

Do discontinuation symptoms predict depression relapse after antidepressant cessation?

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Abstract

Background: Discontinuing antidepressants after recovering from a depressive episode is associated with a risk for two events: discontinuation symptoms and relapse. Little is known about who can discontinue safely and whether discontinuation symptoms constitute a risk factor for relapse. This study investigated risk factors for experiencing discontinuation symptoms and whether discontinuation symptoms are associated with depression relapse.

Methods: 103 patients with a currently remitted major depressive disorder were randomized to continuation or discontinuation of antidepressants. Discontinuation symptoms were assessed with the Discontinuation Emergent Signs and Symptoms (DESS) scale. The discontinuation syndrome (ADS) was defined as experiencing at least 4 DESS symptoms. We investigated the association of clinical factors with the number of discontinuation symptoms in Bayesian linear regressions. After the randomization phase, all patients discontinued their antidepressant and were followed up over 6 months. We investigated the association of discontinuation symptoms and clinical factors with relapse risk in logistic regressions and a cox proportional hazards model.

Results: An ADS was experienced by 29% (95% PI [8.3%, 72%]) of patients. Women reported more discontinuation symptoms than men (factor 1.67 (95% interval [1.06, 2.56])). None of the other prespecified predictors were associated with the risk or severity of ADS. Trait anxiety (Slope = 0.42, 95% PI [-0.01, 0.90]), ADS severity (0.58, 95% PI [0.07, 1.16]) and early depressive symptoms (0.63, 95% PI [0.16, 1.17]) were associated with a higher relapse risk.

Conclusion: Antidepressant discontinuation symptoms were relatively common and experienced mainly by women. Experiencing discontinuation symptoms may adversely impact relapse risk.

Introduction

Antidepressants are a group of psychoactive drugs used for the treatment of a variety of psychiatric conditions including major depressive disorders (MDD). In recent decades, the number of prescriptions has been steadily increasing around the world (Mikulic, 2021). Between 2017 and 2018, 7.3 million adults (17% of the adult population) were prescribed and dispensed antidepressants in the UK (Davies & Read, 2019; Public Health England, 2019; Tomlinson et al., 2019). Long-term antidepressant medication is only indicated for a minority of patients; therefore, antidepressants will eventually need to be ceased in most. Discontinuation may also be necessary due to adverse effects (Bet et al., 2013; Goodwin et al., 2017).

Discontinuing antidepressants carries an elevated risk for relapse of depression (Geddes et al., 2003; Lewis et al., 2021) and can lead to antidepressant discontinuation syndrome (ADS). Although no reliable incidence rate of ADS currently exists, withdrawal reactions are estimated to affect up to 30-60% of patients and can sometimes be severe and last for weeks to months (Fava et al., 2015; Fava et al., 2018; Jha et al., 2018; Davies & Read, 2019; Hengartner et al., 2020; Horowitz & Taylor, 2022). It can involve affective symptoms, such as lowered mood, but compared to a depression relapse, it is thought to entail more prominent somatic symptoms, to have a more abrupt onset, and a faster response to the reinstatement of antidepressant medication (Haddad & Anderson, 2007; Horowitz & Taylor, 2019). However, even though the occurrence of adverse effects upon the cessation of antidepressants has first been described as early as 1961 (Kramer et al., 1961), research into this issue remains scarce.

As such, key uncertainties remain. First, can ADS be effectively differentiated from the re-emergence of depression or anxiety? And if so, how? The similarity with symptoms of depression and anxiety means ADS can easily be misdiagnosed as the re-emergence of the underlying depressive disorder (Lejoyeux et al., 1996; Rosenbaum et al., 1998), which may lead to unnecessarily prolonged medication and continued exposure to potential adverse effects (Haddad and Anderson, 2007; Wilson and Lader, 2015; Horowitz & Taylor, 2022). Second, can ADS be predicted? This would allow early instantiation of appropriate clinical management to prevent its emergence (c.f. Horowitz & Taylor 2019)? Third, does ADS have an influence on the longer-term course, e.g., increasing relapse risk above and beyond symptoms of depression or anxiety? For instance, discontinuation of antidepressants and the emergence of ADS could function as new stressors and increase the susceptibility of patients. Fourth, can discontinuation be optimized? Long-term psychotropic medication may lead to the establishment of a new homeostatic equilibrium (Andrews et al., 2011; Horowitz & Taylor, 2022). A gradual reduction of medication may thus mitigate withdrawal symptoms by reducing the rate at which the equilibrium is perturbed (Ashton et al., 2005; Horowitz & Taylor, 2019). Indeed, previous reports have shown a higher frequency of discontinuation symptoms after abrupt interruption of antidepressants (van Geffen et al., 2005; Himei & Okamura, 2006). Substances with shorter plasma elimination properties, such as paroxetine (Haddad, 1998), carry an elevated risk for ADS (Renoir, 2013) and result in more symptoms (Rosenbaum et al., 1998). Patient-level determinants, such as the age of depression onset and sex, might also influence the risk of ADS (Bogetto et al., 2002).

