



Effectiveness of Supported Self-Help in Recurrent Depression: A Randomized Controlled Trial in Primary Care

DOI:
[10.1159/000472260](https://doi.org/10.1159/000472260)

Document Version
Final published version

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Biesheuvel-Leliefeld, K. E. M., Dijkstra-Kersten, S. M. A., van Schaik, D. J. F., Van Marwijk, H., Smit, F., van der Horst, H., & Bockting, C. L. H. (2017). Effectiveness of Supported Self-Help in Recurrent Depression: A Randomized Controlled Trial in Primary Care. *Psychotherapy and Psychosomatics*, 86(4), 220-230. <https://doi.org/10.1159/000472260>

Published in:
Psychotherapy and Psychosomatics

Citing this paper

Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights

Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy

If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [<http://man.ac.uk/04Y6Bo>] or contact openresearch@manchester.ac.uk providing relevant details, so we can investigate your claim.



Effectiveness of Supported Self-Help in Recurrent Depression: A Randomized Controlled Trial in Primary Care

Karolien E.M. Biesheuvel-Leliefeld^a Sandra M.A. Dijkstra-Kersten^a
Digna J.F. van Schaik^b Harm W.J. van Marwijk^{a,c} Filip Smit^{d–f}
Henriette E. van der Horst^a Claudy L.H. Bockting^g

Departments of ^aGeneral Practice and Elderly Care Medicine and ^bPsychiatry, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands; ^cManchester Academic Health Sciences Centre, NIHR School for Primary Care Research, Manchester, UK; ^dNetherlands Institute of Mental Health and Addiction, Utrecht, Departments of ^eClinical Psychology and ^fEpidemiology and Biostatistics, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, and ^gDepartment of Clinical Psychology, Utrecht University, Utrecht, The Netherlands

Keywords

Primary care · Depression · Prevention · Psychotherapy · Self-help · Recurrence

Abstract

Background: The burden and economic consequences of depression are high, mostly due to its recurrent nature. Due to current budget and time restraints, a preventive, low-cost, accessible minimal intervention is much needed. In this study, we evaluated the effectiveness of a supported self-help preventive cognitive therapy (S-PCT) added to treatment as usual (TAU) in primary care, compared to TAU alone. **Methods:** We conducted a randomized controlled trial among 248 patients with a history of depression, currently in full or partial remission or recovery. Participants were randomized to TAU augmented with S-PCT ($n = 124$) or TAU alone ($n = 124$). S-PCT consisted of an 8-week self-help inter-

vention, supported by weekly telephone guidance by a counselor. The intervention included a self-help book that could be read at home. The primary outcome was the incidence of relapse or recurrence and was assessed over the telephone by the Structured Clinical Interview for DSM-IV axis 1 disorders. Participants were observed for 12 months. Secondary outcomes were depressive symptoms, quality of life (EQ-5D and SF-12), comorbid psychopathology, and self-efficacy. These secondary outcomes were assessed by digital questionnaires. **Results:** In the S-PCT group, 44 participants (35.5%) experienced a relapse or recurrence, compared to 62 participants (50.0%) in the TAU group (incidence rate ratio = 0.71, 95% CI 0.52–0.97; risk difference = 14, 95% CI 2–24, number needed to treat = 7). Compared to the TAU group, the S-PCT group showed a significant reduction in depressive symptoms over 12 months (mean difference –2.18; 95% CI –3.09 to –1.27) and a significant increase in quality of life (EQ-5D) (mean difference 0.04; 95% CI 0.004–0.08). S-PCT

had no effect on comorbid psychopathology, self-efficacy, and quality of life based on the SF-12. **Conclusions:** A supported self-help preventive cognitive therapy, guided by a counselor in primary care, proved to be effective in reducing the burden of recurrent depression.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Major depressive disorder (MDD) is a prevalent mental disorder and is associated with a high risk of relapse and recurrence [1]. MDD is frequently associated with incomplete remission between episodes [2, 3] and is considered to be among the most disabling illnesses [4], negatively affecting many aspects of life [5, 6]. Current guidelines recommend continuation of antidepressant medication (ADM) and/or psychological treatment, e.g., cognitive (behavioral) therapy (CT or CBT), to reduce the risk of relapse and recurrence [7, 8]. The most commonly used strategy is a continuation of ADM [9–12]. The recommendations on ADM are under debate [12] as the optimal duration of the continuation or maintenance phase has not been studied well enough [9, 11]. Also, there is conflicting evidence about the effect of discontinuation of ADM on relapse or recurrence [13] and, furthermore, reported levels of ADM nonadherence have been consistently high [14]. In conclusion, proactive management based on the continuation of ADM alone may not be the most optimal strategy in preventing relapse or recurrence.

Research demonstrates that psychological interventions, specifically aimed at the prevention of relapse and recurrence in patients with a history of depression, offered during the continuation or maintenance phase, are effective in reducing the risk of relapse and recurrence compared to treatment as usual (TAU), active control condition, and/or ADM [15–19]. These interventions are mostly based on C(B)T [20], but add strategies such as modifying dysfunctional metacognitions in preventive CT (PCT) [21] and meditation in mindfulness-based CT [22]. Interpersonal psychotherapy links stressful life events and insufficient social support to relapse and recurrence [23]. The majority of these interventions is offered in secondary care, often relying on the intensive use of therapist's time, and, therefore, they are costly. A minimally supported self-help intervention may help to overcome this problem. We considered the evidence base for CBT-based interventions to be the strongest [17] and expected that a self-help intervention

would be both low threshold and low cost, as was suggested in an ante hoc health economic modeling study which was conducted before the trial-based evaluation. Finally, we expected that a minimally supported intervention would keep dropout rates low. A recent trial by Gilbody et al. [24] showed that the evidence for the effectiveness of standalone E-mental health interventions is limited. Therefore, the intervention included minimal support. Supported self-help has already proved as effective as face-to-face treatments in acutely depressed patients according to a meta-analysis of 21 studies, reporting an effect on symptoms of depression [25]. The integration of supported self-help in primary care, supported by paraprofessionals [25], into current longitudinal primary care systems, would fit best with the recurrent character of depression. The challenges in providing such service in primary care depend on the actual dynamics between the patients, health care professionals, the intervention and the organization of care. Therefore, in this study, we conducted a randomized controlled trial to evaluate the effectiveness of a supported self-help PCT (S-PCT) in primary care in patients with a history of depression, currently not meeting the criteria for depression.

