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| Keywords:        | antidepressants, anxiety disorders, guidelines, meta-analysis, relapse |
Appendix 1. Search strategy Pubmed.


This search strategy has been translated for additional searches in both Embase and Cochrane.
Appendix 4. Funnel plot proportion of relapse

[Image: Funnel Plot of Standard Error by Log odds ratio]

Log odds ratio

Standard Error
Appendix 5. Funnel plot time to relapse
Risk of relapse following antidepressant discontinuation in anxiety disorders, OCD and PTSD.

A systematic review and meta-analysis of relapse prevention trials

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ABSTRACT

OBJECTIVE To examine the risk of relapse and time to relapse following discontinuation of antidepressants in anxiety disorder patients who responded to antidepressants. Exploratory subgroup and meta-regression analyses examine whether risk of relapse might be related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of concurrent psychotherapy.

DESIGN Systematic review and meta-analyses of relapse prevention trials

DATA SOURCES PubMed, Cochrane, Embase and clinical trial registers (from inception to 7-2016).

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Studies including anxiety disorder patients who responded to antidepressants, that randomized patients to either continuing antidepressants or switching to placebo in a double-blind fashion, and that compared relapse rates or time to relapse.

DATA EXTRACTION Two independent raters selected studies and extracted data. Random effect models were used to estimate odds ratios (ORs) for relapse and hazard ratios (HRs) for time to relapse. Subgroup analyses and meta-regression analyses were conducted to assess the impact of various categorical and continuous variables respectively.

RESULTS Twenty-eight studies examining relapse were meta-analyzed (n=5233). Discontinuation increased the odds of relapse compared to continuing antidepressants (summary OR=3.11, 95%CI 2.48 to 3.89, n=28 studies). None of the subgroup analyses and meta-regression analyses showed significance. Drop-out was higher in the placebo-group (summary OR=1.31, 95%CI 1.06 to 1.63, n=27 studies). Eleven studies examined time to relapse (n=3002), which was shorter when discontinuing antidepressants (summary HR=3.63, 95%CI 2.58 to 5.10, n=11 studies).

CONCLUSIONS Given chronic course trajectories of anxiety disorders, long-term considerations should direct treatment. Antidepressants optimize the prognosis of anxiety disorders by preventing relapse up till a period of one year. The lack of evidence after this period should not be interpreted as an explicit advice to discontinue antidepressants after one year. Patients and doctors should discuss which treatment policy seems best at long-term.
INTRODUCTION

In anxiety disorders, chronic course trajectories\(^1\) and relapses following remission\(^2\) are common. Consequently, when combined with high prevalence rates\(^3\) and functional limitations,\(^4\) anxiety disorders score high on burden of disease rankings.\(^5\) Optimizing the long-term prognosis, including prevention of relapse,\(^6\) is an important strategy to decrease the anxiety-related burden of disease.

In addition to cognitive behavioral therapy, antidepressants are a first-line option for the treatment of anxiety disorders,\(^7\) since antidepressants are effective\(^8\) and generally well tolerated.\(^9\) The majority (57%) of patients with anxiety disorders who are being treated use medication.\(^10\) As long-term studies are scarce, it remains largely unknown whether antidepressants should be regarded a first-line treatment option for optimizing long-term prognosis too. International guidelines are therefore consensus-based and advise continuation treatment of variable duration (6-24 months) and subsequent tapering of the antidepressant (for an overview, see\(^11\)). In contrast to the guidelines’ advice, long-term use is increasing, with nearly half of the patients in the United Kingdom and approximately two-thirds of patients in the United States continuing antidepressants for at least two years.\(^12\) It remains unclear whether clinicians are unnecessarily medicalizing their patients or whether guidelines are too optimistic by advising to discontinue antidepressants after sustained remission. This discrepancy calls for clarity regarding long-term use of antidepressants: is it wise to discontinue antidepressants?

A previous meta-analysis, including studies up till 2008, reported that relapse occurred in 26-45% of anxiety disorder patients who discontinued antidepressants.\(^13\) Continuing antidepressants appeared effective to prevent relapse, with protective summary odds ratios ranging from 0.20-0.38 in various anxiety disorders.\(^14\) Superiority of antidepressants vs. placebo was also shown regarding quality of life.\(^15\)

Information on whether specific treatment- or discontinuation strategies influence relapse risk is scant and inconclusive. For example, whereas some studies reported fewer relapses when antidepressants are discontinued after sustained use,\(^16\) other studies reported that relapses also occur frequently when antidepressants are stopped after a prolonged period of use.\(^17\) Likewise, it is unknown whether relapse risk depends on the type of antidepressant, the mode of discontinuation (abrupt vs. tapered), the duration of follow-up, allowing concomitant psychotherapy, and whether comorbidity affects relapse risk after discontinuation of antidepressants.