In this study, we analyzed data from an open randomized study of antidepressant discontinuation with a naturalistic follow-up. First, we aimed at disentangling discontinuation and depressive symptoms. We investigated whether discontinuation symptoms rise before symptoms of depression, and whether these can be statistically distinguished from each other. Next, we tried to identify risk factors for developing ADS. We investigated the effect of both medication- and patient-related factors in predisposing towards discontinuation symptoms. Lastly, we examined the association of ADS severity with relapse of a major depressive episode.

Methods

Ethical approval

Ethical approval for the study was obtained from the cantonal ethics commission Zurich (BASEC: PB_2016-0.01032; KEK-ZH:2014-0355) and the ethics commission at the Campus Charité-Mitte (EA 1/142/14), and procedures were in accordance with the Declaration of Helsinki.

Study Design

We examined data from the AIDA study, which was a two-site (Zurich and Berlin), longitudinal study of antidepressant discontinuation (Berwian et al., 2022). After inclusion, patients underwent a baseline assessment (BA), which involved the registration of patient history and current symptomatology. Patients were randomized to early discontinuation (1W2) and late discontinuation (12W) of antidepressants (1/2 represents the number of the main assessment, “W” signifies withdrawal). Patients in the 1W2 group began antidepressant withdrawal after the first main assessment (MA1), while the second main assessment (MA2) was carried out at least 5 half-lives after completion of the withdrawal. Patients in the 12W group started discontinuing their medication after completing MA2. The tapering duration of up to 18 weeks was determined by treating physicians independent of the researchers. The time interval between MA1 and MA2 in the 12W group was matched with the tapering period in the 1W2 group. After discontinuation was completed, all individuals entered a 26-week follow-up. During this period, patients underwent assessments of depression and discontinuation symptoms at weeks one, two and four with telephone interviews and a final assessment upon study exit. If the telephone interview suggested a potential relapse, patients were invited for a structured clinical evaluation of a depressive episode according to DSM-IV diagnostic criteria (American Psychiatric Association., 2000).

Participants

Participants were included if: (1) they were currently taking antidepressant medication for the treatment of MDD, (2) they had made an informed decision to discontinue antidepressant medication independent of study participation, (3) they had taken an antidepressant during the last depressive episode, (4) they were currently remitted and (5) clinical remission was achieved solely with antidepressant medication without manualized psychotherapy, where remission was defined with 17-item Hamilton Depression Score (HAMD-17) of less than 7 (Williams, 1988).

Patients were excluded if they: (1) had any disease of type or severity that could undermine the planned measurements, (2) were taking psychotropic drugs other than antidepressants, (3) had acute suicidal thoughts, (4) had lifetime or current diagnosis of borderline or antisocial personality disorder, psychotic disorder or bipolar disorder, and (5) had a current diagnosis of post-traumatic stress disorder, obsessive compulsive disorder, eating disorder or drug-use disorder. See Berwian et al. (2022) and the supplementary material for more detailed inclusion and exclusion criteria. Patients received usual care while participating in the study. All participants provided written, informed consent.

Measures

We included measures on demographics, treatment history, current symptoms and variables related to the antidepressant treatment. Depressive symptoms were evaluated with the Inventory of Depressive Symptomatology: Clinician (IDS-C; Rush et al., 1996) and Self-report IDS (IDS-S; Rush et al., 1996), trait anxiety with State-Trait Anxiety Inventory: Trait Version (STAI-T; Spielberger et al., 1970). Discontinuation symptoms were assessed with the Discontinuation Emergent Signs and Symptom Scale (DESS; Rosenbaum et al., 1998). The DESS is a 43-item instrument developed to evaluate new onset symptoms following antidepressant. Somatic DESS symptoms were defined as symptoms 1 to 14, psychological DESS 15 to 43. Relapse of MDD was assessed via clinician-administered diagnostic interviews of the SCID-I.

Statistical analyses

All statistical analyses were conducted in R Studio (Version 1.4.1106). We applied both frequentist and Bayesian methods. Bayesian statistics were applied when estimating the size of a parameter. Frequentist methods were used when testing a sharp null hypothesis and for sensitivity analyses. Bayesian posterior intervals represent 95% central intervals. We predefined the analyses in an analysis plan (<https://github.com/mpc-ucl/aidaShare/tree/master/analysis/DiscontinuationSymptoms>).

Incidence and severity of antidepressant discontinuation syndrome

To estimate the severity of discontinuation symptoms, we compared the DESS scores between the two groups at MA2. At this timepoint, patients in the 1W2 group had discontinued their medication, while patients in the 12W group had not yet started discontinuation. A negative-binomial link function was used as the DESS scale represents count data, MA1 scores were included as predictor for baseline correction. Because the MA2 assessment was conducted at varying times after completion of discontinuation (between 5 and 42 days post withdrawal) we included an interaction between group and time of MA2 assessment. For the estimation of a sex-specific effect, we included an interaction between group and sex.

To estimate the incidence rate of ADS as a categorical variable, we compared the number of patients who reported 4 or more new or worsened symptoms on the DESS scale, following the criteria by Rosenbaum et al. (1998), at time point MA2 between the two groups. For this, we fitted a univariate binomial regression with group as a predictor variable.