Methods

Design

We performed a pragmatic randomized controlled trial with 2 parallel groups of participants comparing TAU augmented with S-PCT, with TAU alone. Participants were observed for 12 months. The design of this study is described in more detail elsewhere [26]. The study was called the PARADE study (Prevention of Recurrent Depression). The study is registered in the Dutch Trial Register, www.trialregister.nl, under NTR3001.

Ethics

The Medical Ethics Committee of the VU University Medical Center Amsterdam approved the study protocol (2011/285), and all participants provided written informed consent.

Terminology

To describe the course of depression, we use the operational criteria of Frank et al. [27]. According to these criteria, the course of depression is described as a series of disease stages in which a patient can move from a symptom-free stage to a stage characterized by some symptoms but not meeting the diagnostic criteria, to a stage with the full-blown disorder, after which the patient can go into remission. When a patient stays in remission for a minimum of 6 months, he or she is considered to be recovered. Subsequently, a relapse is defined as a depressive episode that occurs during remission and before recovery, while a recurrence is defined as a depressive episode that occurs after recovery.

Participants

S-PCT was delivered in primary care, but recruitment took place through general practices in primary care and in mental health care services (secondary care) in the Netherlands. To be included in the trial, participants had to (a) be 18 years or older, (b) be in full or partial remission (meaning the presence of residual symptoms) of recurrent MDD for at least 2 months, but no longer in recovery than 5 years according to the Structured Clinical Interview for DSM-IV axis 1 disorders (SCID-1 3.0) [28], and (c) have experienced 2 or more previous episodes of MDD. The SCID-1 interview was conducted over the telephone by trained researchers and psychologists. Telephone-administered SCIDs are valid and reliable compared to face-to-face administered SCIDs [29], which are considered the gold standard. Exclusion criteria were severe cognitive impairment, current or past mania, hypomania or psychosis, current alcohol or drug abuse, or insufficient mastery of the Dutch language.

Intervention

The intervention is an 8-week supported self-help and is a manualized PCT-based bibliotherapy consisting of a printed self-help book with 8 modules and minimal guidance [30]. It is based on an effective face-to-face PCT [21] and mobile PCT [31]. PCT is an adapted type of cognitive therapy for acute depression [20] and aims to prevent relapse and recurrence in remitted patients with a history of depressive episodes. The intervention prevention program targets underlying cognitive vulnerability factors, such as dysfunctional beliefs. Unlike CT for acutely depressed patients, S-PCT is not primarily directed toward modifying negative thoughts. Instead, it starts with the identification of negative thoughts and dysfunctional attitudes, aided by a self-report questionnaire with examples of attitudes and specific challenging techniques. The focus of the self-help book is then directed on changing these attitudes by using different cognitive techniques such as identification of positive attitudes. Moreover, practice in daily life with alternative attitudes is promoted. Part of the modules is keeping a diary of positive experiences to enhance specific memories of positive experiences, instead of retaining overly general memories. Further specific relapse and recurrence prevention strategies are formulated in the last modules of the S-PCT resulting in a personal prevention plan. Like regular CT, PCT follows a fixed structure with agenda setting, review of homework, explanation of the rationale of each session, and the assignment of homework. Participants complete 1 module per week. Each module includes reading homework plus assignments, to be completed in approximately 60 min. In the current project, the counselor explained the rationale of PCT and coming weeks' planning in a first contact (by phone or face to face), before the start of the intervention. Each week, the counselor contacted the participant by phone to evaluate progress and understanding. This call was strictly protocolled and was designed to last no longer than 15 min. The nature of the contact was solely to support the participant and not to engage in a therapeutic relationship actively.

Counselors

Twenty-four counselors (primary care mental health nurses and psychologists) were trained to guide the intervention. The psychologists were nonspecialized psychologists (i.e., without post-doctoral training in clinical interventions). All counselors attended a 1-day training delivered by experienced clinical psychologists, who developed the intervention and therefore had an intimate

knowledge of S-PCT. Before the start of the trial, the trainers evaluated the competence of the counselors by giving feedback on audiotaped telephone contacts with 2 pilot patients for each counselor during a 1-day supervision session. During the trial, counselors could contact the trainers at any time for additional questions and feedback. To assess adherence, each week, the counselor completed a checklist with 4 items: (1) the number of that week's module (1–8), (2) the compliance of the participants in reading the literature of that week (yes/no plus reason), (3) the compliance of the participants in doing the assignments (yes/no plus reason), and (4) the time spent on the call (min).

Treatment as Usual

There were no restrictions on the type of TAU. Service providers who did not know their patients were enrolled in a study and patients were asked not to tell their service providers about their enrollment.

Current TAU guidelines recommend encouraging a person who has benefited from taking ADM, to continue ADM for at least 6 months after remission of an episode of depression. On psychological interventions, guidelines recommend offering CBT to persons with a significant history of depression plus residual symptoms and mindfulness-based CT to patients with a history of at least 3 episodes of depression [7, 8]. TAU was recorded using the Trimbos and iMTA self-report questionnaire for Costs associated with Psychiatric Illnesses [32].

Treatment Allocation

Once participants had provided informed consent, they received the SCID interview to assess eligibility criteria. When participants were eligible, randomization was conducted by an independent statistician using computer-generated random numbers in blocks of size 2. Participants were randomized on the order in which their baseline SCID interview was conducted by the researchers. Randomization was stratified by the number of previous depressive episodes (2–3 vs. ≥ 4 episodes) because the number of previous episodes is associated with relapse and recurrence [33]. Randomization was concealed from the assessors who conducted interviews during the observation period, as they were not informed about the participants' randomization status, and participants were requested not to disclose randomization status to the assessors.

Blinding

Interviewers were blind to the randomization status of the participants during all measurements. Due to the nature of the intervention, it was not possible to blind the participants. At the start of each interview, participants were asked not to reveal their randomization status to the interviewers.

