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Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial

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Summary

Background Keeping individuals on antidepressants after remission or recovery of major depressive disorder is a common strategy to prevent relapse or recurrence. Preventive cognitive therapy (PCT) has been proposed as an alternative to maintenance antidepressant treatment, but whether its addition would allow tapering of antidepressants or enhance the efficacy of maintenance antidepressant treatment is unclear. We aimed to compare the effectiveness of antidepressants alone, with PCT while tapering off antidepressants, or PCT added to antidepressants in the prevention of relapse and recurrence.

Methods In this single-blind, multicentre, parallel, three-group, randomised controlled trial, individuals recruited by general practitioners, pharmacists, secondary mental health care, or media were randomly assigned (10:10:8) to PCT and antidepressants, antidepressants alone, or PCT with tapering of antidepressants, using computer-generated randomised allocation stratified for number of previous depressive episodes and type of care. Eligible participants had previously experienced at least two depressive episodes and were in remission or recovery on antidepressants, which they had been receiving for at least the past 6 months. Exclusion criteria were current mania or hypomania, a history of bipolar disorder, any history of psychosis, current alcohol or drug abuse, an anxiety disorder that requires treatment, psychological treatment more than twice a month, and a diagnosis of organic brain damage. The primary outcome was time-related proportion of individuals with depressive relapse or recurrence in the intention-to-treat population, assessed four times in 24 months. Assessors were masked to treatment allocation, whereas physicians and participants could not be masked. This trial is registered with the Netherlands Trial Register, number NTR1907.

Findings Between July 14, 2009, and April 30, 2015, 2486 participants were assessed for eligibility and 289 were randomly assigned to PCT and antidepressant (n=104), antidepressant alone (n=100), or PCT with tapering of antidepressant (n=85). The overall log-rank test was significant (p=0·014). Antidepressants alone were not superior to PCT while tapering off antidepressants in terms of the risk of relapse or recurrence (hazard ratio [HR] 0·86, 95% CI 0·56–1·32; p=0·502). Adding PCT to antidepressant treatment resulted in a 41% relative risk reduction compared with antidepressants alone (0·59, 0·38–0·94; p=0·026). There were two suicide attempts (one in the antidepressants alone group and one in the PCT with tapering of antidepressants group) and one death (in the PCT and antidepressants group) not related to the interventions during the 24 months' follow-up.

Interpretation Maintenance antidepressant treatment is not superior to PCT after recovery, whereas adding PCT to antidepressant treatment after recovery is superior to antidepressants alone. PCT should be offered to recurrently depressed individuals on antidepressants and to individuals who wish to stop antidepressants after recovery.

Funding The Netherlands Organisation for Health Research and Development.

Introduction

Major depressive disorder is projected to rank second in 2030 in terms of burden of disease.[1] The extraordinary contribution of major depressive disorder to disability and health-care costs is largely due to its highly recurrent nature.[2,3] Accordingly, efforts to reduce the disabling effects of major depressive disorder should target prevention of recurrence, particularly in high-risk individuals.[4] Several international guidelines[5,6] state that individuals with histories of multiple previous depressive episodes are at high risk of recurrence. For a long time, almost all individuals in remission have been continued on antidepressants for at least a couple of months to prevent relapse (return of the treated episode), and it is

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Research in context

Evidence before this study

We searched Embase, PubMed, PsycINFO, Web of Science, Scopus, and the Cochrane library without language restrictions up to July 3, 2017, using the search terms (preventive cognitive therapy OR PCT OR cognitive therapy OR cognitive behavior therapy OR mindfulness-based cognitive therapy OR MBCT) AND (depress*) AND (antidepressants OR antidepressant medication) AND (recurrence OR recurrent OR relapse OR relapse prevention). We screened abstracts to retrieve full-text articles. We also checked reference lists of relevant studies and reviews for potentially relevant studies. We did not find a three-group, relapse prevention trial in individuals with major depressive disorder comparing the effectiveness of continuation of antidepressants after remission versus cognitive-based therapy, or comparing the effectiveness of adding cognitive-based therapy to antidepressants versus antidepressants alone. We identifed three published trials comparing two groups, in particular the effectiveness of mindfulness-based cognitive therapy (MBCT) after remission, with support to taper or discontinue antidepressants, versus maintenance antidepressants. The relative risk ratio of MBCT versus maintenance antidepressant treatment was 0·76 (95% CI 0·59–0·98), a risk reduction of 24% over 60 weeks. Additionally, we identified one published trial comparing MBCT added to maintenance antidepressant treatment after remission versus maintenance antidepressant treatment alone, with a hazard ratio of 0·87 (95% CI 0·40–1·90) over 15 months for this comparison.

Added value of this study

This study is the first three-group, randomised controlled trial in individuals in remission or recovery at high risk of recurrence to examine whether maintenance antidepressant treatment reduces recurrence risk more than does tapering off antidepressants while adding PCT, and whether adding PCT enhances the preventive efficacy of maintenance antidepressant treatment compared with antidepressants alone. We found no evidence that maintenance antidepressant treatment was superior to discontinuation of antidepressants while receiving PCT over 24 months. We found benefits for the combination of PCT and antidepressants over antidepressants alone in terms of reduced risk of recurrence and secondary outcomes (number and duration of recurrences) over 24 months.