This meta-analysis aims to verify, update and extend current knowledge. We meta-analyzed relapse prevention trials that included anxiety disorder patients who responded to antidepressants, randomized these patients to either continuing the antidepressant or switching to placebo in a double-blind fashion, and compared relapse rates or time to relapse between these groups. Additionally, we explored whether this relapse risk is related to the type of anxiety disorder, type of antidepressant,
mode of discontinuation, duration of prior treatment, duration of follow-up, whether studies allowed concurrent psychotherapy or not, whether studies excluded comorbidity or not, and involvement of pharmaceutical companies. Finally, we briefly report on tolerability issues, given the importance for daily clinical practice.
METHODS AND MATERIALS

Literature search
PubMed, Cochrane and Embase (from inception to July 2016) were searched for studies including anxiety disorder patients who responded to antidepressants, that subsequently randomized patients to either continuing the antidepressant or switching to placebo, and that compared (time to) relapse between these groups. The search was performed by a librarian and NB using (combinations of) free text and keywords indicating anxiety disorders, antidepressants, discontinuation and randomized controlled trials (Appendix 1 provides search terms used). Language was unrestricted. This search was extended by scanning reference lists of relevant papers and searching trial registers including ClinicalTrials.gov, World Health Organization, Cochrane trials, GlaxoSmithKline, Roche, Novartis, and Astrazeneca.

Study selection criteria consisted of: 1) Studies focused on patients with panic disorder (PD); agoraphobia (AG); social phobia (SP); generalized anxiety disorder (GAD); obsessive-compulsive disorder (OCD); post-traumatic stress disorder (PTSD); or specific phobia (SpP). Comorbidity was allowed. 2) Patients were classified as responder after treatment with antidepressants. Studies focusing on pharmacotherapy while allowing concomitant psychotherapy were included. 3) A double-blind placebo-controlled design was used, randomizing patients to long-term use of antidepressants (antidepressant-group) or switching to placebo (placebo-group). 4) Relapse and/or time to relapse were assessed after a follow-up period. 5) Articles not presenting original data or consisting of abstracts only were excluded. We used the definitions of response and relapse as used in the original studies.

Study selection was conducted in accordance with the PRISMA guidelines. Firstly, two independent raters (NB and WS) assessed titles and abstracts for eligibility. Secondly, the method sections of the selected articles were assessed by two independent raters (NB and RB), who resolved disagreements via discussion.

Data extraction
From each study, NB and RB independently extracted the following aspects for the active treatment phase: the anxiety disorder, inclusion and exclusion criteria, the type and dosage of antidepressant, the sample size, duration of treatment, definition of response, and proportion of responders. For the follow-up phase we extracted the following variables: sample size, age, duration of follow-up, definition of relapse, proportion of and time to relapse per treatment arm, corresponding statistics, mode of discontinuation (tapering vs. abrupt), drop-outs, tolerability, and withdrawal symptoms. Discrepancies were resolved by referral to the data of the original article. For each study, the odds ratio (OR), indicating the odds of relapse in the placebo group relative to the odds of relapse in the antidepressant group, was based on the number of relapses per group and the total number of patients per group. This information was also used to calculate the corresponding confidence intervals. For time to relapse, we used the hazard ratio and its corresponding confidence interval as reported by the
Quality assessment and publication bias

To assess the quality of the studies, studies were scored independently by KH and RB using the Cochrane Collaboration tool for assessing risk of bias.30 Studies were scored ‘low risk’, ‘high risk’ or ‘unclear’ on the following domains: random sequence generation and allocation concealment (selection bias); blinding of patients and providers (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias) (Appendix 2). Because the blinding of patients may be breached by the experience of withdrawal symptoms, the risk of bias was considered high when antidepressants were discontinued abruptly, unless it was reported that adverse events following randomisation did not differ between groups. Attrition bias was considered high when 15% or more of the total number of patients dropped out during follow-up. Consensus on the ratings was reached through discussion. A summary score was computed summing the number of items scoring ‘high’ and included in a meta-regression analysis as the variable ‘quality’.