Outcome Measures

Primary Outcome

The primary outcome was the incidence rate of relapse or recurrence of depression. Participants were observed for 12 months beginning with the start of the intervention which took place within 2 weeks after randomization. To reduce recall bias, telephone SCID interviews were conducted over 6 months, at 6 and 12 months and combined into a single outcome (0 = no relapse or recurrence, 1 = relapse or recurrence). The incidence rate ratio (IRR) was calculated by comparing the incidence rates of new ep-

isodes in both conditions. An IRR <1 implies a better risk reduction in the intervention group relative to the control group; the intervention is then deemed successful. IRR = 1 and IRR >1 imply no effect or an adverse effect, respectively. In case participants proved depressive according to the telephone SCID interview, they were advised to contact their primary care physician or mental health caregiver. In the case of suicide thoughts or beliefs, we contacted the general practitioner immediately which was signed for in the informed consent.

Secondary Outcomes

Secondary outcomes were assessed online at baseline and at 6 and 12 months (depressive symptomatology, health-related quality of life) or at 9 and 12 months (comorbid psychopathology, self-efficacy).

Depressive symptoms were assessed using the Dutch translation of the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-sr) [34]. This self-report questionnaire consists of 16 symptom items to be answered on a 4-point Likert scale. A score of 0–5 is categorized as no depressive symptoms, 6–10 as mild, 11–15 as moderate, 16–20 as severe, and 20–27 as very severe depressive symptoms.

Health-related quality of life was examined using the Dutch translations of the 12-Item Short-Form Health Survey (SF-12) [35] and the European Quality of Life Five-Dimensions (3-level) Health Status Questionnaire (EQ-5D) [36]. The SF-12 is a measure of health-related functional status [37] and yields 2 summary measures of physical and mental health. It is the most commonly used health measure and, therefore, outcomes can be easily compared to other studies using the SF-12. The EQ-5D measures health-related quality of life on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety and depression), combined into 1 outcome. Each dimension is rated at 3 levels corresponding to whether a respondent has no problems, moderate or extreme problems. The value of each of the 243 health states is preference weighted using valuations from the Dutch population [38]. Besides the SF-12, we used the EQ-5D because it is the most commonly used health measure in a cost-effectiveness analysis, which we plan to report.

Comorbid symptoms were measured with the Four-Dimensional Symptom Questionnaire [39], which is a self-rating questionnaire that comprises 50 items distributed over 4 scales (distress, depression, anxiety, and somatization).

Perceived *self-efficacy* was assessed with the General Self-Efficacy Scale [40], which consists of 10 items, scored 1–4. Especially in the self-help condition, self-efficacy might change in the course of the intervention and during the observation period.

Sample Size

We combined findings from previous research [16, 41] and assumed a mean relapse or recurrence rate of 40% during the observation period versus 60% in the controls. To detect this 20% risk reduction in a 2-sided test at $\alpha = 0.05$ and a power of $1 - \beta = 0.80$, 107 participants in each condition were required. Compensating for loss to follow-up of 10% over the whole 12-month observation period required at least $(107/0.90 =)$ 119 participants at baseline in each trial arm. Our own experience with randomization of patients at general practice level [42, 43] indicates that clustering of patients within practices has no impact on the power of the trial. Therefore, we did not take clustering effects into account.

Statistical Analyses

We investigated whether baseline characteristics differed between conditions. In addition, we compared the baseline characteristics of dropouts and those who completed all measurements during the 12-month observation period by performing logistic regression analysis. Data were primarily analyzed on the basis of the intention-to-treat (ITT) principle. Missing values on outcome measures were imputed using multiple (10-fold) imputation by chained equations [44]. The analyses were performed in each of the 10 data sets, and the results of the analyses were pooled using the Rubin rules [45].

To compare risk on relapse or recurrence in both conditions, we performed a Poisson regression analysis of the incidence of relapse or recurrence on the treatment condition. In this manner, we obtained an IRR. Because the use of Poisson regression tends to provide conservative results [46, 47] and overestimates error [47], we used the Hubert-White sandwich estimator as implemented in STATA [48]. Results were adjusted for baseline (residual) depressive symptoms (QIDS-sr). Previous trials indicated that depression status is associated with relapse/recurrence, and therefore we adjusted to improve our estimates [49, 50].

Estimates of the intervention effects on the secondary outcome measures (all continuous) were obtained over 12 months from linear mixed models. Randomization status, R , time of measurements, T , and randomization-by-time interaction ($R \times T$) were included as fixed effects in the models. The participants' identification was included as random term because in the long data set the same participant could have contributed to the data set at some or all time points. We assessed the overall effect of the intervention by testing the interaction between randomization and time of measurement that was associated with outcome. Means were adjusted for baseline level of the outcome. In linear mixed models, imputation of missing data is not necessary. The results of the ITT analysis were compared with the results of the per-protocol analysis, including those participants who completed at least 80% of the intervention (5 modules). All analyses were performed with STATA (version 12). Statistical significance was tested 2-tailed.

Results

Recruitment

Details of enrollment are shown in Figure 1. Recruitment took place between September 2012 and April 2014. Medical records of 22 family practices and 4 specialized mental health care institutions were screened for eligible patients. This led to the selection of 5,489 patients, who received a short information letter. Finally, 248 patients met all inclusion criteria and signed an informed consent. They were randomly allocated to the S-PCT group (124) or to the TAU group (124). In primary care, 3,517 invitation letters led to 129 participants (3.7%), and in secondary care 1,971 letters led to 109 (5.6%). Primary care patients had a mean QIDS-sr score of 9.13 (SD = 4.58), and secondary care patients scored 9.31 (SD = 5.24).