Implications of all the available evidence

PCT might be an alternative to maintenance antidepressant treatment in individuals with recurrent depression who wish to discontinue medication after recovery or who intend to continue on antidepressants.

becoming common practice to maintain high-risk individuals with a history of multiple previous episodes on antidepressants indefinitely to guard against recurrence (onset of a new episode).[4] Meta-analyses[7–10] have shown that keeping individuals on antidepressants reduces the risk of symptom return (odds ratios [ORs] ranging from 0·30 to 0·48 *vs* switching to placebo after treatment with antidepressants). However, most (70–80%) at-risk individuals are not willing to stay on antidepressants for extended periods of time,[11,12] and there are indications that some individuals might become resistant to the prophylactic properties of antidepressants with increasing duration of exposure.[8]

Cognitive therapy is an effective treatment for major depressive disorder and reduces the risk of recurrence.[13–17] Sequential treatment with cognitive therapy after acute-phase remission is effective in preventing subsequent relapse and recurrence in individuals with recurrent major depressive disorder, and this beneficial effect might be increased if cognitive therapy were given without antidepressants, as suggested in non-randomised studies.[13,15] In our previous multicentre, randomised controlled trial[16,17] in individuals in remission of depression who had a history of recurrence, adding preventive cognitive therapy (PCT) to treatment as usual reduced the risk of recurrence over the following decade in highly recurrent individuals with more than three previous major depressive episodes. Additionally, the preventive effect of PCT in primary care was confirmed in participants in remission who had experienced previous major depressive episodes.[18]

In our previous two-group trial,[16–18] we did not randomly assign participants to continued or tapered antidepressants. An earlier trial[19] in participants with recurrent depression who had recently remitted on antidepressants reported a 50% reduction in recurrence with clinical management while tapering off antidepressants compared with wellbeing therapy (40% *vs* 90%) over 6 years of follow-up. This finding suggests that cognitive therapy might have long-term preventive effects in individuals tapering off antidepressants. A meta-analysis[13] in participants with major depressive disorder who responded to acute treatment with cognitive therapy found promising preventive effects for cognitive therapy compared with acute-phase treatment with antidepressants and non-active controls.

Three randomised controlled trials[20–22] compared the effectiveness of mindfulness-based cognitive therapy (MBCT) after remission, including support to taper off or discontinue antidepressants, with maintenance antidepressant treatment. The aggregated results of these trials indicated no significant difference between MBCT and maintenance antidepressant treatment (relative risk ratio 0·76, 95% CI 0·59–0·98).[22] Additionally, in one study[23] in 68 remitted individuals with recurrent depression, no effect was seen in adding MBCT to maintenance antidepressant treatment after remission compared with maintenance antidepressants alone

(hazard ratio [HR] over 15 months was 0·87 [95% CI 0·40–1·90]).

In this study, we aimed to establish whether staying on maintenance antidepressant treatment offers better protection against recurrence than does receiving PCT while tapering off antidepressants, and whether adding PCT to antidepressants enhances protection against recurrence compared with antidepressants alone.

Methods

Study design and participants

The Disrupt the Rhythm of Depression (DRD) study was a three-group, multicentre, single-blind, parallel, randomised controlled trial in individuals with a history of depressive episodes who were in remission or recovery and had a high risk of recurrence.[5,6] Participants were recruited via general practitioners (GPs), pharmacists, secondary mental health care, and media. Eligible individuals had at least two previous episodes of major depressive disorder and had been in remission for at least 8 weeks but no longer than 2 years according to DSM-IV criteria, assessed with the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I).[24] Additionally, recovery had to have been achieved with acute antidepressant treatment, and participants had to have been on antidepressants for at least the past 6 months. Remission was defined as having a score of 10 or lower on the 17 item Hamilton Rating Scale for Depression (HRSD)[25] and the last major depressive episode having ended at least 2 months and no longer than 2 years before study entry. For the full definition of remission, see the appendix.

Exclusion criteria, as assessed with SCID-I, were current mania or hypomania; a history of bipolar disorder; any history of psychosis, including major depressive episode with psychotic features; current alcohol or drug abuse; predominant anxiety disorder; receiving psychological treatment more than twice a month; and a diagnosis of organic brain damage.

Interested individuals were screened and informed about the study. If suitable, they were assessed by the researchers for eligibility and current and past diagnostic status using the telephone version of SCID and HRSD. Individuals were enrolled only after meeting all inclusion criteria.

On Dec 1, 2011, we discarded our prespecified inclusion criterion[26] of having experienced at least two depressive episodes within the past 5 years on the basis of findings from studies[4] showing that individuals with multiple episodes over a longer period of time might also benefit from relapse prevention strategies. Furthermore, discordant with the protocol,[26] we offered PCT in both group and individual formats because a substantial proportion of the participants were not able to attend group meetings for practical reasons. We examined whether group versus individual PCT had an effect on the results in our analysis. These protocol changes were approved by The Netherlands Organisation for Health Research and Development.

A patient organisation (Depressie Vereniging, Amersfoort, Netherlands) was involved in the study design, development of prevention strategies for relapse, participant recruitment, and in discussing the interpretation of the results. An independent medical ethics committee for all included sites (METIGG) approved the DRD trial protocol.[26] The trial was done in accordance with CONSORT guidelines. All participants provided written informed consent.