Temporal course of depressive and discontinuation symptoms

To examine whether discontinuation symptoms rose earlier than depressive symptoms following antidepressant discontinuation, we conducted two sets of analyses. First, we compared the time point at which each patient's maximum DESS/IDS score was reached in a paired Wilcoxon rank-sum test. Secondly, we fitted a quadratic regression to the DESS/IDS values over time and compared the maxima of these functions. A negative binomial link function was used, because both DESS and IDS scores represent zero-inflated count data and are non-normally distributed. The DESS and IDS values that were recorded before the discontinuation were used as baseline values with their time value set to 0. We repeated the analysis with a normal link function in a Bayesian and a frequentist framework.

Correlation of IDS and DESS scores

To test whether depressive symptoms are distinguishable from discontinuation symptoms, we analyzed whether DESS scores at a given time point (weeks 2 and 4) were more strongly associated with the IDS scores at the same timepoint or the DESS scores at the previous assessment. We fitted a linear regression with a negative binomial link function to the DESS scores at time point t with $IDS(t)$ or $DESS(t-1)$ as a predictor. For reasons of interpretability, the predictors were z-scored.

Association of medication and personal factors with ADS

We conducted linear regressions with a negative binomial link function in order to assess the association of medication and personal factors with discontinuation symptoms. Predefined predictor variables were tapering duration, drug half-life, treatment duration, dosage level, trait anxiety, sex, age of disease onset, and the interaction between tapering duration and drug half-life. For the estimation of severity by antidepressant class and type, we used a varying intercept model with partial pooling, where the intercept for each antidepressant was allowed to vary within each class. We used vaguely informative priors for all analyses. Antidepressant classes were defined as follows:

Selective serotonin reuptake inhibitors (SSRIs): Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, Vortioxetine

Serotonin and norepinephrine reuptake inhibitors (SNRIs): Duloxetine, Venlafaxine

Dopamine reuptake inhibitors (DNRI): Bupropion

Other: Agomelatine

To test a potential predictive value of the above-mentioned medication and patient characteristics regarding the severity of ADS, we conducted a multiple regression using Zurich as a training sample and Berlin as a hold-out sample for out-of-sample validation.

Influence of ADS on relapse risk

We examined the potential role of discontinuation symptoms as a stressor for relapse in a logistic regression. We hypothesized trait anxiety (STAI-T) to be a common cause of discontinuation symptoms and relapse. It was therefore included as a predictor in a multiple regression. Secondly, we conducted a univariate Cox proportional hazard (PH) regression relating DESS values to time-to-relapse with two distinct counting approaches. In model one, we selected 14 days after withdrawal as the time-origin from which patients were considered at risk of relapse, and DESS values were averaged across assessments conducted in the first 14 days (early DESS). In model two, we set 35 days after discontinuation as time-zero and used the mean DESS values of all measures during the first 35 days as the predictor (early and late DESS). Of note, we excluded individuals who dropped out or relapsed before time-origins from the analysis. To ensure relapse risk was related to discontinuation symptoms arising from antidepressant withdrawal and not due to trait anxiety, we incorporated pre- and post-discontinuation DESS scores, as well as STAI-T at baseline (BA) into the Cox regression models as predictors.

Relapse prediction

Lastly, we explored whether a clinically informative relapse prediction model could be derived from clinical characteristics. Using the Zurich sample as the training set, we fitted a logistic regression model with the averaged post-withdrawal DESS score, STAI-T, and their interaction as predictors. The model performance was evaluated using 10-fold cross-validation with 10 repetitions. We then examined the predictive power of the logistic model by using the Berlin data as an external validation set. Here, the logistic regression weights determined in the Zurich sample were used to predict the relapse status of Berlin patients.

Results

Sample description

103 patients were included in the study. 50 and 53 were randomized to the discontinuation (1W2) and continuation group (12W), respectively; 75 patients were in Zurich, 28 were in Berlin. Demographics and treatment characteristics were comparable across two study groups and sites (Table 1). 14 patients dropped out and 1 patient relapsed before any assessment after discontinuation and were excluded from all analyses. Among the included patients, 54 (65%) remained well and 29 (35%) relapsed (missing data for 5 patients). Supplementary table 1 shows the frequency of the 10 different antidepressants used and the respective percentage of patients not completing the discontinuation phase.

	Site	N	Missing	Mean	SD	Min	Max	P value
Age	Berlin	28	0	37.3	12.2	20	57	0.22
	Zurich	75	0	34.0	10.6	19	53	
No of episodes	Berlin	28	0	2.0	1.4	1	5	0.07

	Zurich	75	0	2.5	1.3	1	5	
Age of onset	Berlin	28	0	25.6	10.8	12	53	0.13
	Zurich	75	0	22.1	7.5	12	47	
IDS at baseline	Berlin	28	0	3.9	3.7	0	12	0.69
	Zurich	75	0	4.2	3.4	0	13	
Tapering duration (days)	Berlin	27	1	47.5	29.0	0	113	0.72
	Zurich	66	9	50.3	42.5	0	216	
Treatment duration (months)	Berlin	28	0	41.9	27.7	8	109	0.08
	Zurich	75	0	30.4	33.2	3	168	

Table 1. Demographic, clinical and medication related variables at baseline. P values refer to difference between Berlin and Zurich samples, to which patients were not randomized.