To assess publication bias, funnel plots were created and Duval and Tweedie’s trim and fill29 procedure was used to provide an estimate of the odds ratios (ORs) and hazard ratios (HRs). Importantly, funnel plot asymmetry can result from (a combination of) publication or other selection biases, poor methodological quality in small studies, but may also be due true heterogeneity, artefacts, and chance.31,32 Additionally, as the Duval & Tweedie trim and fill method relies on the assumption that publication bias is the only reason for funnel plot asymmetry,31 results should be interpreted with caution.

Meta-analysis

A random effects meta-analysis (DerSimonian-Laird [DL] method) was performed to summarize the difference in ‘proportion of relapse’ between antidepressants and placebo. ORs and corresponding 95% confidence intervals (ORs; 95%CI) were used to summarize data. Although the DL-method is widely used, this method tends to provide CI’s which are too narrow, thus resulting in inappropriate numbers of type I errors. To overcome this, reported confidence intervals are adjusted by means of the Hartung-Knapp-Sidik-Jonkman (HKSJ) method.33-35 P-values for the random-effects subgroup analyses are based on the Q-test for heterogeneity using the HKSJ-adjusted variance per subgroup.33-36 Meta-analysis was based on ITT samples and, if not available,37,38 on responder samples.

Subgroup analyses were defined a priori and conducted on the following categorical variables: type of anxiety disorder according to DSM-IV (GAD; SP; PD; OCD; PTSD); with a separate analysis on anxiety disorders according to DSM-5 (which excludes OCD and PTSD); type of antidepressant (SSRI; SNRI; other); mode of discontinuation (abrupt; taper or fluoxetine (which tapers by itself)); concurrent psychotherapy allowed (no/yes); whether (most) comorbidity was excluded (no/yes); and involvement of pharmaceutical companies. Meta-regression analysis (method of moments) was used to estimate the influence of the year of publication, the quality of individual studies, the duration of
treatment, and the duration of follow-up on the outcomes of studies.

In a separate random effects meta-analysis, we examined the ‘time to relapse’. HRs and corresponding 95% confidence intervals (HRs; 95%CI) were used to summarize these data, with HRs reflecting the hazard rate of time to relapse in the placebo-group divided by the hazard rate of time to relapse in the antidepressant-group.

We used random effect models for the meta-analyses because we expected heterogeneity across studies. The Q statistic and $I^2$ were reported as measures for heterogeneity between studies. $I^2$ reflects observed heterogeneity in percentages, with 0% indicating no heterogeneity and 25%, 50% and 75% considered as a low, medium and high level of heterogeneity respectively. Forest plots were produced to visualize summary ORs, summary HRs and their corresponding CIs. Analyses were conducted using the software package Comprehensive Meta Analysis, version 3.3.070.

Number Needed to Treat

The number needed to treat to prevent one relapse provides insight into the clinical relevance of the outcome. It refers to the number of patients that would need to be on continuation treatment with antidepressants instead of discontinuing antidepressants to prevent one additional relapse. Thus, the lower the NNT, the better. In general, a NNT below 10 is regarded acceptable. The NNT-value is based on $1/(\text{proportion of relapse in the placebo group} - \text{proportion or relapse in the antidepressant group})$ and rounded up to the next whole number. For calculations of the confidence intervals, we refer to.

Patient involvement

The Dutch patient association for anxiety disorders (angst, dwang en fobiestichting, www.adfstichting.nl) frequently receives questions regarding medication policies after the acute phase, and therefore welcomes the present meta-analysis. They will inform patients about the results. Because the study at hand is a meta-analysis, no patients were involved in the design. No patient involvement was reported in original studies.
RESULTS

Flowchart
The literature search resulted in 2934 records. Of these, 50 full-text articles were assessed for eligibility and a total of 24 were included (Figure 1). Six unpublished studies were identified via hand-searching and by searching clinical trials registers. Of these, two could not be included due to missing data, as data were not provided upon request. One of the articles with missing data concerned a negative study, conducted by Hackett et al, 2000 described by, the other is registered on clinicaltrials.gov (identifier: NCT00215137 by Wang, Davidson, Connor, Li, and Zhang), results are not described. The remaining four unpublished studies were included, all were conducted by GlaxoSmithKline. This resulted in a total of 28 studies meeting inclusion criteria for proportion of relapse. Eleven of these also reported on time to relapse. Data about the corresponding 95% CI of the HRs was incomplete in two studies and not provided by the authors upon request, therefore estimations of the 95% CI were based on methods described by.