Randomisation and masking

Independent psychologists or research assistants interviewed all potential participants. An independent research assistant masked to the randomisation sequence entered the stratification characteristics and implemented the automated permuted-block randomisation using computer-generated random numbers with a predefined allocation ratio of 10:10:8 to PCT and antidepressants, antidepressants alone, and PCT while tapering off antidepressants. Randomisation was stratified for number of previous major depressive episodes (two *vs* three or more) and type of care (GP *vs* secondary mental health care). Subsequently, participants were informed of their group assignment by a researcher (GDvR, HJE, or CS) who was not involved in the follow-up interviews. Trained assessors masked to treatment allocation did all subsequent follow-up assessments.

Participants and physicians were aware of treatment allocation. We assessed the fidelity of masking, which was found to be moderate to good (43·7% of assessments of treatment allocation were correctly guessed).

See Online for appendix

Procedures

For the baseline assessment, we asked participants to complete the web-based self-report questionnaires (see the study protocol[26] for an overview). Participants in the two PCT groups received the intervention by therapists. PCT, based on a treatment manual,[4,27] comprised eight weekly group or individual sessions. Unlike most psychological treatments for acute depression, the main components of PCT are identification and evaluation of dysfunctional attitudes and schemas that activate positive affect and emotions through identification of wishful beliefs,[4] enhancement of memories of positive experiences, and formulation of prevention strategies. By contrast with MBCT, meditation was not included. Therapists were psychologists fully trained in cognitive behavioural therapy who received an additional 16 h of training specific to this study. To maintain treatment integrity, therapists followed a PCT manual[4,27] and were supervised by a fully trained cognitive behavioural therapist or a licensed psychologist. Adherence issues were resolved through supervision (three adherence issues were detected and resolved). An independent research assistant listened to all eight sessions of one

randomly selected participant per therapist from ten randomly selected therapists to assess therapist adherence to the PCT manual. A specific questionnaire (available from CLHB) that comprised all elements of PCT was developed, in which all PCT elements were independently scored on a dichotomous scale (present or absent). The total score was transformed into percentages, indicating a high adherence of 87·2% (range 81·0–95·0). We also assessed attendance at the sessions.

In the two groups that received maintenance antidepressant treatment, GPs and psychiatrists were advised to continue guidance and prescription of antidepressants at minimally required adequate doses or higher (≥20 mg fluoxetine equivalent[12]), as recommended by guidelines.[5,6] Participants were encouraged to use antidepressants as prescribed, and GPs and psychiatrists were encouraged to prescribe therapeutic doses and to discuss problems with adherence.

In the group tapering off antidepressants, GPs and psychiatrists were advised to taper antidepressants over a period of 4 weeks. This time frame was chosen in line with the recommendation of a 2009 international guideline from the National Institute for Health and Care Excellence.[6] However, most (60%) individuals tapered the antidepressants with their doctors over 6 months, indicating that a time frame of 4 weeks was not considered feasible for many individuals. The GP or psychiatrist and participant received a letter with instructions to guide tapering and a tapering schedule per type of drug. In this group, participants were asked for an intention to taper antidepressants. However, study participants were allowed to re-start antidepressants at any time, which was monitored.

Doses of antidepressants were assessed in all participants with the Trimbos and Institute for Medical Technology Assessment questionnaire on costs associated with psychiatric illness.[28] Participants in the tapering group were also monitored via telephone by an independent researcher on their progress. For all antidepressants, equivalent doses in mg of fluoxetine were computed.

Participants could withdraw from the treatment or study at any time. Nevertheless, we asked those who did withdraw from the trial whether they were willing to attend all the remaining research appointments.

Outcomes

The primary outcome was time-related proportion of participants with recurrence over a follow-up of 24 months, analysed in terms of time to recurrence. Participants were assessed for remission by trained assessors at baseline and after 3, 9, 15, and 24 months using DSM-IV-TR criteria assessed with SCID-I, including retrospective parts and information from monthly ratings on the Inventory of Depressive Symptomatology–Self Report (IDS-SR).[29] Four trained interviewers (NSK, CS, and two research assistants) rated a subset of 50 interviews, resulting in an inter-rater agreement of 0·96, indicating excellent agreement.

Secondary outcomes included the number, duration, and severity of depressive recurrences during the 24 months' follow-up, as assessed with SCID-I. Additionally, we did predefined, exploratory subgroup analyses to investigate whether treatment effects were modified by the number of previous major depressive episodes (assessed with SCID), the severity of the last major depressive episode (assessed with SCID), sex, and the level of residual symptoms (assessed with HRSD). We examined differential predictors of time to recurrence using Cox regression. Potential predictors were illness-related (IDS-SR and HRSD), stress-related (Negative Life Events Questionnaire and Everyday Problem Checklist), cognitive-related (Ruminative Responses subscale of the Response Styles Questionnaire [RRS], Dysfunctional Attitude Scale [DAS], and Leiden Index of Depression Sensitivity [LEIDS]), and non-adherence to antidepressants (Medication Adherence Questionnaire). In another exploratory analysis, we examined whether treatment effects could be explained by mediating time-specific covariates in the Cox regression. We could not analyse the results of the Implicit Associations Test because data collection with the online version of the test was problematic (no data for 66% of participants, mainly due to practical issues). Cost-effectiveness results will be reported elsewhere.