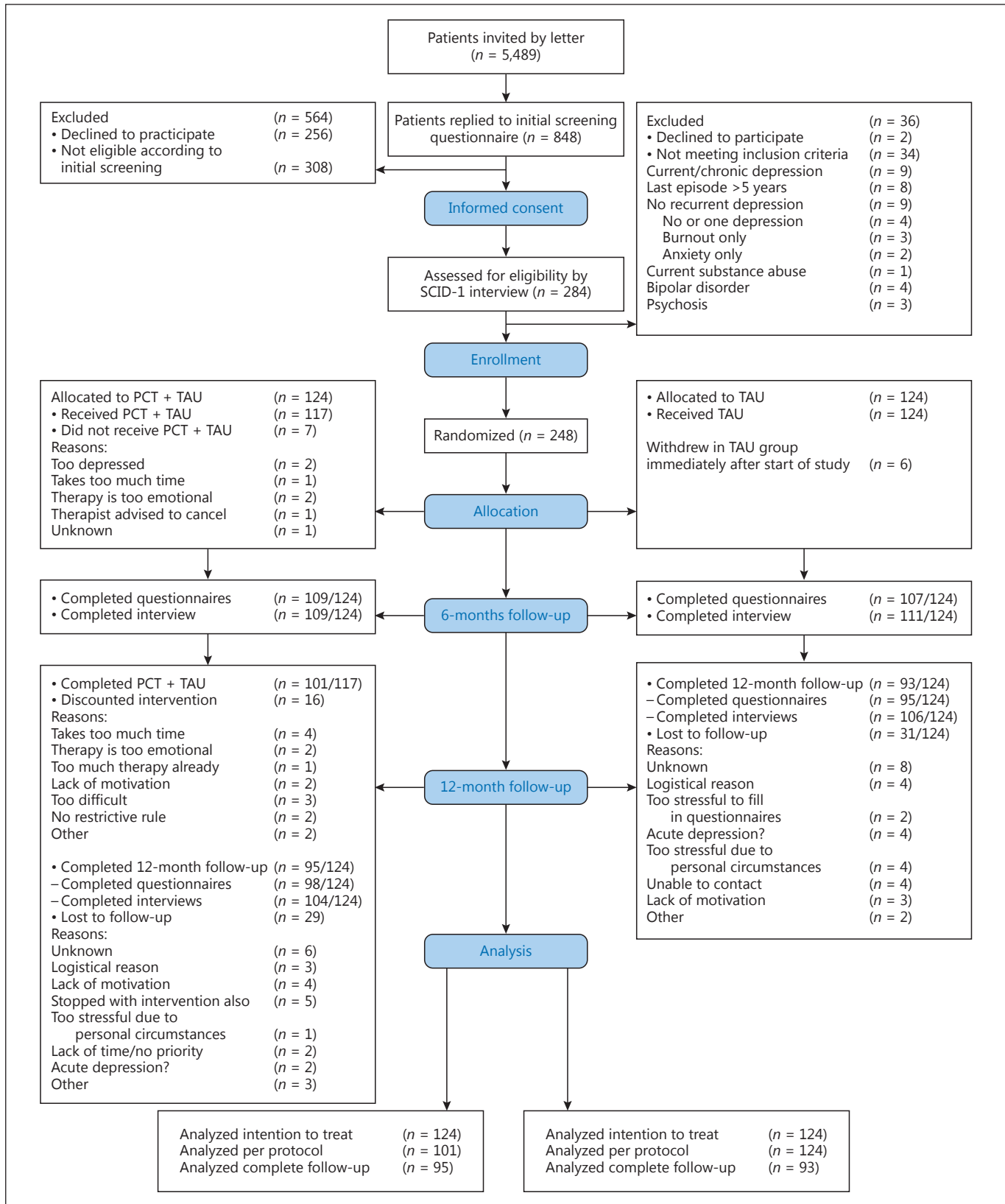


Fig. 1. Participant flow diagram.

Table 1. Baseline demographic and descriptive characteristics of the study population according to randomized group

Characteristics	S-PCT (n = 124)	TAU (n = 124)	All participants (n = 248)
Age, years	48.6±11.9	48.8±11.4	48.7±11.7
Females, n (%)	89 (71.8)	84 (67.7)	173 (69.8)
Previous episodes, %			
2 or 3	53.2	49.9	51.6
4 or more	46.8	50.1	48.4
Marital status, %			
Partner	64.9	64.9	64.9
Education, %			
High education ^a	42.7	35.5	39.1
Age at onset, years	28.2±11.4	27.5±12.3	27.8±11.9
Depressive symptoms (QIDS-sr)	9.6±4.8	8.9±5.0	9.3±4.9
Quality of life			
Mental health (SF-12)	53.6±12.2	53.5±11.6	53.5±11.9
Physical health (SF-12)	59.4±11.4	57.6±11.7	58.5±11.6
EQ-5D	0.77±0.21	0.78±0.20	0.77±0.2
Comorbid psychopathology (4-DSQ)			
Anxiety	3.2±3.9	3.2±4.3	3.2±4.1
Distress	13.0±7.6	12.7±8.0	12.8±7.8
Somatization	8.1±5.5	8.9±5.7	8.5±5.6
Pain (MPQ)	2.5±3.6	3.2±4.2	2.8±3.9
Fatigue (FSS)	3.8±1.5	3.9±1.6	3.8±1.6
Self-efficacy (GSES)	28.6±5.9	28.3±6.2	28.4±6.0
ADM use past 3 months, %	51.8	56.7	54.2

Results are expressed as means ± SD unless indicated otherwise. TAU, treatment as usual; SD, standard deviation; ADM, antidepressant medication; SF-12, 12-Item Short-Form Health Survey; MPQ, MacGill Pain Questionnaire; FSS, Fatigue Severity Scale; GSES, General Self-Efficacy Scale; EQ-5D, European Quality of Life Five-Dimensions Health Status Questionnaire; QIDS-sr, Quick Inventory of Depressive Symptoms Self-Report; 4-DSQ, Four-Dimensional Symptom Questionnaire. Standard deviations for multiply imputed data were computed from the standard errors: $SD = \sqrt{_{b}[\text{var}^2] - _b[\text{var}] \times _b[\text{var}]}$. ^aHigh education is defined as bachelor's or master's degree.

Baseline Characteristics

In Table 1, baseline sociodemographic and clinical characteristics of the ITT group are presented. No relevant baseline imbalances were found. At baseline, all participants were in (partial) remission or recovery of recurrent MDD and experienced mild depressive symptoms (mean QIDS-sr = 9.3, SD = 4.9). The intervention group had a mean QIDS-sr score of 9.6 (SD = 4.8) and the controls one of 8.9 (SD = 5.0), indicating moderate residual symptoms.

