Preventive Cognitive Therapy With Antidepressant Discontinuation During Pregnancy:
Results From a Randomized Controlled Trial

Nina M. Molenaar, MD, PhD[a,b,‡]; Marlies E. Brouwer, PhD[c,‡]; Huibert Burger, MD, PhD[c,d]; Astrid M. Kamperman, PhD[b,e]; Veerle Bergink, MD, PhD[a,b]; Witte J. G. Hoogendijk, MD, PhD[b]; Alishia D. Williams, PhD[f]; Claudi L. H. Bockting, PhD[c]; and Mijke P. Lambregtse-van den Berg, MD, PhD[b,g]

Major depressive disorder (MDD) is a highly prevalent and recurrent mental disorder that can also affect women in the perinatal period.[1] As antidepressants are regarded as effective treatments for MDD,[2] use during the perinatal period is common, with prevalence rates ranging between 1.6% and 5.5%.[3] Many women are reluctant to continue antidepressants during pregnancy and express a strong preference for nonpharmacologic treatment,[4,5] as possible consequences for the unborn child cannot be ruled out.[6,7] Approximately half of women therefore decide to discontinue their antidepressants prior to or during pregnancy.[8–10]

While the wish to avoid in utero antidepressant exposure to the fetus is understandable, discontinuation of medication may lead to relapse.[11] Depressive relapse in the perinatal period can have a profound negative impact on the health of both the mother and the child.[12] Currently, most women who decide to discontinue antidepressants are not offered a substitute nonpharmacologic treatment to prevent relapse, while in the general population, there is evidence that continuation of antidepressants is not superior to Preventive Cognitive Therapy (PCT) or Mindfulness Based Cognitive Therapy (MBCT).[13–17] We present the first randomized controlled trial that evaluated the efficacy of PCT with gradual, guided discontinuation of antidepressants during pregnancy as compared to continuation of antidepressants.

[a]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York
[b]Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands
[c]Department of Psychiatry, Amsterdam University Medical Centers, location AMC, University of Amsterdam, Amsterdam, The Netherlands
[d]Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[e]Epidemiological and Social Psychiatric Research Institute, Erasmus Medical Center, Rotterdam, the Netherlands
[f]Faculty of Science, School of Psychology, The University of New South Wales, Sydney, Australia
[g]Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Sophia's Children Hospital, Rotterdam, The Netherlands
‡Shared first authorship.
*Corresponding author: Nina M. Molenaar, MD, PhD, Icahn School of Medicine at Mount Sinai, Department of Psychiatry, 1425 Madison Ave, New York, NY 10029 (nina.molenaar@mssm.edu).

J Clin Psychiatry 2020;81(4):19l13099

To cite: Molenaar NM, Brouwer ME, Burger H, et al. Preventive cognitive therapy with antidepressant discontinuation during pregnancy: results from a randomized controlled trial. *J Clin Psychiatry*. 2020;81(4):19l13099.