Incidence and profile of withdrawal symptoms

At MA2, 50% of patients in the discontinuation group and 21% in the control group fulfilled the criteria for an antidepressant discontinuation syndrome, as defined by 4 or more symptoms on the DESS scale (estimated incidence rate 29% (95% PI [8.3%, 72%])). Patients who had discontinued experienced more symptoms than those on continued treatment (5.1 vs. 2.0. Mean difference (MD) = 3.12, 95% PI [1.06, 6.70], Cohen's d = 0.67. Figure 1). The increase was more pronounced for psychological (2.2 vs. 0.7. MD = 1.62, 95% PI [0.45, 3.88], d = 0.74) than for somatic symptoms (2.9 vs. 1.3. MD = 1.33, 95% PI [0.14, 3.45], d = 0.52), although somatic and psychological DESS symptoms were strongly correlated (Pearson's r = 0.73, p = 2.6*10⁻⁸). IDS scores increased by roughly 3 points in response to antidepressant discontinuation (7.6 vs 4.6. MD = 3.06, 95% PI [1.12, 5.75], d = 0.64).

In the discontinuation group, the assessment was conducted at an average of 18 days (range 5 to 42 days) after discontinuation. Earlier assessments were associated with more symptoms (Mean for factor time (days) = 0.95, 95% PI [0.92, 0.98]). We did not detect an influence of baseline DESS scores on DESS points after withdrawal (group-by-baseline interaction). All differences were estimated in a linear regression with correction for baseline.

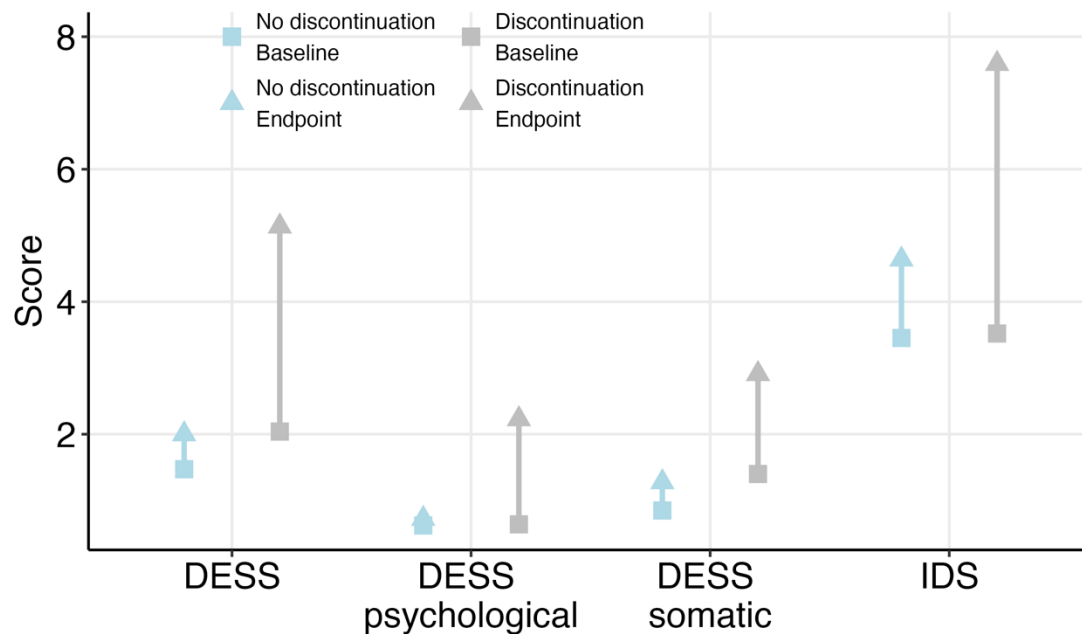


Figure 1. Baseline and endpoint means of total, psychological, somatic DESS symptoms and IDS. Baseline = main assessment 1, endpoint = main assessment 2. Discontinuation = group 1W2. No discontinuation = group 12W.

Discontinuation symptoms were primarily reported by women (Mean difference (MD) = 3.84, 95% PI [1.26, 8.59]), while there was no discernable difference between the two groups in men (MD = 0.20, 95% PI [-0.95, 3.80]).

The most frequently reported symptoms were dizziness (31.8 vs 4.3%) and irritability (38.6 vs 12.8%). Ten symptoms were only seen in the discontinuation group, nine of which were physical. 20.5% of patients in the discontinuation group had at least one specific symptom. Supplementary table 2 shows the incidence rates for each of the 43 DESS symptoms.

Withdrawal symptoms rise earlier than depressive symptoms

Maximum DESS scores were reached earlier than maximum IDS scores after discontinuation (days 15.85 (SD=13.54) versus 21.41 (SD=14.04). Paired Wilcoxon rank-sum test: mean difference = - 5.6 days, Z=-3.5, p=0.001). Fitting a quadratic function to the time course of DESS and IDS scores yielded maximum DESS scores at day 21.3 versus day 28.2 days for IDS scores (figure 2). Using a normal outcome distribution with both frequentist and Bayesian estimation yielded similar results.