We recorded suspected serious adverse events and reported them to the multicentre ethics committee (METIGG), according to their guidelines.

Statistical analysis

289 participants were included in the study, providing 80% power (two-sided α of 0·05) to detect a clinically significant difference of at least 20% in the primary outcome between the PCT with antidepressants group and the antidepressants alone group (assuming 50% recurrence in participants assigned to antidepressants *vs* 30% in those assigned to PCT and antidepressants) in a survival analysis after 24 months. This calculation was based on clinically significant differences reported in relapse prevention studies.[8,13] Taking into account 15% attrition for this comparison, 98 participants were needed in each of the PCT with antidepressants and antidepressants alone groups. To detect a clinically significant difference of at least 15% in the primary outcome (assuming 50% recurrence in participants on antidepressants alone) between the group that was tapered off antidepressants while receiving PCT and the group that received antidepressants alone, 80 participants were needed in the group tapered off antidepressants.[7–10] This number was based on a steeper drop in the survival curve of participants in this group during the first 3 months in relapse-prevention studies.[16,17]

Primary analyses were done by intention to treat. We also did two per-protocol analyses (appendix). In the first per-protocol analysis, only participants who had received five or more sessions of PCT were included in the

analysis. In the second per-protocol analysis, the tapering off antidepressants group included only those who had reduced their antidepressant dose by at least 50% within 6 months, and the maintenance anti-depressants groups included only those who were using a minimal therapeutic dose of antidepressant (equivalent to at least 20 mg fluoxetine) at 24 months, as recommended by international guidelines.[5,6] We constructed Kaplan-Meier curves to display the time-related proportions of participants with recurrence of major depressive disorder by treatment. For the primary analysis, we used Cox proportional hazards models with time to recurrence as a dependent variable and treatment group and stratification factors as independent variables. In these analyses, participants who dropped out during follow-up or had not experienced a recurrence by 24 months were considered right-censored. The results of the Cox models are expressed as HRs with 95% CIs. To assess whether the proportional hazards assumption held, we examined log-minus-log plots.

In a predefined exploratory analysis, we examined whether treatment effects were modified by the number of previous major depressive episodes through assessing the significance of the interaction term treatment condition × number of previous episodes as a continuous variable in the Cox models. If significant, we re-did the analyses in subgroups of participants with fewer than the median number of episodes (two to four episodes) and in those with five or more. This cutoff was arbitrary and was defined before the analyses. We used Poisson regression analysis to analyse differences in number of recurrences between the groups. The mean severity of recurrences was compared between the groups with a linear regression model. Duration of recurrences was non-parametrically compared with the Mann-Whitney *U* test because of its distributional properties.

The same approach as used for duration of recurrences was used to assess the potential treatment effect modification by baseline scores on IDS-SR, Negative Life Events Questionnaire, Everyday Problem Checklist, RRS, DAS, and LEIDS scales and medication adherence (dichotomised as medium to low *vs* high). Clinical secondary outcomes that were assessed more than twice (IDS-SR and HRSD) during follow-up were investigated in terms of change over time and were analysed with linear mixed-effect models with unstructured variance–covariance matrices. In these analyses, we added a random intercept and, if it significantly improved the model, a random slope for participants. Treatment effects were quantified by entering group-by-time interaction terms.

Our study was not powered for a mediation analysis. Therefore, we only explored whether treatment effects that were significant could be explained by changes in the scores on DAS, LEIDS, RRS, and Everyday Problem Checklist from baseline to end of treatment (3 months of follow-up).[24] This analysis was done by entering the mediator as an independent variable in the Cox regression model and assessing the relative attenuation of the HR for relapse. For all analyses, significance was set at 0·05 (two-sided) and SPSS version 23 was used. Information about sensitivity analyses can be found in the appendix.

The trial is registered with the Netherlands Trial Register, number NTR1907.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 14, 2009, and April 30, 2015, 289 participants with recurrent major depressive disorder who were in remission or recovery and on antidepressants were randomly assigned to PCT and antidepressants (n=104), PCT while tapering off antidepressants (n=85), or antidepressants alone (n=100; figure 1). 200 (69%) of 289 participants had at least 4 months of sustained remission, 28 (10%) had 3 months, and 60 (21%) had 8 weeks; no data were available for one participant. 220 (76%) of 288 participants had experienced two or more episodes in the past 5 years. Participants were recruited via GPs (n=5), pharmacists (n=46), secondary mental health care (n=55), media (n=180), or by other means (n=3). 200 (69%) of 288 participants had received antidepressants from their GP.

In 43 (23%) of 189 participants assigned to PCT, the intervention was not started and follow-up data were not available because the travel time was too long to visit the PCT group or the group sessions were planned at a time they could not attend. Therefore, from February, 2013, we decided to offer individual sessions as well as group sessions. In addition to these 43 participants, 16 in the PCT groups and 21 in the antidepressants alone group dropped out for other reasons. Thus, 209 participants were followed up for 1 day or more after randomisation. The proportion of participants with missing covariates was less than 5%. During the 24 months' follow-up, one participant assigned to PCT and antidepressants died because of cancer and two suicide attempts were reported, including one participant in the antidepressants alone group 10 months after study initiation and one participant in the PCT with tapering of antidepressants group 7 months after study initiation. The participant who attempted suicide while receiving PCT and being tapered off antidepressants did not adhere to the tapering protocol and discontinued the antidepressant (fluoxetine) abruptly after 3 months. The suicide attempt was 4 months after non-adherence to the tapering protocol, and treatment with the same antidepressant was re-initiated after the attempt. There was no indication that these events were related to the relapse prevention strategies.

