Effectiveness of supported self-help for recurrent depression: a randomised controlled trial in primary care

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ABSTRACT

Purpose: The burden of depression is high, mostly due to its recurrent nature. In this study we evaluated the effectiveness of a supported Self-help Preventive Cognitive Therapy (S-PCT) aimed at the prevention of recurrence, compared to treatment-as-usual (TAU) in primary care.

Methods: We conducted a randomised controlled trial among 248 patients with a history of depression, currently in remission. Participants were randomised to TAU augmented with S-PCT (n=124) or TAU alone (n=124). S-PCT consisted of a self-help intervention, supported by weekly telephone guidance by a counsellor. Primary outcome was incidence of recurrence over the full 12 months follow-up. Secondary outcomes were depressive symptoms, quality of life (EQ-5D and SF-12), co-morbid psychopathology, and self-efficacy.

Results: In the S-PCT group, 44 participants (35.5%) experienced a recurrence, compared to 62 participants (50.0%) in the TAU group (incidence rate ratio=0.71, 95% CI 0.52 to 0.97; risk difference=14, 95% CI 2-24, number needed to treat=8). 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 to 0.08). S-PCT had no effect on co-morbid psychopathology, self-efficacy, and quality of life based on the SF-12.

Conclusions: A supported self-help preventive cognitive therapy in primary care proved to be effective in reducing the burden of recurrent depression.
INTRODUCTION

Major depressive disorder (MDD) is a prevalent mental disorder and is associated with a high risk of relapse and recurrence. MDD is frequently associated with incomplete remission between episodes and is considered to be among the most disabling illnesses, negatively affecting many aspects of life. Current guidelines recommend continuation of antidepressant medication (ADM) and/or psychological treatment (e.g., Cognitive (behavioural) Therapy (CT)) to reduce the risk of relapse and recurrence. The most commonly used strategy is continuation of ADM. Yet, the recommendations on ADM are under debate as the optimal duration of the continuation- or maintenance phase has not been studied well enough. Also, there is conflicting evidence about the effect of discontinuation of ADM on relapse or recurrence and, furthermore, reported levels of ADM non-adherence have been consistently high. In conclusion, proactive management based on 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 TAU and/or ADM. These interventions are mostly based on C(B)T, but add strategies such as modifying dysfunctional meta-cognitions in preventive CT (PCT), meditation in Mindfulness Based CT (MBCT) and linking stressful life events and insufficient social support to relapse and recurrence in Interpersonal Therapy (IPT). The majority of these interventions is offered in secondary care, often relying on intensive use of therapist's time, and, therefore, are costly. A minimally supported self-help may help to overcome this problem and has already proved as effective as face-to-face treatments in acute depressed patients. The integration of a supported self-help in primary care, supported by para-professionals, into current longitudinal primary care systems, would fit best with the recurrent character of depression. In the Netherlands, as in most western countries, primary care professionals have regular contact with the vast majority of the population, learn about the patients’ social situation and provide continuous care. Besides, the prevalence of patients with MDD or depressive feelings in primary practice is around 21%. Therefore, in this study, we conducted a randomised controlled trial (RCT) to evaluate the real-life effectiveness of a supported self-help PCT (S-PCT) in primary care in patients with a history of depression, currently in remission.
METHODS

Design
We performed a pragmatic randomised controlled trial with two parallel groups of participants comparing TAU augmented with S-PCT, with TAU alone. The design of this study is described in more detail elsewhere\textsuperscript{28}. The study was called the PARADE-study (Prevention of Recurrent DEpression). The study is registered in the Dutch Trial Register, www.trialregister.nl, NTR3001.

Ethics
The Medical Ethics Committee of the VU University Medical Center Amsterdam approved the study protocol and all participants provided written informed consent.

Terminology
To describe the course of depression, we use the operational criteria of Frank et al \textsuperscript{29}. 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 six 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
Participants were recruited through general practices and mental health care services 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 two months, but no longer in recovery than five years according to the Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID-1 3.0) \textsuperscript{30} and c) have experienced two or more previous episodes of MDD. The SCID-I interview was conducted over the telephone by trained researchers and psychologists. 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.

Counsellors
Twenty-four counsellors (primary care mental health nurses and psychologists) were trained to guide the intervention. The psychologists were non specialised psychologists (i.e. without postdoctoral training in clinical interventions). All counsellors attended a one-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 counsellors by giving feedback on audiotaped telephone contacts with two pilot-patients for each counsellor during a one-day supervision session. During the trial, counsellors could contact the trainers at any time for additional questions and feedback. To assess adherence, each week, the counsellor 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 (minutes).