Insert Figure 1 here

Characteristics of population
The 28 included studies examining relapse were published between 1995 and 2012 (Appendix 3). Sample sizes of the relapse prevention phase ranged from n=15 to n=561, resulting in n=2625 patients in the antidepressant-group and n=2608 patients in the placebo-group (total n=5233). Six studies focused on PD, five on SP, six on GAD, seven on OCD and four on PTSD. Between studies, the duration of the treatment ranged from eight to 52 weeks, as did the duration of follow-up. Two studies had a variable duration of follow-up of 24-76 and 24-56 weeks respectively. Because in these two studies all patients had an assessment at 24 weeks, we used data at 24 weeks as outcome for these studies. The second meta-analysis examining time to relapse was based on eleven studies with n=1511 patients in the antidepressant-group and n=1491 patients in the placebo-group (total n=3002).

Proportion of relapse
The summary OR of relapse was 3.11 (95%CI 2.48 to 3.89, n=28 studies) for patients in the placebo-group (36.4% relapsed) relative to patients in the antidepressant-group (16.4% relapsed) (Table 1; Figure 2), indicating that more patients relapsed after discontinuation of antidepressants than when antidepressants were continued. The Q statistics provided no indications for significant dispersion across studies (Q=29.37, df=27, p=0.34). Based on , 8.07% of the total variance was related to true heterogeneity between studies. Inspection of the funnel plot (Appendix 4) seems to show some asymmetry, which could indicate small study effects. The Duval & Tweedie trim and fill procedure suggested little change regarding the OR after adjustment (summary OR adjusted =2.98, 95%CI 2.39 to 3.72, n=28 studies).
Insert Table 1 and Figure 2 here

Legend Table 1:
Abbreviations: GAD = Generalised Anxiety Disorder; OCD = Obsessive-Compulsive Disorder; PD = Panic Disorder with or without agoraphobia; PTSD = Post-Traumatic Stress Disorder; SP = Social Phobia; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Selective Serotonin and Noradrenalin Reuptake Inhibitor. All confidence intervals are Hartung-Knapp-Sidik-Jonkman adjusted.

Subgroup analyses and meta-regression analyses
Several exploratory subgroup analyses were performed (Table 1). In line with the indications of limited heterogeneity across studies by Q and $I^2$, type of anxiety disorder, type of antidepressant, mode of discontinuation, allowing concurrent psychotherapy, and the exclusion of comorbidity did not critically influence the OR of relapse. Likewise, outcomes seemed unrelated to year of publication ($p=0.25$), quality of the studies based on GRADE method ($p=0.44$), duration of treatment ($p=0.95$), or duration of follow-up ($p=0.24$). Although planned, no subgroup analysis on the involvement of pharmaceutical companies was conducted, as these were involved in all but two small studies.

Time to relapse
Analysis showed that antidepressant discontinuation resulted in a shorter time to relapse in the placebo group compared to the antidepressant group (summary HR=3.63, 95%CI 2.58 to 5.10, n=11 studies) (Figure 3). The Q statistic provided no indications of significant dispersion across studies ($Q=9.85$, df=10, $p=0.45$). Further, $I^2$ is set to zero as the number of degrees of freedom is higher than the value of Q. Due to the limited number of studies, no subgroup analyses or meta-regression analyses were conducted. Based on the funnel plot, there appeared to be little indication of small study effects, though the small number of studies precluded a firm conclusion (Appendix 5).

Tolerability and withdrawal symptoms
Most studies reported to some extent on adverse events during follow-up and concluded that antidepressants were well tolerated over time. Drop-outs (excluding those for lack of efficacy) were 17.2% in the antidepressant-group vs. 21.9% in the placebo-group (summary OR=1.31, 95%CI 1.06 to 1.63) (based on n=27 studies). This could possibly be due to withdrawal symptoms in the placebo-group. However, four studies, which specifically reported on withdrawal symptoms, stated that there were generally no differences between groups, thereby suggesting that adverse effects of antidepressants in the antidepressant-group and withdrawal symptoms in the placebo-group were balanced. Alternatively, the higher drop-out rates in the placebo-group might be a masked effect of lack of efficacy. A 'lack of efficacy' can be interpreted as a (partial or beginning) relapse because all patients were classified as responder prior to randomization. If those who discontinue antidepressants drop out of treatment more frequently because of lack of efficacy, this would only strengthen our conclusion that those who discontinue antidepressants run a higher risk for relapse.
Number needed to treat