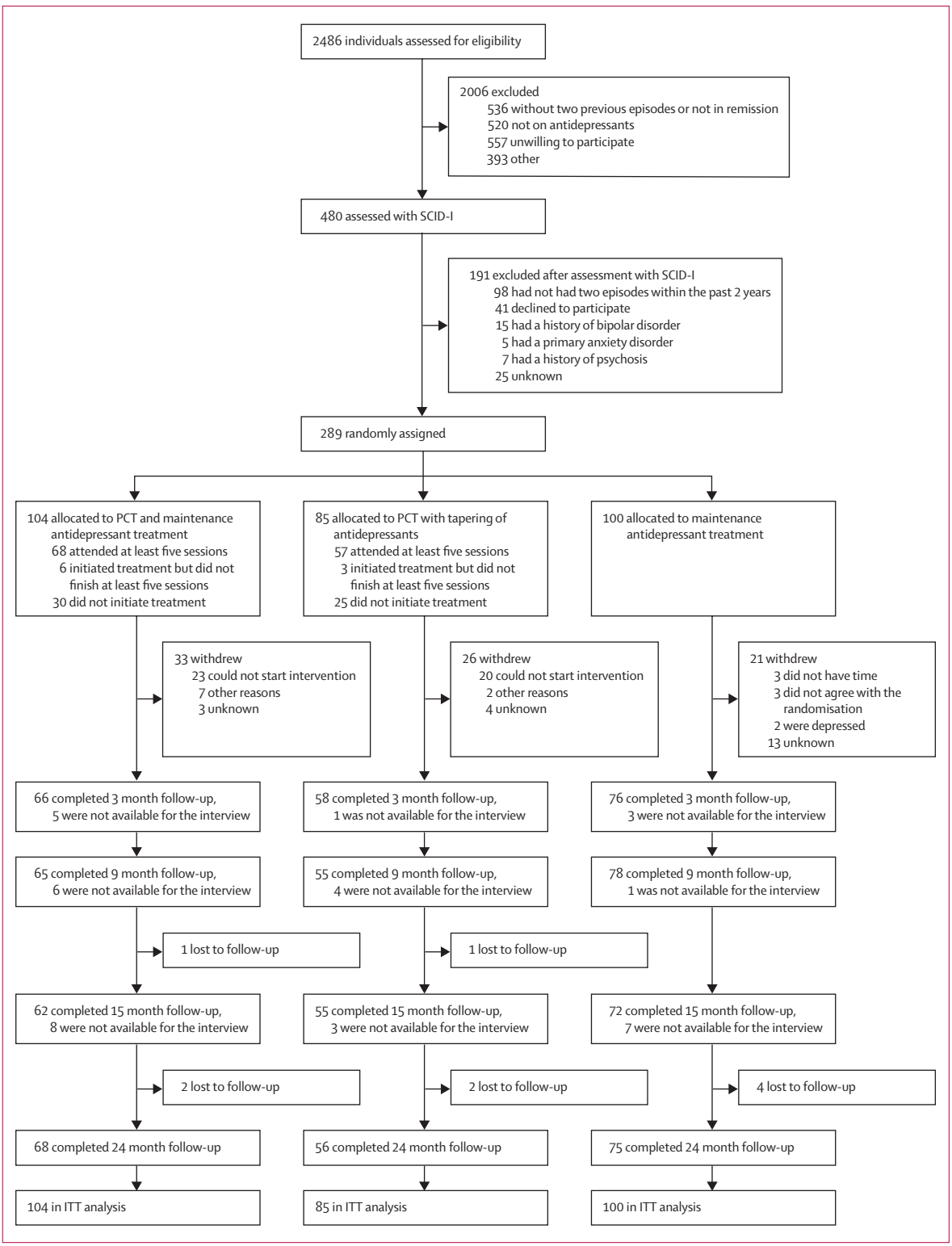

Figure 1: **Trial profile**
SCID-I=Structured Clinical Interview for DSM-IV Axis-I Disorders. PCT=preventive cognitive therapy. ITT=intention to treat.

The baseline demographic and clinical characteristics of the entire intention-to-treat population (table), and of the population with follow-up data (appendix), appeared to be similar and balanced across the groups, except for a slight imbalance in employment status, marital status, and education. 233 (81%) of 287 participants used SSRIs. This distribution in type of antidepressant used remained consistent throughout the 24 months of the study. During the study, two participants in each group received in-patient treatment, and 21 participants in the PCT and antidepressants group, 18 in the antidepressants alone group, and 16 in the PCT with tapering of antidepressants group received additional psychological or psychotherapeutic treatment.

More than half of participants still in the study after 6 months adhered to the antidepressant protocol (30 [60%] of 50 participants in the PCT with tapering of antidepressants group, 36 [65%] of 55 in the combined treatment group, and 38 [58%] of 66 in the antidepressants alone group; appendix). Additionally, most participants receiving PCT completed at least five sessions (68 [88%] of 77 participants receiving the combined treatment and 57 [90%] of 63 who were tapered off antidepressants; appendix).