**Intervention**

The intervention is a supported self-help, and is a manualised PCT-based bibliotherapy consisting of a printed self-help book with eight modules and minimal guidance. It is based on an effective face-to-face PCT and mobile PCT. PCT is an adapted type of cognitive therapy for acute depression 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 in order 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 one module per week. Each module includes reading homework plus assignments, to be completed in approximately 60 minutes. In the current project the counsellor explained the rationale of PCT and coming week’s planning in a first contact (by phone or face-to-face), prior to the start of the intervention. Each week, the counsellor contacted the participant by phone to evaluate progress and understanding. This call was strictly protocolled and was designed to last no longer than 15 minutes. The nature of the contact was solely to support the participant and not to actively engage in a therapeutic relationship.
Chapter 6

Treatment-as-usual
There were no restrictions to type of TAU. Care providers were not aware of randomization status.

Current TAU guidelines recommend to encourage a person who has benefited from taking ADM, to continue ADM for at least 6 months after remission of an episode of depression. With respect to psychological interventions, guidelines recommend to offer CBT to persons with a significant history of depression plus residual symptoms, and MBCT to patients with a history of at least three episodes of depression. TAU was recorded using the Trimbos and iMTA self-report questionnaire for costs associated with Psychiatric Illnesses (TiC-P).

Treatment allocation
After inclusion, participants were randomised using computer generated blocks and allocation concealment, stratified by the number of previous depressive episodes (2-3 episodes versus ≥4 episodes) because the number of previous episodes is associated with relapse and recurrence.

Blinding
Interviewers were blind for 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 allocation status to the interviewers.

Outcome measures

Primary outcome
Primary outcome was the incidence rate of relapse or recurrence of depression over the 12 months follow-up period. 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 episodes 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. An IRR = 1 and IRR > 1 imply no effect or an adverse effect, respectively.

Secondary outcomes
Secondary outcomes were assessed online at baseline and after 6 and 12 months (depressive symptomatology, health related quality of life) or after 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)\textsuperscript{37}. This self-report questionnaire consists of 16 symptom items to be answered on a 4-point Likert-scale. A score of 0-5 is categorised 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 (HRQoL) was examined using the Dutch translations of the 12-Item Short-Form Health Survey (SF-12)\textsuperscript{38} and the European Quality of Life Five Dimensions (three level) health status questionnaire (EQ-5D-3L)\textsuperscript{39}. The SF-12 is a measure of health-related functional status\textsuperscript{40} and yields two 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 HRQoL on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety and depression), combined into one outcome. Each dimension is rated at three 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\textsuperscript{41}. 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 (4DSQ)\textsuperscript{42}. The 4DSQ is a self-rating questionnaire that comprises 50 items distributed over four scales (distress, depression, anxiety, and somatisation).

Perceived self-efficacy was assessed with the General Self Efficacy Scale (GSES)\textsuperscript{43}. The GSES consists of 10 items, scored 1–4. Especially in the case of self-help, self-efficacy might change in the course of the intervention and during follow-up.

Sample size
We combined findings from previous research\textsuperscript{18,44}, and assumed a mean relapse or recurrence rate of 40% after 1 year of follow-up 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 months follow-up, 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\textsuperscript{45,46} 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 12-month follow-up by performing logistic regression analysis.
Data were primarily analysed 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 (MICE)\textsuperscript{47}. The analyses were performed in each of the 10 datasets, and the results of the analyses were pooled using the Rubin rules\textsuperscript{48}.

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 incidence rate ratio (IRR). Because the use of Poisson regression tends to provide conservative results\textsuperscript{49–51} and overestimates error\textsuperscript{50}, we used the Hubert-White sandwich estimator as implemented in STATA.\textsuperscript{52} Results were adjusted for baseline (residual) depressive symptoms (QIDS-sr) because these symptoms are well-known to be a risk factor for relapse or recurrence\textsuperscript{53–55}.

Estimates of the intervention effects on the secondary outcome measures (all continuous) were obtained from linear mixed models (LMM). 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’ identifier, ID, was included as random term, because in the long dataset the same participant could have contributed to the dataset 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 LMM, imputation of missing data is not necessary. The results of the ITT analysis were compared with the results of the per protocol (PP) analysis, including those participants who completed at least 80% of the intervention (5 modules). All analyses were performed with STATA (version 12).

RESULTS

Participants flow and recruitment
Details of enrolment are shown in Figure 1. Recruitment took place between September 2012 and April 2014. Medical records of 22 family practices and 4 specialised 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 informed consent. They were randomly allocated to the S-PCT group (124) or to the TAU group (124).