Based on the proportions of relapse in the placebo-group (0.364) and in the antidepressant-group (0.164), the number needed to treat to prevent one relapse is 5 (based on: 1/(0.364-0.164)=4.98 and rounded to the next whole number) with a corresponding 95% CI of 5 to 6 (unrounded: 4.46 to 5.64).
DISCUSSION

Main Findings
Optimizing the long-term prognosis should be an overriding priority when treating patients with anxiety disorders because relapse and chronicity are common. This meta-analysis examined the risk of relapse when discontinuing antidepressants in anxiety disorder patients who responded to antidepressant treatment. Based on many randomized controlled trials of high quality, a clear benefit of continuing medication compared to discontinuation was shown for both relapse and time to relapse (summary OR=3.11 (95%CI 2.48 to 3.89, n=28 studies); summary HR=3.63 (95%CI 2.58 to 5.10, n=11 studies)). Five patients need to be treated to prevent one relapse. None of the subgroup analyses nor meta-regression analyses were significant.

It should be noted that certain aspects of the study population and design may have affected outcome in either or both conditions.
First, we have presented ORs to measure the magnitude of the effect of antidepressant discontinuation on the risk of relapse. Because the event under study (i.e. relapse) is fairly common, the odds ratio may overestimate the risk ratio. To avoid overestimating results, we also summarized the relative risks for relapse. Indeed, the summary relative risk was 2.21 (95% CI 1.85 to 2.64), which is lower than the OR (3.11; 95%CI 2.48 to 3.89).
Second, most studies in this meta-analysis excluded comorbidity to some extent. Given that comorbidity in anxiety disorders is common and associated with chronicity, 1 relapse rates in clinical practice are presumably higher. In our subgroup analysis no impact of comorbidity on relapse rates was found. However, in their randomized controlled trial, Geller and colleagues 56 found that comorbidity primarily increased relapse rates in the placebo group; e.g. in the placebo group relapse was 33% in those without comorbid disorders, and 55% and 77% for those with one or more, and two or more disorders respectively. Gellers findings suggest that the benefits of continuing medication are greater for patients with comorbidity compared to patients without comorbidity.
Third, relapse was 36.4% vs. 16.4% in the placebo-group and antidepressant-group respectively. Falsely interpreting withdrawal symptoms in the placebo-group as relapse would overestimate the protective effect of continuing antidepressants. However, it seems unlikely that the higher relapse rate in the placebo group is attributable to withdrawal symptoms, i.e. the majority of studies tapered antidepressants thereby diminishing withdrawal symptoms. In addition, ten studies required symptoms to be present on successive visits, 24,38,47,50,58,61-63,68,72 whereas withdrawal symptoms are transient. 73 Also, five studies 50,53,54,61,67 conducted post-hoc analyses excluding relapses occurring when withdrawal symptoms are most likely (i.e. the first 7, 14 or even 28 days following discontinuation) and reported that superiority of antidepressants over placebo remained similar.
Fourth, various criteria for response and relapse have been used in the individual studies. Using a low threshold to define responders will include patients with residual symptoms in the discontinuation phase, who may run a higher risk for relapse, 74 and hence relapse rates may increase.
Fifth, only relapses of the disorder under study have been included. Given the low stability of anxiety
disorders over time, the development of ‘any disorder’ is likely to be substantially higher.

**Strengths and weaknesses**

This meta-analysis summarized findings of 28 studies, including a total of 5233 patients. This produces more robust estimates compared to individual studies. By conducting the current meta-analysis, we verified, updated and extended a previous meta-analysis on this subject by (i) including 6 additional studies increasing the total number of patients from 4121 to 5233, (ii) summarizing studies of all anxiety disorders combined, (iii) assessing time to relapse as additional outcome parameter; (iv) using a more conservative random effects model, (v) assessing publication bias, (vi) conducting exploratory subgroup analyses and meta-regression analyses, (vii) assessing quality of the included studies, (viii) considering dropout ratios, and (ix) presenting adverse events in the follow-up phase. Another strength of the current study is that only trials with a fixed treatment period were included. By contrast, observational studies, allowing a flexible duration of the open label phase, are prone to bias favoring continuation treatment.