To share: https://doi.org/10.4088/JCP.19l13099

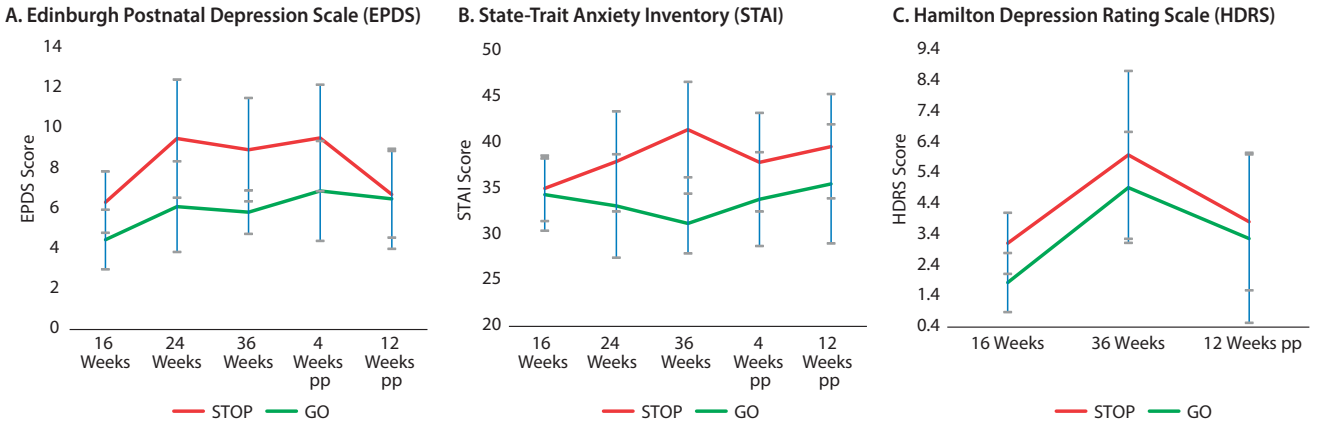
Methods

Details about the study design can be found elsewhere.[18] We included 44 women between 12 and 16 weeks pregnant, with a history of MDD (assessed with the Structured Clinical Interview for *DSM-IV* Axis I Disorders [SCID-I]),[19] currently remitted, and with use of an antidepressant (Supplementary Methods). Comorbid medication was permitted. Women with a history of bipolar or psychotic disorder were excluded. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center. Participants were randomized with a stratified block-randomization allocation to either discontinuation of antidepressants with PCT (STOP; n = 24) or continuation of antidepressant and care as usual (GO; n = 20). Women were followed throughout their pregnancy and up to 3 months postpartum to evaluate relapse of MDD using the SCID-I. Trained assessors masked to treatment allocation conducted all follow-up assessments. Continuous longitudinal self-report outcome measures, including the Edinburgh (Postnatal) Depression Scale,[20] State-Trait Anxiety Scale,[21] and the Hamilton Depression Rating Scale,[22] were collected at baseline, 24 and 36 weeks of pregnancy, and 4 and 12 weeks postpartum. Analyses were carried out according to the intention-to-treat principle. Relapse risk was compared using a 1-tailed Fisher exact test. Odds ratio (OR) and 95% confidence interval (CI) are reported. The difference in time-related proportions of participants with relapse or recurrence by treatment was tested using the log-rank test. We deployed linear mixed models with random intercepts for the continuous variables (Supplementary Methods).

Results

Demographic and clinical data of participants are presented in Supplementary Table 1. Six women (13.6%) experienced a recurrence of depression during study participation, 3 in the GO group (15.0%) and 3 in the STOP group (12.5%; OR = 1.24; 95% CI = 0.22–6.92; $P = .58$). Overall mean time to relapse from baseline (T0) was 143 days (STOP: 101 days, GO: 185 days). The log-rank test showed no statistically significant difference in time to recurrence ($P = .93$). We observed no differences in mood

Figure 1. Outcomes of Discontinuation of Antidepressants With PCT (STOP) vs Continuation of Antidepressants (GO) in Pregnant Women[a]



[a]Error bars indicate 95% confidence intervals.
Abbreviations: PCT = Preventive Cognitive Therapy, pp = postpartum.

symptoms between the two groups over time (Figure 1 and Supplementary Table 2).

Conclusion

We found no evidence that Preventive Cognitive Therapy with gradual discontinuation of antidepressants during pregnancy altered the risk of maternal relapse of depression as compared to continuation of antidepressants. Although our findings need to be replicated in a larger trial, our study is a first step to study continuation versus discontinuation of antidepressants during pregnancy and should encourage further research on alternative strategies to continuation of antidepressants for pregnant women who have recovered from depression.

Published online: June 23, 2020.

Potential conflicts of interest: The authors report no financial or other relationship relevant to the subject of this report.

Funding/support: This work was supported by a grant from the Netherlands Organization for Health Research and Development (836021011), Den Haag, The Netherlands. Additional funding was available from the Erasmus Medical Center, Department of Psychiatry, Rotterdam, The Netherlands.