Numbers Analyzed

Complete data for the 12-month observation period were collected from 95/124 participants (77%) in the intervention group and 93/124 participants (75%) in the control group, which was not statistically different

[$\chi^2(247) = 0.088$]. Loss to follow-up was significantly associated with more fatigue at baseline [difference in mean = 0.602, 95% CI 0.115–1.089, $t(235) = 2.437$, $p = 0.016$].

Primary Outcome

Incidence of Relapse or Recurrence of Depression

Twelve months after randomization, a new relapse or recurrence of depression had occurred in 44 (35.5%) participants in the intervention group and 62 (50.0%) participants in the control group (Table 2). The IRR was therefore $35.5/50.0 = 0.71$ [95% CI 0.52–0.97, $t(234.4) = -2.16$, $p = 0.032$]. The risk difference between the TAU group and the S-PCT group was $50.0 - 35.5 = 14.5\%$ [95% CI 2–24, $t(167.7) = -2.25$, $p = 0.025$] which corresponds to a number needed to treat of 7 (Table 3).

Table 2. Descriptive unadjusted statistics at baseline, 6 and 12 months: ITT analysis and per-protocol (PP) analysis

	ITT analysis		PP analysis	
	S-PCT (<i>n</i> = 124)	TAU (<i>n</i> = 124)	S-PCT (<i>n</i> = 101)	TAU (<i>n</i> = 124)
<i>Primary outcome</i>				
Relapse or recurrence after 12 months	44/124 (35.5)	62/124 (50.0)	35/101 (34.7)	62/124 (50)
<i>Secondary outcomes</i>				
Depressive symptoms (QIDS-sr)				
Baseline	9.6±4.8	8.9±5.0	10.1±4.8	8.9±5.0
6 months	6.3±4.3	8.7±4.9	6.3±4.3	8.7±4.9
12 months	7.2±4.9	7.7±5.3	7.3±4.8	7.7±5.3
Functional impairment (SF-12, mental)				
Baseline	53.6±12.2	53.5±11.6	53.5±12.1	53.5±11.6
6 months	53.3±10.7	51.7±11.8	53.1±10.6	51.7±11.8
12 months	53.4±10.4	54.4±12.2	53.2±10.6	54.4±12.2
Functional impairment (SF-12, physical)				
Baseline	59.4±11.4	57.6±11.7	59.3±11.6	57.6±11.7
6 months	58.7±10.8	56.8±11.5	58.9±10.4	56.8±11.5
12 months	60.5±11.5	58.8±12.6	60.3±11.6	58.8±12.6
Health-related quality of life (EQ-5D)				
Baseline	0.77±0.21	0.78±0.20	0.74±0.22	0.78±0.20
6 months	0.81±0.19	0.77±0.20	0.81±0.19	0.77±0.20
12 months	0.80±0.19	0.78±0.24	0.79±0.19	0.78±0.24
Anxiety (4-DSQ)				
Baseline	3.2±3.9	3.2±4.3	3.5±4.0	3.2±4.3
9 months	3.0±3.7	2.6±4.1	3.1±3.7	2.6±4.1
12 months	2.8±3.7	2.9±4.2	2.9±3.7	2.9±4.2
Distress (4-DSQ)				
Baseline	13.0±7.6	12.7±8.0	13.7±7.7	12.7±8.0
9 months	12.3±8.1	11.5±8.8	12.4±8.0	11.5±8.8
12 months	11.9±8.8	11.6±8.7	12.1±8.8	11.6±8.7
Somatization (4-DSQ)				
Baseline	8.1±5.5	8.9±5.7	8.4±5.8	8.9±5.7
9 months	8.2±5.8	8.4±6.0	8.4±5.9	8.4±6.0
12 months	7.6±5.4	7.6±5.4	7.8±5.4	7.6±5.4
Self-efficacy (GSES)				
Baseline	28.6±5.9	28.3±6.2	28.3±6.2	28.3±6.2
9 months	28.8±6.8	29.3±6.2	28.8±6.7	29.3±6.2
12 months	28.6±7.1	28.8±7.0	28.5±7.0	28.8±7.0

Primary outcomes are expressed as *n* (%) and secondary outcomes as means ± SD. EQ-5D, European Quality of Life Five-Dimensional Health Status Questionnaire; ITT, intention-to-treat; QIDS-sr, Quick Inventory of Depressive Symptoms Self-Report; GSES, General Self-Efficacy Scale; 4-DSQ, Four-Dimensional Symptom Questionnaire; SF-12, 12-Item Short-Form Health Survey; TAU, treatment as usual; S-PCT, self-help preventive cognitive therapy; SD, standard deviation.

Secondary Outcomes

Depressive symptom scores in the intervention group decreased significantly compared to TAU over 12 months with 2.18 QIDS-sr points (95% CI −3.09 to −1.27, *Z* = −4.70, *p* < 0.001). This longitudinal between-group mean difference (with an SD of 7.3) translates into

a clinically small standardized effect size of *d* = 0.30 [51]. Quality of life improved significantly with a between-group mean difference of 0.04 EQ-5D points (95% CI 0.004–0.08, *Z* = 2.18, *p* = 0.029). No significant effects were found on any of the other secondary outcomes (Table 2).

Table 3. Testing the between-group differences over 12 months using Poisson regression and linear mixed modeling adjusting for the baseline values of the dependent variable (ITT analysis and per-protocol, PP, analysis)