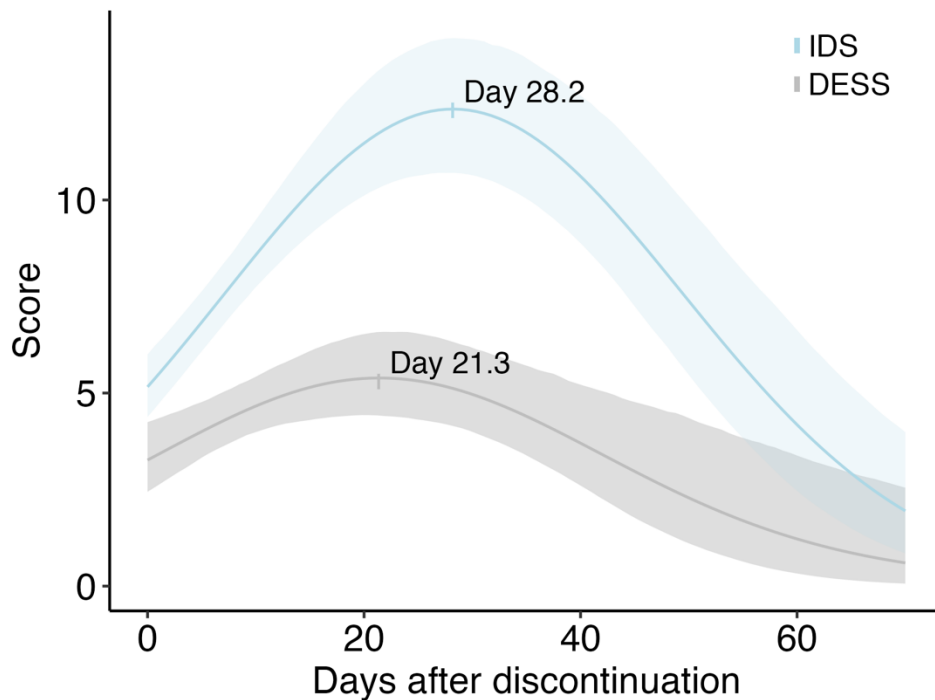


Figure 2. Temporal distributions of DESS and IDS: Lines represent the quadratic fits with a negative binomial link function; marking ticks represent time values (x-axis) corresponding to maximum instrument scores (y-axis). Shaded areas indicate 95% posterior intervals of means.

IDS and DESS are strongly correlated

In line with the notion that withdrawal and depressive symptoms overlap, DESS scores at a particular time point (week 1 or 2) did not systematically predict DESS scores at the following assessment better than IDS scores (Supplementary figure 3). Using only somatic symptoms of the DESS scale yielded similar results. Conversely, IDS and DESS scores were strongly correlated at weeks 1, 2 and 4 (Coefficient of correlation = 0.74, 0.66 and 0.61, respectively).

Clinical and medication factors associated with discontinuation symptoms

The association of patient and medication characteristics with the number of reported DESS symptoms was investigated. Note, that the following analyses include all patients and hence lack a control condition. Univariate regression suggested that female patients reported 1.67 (95% interval [1.06, 2.56]) times as many symptoms on the DESS as males in the 3 post-withdrawal assessments. The mean number of total new or worsened symptoms was 17.3 for females and 10.4 for males. This relationship remained unchanged when including anxiety (STAI-T score) and its interaction as predictors (Supplementary figure 4). None of the other predefined predictors showed a clear relationship with the number of DESS symptoms after withdrawal (Table 2). Of note, slower discontinuation was not associated with fewer discontinuation symptoms (1.10, 95% PI [0.98, 1.27]).

	Slope	95% Interval
Tapering duration (months)	1.10	[0.98, 1.27]
Drug half-life (days)	1.07	[0.90, 1.30]
Duration of treatment (years)	1.00	[0.94, 1.08]
Medication load (z-score)	1.00	[0.85, 1.29]
Age of illness onset (decades)	0.68	[0.12, 4.67]
Sex (female)	1.67	[1.06, 2.56]
STAI-T (z-score)	1.09	[0.92, 1.31]

Table 2. Posterior mean and 95% intervals for univariate regressions with different predictors. Total number of DESS symptoms (sum of weeks 1, 2 and 4) as outcome with negative-binomial link function. Coefficients are multiplicative, meaning for each unit increase in predictor value, the outcome is multiplied by the factor slope. Sensitivity analyses were conducted. Using the average DESS scores after discontinuation and a normal link function yielded similar results (supplementary table 3).

Type of antidepressant and discontinuation symptoms

The estimated mean number of discontinuation symptoms was higher for SSRIs (16.0 (95% PI [12.6, 19.9])) and SNRIs (15.7 (95% PI [10.9, 22.5])) than for Bupropion (12.7 (95% PI [4.8, 31.7])) and Agomelatine (11.5 (95% PI [2.3, 42.0])). Due to the small sample sizes for Agomelatine (n = 1) and Bupropion (n = 4), no meaningful statistical inferences could be drawn. Figure 3 shows the posterior intervals and total DESS symptoms for each antidepressant class. Supplementary figure 5 shows the estimated number of DESS symptoms for each individual SSRI.