Role of the sponsor: The funding sources were not involved in the design and conduct of the study, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev*. 2007;27(8):959–985.
2. National Institutes of Excellence (NICE). Depression in Adults: Recognition and Management. https://www.guidelines.co.uk/mental-health/depression-in-adults-recognition-and-management/454977.article. Published April 1, 2018.
3. Molenaar NM, Bais B, Lambregtse-van den Berg MP, et al. The international prevalence of antidepressant use before, during, and after pregnancy: a systematic review and meta-analysis of timing, type of prescriptions and geographical variability. *J Affect Disord*. 2020;264:82–89.
4. Battle CL, Salisbury AL, Schofield CA, et al. Perinatal antidepressant use: understanding women's preferences and concerns. *J Psychiatr Pract*. 2013;19(6):443–453.
5. Kothari A, de Laat J, Dulhunty JM, et al. Perceptions of pregnant women regarding antidepressant and anxiolytic medication use during pregnancy. *Australas Psychiatry*. 2019;27(2):117–120.
6. Campagne DM. Antidepressant use in pregnancy: are we closer to consensus? *Arch Women Ment Health*. 2019;22(2):189–197.
7. Hendrick V, Stowe ZN, Altshuler LL, et al. Placental passage of antidepressant medications. *Am J Psychiatry*. 2003;160(5):993–996.
8. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. *BJOG*. 2015;122(7):1010–1020.
9. Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth*. 2014;14(1):242.
10. Molenaar NM, Lambregtse-van den Berg MP, Bonsel GJ. Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. *Arch Women Ment Health*. 2020;23(1):71–79.
11. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006;295(5):499–507.
12. Alder J, Fink N, Bitzer J, et al. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? a critical review of the literature. *J Matern Fetal Neonatal Med*. 2007;20(3):189–209.
13. Bockting CLH, Klein NS, Elgersma HJ, et al. 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. *Lancet Psychiatry*. 2018;5(5):401–410.
14. Kuyken W, Byford S, Taylor RS, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol*. 2008;76(6):966–978.
15. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet*. 2015;386(9988):63–73.
16. Fava GA, Ruini C, Rafanelli C, et al. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *Am J Psychiatry*. 2004;161(10):1872–1876.
17. Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. *Arch Gen Psychiatry*. 2010;67(12):1256–1264.
18. Molenaar NM, Brouwer ME, Bockting CLH, et al. Stop or go? preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicentre non-inferiority randomized controlled trial. *BMC Psychiatry*. 2016;16(1):72.
19. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
20. Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh Depression Scale during pregnancy. *J Psychosom Res*. 2011;70(4):385–389.
21. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *Br J Clin Psychol*. 1992;31(3):301–306.
22. Hamilton M. Rating depressive patients. *J Clin Psychiatry*. 1980;41(12 Pt 2):21–24.

See supplementary material for this report at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Letter Title: Preventive Cognitive Therapy With Antidepressant Discontinuation During Pregnancy: Results From a Randomized Controlled Trial

Author(s): Nina M. Molenaar, MD, PhD; Marlies E. Brouwer, PhD; Huibert Burger, MD, PhD; Astrid M. Kamperman, PhD; Veerle Bergink, MD, PhD; Witte J. G. Hoogendijk, MD, PhD; Alishia D. Williams, PhD; Claudi L. H. Bockting, PhD; and Mijke P. Lambregtse-van den Berg, MD, PhD

DOI Number: 10.4088/JCP.19l13099

List of Supplementary Material for the Brief Report

1. Supplementary Methods
2. Table 1 Baseline Characteristics
3. Table 2 Effects (Unadjusted and Adjusted) of Treatment Allocation on the Course of Symptoms Throughout Pregnancy Up To 3 Months Postpartum

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published brief report. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

SUPPLEMENTARY MATERIAL

Supplementary methods

Study design

We conducted a CONSORT compliant, pragmatic multicenter randomized controlled non-inferiority trial that compared two strategies for preventing relapse or recurrence of depression in pregnant women with a history of depression. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Medical Ethical Committee of the Erasmus Medical Center. Written informed consent was obtained from all subjects. Trial Registration: Dutch Trial Register, NTR4694, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4694

Participants

Eligible participants were women between 12 and 16 weeks pregnant, with a history of depression (as assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[1], currently remitted, and with use of a Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin Noradrenaline Reuptake Inhibitor (SNRI) or Tricyclic Antidepressant (TCA) for at least 4 months prior to inclusion. Remission was defined as an absence of depression for at least two months as diagnosed with the SCID-I and having a score of 10 or lower on the 17-item Hamilton Depression Rating Scale (HDRS)[2,3], in line with other relapse prevention studies[4–6]. Women were excluded if they had a (1) multiple pregnancy, (2) insufficient proficiency in Dutch or English, (3) severe medical conditions, such as oncology-related conditions or conditions that need urgent medical interventions, which involve treatment decisions overriding research participation, (4) history of or current mania, hypomania or bipolar disorder, (5) current suicidality or self-harm, (6) history of or current psychotic disorder, (7) current alcohol or drug misuse, or (8) current psychological treatment for depressive symptoms equal to or more than once a week. Detailed information on recruitment, screening of eligibility and the informed consent procedure is provided in the study protocol[7].