Pharmaceutical companies were involved in all except two small studies. Hence, we should be aware of the probability of both publication bias and sponsorship bias. To limit potential bias, we thoroughly searched for non-published studies and included these if sufficient information was available. Six unpublished studies were found, four with negative results, one with positive results and one unknown, thereby suggesting publication bias. Indeed, excluding the unpublished studies resulted in a higher OR as compared to including (the four) unpublished studies; (e.g. excluding unpublished studies OR=3.38 (95% CI 2.76 to 4.12) vs. including unpublished studies OR=3.11 (95% CI 2.50 to 3.86)). To further assess potential biases, we examined whether selective reporting was present in individual studies. Several indications for selective reporting were found. In four articles, the abstract was incomplete. In addition, one study had planned to analyse time to relapse with a Cochran-Mantel-Haenzel test, but did not report test results, and three studies reported the HR for time to relapse, but information about the 95% CI was incomplete. Irrespective of whether these shortcomings are related to the involvement of pharmaceutical companies, it seems unlikely that these shortcomings change our conclusion for the following reasons: (i) we most likely included the majority of unpublished studies in the meta-analysis, (ii) adjusting ORs attenuated the strength of the association, but the protective effect of continuing AD remained substantial, (iii) missing confidence intervals were estimated and included in meta-analysis, and (iv) a meta-regression on the quality of studies (including the aspect of selective reporting) was non-significant.

We conducted subgroup analyses which revealed no statistical significant differences. Findings of subgroup analyses should however be interpreted cautiously, because these are observational comparisons; i.e. studies included in the subgroup analysis may differ on other aspects too. Only direct comparisons may verify whether risk of relapse might be related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of concurrent psychotherapy.

A final limitation is that the maximum duration of treatment was limited to 52 weeks. Randomised studies with a longer duration are non-existent. Up till one year, a clear advantage of continuing...
antidepressants was found. However, based on the present meta-analysis, we cannot determine
whether there is a relatively ‘safe’ period after 52 weeks of treatment when antidepressants can be
discontinued without the associated risk for relapse.

Clinical implications and guideline recommendations

Altogether our results imply that, for a treatment duration up till one year, antidepressants outperform
placebo in preventing relapse and are well tolerated over time. Additionally, antidepressants seem to
be superior to placebo regarding quality of life (e.g.\textsuperscript{23}), and direct medical costs associated with
relapse might offset the costs of antidepressants.\textsuperscript{77} The number needed to treat is quite acceptable.
These results thus suggest that continuation should be advised for at least one year following
response on antidepressants. Some guidelines advise shorter periods for specific anxiety disorders
(e.g. panic disorder\textsuperscript{14,18,78}), these recommendations may need reconsideration.

Patients may however prefer discontinuation even within a year, because of an aversion to
antidepressants or because they view long-term use as problematic.\textsuperscript{79,80} There is no definite answer
as to whether it is unwise to discontinue antidepressants earlier. Our exploratory meta-regression
analysis assessing the impact of duration of treatment was non-significant. In line with this, it was
found that time to restart an antidepressant was similar in patients who discontinued antidepressants
within 6 months and in patients who continued antidepressants for 6-12 months.\textsuperscript{81}

Additionally, results can be compared to the well-known glass of water which is either half full or half
empty; when 36.4% of the patients relapse, 63.6% does not. Also, relapse may also occur during
continuation of antidepressants (16.4% within follow-up). Doctors and their patients should consider
whether the benefits of discontinuation are worth the substantial risk of relapse.

Studies included in this meta-analysis have a treatment duration up till one year. Because studies with
longer durations are lacking, it is unknown whether after this period patients should continue or can
safely discontinue their antidepressants. On the one hand, it can be hypothesized that with longer
durations of treatment, improvement continues and functioning improves thereby drifting further away
from a relapse. On the other hand, in a study with a naturalistic design, relapse rates following
discontinuation were high, even after three years of sustained remission on medication.\textsuperscript{26} Given the
importance of this for daily clinical care, randomized controlled trials with long treatment durations are
needed in patients who responded to antidepressants. These studies should directly compare various
durations of treatment. To date, such studies have been conducted by Rickels and colleagues\textsuperscript{24} and
by Mavissakalian and Perel.\textsuperscript{28} Both studies had small sample sizes, and additionally, in part of the
sample of Mavissakalian and Perel, discontinuation was not blinded. Results were contradictory.
Rickels and colleagues found significantly higher relapse rates following discontinuation in patients
treated for six months (53.7%) as compared with patients treated for twelve months (32.4%).\textsuperscript{24} In
contrast, Mavissakalian and Perel found similar relapse rates in patients who were treated for 6
months and in patients who were treated for 12-30 months prior to discontinuation.\textsuperscript{28} Until more data
become available, no rational advice can be provided to patients to optimize their long-term prognosis.
after this period of one year. We would like to emphasize that the guidelines advice to continue medication for a year, should not be interpreted as an advice to taper medication after this period. Thus, by suggesting to taper medication following sustained remission, current guidelines are too optimistic. Unfortunately, the discussion whether or not it is wise to discontinue antidepressants does often not take place between doctors and their patients.82