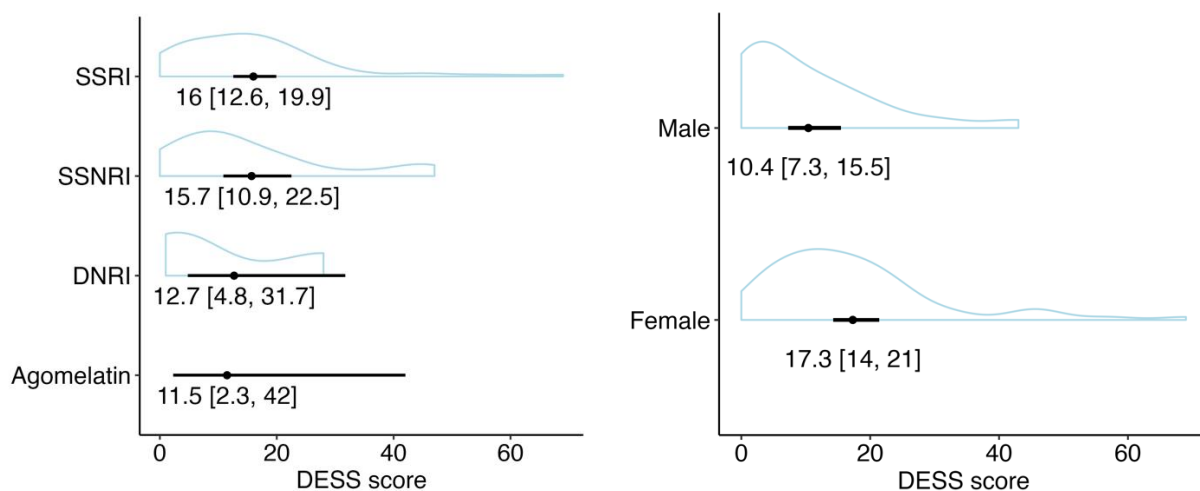


Figure 3. Violin plots showing frequencies of total number of DESS symptoms after AD discontinuation. Posterior means and 95% intervals (Black dots and lines) were estimated in a negative-binomial regression with partial pooling. Missing values were imputed using last-observation-carried-forward (LOCF).

Prediction of ADS severity

We investigated whether medication- or patient-related factors have a predictive value regarding the severity of antidepressant withdrawal syndrome. To this end, the Zurich sample was used for model fitting, while the independent Berlin sample served as a validation set. Neither medication- nor patient-related factors showed predictive information regarding ADS severity. Using all hypothesized relevant factors as predictors, the mean absolute error (MAE) of predicted and observed DESS scores was 15.38, while the mean absolute deviation from the Berlin sample mean was 10.55 (supplementary figure 7). Using only medication- or patient-related factors did not produce better results.

Association of ADS with relapse of depression

DESS scores, IDS scores and trait anxiety were positively associated with relapse risk, while no such association was detected for patient sex. Including STAI-T, as well as the interaction of DESS and STAI-T as predictors did not change the positive association of DESS scores and relapse risk. This analysis was conducted to control for potential confounding, as we hypothesized that high DESS scores and relapse risk might be a common consequence of STAI-T.

We conducted best-worst, as well as multiple random imputations to account for missing data regarding relapse status. 32, 66 and 100% of intervals were credibly greater 0 for STAI-T, DESS and IDS, respectively (supplementary tables 5 and 6).

	Coefficient	Risk difference (%)	Multiple regression	
Sex	-0.07 [-1.09, 0.98]	- 0.2 [-17.8, 20.3]	DESS (average)	0.60 [0.08, 1.25]
IDS (average)	0.63 [0.16, 1.17]	15.2 [3.8, 28.3]	STAI-T	0.41 [-0.07, 0.94]
DESS (average)	0.58 [0.07, 1.16]	13.9 [1.7, 28.1]	Interaction	-0.37 [-0.91, 0.14]
DESS (< 14 days)	0.50 [-0.06, 1.14]	12.4 [-1.4, 27.7]		
DESS (day 15-30)	0.45 [-0.03, 0.99]	11.2 [-0.8, 24.2]		
DESS (somatic symptoms only)	0.48 [0.01, 1.01]	11.6 [0.2, 24.8]		
STAI-T	0.42 [-0.01, 0.90]	10.1 [-0.2, 21.9]		

Table 3. Posterior estimates for univariate and multiple logistic regressions for various predictors. Predictors were z-scored for better interpretability. Complete case analysis. Risk difference refers to the absolute increase in relapse risk for 1 unit (SD) increase in predictor value. In the case of sex: female = 0, male = 1. Brackets represent 95% posterior intervals. Average scores are mean of three post withdrawal assessments (weeks 1,2 and 4).