The overall log-rank test in the Kaplan-Meier analysis was significant (p=0·014; figure 2), indicating differences in the primary outcome between the groups. The Kaplan-Meier curves were generally similar for the antidepressants alone and PCT with tapering of antidepressants groups, although the group tapered off antidepressants had a somewhat higher recurrence rate than did the antidepressants alone group during the first 140 days of follow-up (appendix). The recurrence rate in the PCT and antidepressants group was significantly lower than the recurrence rates in the other two groups. After 2 years of follow-up, cumulative recurrence rates according to Kaplan-Meier estimates were 55·1% for the entire intention-to-treat group, 60·0% for the antidepressants alone group, 63·3% for the PCT with tapering of antidepressants group, and 42·6% for the PCT and antidepressants group.

In the Cox regression analyses, antidepressants alone were not superior to PCT with tapering of antidepressants (HR 0·86, 95% CI 0·56–1·32; p=0·502). The recurrence risk was 41% lower in the PCT and antidepressants group than in the antidepressants alone group (0·59, 0·38–0·94; p=0·026). Log-minus-log plots showed no violation of the proportional-hazards assumption. Additionally, the recurrence risk was lower with the combined treatment than with PCT while tapering off antidepressants (0·54, 0·33–0·87; p=0·011). Sensitivity analyses yielded similar results for the comparison of antidepressants alone versus PCT while tapering off antidepressants, whereas the comparison of PCT and antidepressants versus antidepressants alone lost significance (p>0·05) in two of the three sensitivity analyses (appendix).

In prespecified secondary analyses, the number of previous episodes and treatment condition did not significantly interact in the comparison of antidepressants alone versus PCT with tapering of antidepressants (HR 0·96, 95% CI 0·87–1·06; p=0·419). However, an interaction with the number of previous episodes was found for the comparison of PCT and antidepressants versus antidepressants alone (1·11, 1·02–1·22; p=0·019). In subgroup analyses, HRs were 0·33 (95% CI 0·16–0·66; p=0·002) for participants with two to four previous

	PCT and antidepressants (n=104)	PCT with tapering of antidepressants (n=85)	Antidepressants alone (n=100)
Age, years*	47·0 (9·3)	47·7 (11·1)	47·2 (10·5)
Sex			
Women	72 (69%)	53 (62%)	64 (64%)
Men	32 (31%)	32 (38%)	36 (36%)
Dutch nationality†	101 (97%)	82/84 (98%)	95/99 (96%)
Marital status†			
Single	27/103 (26%)	28/84 (33%)	32/99 (32%)
Married or cohabiting	69/103 (67%)	46/84 (55%)	59/99 (60%)
Divorced or widowed	7/103 (7%)	10/84 (12%)	8/99 (8%)
Education†			
Primary or secondary	20 (19%)	12/84 (14%)	25/99 (25%)
Vocational	31 (30%)	23/84 (27%)	28/99 (28%)
Higher	53 (51%)	49/84 (58%)	46/99 (46%)
Employed†	73/103 (71%)	53/84 (63%)	65/98 (66%)
Treatment as usual			
Specialised mental health care	32 (31%)	26 (31%)	31 (31%)
General practitioner	72 (69%)	59 (69%)	69 (69%)
Experience with cognitive therapy†	45/99 (45%)	41/79 (52%)	49/98 (50%)
Current psychological or psychotherapeutic treatment†	21/104 (20%)	16/85 (19%)	18/99 (18%)
Number of previous depressive episodes	5 (3–6)	5 (3–6)	4 (3–6)
Time in remission, months	8·3 (6·8)	7·5 (5·9)	8·4 (6·4)
HRSD score	3·6 (3·1)	3·6 (3·0)	3·8 (3·1)
IDS-SR score	20·4 (11·5)	20·6 (12·1)	18·5 (10·8)
Type of antidepressant†			
SSRI	85/103 (83%)	69/85 (81%)	79/99 (80%)
SNRI	1/103 (1%)	1/85 (1%)	8/99 (8%)
Tricyclic antidepressant	7/103 (7%)	10/85 (12%)	7/99 (7%)
Atypical antidepressant	5/103 (5%)	3/85 (4%)	2/99 (2%)
Monoamine oxidase inhibitor	0 (0%)	0 (0%)	1/99 (1%)
More than one antidepressant	5/103 (5%)	2/85 (2%)	2/99 (2%)
Other medication†			
Mood stabilisers	2/74 (3%)	1/62 (2%)	2/74 (3%)
Antipsychotics	2/74 (3%)	2/62 (3%)	2/74 (3%)
Anxiety medication	9/74 (12%)	9/62 (15%)	6/74 (8%)
Other psychotropic medication	1/74 (1%)	2/62 (3%)	2/74 (3%)
Medication for physical illness	36/74 (49%)	25/62 (40%)	36/74 (49%)
Chronic somatic illness†	17/77 (22%)	13/63 (21%)	15/80 (19%)

Data are mean (SD), median (IQR), n (%), or n/N (%). HRSD=Hamilton Rating Scale for Depression. IDS-SR=Inventory of Depressive Symptomatology Self-Report. *Two participants were older than 65 years at baseline. †Data were not available for all randomised participants.