Recruitment took place between April 2015 and February 2018 on a national level in the Netherlands. Women were referred by their obstetrician, midwife, psychiatrist, psychologist or general practitioner or signed up through social media. During the recruitment phase, a total of 478 pregnant women were referred for further counseling. Thirty-one women (6.5%) were excluded because they were unreachable for further counseling, 204 women (42.7%) were excluded for not fulfilling in- and exclusion criteria, and 198 women (41.6%) were excluded because they did not want to participate, mostly because they felt strongly for either continuation or discontinuation of antidepressants. This resulted in a study population of 44 women (9.2%). Recruitment was stopped due to time constraints and was not associated with trial outcome.

Randomization and masking

Eligible participants were randomized with a stratified block-randomization allocation to either discontinuation of antidepressants with PCT (STOP) or continuation of antidepressant and care as usual (GO). Randomization was done by independent research personnel following baseline assessment with a web based computer-generated randomization schedule (a validated TENALEA Clinical Trial Data Management System; http://www.formsvision.com/) using permuted blocks or random size with a minimum of 2 and a maximum of 16 and stratified for the number of previous depressive episodes (three or less vs. four or more[2]). Participants and physicians were aware of treatment allocation. Trained assessors masked to treatment allocation conducted all subsequent follow-up assessments after baseline assessments.

Interventions

Women assigned to the STOP group were referred to a psychiatrist or their general practitioner (GP), who was instructed by the principal investigator, for discontinuation guidance of their antidepressant. The specialists were instructed to taper the antidepressant over a period of 4 weeks, based upon an expert-based discontinuation protocol and in accordance with the recommendation of a 2009 international guideline from the National Institute for Health and Care Excellence[8]. Participants were allowed to restart antidepressants at any time, which was monitored.

In addition, women in this group received individual PCT by a trained and licensed clinical psychologist. In short, PCT uses techniques focused on dysfunctional beliefs and schema using cognitive challenging techniques, including phantasy (activation of positive network), enhance the recall of specific memories of positive experiences, positive feeling and thoughts, and formulating relapse prevention strategies[9]. This psychological intervention has proven to be effective in relapse prevention[4,10–15] The intervention was applied through VSee (www.vsee.nl), a HIPAA-compliant telehealth app. It consisted of eight weekly VSee sessions of approximately 30 minutes. For each session the participant received an assignment of approximately 10 minutes per day. Therapists were psychologists fully trained in cognitive behavioral therapy who received an additional 10h of training specific to this study. To maintain treatment integrity, therapists followed a PCT treatment manual[61] and received supervision. Treatment adherence was monitored.

Women assigned to the GO group were instructed to continue consulting their prescribing clinician as they regularly did. Research personnel informed the prescribing clinician about their patient's study participation and treatment allocation, and asked to contact the study team in case of adverse events.

Both randomized groups received obstetric care as usual and all care alongside the study interventions was completely registered. In line with the pragmatic nature of the study, once randomized, we did not impose any restrictions with regards to additional care or psychiatric co-medication used during study follow-up by participants from either randomized group. Participants and their treating clinicians from both groups were free to alter treatment management (e.g. re-start of medication), without any interference of study personnel.

Outcome measures

The primary outcome was relapse risk defined as the cumulative incidence of relapse or recurrence of depression, as defined by the SCID-I, during pregnancy and up to 12 weeks postpartum. The SCID-I was standardly assessed at baseline and 12 weeks postpartum. If, based on assessment with the HDRS at fixed time points, relapse/recurrence was suspected (HDRS>13), the SCID-I was performed in the intervening period as well. Interviewers received a minimum of two days of training followed by taped practice interviews and supervised interviews before being eligible to conduct independent interviews. Any inconsistencies, unresolved information, or missing information after interview completion resulted in a call-back to the participant by a second interviewee.

Additionally, secondary repeated continuous outcomes were examined. For registration of severity of depressive symptoms, the HDRS was telephonically assessed at baseline (T0), at 36 weeks of gestation (T3), and at 12 weeks postpartum (T6). For self-reported measures, questionnaires were administered at baseline (T0), 24 and 36 weeks of gestation (T2 & T3) and 4 and 12 weeks postpartum (T5 & T6). For self-reported symptoms of depression, the Edinburgh Postnatal Depression Scale (EPDS) was administered[16]. For symptoms of anxiety, the short version of the State Trait Anxiety Inventory (STAI) was used[17].

Intended sample size

We used a non-inferiority margin of 15%[7]. With this margin, and the assumption that the overall absolute risk of relapse would be around 15%[6], we needed 178 women, given alpha .025, power 80%, and a one-sided test. Unfortunately, we did not reach our intended sample size, due to difficulties with recruitment.