To weight the advantages and disadvantages of discontinuation, several related issues need to be discussed and taken into account. First, patients may be willing to take the risk of relapse if reinstating the antidepressant will reverse the deterioration. Though some have reported regular efficacy after reinstating antidepressants,24 others have reported limited response, a phenomenon sometimes called tachyphylaxis.83,84 More research in this area may add to the decision to either continue or discontinue antidepressants. Second, patients may consider discontinuation more readily if concomitant psychotherapy counteracts relapse risk. Surprisingly, the merits of psychotherapy in the context of discontinuation are largely unknown. In two small studies focusing on current disorders, symptom levels remained similar when concomitant cognitive behavioral therapy (CBT) was provided during the period of discontinuation.85,86 However, in their study on panic disorder, Barlow and colleagues did not find protective effects of CBT when discontinuing antidepressants.87 Given the scarcity of studies, further research should examine the merits of psychotherapy in the context of discontinuation of antidepressants. Third, a personalized risk-estimate may facilitate the decision to discontinue antidepressants. However, research on predictors of relapse in anxiety disorders is scarce,5 and results are inconclusive, for example concerning functional impairment/quality of life,5,72 and concerning residual symptoms.74,88 Likewise, little is known about predictors related to the antidepressant treatment itself, but it has been suggested that higher dosages are associated with an increased relapse risk.89 Clinical care would clearly benefit from research in this area.

Conclusion
Anxiety disorders often run a chronic course, therefore long-term considerations should direct treatment. In the acute phase, both cognitive behavioural therapy and antidepressants can be considered. When considering antidepressants in acute phase treatment, the relapse risk in the case of discontinuing later on needs to be discussed and evaluated straight from the start of the treatment. Based on the evidence presented here, the advice is to continue antidepressants for at least a year. After this period no evidence-based advice can be provided. The lack of evidence after this period should not be interpreted as an explicit advice to discontinue antidepressants after one year. Guidelines which suggest tapering antidepressants following sustained remission should be reworded. It is up to patients and their doctors to exchange views on what seems best for the individual patient at long-term.
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Contributorship statement NB, AM, WS, KH and AvB devised the concept and design of the study. NB, WS and RB assessed studies for eligibility and extracted the information from all articles, RB and AM conducted the analyses and all authors interpreted the data. NB and RB drafted the article. All revised it critically for important intellectual content and all approved the version to be published. NB and AvB are the guarantors for the study.

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Competing interest All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf they have no relationships with companies that might have an interest in the submitted work in the previous 3 years; their spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and they have no non-financial interests that may be relevant to the submitted work.

Ethical approval Not required.

Data sharing No additional data available.

Transparency NB and AvB affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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REFERENCE LIST


What is already known on this topic

- Antidepressants are a first-line treatment option for the acute treatment of anxiety disorders but their benefits in optimizing long-term prognosis are less well known. International guidelines are therefore consensus-based and advise continuation treatment of variable duration (6-24 months) and subsequent tapering of the antidepressant.
- Previous studies have shown high risk of relapse following discontinuation of antidepressants, but information on whether specific treatment- or discontinuation strategies influence relapse risk is scant and inconclusive.

What this study adds

- This study meta-analyzed results of 28 relapse prevention trials in patients with remitted anxiety disorders. A clear benefit of continuing medication (relapse 16.4%) compared to discontinuation (relapse 36.4%) was shown for both relapse and time to relapse (summary OR=3.11 (95%CI 2.48 to 3.89); (summary HR=3.63, 95%CI 2.58 to 5.10, n=11 studies)).
- Subgroup analyses and meta-regression analyses provided no evidence that type of anxiety disorder, duration of prior treatment, duration of follow-up, mode of discontinuation, and allowance of concurrent psychotherapy significantly influenced relapse risk.