Modelling relapse in a proportional hazards model yielded similar results (table 4). Both DESS and IDS had a statistically significant influence on the hazard rate. Removing all patients relapsing within 30 days did not change the results (IDS: 1.44 [1.08, 1.95]). We visualized the effect of discontinuation symptoms and early depressive symptoms on relapse risk using Kaplan-Meier curves. Patients were stratified by median-split.

	HR (95% Interval)	p-value	FDR p-value
Average DESS	1.35 [1.03, 1.78]	0.032	0.07
DESS (< 14 days)	1.25 [0.87, 1.79]	0.22	0.28
DESS (day 15-30)	1.36 [1.01, 1.89]	0.046	0.08
Average IDS	1.49 [1.12, 1.98]	0.006	0.03
IDS (< 14 days)	1.66 [1.18, 2.32]	0.0037	0.02
IDS (days 15-30)	1.53 [1.15, 2.05]	0.0037	0.02
Sex	1.09 [0.46, 2.54]	0.85	0.92
STAI-T	1.31 [0.96, 1.80]	0.087	0.15
Age of depression onset	1.19 [0.87, 1.62]	0.28	0.33

Table 4. Results of univariate cox regression. Predictors were z-scored for better interpretability. Hazard ratio signifies change in relapse risk for each SD increase in predictor value.

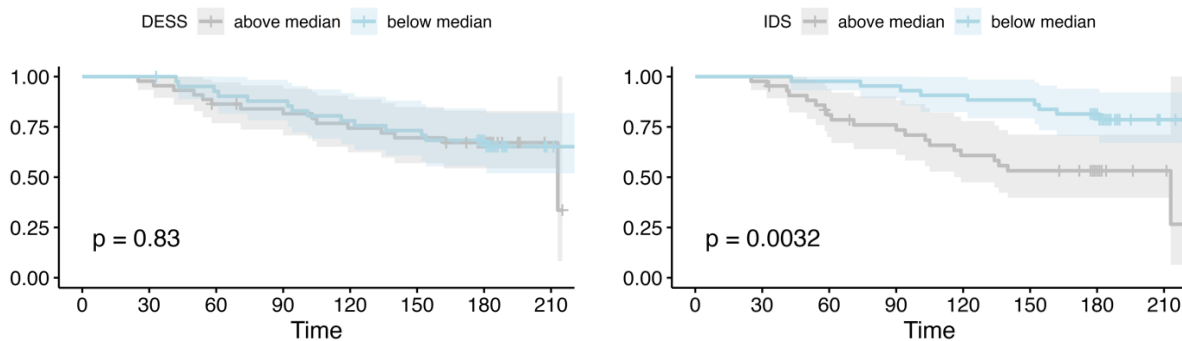


Figure 4. Kaplan-Meier estimates for relapse of a depressive episode. Univariate analysis with post-discontinuation average scores of DESS (a) and IDS (b) as predictors. Strata were generated via median-split.

Relapse prediction analysis

We used a multiple regression model with predefined predictor variables to assess the possibility of predicting relapse after withdrawal. With repeated cross-validation, in which resampling occurs with each iteration, the multiple logistic regression model correctly classified 521 out of 830 resampled observations (balanced accuracy = 0.52). Specifically, 48 out of 290 relapsed and 437 out of 540 non-relapsed observations were correctly predicted (sensitivity = 0.17, specificity = 0.88). The area under the ROC curve (AUC) was 0.6, not suggestive of an acceptable performance. The logistic model where regression coefficients were estimated using all 59 patients from Zurich correctly predicted the relapse-state of 15 (out of 24) patients in Berlin with a balanced accuracy of 0.56 and an AUC of 0.67. The model correctly classified 1 out of 9 relapsed (sensitivity = 0.11) and 14 out of 15 non-relapsed patients (specificity = 0.93).

Discussion

Early detection and differential diagnosis of discontinuation symptoms and depression relapse after antidepressant discontinuation is crucial. While a wait-and-see approach or symptomatic treatment and adjustment of tapering speed is appropriate for the former, diagnosis of relapse may require recommencement of antidepressant medication (Henssler et al., 2019).

In this study, 103 patients predominately using SSRI and SNRI gradually withdrew over an average of 50 days, reporting comparable rates of ADS to previous reviews (Fava et al., 2015; Fava et al., 2018; Jha et al., 2018). While patients in the withdrawal group experienced significantly more symptoms than those on continued medication during the randomized phase, increases in total DESS scores were not specific to antidepressant discontinuation. The fact that one fifth of patients on continued medication fulfilled the symptom-level criteria of an ADS suggests the current ADS definitions may be too lenient.

The increase in psychiatric symptoms was more pronounced than that for somatic symptoms, representing the commonness of affective discontinuation symptoms. For instance, in the RCT by Rosenbaum et al. (1998), the first three most prevalent withdrawal signs were psychological: worsened mood, irritability, and agitation. Nevertheless, it cannot be ruled out that the affective symptoms are early signs of a depressive episode. Indeed, early increases of IDS scores (as early as within 2 weeks) after withdrawal were associated with future diagnosis of a depressive episode.