Statistical analysis

Analyses were carried out according to the intention-to-treat principle. The primary outcome was compared between the groups by using a one-tailed Fisher's exact test. Odds Ratio (OR) and 95% Confidence Interval (CI) are reported. We constructed Kaplan-Meier curves to display the time-related proportions of participants with relapse/recurrence by treatment, and tested differences using the log-rank test. Patients who dropped out during follow-up or had not experienced a relapse at 12 weeks postpartum were considered right-censored.

For the secondary repeated continuous outcomes (HDRS, EPDS, and STAI) linear mixed models were deployed. In a series of random-intercept models, we included time, treatment allocation (discontinuation/continuation), and the time x treatment allocation interaction, the latter indicating the intervention effect. Subsequently, we added the standardized baseline score of the HDRS, EPDS or STAI, as baseline symptoms are an important predictor for treatment outcomes. We used random intercepts only as random slopes did not improve model fit as estimated with the Akaike Information Criterion (AIC). Unadjusted and adjusted regression coefficients including 95%CI and p-values are reported. A coefficient of <0.2 indicates a small effect, around 0.5 a moderate effect and of >0.8 a large effect[18]. No imputation of missing values was required, as mixed models allow data for all subjects to be included in the analysis regardless of whether they completed all study time points. In additional models, we adjusted for prognostically important factors in the pertaining regression models: age, ethnicity, education level, multiparity, planned pregnancy, duration of antidepressant use, psychiatric institute admission in the history, number of psychiatric co-morbidities and number of depressive episodes. Due to the limited sample size, no subgroup analyses were performed. All analyses were performed with SPSS, version 25.0.

Supplementary Table 1. Baseline Characteristics

	Overall (n = 44)	STOP (n =24)	GO (n = 20)
Age in years, mean (SD)	32.2 (4.9)	32.3 (5.3)	32.0 (4.5)
Ethnicity, n (%)			
Dutch	31 (70.5)	19 (79.2)	12 (60.0)
Turkish	1 (2.3)	0 (0.0)	1 (5.0)
Surinamese	2 (4.5)	1 (4.2)	1 (5.0)
Other Western	6 (13.6)	3 (12.4)	3 (15.0)
Other non-Western	4 (9.1)	1 (4.2)	3 (15.0)
Level of education, n (%)			
Low	21 (47.7)	12 (50.0)	9 (45.0)
High	23 (52.3)	12 (50.0)	11 (55.0)
Partner, yes (%)	41 (95.3)	23 (95.8)	18 (94.7)
Parity, median (range)	2.0 (1-5)	2.0 (1-5)	2.0 (1-4)
Planned pregnancy, yes (%)	28 (63.3)	15 (62.5)	13 (65.0)
Antidepressant used, n (%)			
Citalopram	19 (43.2)	10 (41.7)	9 (45.0)
Escitalopram	7 (15.9)	3 (12.5)	4 (20.0)
Fluoxetine	1 (2.3)	1 (4.2)	0 (0.0)
Paroxetine	5 (11.4)	2 (8.3)	3 (15.0)
Sertraline	10 (22.7)	8 (33.3)	2 (10.0)
Venlafaxine	2 (4.5)	0 (0.0)	2 (10.0)
Duration of antidepressant use in months, median (range)	38.5 (4-168)	27.5 (4-168)	44.5 (4-168)
Current psychiatric co-medication, n (%)	1 (2.3)	1 (4.2)	0 (0.0)
No. of depressive episodes, median (range)	1.5 (1-7)	2.0 (1-4)	1.0 (1-7)
No. of psychiatric co-morbidities, median (range)	1.0 (0-6)	1.0 (0-4)	1.5 (0-6)
History of psychiatric institute admission, n (%)	8 (18.2)	6 (25.0)	2 (10.0)

Supplementary Table 2. Effects (unadjusted and adjusted) of treatment allocation[a] on the course of symptoms throughout pregnancy up to 3 months postpartum