Primary outcome	ITT analysis (S-PCT: <i>n</i> = 124; TAU: <i>n</i> = 124)			PP analysis (S-PCT: <i>n</i> = 101; TAU: <i>n</i> = 124)		
	IRR ^a (95% CI)	RD ^b (95% CI)	NNT	IRR ^c (95% CI)	RD ^d (95% CI)	NNT
Relapse or recurrence	0.71 (0.52 to 0.97)	14 (2 to 24)	7	0.68 (0.50 to 0.93)	15 (4 to 25)	7
Secondary outcomes	Mean group difference ¹ (95% CI)	Z value	<i>p</i>	Mean group difference ¹ (95% CI)	Z value	<i>p</i>
Depressive symptoms (QIDS-sr)	-2.18 (-3.09 to -1.27)	-4.70	<0.001	-2.31 (-3.26 to -1.37)	-4.81	<0.001
Health-related quality of life (SF-12, mental)	0.67 (-1.33 to 2.67)	0.65	0.513	0.44 (-1.62 to 2.50)	0.42	0.675
Health-related quality of life (SF-12, physical)	1.05 (-0.81 to 2.91)	1.10	0.270	0.89 (-1.01 to 2.80)	0.92	0.359
Health-related quality of life (EQ-5D)	0.04 (0.004 to 0.08)	2.18	0.029	0.04 (0.003 to 0.81)	2.10	0.036
Anxiety (4-DSQ)	-0.05 (-0.68 to 0.59)	-0.14	0.887	-0.05 (-0.71 to 0.60)	-0.16	0.872
Distress (4-DSQ)	-0.21 (-1.81 to 1.39)	-0.26	0.798	-0.25 (-1.90 to 1.41)	-0.29	0.769
Somatization (4-DSQ)	0.38 (-0.64 to 1.39)	0.73	0.464	0.42 (-0.63 to 1.48)	0.79	0.432
Self-efficacy (GSES)	-0.68 (-1.91 to 0.55)	-1.08	0.280	-0.57 (-1.81 to 0.67)	-0.91	0.36

QIDS-sr, Quick Inventory of Depressive Symptoms Self-Report; CI, confidence Interval; GSES, General Self-Efficacy Scale; 4-DSQ, Four-Dimensional Symptom Questionnaire; EQ-5D, European Quality of Life Five-Dimensional Health Status Questionnaire; SF-12, 12-Item Short-Form Health Survey; IRR, incidence rate ratio; ITT, intention-to-treat; NNT, number needed to treat; RD, risk difference; TAU, treatment as usual; S-PCT, supported self-help preventive cognitive therapy.

ITT: ^a *p* = 0.032; an IRR <1 means that over 12 months more patients in the TAU group recurred compared to the S-PCT group; scores were adjusted for depressive symptoms (QIDS-sr) at baseline; ^b *p* = 0.025; RD is the percentage risk difference in relapse and recurrence rate between S-PCT and TAU over the 12-month observation period. PP: ^c *p* = 0.017; scores were adjusted for depressive symptoms (QIDS-sr) at baseline; ^d *p* = 0.011; RD is the percentage risk difference in relapse and recurrence rate between S-PCT and TAU over the 12-month observation period. ¹ Scores were adjusted for baseline level of the outcome and estimated with linear mixed modeling.

The Supported Self-Help Intervention

Seven participants did not start the supported self-help intervention (7/124 = 6%). Two participants dropped out after the first contact (2%), and 5 participants dropped out after the first S-PCT meeting (4%). Reasons for drop-out are shown in Figure 1. From the 117 participants who started the intervention, 16 (18.5%) dropped out during the intervention, all before week 6 of the intervention. In total, 101 participants (81%) completed at least 5 modules (80%), and were labeled as “completers.” At baseline, completers experienced more depressive symptoms [mean difference = 2.22, 95% CI 0.010–4.35, *t*(236) = 2.06, *p* = 0.04], more distress [mean difference = 3.46, 95% CI 0.02–6.90, *t*(235) = 1.98, *p* = 0.049] and a lower quality of life (EQ5D) [mean difference = -0.11, 95% CI 0.02–0.20, *t*(236) = -2.52, *p* = 0.012] than noncompleters.

Participants were supported by a primary care mental health nurse (31.5%) or by a nonspecialized psychologist (68.5%). The first contact was organized face to face (40.3%) or by telephone (59.1%). The mean amount of time spent per phone call per participant by the counselor was 13.8 min (SD = 5.42), totaling a mean of 110.2 min of attention per participant per treatment. Adjusting for the type of counselor, the type of first contact or the mean

length of time spent per phone call per participant did not influence the results on effectiveness. No adverse events were observed.

According to the checklist of the counselors, in 6% of all contacts, the participant had not read the literature belonging to that week’s module. Reasons for not reading the literature were (more than 1 reason per participant was possible): lack of time (19), too difficult (10), practical considerations (7), too depressed (6), did not feel like it (1), other (3). In 11% of all contacts, the participants declared they did not complete the assignments for that week’s module. Reasons for not doing assignments were: lack of time (28), too difficult (21), too depressed (11), practical considerations (11), did not feel like it (5), physical illness (5), intervention does not meet expectations (2), other (2).

Treatment as Usual

At the end of the 12-month observation period, the percentage of participants in the S-PCT group and TAU group who received ADM at any moment during the past 3 months was 47% for both groups [$\chi^2(1) = 0.0001$, *p* = 0.994]. Compared to baseline, relatively more participants in the TAU group stopped using ADM than in the

S-PCT group during the observation period, but this difference was not significant ($p = 0.742$). At the end of the 12-month observation period, 43% of the participants in the S-PCT group received additional counseling from a psychiatrist/psychologist/psychotherapist versus 40% of the participants in the TAU group [$\chi^2(1) = 0.172$, $p = 0.678$].

Per-Protocol Analysis

The per-protocol analysis included only those participants who completed at least 80% (5 modules) of the intervention (81%; 101/124 participants). The results were roughly comparable to the results of the ITT analysis. The difference in incidence rate of relapse or recurrence between the S-PCT group and the TAU group was more pronounced than in the ITT analysis [IRR = 0.68, 95% CI 0.50–0.93, $t(370.3) = -2.39$, $p = 0.017$; risk difference = 15%, 95% CI 4–25, number needed to treat = 7] (Table 3). Similar to the ITT analysis, both the depressive symptoms score and quality of life score (EQ5D) changed significantly over 12 months in the intervention group compared to the TAU group (–2.31 QIDS-sr points, 95% CI –3.26 to –1.37, $Z = -5.87$, $p < 0.001$; 0.04 points, 95% CI 0.003–0.81, $Z = 2.10$, $p = 0.036$, respectively).