However, the correlation of somatic DESS items with depressive symptoms suggests that a fraction of affective symptoms might originate from the same pharmacological effect following drug cessation. These affective discontinuation symptoms might be misinterpreted as a relapse of depression in some patients. Rating scales such as the IDS and DESS should therefore be applied with caution, as they cannot reliably distinguish between discontinuation symptoms, rebound depression and relapse.

Our results indicate that discontinuation symptoms rise earlier than depressive symptoms and that some physical symptoms, such as incoordination, blurred vision and shaking, are specific to discontinuation. Differential diagnosis should thus involve the time course, as well as the occurrence of specific symptoms rather than total symptom scores.

Factors associated with ADS severity

We did not replicate the association between treatment duration, tapering duration or antidepressant plasma half-life and discontinuation-emergent events (Horowitz & Taylor, 2019; Renoir, 2013). Longer tapering duration tended to be associated with more, rather than fewer, discontinuation-emergent events. This could be due to reverse causation, where more symptoms might have led to slower tapering.

Alternatively, an influence of tapering duration on ADS severity might be detected only with much longer tapering periods that did not occur in this study (Horowitz & Taylor, 2019). Randomized controlled trials are needed to investigate the influence of tapering speed on discontinuation symptoms. To date, trials comparing different tapering speeds in a randomized fashion are lacking.

SSRI and SNRI tended to be associated with more severe ADS than bupropion and agomelatine. Due to the small sample sizes of the latter two, we were not able to accurately assess these differences. However, the drop-out rates differed between antidepressants. Patients may have dropped out because of more severe symptoms thereby reducing apparent differences between medications.

We found evidence indicating that women experience more withdrawal symptoms than men, in line with previous publications (Lincoln et al., 2021). In fact, no discernible difference in DESS scores between discontinuation and continuation group was found for men. More studies are needed before drawing firm conclusions.

Association of discontinuation symptoms and trait anxiety on relapse risk

Elevation of stress-related hormones was shown during the antidepressant interruption, and ADS was coupled with bio-behavioural stress-responses (Berwian et al., 2017; Harvey & Slabbert, 2014b; Michelson et al., 2000a). These could predispose patients to experiencing relapse. Our results suggest that discontinuation symptoms might be associated with a higher relapse risk. This association persisted after correcting for trait anxiety. While a causal relationship might seem plausible, randomized controlled trials would be required to investigate whether mitigating withdrawal symptoms, e.g. by slower tapering, reduces this elevated relapse risk. Patients with higher trait anxiety showed an increased relapse risk after discontinuation. This accords with existing evidence that individuals with co-morbid anxiety disorders have higher relapse rates, including after antidepressant discontinuation (Joliat et al., 2004; Wilhelm et al., 1999). These could predispose patients to experiencing relapse. We did not find evidence for withdrawal symptoms as a stressor in predisposed (high STAI-T scores) individuals, as we did not detect an interaction effect of these variables. The strongest association with future relapse was found for early depressive symptoms. While this could merely represent early detection of depressive relapse, rebound depressiveness due to antidepressant discontinuation might be partly responsible for this association.

Strength and limitation

A major strength of this study is the use of individualized tapering regimens. This allowed for the investigation of discontinuation symptoms in a real-world setting. Secondly, discontinuation symptoms were assessed over a course of 4 weeks after discontinuation, which covers the time needed for most antidepressants to be eliminated from the body [which ranges from 1 day (venlafaxine) to 25 days (fluoxetine)]. Studies assessing discontinuation symptoms too early after the discontinuation might underestimate symptom severity for antidepressants with longer half-

lives, as discontinuation symptoms typically emerge after 90% of the drug has been cleared (Glenmullen, 2006; Harvard Health Publishing, 2020).

We would like to touch on several limitations of our study. Due to the open label design of the trial, we cannot rule out that placebo effects or inflation due to biased reporting affected the number of discontinuation-related symptoms. We could not develop an accurate and clinically useful prediction model, which might be due to the small sample size and small number of predictor variables in this study (Patel et al., 2016). Furthermore, differences between different antidepressants could not be established.

Future directions and clinical implications

The substantial correlation between discontinuation and depressive symptoms points to the potential of misinterpreting discontinuation symptoms as depression relapse in clinical settings and vice versa. The relatively high incidence of discontinuation symptoms in the non-discontinuation group suggests a less lenient approach to discontinuation symptoms in general. Focusing on more distinctive physical and somatic dimensions of discontinuation symptoms and their time course might improve the diagnostic precision. In future research, factor analysis with a large sample size should be applied to identify specific symptom clusters and trajectories.

Randomized controlled trials should investigate whether slower tapering can mitigate the increased relapse rate via reduction of discontinuation symptoms. Importantly, patients should be informed of the possibility of discontinuation-emergent events before initiation of treatment with antidepressants. Lastly, our finding suggests that trait anxiety may be a risk factor for depression relapse after antidepressant discontinuation. Treatments such as cognitive behavioral therapy and mindfulness-based cognitive therapy have shown effectiveness in managing trait anxiety (Ninomiya et al., 2020; Salzer et al., 2011), and may be relevant in this setting.

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Author contributions

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Funding acquisition: HW and QJMH

Statistical analyses: CV and SA, with supervision by QJMH and HW.

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