Implications for practice

- Given chronic course trajectories of anxiety disorders, long-term considerations should direct treatment. For a treatment duration up till one year, antidepressants optimize the long-term prognosis of anxiety disorders by preventing relapse.
- After one year of treatment, no evidence-based advice can be provided. This lack of evidence should not be interpreted as an explicit advice to taper antidepressants after one year. Guidelines which suggest tapering antidepressants following sustained remission should be reworded.
- Current clinical practice needs to change, i.e. when considering antidepressants in acute phase treatment, the risk of relapse in case of discontinuation later on needs to be discussed straight from the start of the treatment, and after one year, patients and their doctors should decide what seems best for the individual patient.
Figure 1. Flowchart

Records identified through PubMed, n=667

Records identified through Embase, n=2473

Records identified through Cochrane, n=402

Duplicate records, n=608

Records after duplicates removed, n=2934

Records removed based on title and abstract, n=2884

Full-text articles assessed for eligibility, n=50

Not fulfilling inclusion criteria, n=7
- Design inadequate, n=6
- No anxiety diagnosis, n=1

Not presenting original data, n=15
- Subsample analysis, n=10
- Not research paper, n=5

Additional search (hand search and search trial registers), n=6, included n=4, n=2 excluded due to missing data despite data request

Studies included in meta-analysis, n=28

Duplicating studies, n=2

Missing data for meta-analysis despite data request, n=2 (for time to relapse)
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**Subgroup analysis of relapse**

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<td>PTSD</td>
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<td>6.50</td>
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<tr>
<td>SP</td>
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<td>3.19 (1.02 to 9.95)</td>
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**Anxiety DSM-V**

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**Antidepressant**

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**Discontinuation**

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<td>Taper</td>
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**Concurrent psychotherapy allowed**

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Figure 2: Forest plot representing proportion of relapse per study.

Time point indicates duration of follow-up in weeks.
Figure 3: Forest plot time to relapse per study. Time point indicates duration of follow-up per study.

<table>
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<tr>
<th>Study name</th>
<th>Time point</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Relative weight</th>
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<td>Aiguiander et al., 2009</td>
<td>24 weeks</td>
<td>1.90</td>
<td>2.54</td>
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<td>Baldwin et al., 2012</td>
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<td>1.80</td>
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<td>Davidson et al., 2001</td>
<td>28 weeks</td>
<td>6.35</td>
<td>1.32</td>
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<td>Fineberg et al., 2007</td>
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<td>2.74</td>
<td>1.89</td>
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<td>Horvander et al., 2003</td>
<td>26 weeks</td>
<td>2.70</td>
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<td>Montgomery et al., 2005</td>
<td>24 weeks</td>
<td>2.83</td>
<td>1.95</td>
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<td>Rickels et al., 2010</td>
<td>26 weeks</td>
<td>9.73</td>
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<td>Stein et al., 2002</td>
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<td>1.01</td>
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<td>Stocchi et al., 2003</td>
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<td>4.68</td>
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<td>Walker et al., 2000</td>
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<td>10.20</td>
<td>1.29</td>
<td>80.36</td>
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## Supplement 2: Characteristics of included studies.

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<tr>
<th>Reference</th>
<th>Anxiety Disorder</th>
<th>Age</th>
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<th>Placebo</th>
<th>Dose (mg/day)</th>
<th>Discontinuation</th>
<th>Duration treatment before randomisation (in weeks)</th>
<th>Duration follow-up (in weeks)</th>
<th>N treatment</th>
<th>N follow-up</th>
<th>N relapse during follow-up</th>
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<th>Comorbidity mostly excluded</th>
<th>Role pharmaceutical companies</th>
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<td>[53] GAD</td>
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<td>42 (18-64)*</td>
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<td>Taper</td>
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- *Studies with an "*" report mean age and age range, all other studies report mean age and standard deviation.
- Fluoxetine was discontinued abruptly in all studies, however given the relatively long half-life time of fluoxetine, this medication is considered to taper itself.
- [53] had a minimum follow-up duration of 24 weeks, and depending on when a participant was included, a maximum follow-up of 76 weeks.
- [54] had a minimum follow-up duration of 24 weeks, and depending on when a participant was included, a maximum follow-up of 56 weeks.
### Appendix 3: Quality assessment per study according to GRADE method.

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