Table: **Demographic and clinical characteristics of the intention-to-treat population**

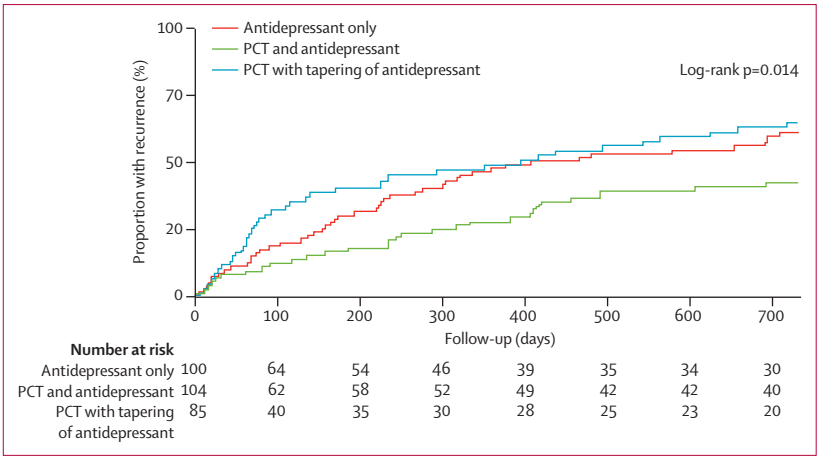

Figure 2: **Time to recurrence of depression over 24 months according to treatment (n=289)**
PCT=preventive cognitive therapy.

episodes and 1·03 (0·53–1·97; p=0·942) for those with five or more (appendix). None of the other secondary analyses or analyses of treatment effect modification showed significant results. The effect of antidepressants and PCT versus antidepressants alone was explained to a small extent by a change in DAS score between baseline and 3 months of follow-up; the HR attenuated by 7% (change from 0·59 to 0·63) and lost significance (from p=0·026 to p=0·64). For the remaining potential mediators, no such pattern was observed (appendix).

More than one recurrence of major depressive disorder was reported in 47 (24%) of 199 participants who completed 24 months' follow-up, including 11 (16%) of 68 participants who received PCT and antidepressants, 13 (23%) of 56 participants who were tapered off antidepressants while receiving PCT, and 23 (31%) of 75 participants who received antidepressants alone. The number of recurrences was 37% lower in the PCT and antidepressants group than in the antidepressants alone group (incidence rate ratio [IRR] 0·63, 95% CI 0·44 to 0·91; p=0·014). No significant difference in the number of recurrences was observed between the antidepressants alone group and the PCT with tapering of antidepressants group (1·16, 0·82 to 1·66; p=0·404). Similarly, no significant difference in severity of recurrences was found between the group that received antidepressants alone and the group that received PCT while being tapered off antidepressants (p=0·47) or the group that received PCT and antidepressants (p=0·12). Finally, the median duration of recurrence did not differ significantly between the antidepressants alone group (84·3 days [IQR 43·3–143·5]) and the PCT with tapering of antidepressants group (84·0 days [47·0–182·5]; p=0·48) or the PCT with antidepressants group (62·3 days [32·7–129·3]; p=0·51).

Discussion

Our findings suggest that PCT might be a viable alternative to maintenance antidepressant treatment for individuals with recurrent depression. Although risk of recurrence was slightly higher during the first few months after tapering of medication, overall, recurrence rates did not significantly differ between those who received PCT while being tapered off antidepressants and those who stayed on maintenance antidepressant treatment over 2 years. This effect was not modified by number of previous episodes and type of care. Thus, maintenance antidepressant treatment is not superior to discontinuation of antidepressants while receiving PCT in reducing risk of recurrence.

Adding PCT to maintenance antidepressant treatment reduced recurrence risk substantially (by 41%) and had beneficial effects on secondary outcomes, including reduced number of recurrences and shorter duration of recurrences, compared with continuation of antidepressants alone. This effect was modified by the number of previous episodes, indicating a decreasing preventive effect for the combined strategy with increasing number of previous episodes. However, this analysis was exploratory and should be interpreted with caution. Therefore, for individuals with recurrent depression who are willing to stay on maintenance antidepressant treatment, adding PCT could provide additional protection against subsequent recurrence.

Our finding that maintenance antidepressant treatment is not superior to PCT is in line with three previous studies[20–22] that found no clinically meaningful differences in time to recurrence over 15–24 months between MBCT and maintenance medication. This finding is of clinical importance for individuals with recurrent depression, GPs, and mental health-care providers, given that maintaining treatment with an antidepressant for years after remission while on an antidepressant is the most frequently used preventive strategy in recurrent major depressive disorder. In view of the limitations of maintenance antidepressant treatment, including side-effects[8,11,12] and non-adherence,[11,12] PCT might be an alternative for individuals with recurrent major depressive disorder who would like to or have already stopped maintenance medication after recovery. Although the risk of recurrence initially increased during the first few months after initial tapering, over time, antidepressants alone was not superior to adding PCT. This finding indicates that it is important for GPs and psychiatrists to closely monitor and guide tapering of antidepressants in the first few months, and also that PCT is valuable in the tapering phase.