Discussion

The patient group in our trial was clearly vulnerable as no less than 50% of the participants who received usual care experienced a relapse or recurrence of depression within 12 months. In the intervention group this percentage was reduced, but still, one third of the patients in the S-PCT group relapsed, which underlines the public health significance of ongoing development of proactive strategies. The IRR of 0.71 that we found was somewhat higher (i.e., the intervention may have been less effective) than the IRR we found in our meta-analysis (0.64) comparing psychological interventions to usual care [17]. Participants in our trial experienced a higher level of residual symptoms than participants in the studies that were included in the meta-analysis, and therefore, the a priori chance of relapse or recurrence might have been higher in our trial. An average health gain of 0.04 quality-adjusted life years in the intervention group is perhaps only just noticeable by the participants as a subjectively felt improvement of the quality of their lives [52].

The reach of possible eligible patients may have worked better in secondary than in primary care because of the higher motivation and because diagnoses are more ex-

plicit. Relapse prevention offered shortly after the depression has remitted is most successful because the motivation to participate might be optimal at that time [17].

Loss to follow-up was around 24% in both arms instead of an assumed loss to follow-up of 10%. Perhaps, a self-help approach is too “light-weighted,” and the same characteristics that lead to a patient’s vulnerability to depression (feelings of worthlessness, loss of interest, etc.) may cause an earlier dropout in this type of intervention.

Finally, results of the ITT analysis and the per-protocol analysis appeared quite similar. These results might imply that receiving the suggested number of sessions has a limited impact on the final results.

A strength of our study is that our operationalization of depression and relapse or recurrence was based on a structured clinical interview (SCID-1). A further strength is that our participants achieved remission and/or recovery on antidepressants, other psychotherapies, psychiatric help, counseling, or no treatment at all, as typically present in clinical practice. Moreover, there were no restrictions in using medication at entry to the study. Therefore, this study was designed to maximize external validity, which suggests good generalizability of the findings. Third, very few prevention studies have been performed at the interface of primary and secondary care.

Our study also has limitations. First, though the nature of the contact between the counselor and the participant was solely to support the participant and not to actively engage in a therapeutic relationship, still the interpersonal relationship may have served as an effective element of therapy in and of itself. Secondly, we did not adjust for the fact that some forms of TAU could in and by themselves be more effective in reducing relapses and recurrences than others, which may have partially caused superiority of S-PCT. Yet, over 12 months the use of antidepressant medication, which is the first-step treatment in guidelines for recurrent depression, was not associated with treatment condition in the study. Thirdly, survival analyses, with time to recurrence as the outcome measure, would have allowed better comparisons to the literature, would have opened the exploration of the distribution of the hazards over time and given us an idea how long it takes for the intervention to work. Fourth, we did not adjust for risk factors for developing depression such as chronic medical conditions and must assume that randomization has led to a balanced distribution of such factors across the conditions. Fifth, the intervention in our trial was offered at a random moment during remission or recovery: some participants had been recovered for up to 5 years (and thus were at low risk for recurrence) while others

were in remission or partial remission for only 2 months (and thus were at high risk for relapse). This clinical heterogeneity might have impacted overall results.

Acknowledgments

We are very grateful to all participants. We would also like to thank all recruitment sites for their efforts – GGZ NHN, GGZ Amstelveen, GGZ Zuiderpoort, GGZ Rivierduinen, de Bosgroep – and the participating general practitioners. We also thank all counselors for their guidance. Finally, we are grateful to Evelien van Valen for her help.

References

- 1 Burcusa SL, Iacono WG: Risk for recurrence in depression. *Clin Psychol Rev* 2007;27:959–985.
- 2 Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ: Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychol Med* 2010;40:41–50.
- 3 Conradi HJ, Ormel J, de Jonge P: Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med* 2011;41:1165–1174.
- 4 Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, Charlson F, Davis A, Degenhardt L, Dicker D, Duan L, Erskine H, Feigin VL, Ferrari AJ, Fitzmaurice C, Fleming T, Graetz N, Guinovart C, Haagsma J, Hansen GM, Hanson SW, Heuton KR, Higashi H, Kassebaum N, Kyu H, Laurie E, Liang X, Lofgren K, Lozano R, MacIntyre MF, Moradi-Lakeh M, Naghavi M, Nguyen G, Odell S, et al: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
- 5 Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W: Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. *Arch Gen Psychiatry* 2004;61:387–392.
- 6 Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J: The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA* 1989;262:914–919.
- 7 National Collaborating Centre for Mental Health: Depression: the treatment and management of depression in adults (updated edition). NICE Clinical Guidelines, No 90. Leicester, British Psychological Society, 2009.
- 8 APA: Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000;157:1–45.
- 9 Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM: Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003;361:653–661.
- 10 Hansen R, Gaynes B, Thieda P, Gartlehner G, Deveaugh-Geiss A, Krebs E, Lohr K: Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatr Serv* 2008;59:1121–1130.
- 11 Kaymaz N, van Os J, Loonen AJ, Nolen WA: Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 2008;69:1423–1436.
- 12 Fava GA: Rational Use of Antidepressant Drugs. *Psychother Psychosom* 2014;83:197–204.
- 13 Bockting CL, ten Doesschate MC, Spijker J, Spinhoven P, Koeter MW, Schene AH: Continuation and maintenance use of antidepressants in recurrent depression. *Psychother Psychosom* 2008;77:17–26.
- 14 Ten Doesschate MC, Bockting CL, Schene AH: Adherence to continuation and maintenance antidepressant use in recurrent depression. *J Affect Disord* 2009;115:167–170.
- 15 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;173:128–137.
- 16 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;75:475–488.
- 17 Biesheuvel-Liefveld KEM, Kok GD, Bockting CLH, Cuijpers P, Hollon SD, van Marwijk HWJ, Smit F: Effectiveness of psychological interventions in preventing recurrence of depressive disorder: meta-analysis and meta-regression. *J Affect Disord* 2015;174:400–410.
- 18 Jarrett RB, Minhajuddin A, Gershenfeld H, Friedman ES, Thase ME: Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. *JAMA Psychiatry* 2013;70:1152–1160.
- 19 Stangier U, Hilling C, Heidenreich T, Risch AK, Barocka A, Schösser R, Kronfeld K, Ruckes C, Berger H, Rösche J, Weck F, Volk S, Hambrecht M, Serfling R, Erkwow R, Stirn A, Sobanski T, Hautzinger M: Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: a multicenter prospective randomized controlled trial. *Am J Psychiatry* 2013;170:624–632.
- 20 Beck AT, Rush AJ, Shaw BF, Emery G: *Cognitive Therapy of Depression*. New York, Guilford, 1979.
- 21 Bockting CLH, Schene AH, Spinhoven P, Koeter MWJ, Wouters LF, Huyser J, Kamphuis JH: Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. *J Consult Clin Psychol* 2005;73:647–657.
- 22 Kuyken W, Watkins E, Holden E, White K, Taylor RS, Byford S, Evans A, Radford S, Teasdale JD, Dalgleish T: How does mindfulness-based cognitive therapy work? *Behav Res Ther* 2010;48:1105–1112.
- 23 Spanier CA: The prevention of depression: protective mechanisms of maintenance interpersonal psychotherapy. *Diss Abstr Int Sect B Sci Eng* 1998;68:5657.
- 24 Gilbody S, Littlewood E, Hewitt C, Brierley G, Tharmanathan P: Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *BMJ* 2015;351:h5627.

