücker G. Meta-analysis of proportions. In: Evangelou E, Veroniki AA, eds. Meta-research: methods and protocols. New York, NY: Springer USA, 2022:159–72.

24 Zajecka J, Fawcett J, Amsterdam J, et al. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 1998; **18:** 193–97.

25 Kramer JC, Klein DF, Fink M. Withdrawal symptoms following dicontinuation of imipramine therapy. *Am J Psychiatry* 1961; **118:** 549–50.

26 Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6:** 538–46.

27 Groot PC, van Os J. Successful use of tapering strips for hyperbolic reduction of antidepressant dose: a cohort study. *Ther Adv Psychopharmacol* 2021; **11:** 20451253211039327.

28 Selvaraj S, Jauhar S, Baldwin DS, et al. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6:** 560–61.

29 Kronenberg G, Desai D, Anghelescu I. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6:** 560.

30 Ruhe HG, Horikx A, van Avendonk MJP, Groeneweg BF, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6:** 561–62.

31 Horowitz MA, Framer A, Hengartner MP, Sørensen A, Taylor D. Estimating risk of antidepressant withdrawal from a review of published data. *CNS Drugs* 2023; **37:** 143–57.