We found that the strategy of PCT with antidepressants led to the greatest reduction in recurrence risk over 24 months. This finding is consistent with previous studies that examined the effect of sequential cognitive therapy started after remission,[15] but contrasts with the findings of a randomised controlled trial[23] showing no additional protective effect of adding MBCT to maintenance antidepressant treatment compared with antidepressants alone. Furthermore, the beneficial effect of PCT is consistent with studies[13,15] showing long-term

prophylactic effects for acute-phase cognitive behavioural therapy in acute major depressive disorder.

Future research should examine why the recurrence risk was not lower in individuals who received PCT while being tapered off antidepressants than in individuals who used antidepressants alone, whereas adding PCT to maintenance antidepressant treatment offered additional protection. One explanation could be that individuals benefit less from PCT during tapering of antidepressants, which is characterised by a (temporary) imbalance (such as flu-like and other symptoms as part of discontinuation syndrome and psychological factors, including fear of recurrence) for many individuals. A review[30] indicated that a variety of symptoms with different onsets (early *vs* late) and durations (short *vs* long) emerge as an individual is tapered off antidepressants. Three different types of withdrawal have been described that could have affected the tapering group: new withdrawal symptoms, rebound, and post-withdrawal persistent disorders.[31] Additionally, the withdrawal symptoms for SSRIs can be different to other types of antidepressants, including SNRIs. Future studies should examine the optimal timing of PCT, either before or after tapering of several types of maintenance antidepressants, and examine the type, timing, and duration of withdrawal symptoms and how they can be differentiated from a depressive relapse. Alternatively, the findings could also be explained by the iatrogenic antidepressants hypothesis, which states that antidepressants reduce depressive symptoms, but that the risk of recurrence is heightened after stopping the drug.[32] Although some support exists for this hypothesis,[32] a placebo-controlled randomised trial is needed that includes participants in the acute phase who have not previously used antidepressants. Moreover, studies are needed to investigate the best relapse prevention strategy at the level of the individual (personalisation).

This study has limitations. First, we included only participants with at least two previous episodes, for whom clinical guidelines recommend long-term antidepressant use. Therefore, the results might not be generalisable to individuals who have had a single depressive episode. Second, because 81% of the participants in our study used SSRIs, it was not be possible to estimate separate effects for SSRIs and other antidepressants. Third, the sensitivity analyses using multiple imputation showed a small attenuation in the effect of adding PCT to antidepressants. However, this result has to be interpreted with caution because its validity depends on the untestable assumption that data were missing at random. Similarly, the per-protocol analyses need cautious interpretation because they were susceptible to selection bias. Fourth, as in many randomised controlled trials, the subgroup and mediation analyses in our study were probably underpowered because the sample size calculation was based on main treatment effects only, which might have led to an increased risk of false-negative results. Thus, all subgroup analyses must be interpreted with caution. Fifth, we did not include a pill-placebo control group or a control group for PCT to examine the specific effects of antidepressants and PCT. Given that keeping individuals with a history of recurrence on antidepressants after remission or recovery has been shown to have preventive effects (OR ranging from 0·30 to 0·48),[7–10] we did not believe that it was ethical to include a purely placebo group (ie, no antidepressant and no psychological treatment). Although we cannot conclude that the preventive effects of PCT while tapering off antidepressants are specific to PCT in the absence of such a control group, we believed that it was better to find an effect that requires a subsequent explanation than to not find an effect in a study that is underpowered because of incorporation of additional controls. However, in line with previous studies,[16–18] we did find that PCT had additional preventive effects over maintenance antidepressant treatment, indicating enduring effects of this psychological intervention.

In conclusion, we found no evidence that maintenance antidepressant treatment is superior to PCT after recovery. Our findings suggest that PCT while tapering off antidepressants might be an alternative strategy to long-term continuation of antidepressants in individuals who wish to stop medication after recovery. Adding eight sessions of PCT to antidepressant treatment after recovery yielded substantial protective effects compared with antidepressants alone (and PCT alone). Therefore, PCT should be offered to individuals with recurrent depression on maintenance antidepressant treatment and to individuals who wish to stop antidepressant treatment after recovery.

Contributors

HJE, GDvR, and CS assisted in collecting the data and writing the report. JO, NSK, EB, JD, PJdJ, WAN, AHS, and SDH were involved in designing and initiating the study, planning the analyses, interpreting the results, and writing the report. CLHB, as the principal investigator, was responsible for designing, initiating, and managing the study; collecting the data; performing the analyses; interpreting the results; and writing the report. NSK and HB were involved in planning and performing the analyses, interpreting the results, and writing the report. All authors approved the final version of the manuscript.

Declaration of interests

CLHB is co-editor of *PLOS One* and receives no honorarium for this role. CLHB is also co-developer of the Dutch multidisciplinary clinical guideline for anxiety and depression, for which she receives no remuneration. She is also a member of the scientific advisory board of the National Insure Institute, for which she receives an honorarium, although this role has no direct relation to this study. CLHB has presented keynote addresses at conferences, such as the European Psychiatry Association and the European Conference Association, for which she sometimes receives an honorarium. She has presented clinical training workshops, some of which include a fee. CLHB receives royalties from her books and co-edited books, and she developed PCT on the basis of the cognitive model of A T Beck. WAN has received grants from the Netherlands Organisation for Health Research and Development and the European Union and honoraria and speaker's fees from Lundbeck and Aristo Pharma, and has served as a consultant for Daleco Pharma. All other authors declare no competing interests.

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