Disclosure Statement

The authors have no competing interests to report.

Funding Sources

This research was funded by ZonMW (the Netherlands Association for Health Research and Development), Department Disease Management of Chronical Illnesses, grant No. 80-82310-97-11087 OR 171102002. The funding source did not play any role in the collection, analysis, and interpretation of the data, writing the manuscript or the decision to submit for publication.

- 25 Cuijpers P, Donker T, van Straten A, Li J, Andersson G: Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychol Med* 2010;40:1943–1957.
- 26 Biesheuvel-Leliefeld KE, Kersten SM, van der Horst HE, van Schaik A, Bockting CL, Bosmans JE, Smit F, van Marwijk HW: Cost-effectiveness of nurse-led self-help for recurrent depression in the primary care setting: design of a pragmatic randomised controlled trial. *BMC Psychiatry* 2012;12:59.
- 27 Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weismann MM: Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991;48:851–855.
- 28 First MB, Gibbon M, Spitzer RL, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, American Psychiatric Press, 1996.
- 29 Prescott MR, Tamburrino M, Calabrese JR, Liberzon I, Slembariski R, Shirley E, Fine T, Goto T, Wilson K, Ganocy S, Chan P, Derus A, Serrano MB, Sizemore J, Kauffman J, Galea S: Validation of lay-administered mental health assessments in a large Army National Guard cohort. *Int J Methods Psychiatr Res* 2014;23:109–119.
- 30 Bockting CLH, van Valen E: Ingredients of Mobile Preventive Cognitive Therapy for Recurrent Depression. Groningen, University of Groningen, 2009.
- 31 Kok G, Burger H, Riper H, Cuijpers P, Dekker J, van Marwijk H, Smit F, Beck A, Bockting CL: The three-month effect of mobile internet-based cognitive therapy on the course of depressive symptoms in remitted recurrently depressed patients: results of a randomized controlled trial. *Psychother Psychosom* 2015; 84:90–99.
- 32 Hakkaart-van Roijen L, Van Straten A, Donker M: Manual: Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness (in Dutch). Rotterdam, Erasmus University, 2002.
- 33 Beshai S, Dobson KS, Bockting CL, Quigley L: Relapse and recurrence prevention in depression: current research and future prospects. *Clin Psychol Rev* 2011;31:1349–1360.
- 34 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB: The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573–583.
- 35 Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M: Cross-validation of item selection and scoring for the SF-12 health survey in nine countries. *J Clin Epidemiol* 1998;51:1171–1178.
- 36 Brooks R: EuroQol: the current state of play. *Health Policy* 1996;37:53–72.
- 37 Ware J Jr, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–233.
- 38 Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ: Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneesk* 2005;149:1574–1578.
- 39 Terluin B, van Marwijk HW, Ader HJ, de Vet HC, Penninx BW, Hermens ML, van Boeijen CA, van Balkom AJ, van der Klink JJ, Stalman WA: The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. *BMC Psychiatry* 2006;6:34.
- 40 Schwarzer R, Jerusalem M: Generalized self-efficacy scale; in Weinman J, Wright S, Johnston M (eds): *Measures in Health Psychology: A User's Portfolio Causal and Control Beliefs*. Windsor, Nfer-Nelson, 1995, pp 35–37.
- 41 Romijn G, Ruiters M, Smit F: Meer effect met depressiepreventie? Strategieën voor publieksvoorlichting, vroegherkenning en terugvalpreventie. Wetenschappelijke Onderbouwing Depressiepreventie. Utrecht, Trimbos-Instituut, 2008.
- 42 Willemse GR, Smit F, Cuijpers P, Tiemens BG: Minimal-contact psychotherapy for sub-threshold depression in primary care. Randomised trial. *Br J Psychiatry* 2004;185:416–421.
- 43 Bakker IM, Terluin B, van Marwijk HW, van der Windt DA, Rijmen F, van Mechelen W, Stalman WA: A cluster-randomised trial evaluating an intervention for patients with stress-related mental disorders and sick leave in primary care. *PLoS Clin Trials* 2007;2:e26.
- 44 Van Buuren S, Oudshoorn CGM: *Multivariate Imputation by Chained Equations*. Leiden, Netherlands Organization for Applied Scientific Research, 2000.
- 45 Rubin DB: *Multiple Imputation for Nonresponse in Surveys*. New York, Wiley & Sons, 1987.
- 46 McNutt L-A, Wu C, Xue X, Hafner JP: Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003;157:940–943.
- 47 Zocchetti C, Consonni D, Bertazzi PA: Estimation of prevalence rate ratios from cross-sectional data. *Int J Epidemiol* 1995;24:1064–1067.
- 48 Royall RM: Model robust confidence intervals using maximum likelihood estimators. *Int Stat Rev* 1986;54:221–226.
- 49 Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995;25:1171–1180.
- 50 Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, Maser JD, Mueller T, Solomon DA, Keller MB: Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry* 2000;157:1501–1504.
- 51 Lipsey MW, Wilson DB: The efficacy of psychological, educational, and behavioral treatment. Confirmation from meta-analysis. *Am Psychol* 1993;48:1181–1209.
- 52 Walters SJ, Brazier JE: Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–1532.