	β	95% CI	*p*-value
Outcome: Edinburgh (Postnatal) Depression Scale (EPDS)			
Unadjusted	0.34	-0.54; 1.23	0.45
Partially adjusted[b]	0.43	-0.49; 1.35	0.36
Fully adjusted[c]	0.40	-0.55; 1.34	0.41
Outcome: State Trait Anxiety Inventory (STAI)			
Unadjusted	-0.70	-2.51; 1.12	0.45
Partially adjusted	-0.53	-2.38; 1.32	0.57
Fully adjusted	-1.31	-3.31; 0.68	0.20
Outcome: Hamilton Depression Scale (HAM-D)			
Unadjusted	0.24	-1.27; 1.74	0.76
Partially adjusted	0.21	-1.41; 1.83	0.80
Fully adjusted	-0.58	-2.02; 0.85	0.42

[a] Estimates are given for the continuation group (discontinuation as reference) [b] Included time, treatment allocation, time x treatment allocation interaction, and standardized baseline score. [c] Additionally included age, ethnicity, education level, multiparity, planned pregnancy, duration of antidepressant use, psychiatric institute admission in the history, number of psychiatric co-morbidities and number of depressive episodes.

1. First MB, Spitzer R, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. New York; 2002.
2. Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence. *Clin Psychol Rev*. 2015;41:16-26. doi:10.1016/j.cpr.2015.02.003
3. Hamilton M. Rating depressive patients. *J Clin Psychiatry*. 1980;41(12 II):21-24.
4. Bockting CLH, Klein NS, Elgersma HJ, et al. 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. *The lancet Psychiatry*. 2018;5(5):401-410. doi:10.1016/S2215-0366(18)30100-7
5. De Jonge M, Bockting CLH, Kikkert MJ, et al. Preventive cognitive therapy versus care as usual in cognitive behavioral therapy responders: A randomized controlled trial. *J Consult Clin Psychol*. 2019;87(6):521-529. doi:10.1037/ccp0000395
6. Bockting CLH, Smid NH, Koeter MWJ, Spinhoven P, Beck AT, Schene AH. Enduring effects of Preventive Cognitive Therapy in adults remitted from recurrent depression: A 10 year follow-up of a randomized controlled trial. *J Affect Disord*. 2015;185:188-194. doi:10.1016/j.jad.2015.06.048
7. Molenaar NM, Brouwer ME, Bockting CLH, et al. Stop or go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: Study protocol of a pragmatic multicentre non-inferiority randomized controlled trial. *BMC Psychiatry*. 2016;16(1):72.
8. National Institute for Health and Care Excellence. *Depression: The Treatment and Management of Depression in Adults (Update)*.; 2009.
9. Bockting CLH. *Preventieve Cognitieve Training Bij Terugkerende Depressie*. Houten, The Netherlands: Bohn Stafleu Van Loghum: Springer; 2009.
10. Bockting CLH, Schene AH, Koeter HWJ, et al. Preventing relapse/recurrence in recurrent depression with cognitive therapy: A randomized controlled trial. *J Consult Clin Psychol*. 2005;73(4):647-657. doi:10.1037/0022-006X.73.4.647
11. Bockting CLH, Spinhoven P, Wouters LF, Koeter MWJ, Schene AH. Long-term effects of preventive cognitive therapy in recurrent depression: A 5.5-year follow-up study. *J Clin Psychiatry*. 2009;70(12):1621-1628. doi:10.4088/JCP.08m04784blu
12. Bockting CLH, Elgersma HJ, van Rijsbergen GD, et al. Disrupting the rhythm of depression: Design and protocol of a randomized controlled trial on preventing relapse using brief cognitive therapy with or without antidepressants. *BMC Psychiatry*. 2011;11. doi:10.1186/1471-244X-11-8
13. Guidi J, Fava GA, Fava M, Papakostas GI. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: A preliminary meta-analysis. *Psychol Med*. 2011;41(2):321-331. doi:10.1017/S0033291710000826
14. Guidi J, Tomba E, Fava GA. The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: A meta-analysis of the sequential model and a critical review of the literature. *Am J Psychiatry*. 2016;173(2):128-137. doi:10.1176/appi.ajp.2015.15040476
15. Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing Relapse and Recurrence in Unipolar Depression: A Comparative Meta-Analysis of Cognitive-Behavioral Therapy's Effects. *J Consult Clin Psychol*. 2007;75(3):475-488. doi:10.1037/0022-006X.75.3.475
16. Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh Depression Scale during pregnancy. *J Psychosom Res*. 2011;70(4):385-389. doi:10.1016/j.jpsychores.2010.07.008
17. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). *Br J Clin Psychol*. 1992;31(3):301-306. doi:10.1111/j.2044-8260.1992.tb00997.x
18. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. (Lawrence Erlbaum Associates, ed.). New Jersey, NY, USA; 1988.