Baseline characteristics
In Table 1, baseline socio-demographic and clinical characteristics of the ITT group are presented. No relevant baseline imbalances were found. At baseline, all participants were in (partial) remission of recurrent MDD and experienced mild depressive symptoms (mean QIDS-sr=9.2, SD 4.8).
Effectiveness of supported self-help for recurrent depression

Figure 1. Participant flow diagram
Table 1. Baseline demographic and descriptive characteristics of the study population according to randomised group*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>S-PCT (n=124)</th>
<th>TAU (n=124)</th>
<th>All participants (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>48.6 (11.9)</td>
<td>48.8 (11.4)</td>
<td>48.7 (11.7)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>89 (71.8%)</td>
<td>84 (67.7%)</td>
<td>173 (69.8%)</td>
</tr>
<tr>
<td>N° previous episodes, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or 3</td>
<td>53.2%</td>
<td>49.9%</td>
<td>51.6%</td>
</tr>
<tr>
<td>4 or more</td>
<td>46.8%</td>
<td>50.1%</td>
<td>48.4%</td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>64.9%</td>
<td>64.9%</td>
<td>64.9%</td>
</tr>
<tr>
<td>Education**, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High education</td>
<td>42.7%</td>
<td>35.5%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Age of onset, mean (SD)</td>
<td>28.2 (11.4)</td>
<td>27.5 (12.3)</td>
<td>27.8 (11.9)</td>
</tr>
<tr>
<td>Depressive symptoms (QIDS-sr), mean (SD)</td>
<td>9.6 (4.8)</td>
<td>8.9 (5.0)</td>
<td>9.3 (4.9)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health (SF12, mean (SD))</td>
<td>53.6 (12.2)</td>
<td>53.5 (11.6)</td>
<td>53.5 (11.9)</td>
</tr>
<tr>
<td>Physical health (SF12, mean (SD))</td>
<td>59.4 (11.4)</td>
<td>57.6 (11.7)</td>
<td>58.5 (11.6)</td>
</tr>
<tr>
<td>EQ-5D, mean (SD)</td>
<td>0.77 (0.21)</td>
<td>0.78 (0.20)</td>
<td>0.77 (0.2)</td>
</tr>
<tr>
<td>Comorbid psychopathology (4DSQ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety, mean (SD)</td>
<td>3.2 (3.9)</td>
<td>3.2 (4.3)</td>
<td>3.2 (4.1)</td>
</tr>
<tr>
<td>Distress, mean (SD)</td>
<td>13.0 (7.6)</td>
<td>12.7 (8.0)</td>
<td>12.6 (7.8)</td>
</tr>
<tr>
<td>Somatisation, mean (SD)</td>
<td>8.1 (5.5)</td>
<td>8.9 (5.7)</td>
<td>8.5 (5.6)</td>
</tr>
<tr>
<td>Pain (MPQ), mean (SD)</td>
<td>2.5 (3.6)</td>
<td>3.2 (4.2)</td>
<td>2.8 (3.9)</td>
</tr>
<tr>
<td>Fatigue (FSS), mean (SD)</td>
<td>3.8 (1.5)</td>
<td>3.9 (1.6)</td>
<td>3.8 (1.6)</td>
</tr>
<tr>
<td>Self-efficacy (GSES), mean (SD)</td>
<td>28.6 (5.9)</td>
<td>28.3 (6.2)</td>
<td>28.4 (6.0)</td>
</tr>
<tr>
<td>ADM use past 3 months, %</td>
<td>51.8%</td>
<td>56.7%</td>
<td>54.2%</td>
</tr>
</tbody>
</table>

Abbreviations: ADM, anti-depressant medication; EQ, EuroQol; FSS, Fatigue Severity Scale; GSES, General Self Efficacy Scale; MPQ, MacGill Pain Questionnaire; QIDS-sr, Quick Inventory of Depressive Symptoms self-report; SD, standard deviation; SF, short form 12-Item Short Form Health Survey; S-PCT, supported self-help preventive cognitive therapy; TAU, treatment-as-usual; 4DSQ, Four Dimensional Symptom Questionnaire

*Standard deviations for multiply-imputed data were computed from the standard errors:
\[(sd= sqrt(\_b[\_var] - \_b[\_var]*\_b[\_var]))\]

**Education is defined as bachelor’s or master’s degree

Numbers analysed

Complete follow-up data 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 (\(\chi^2 = 0.088, df=247\)). Loss to follow up was significantly associated with more fatigue at baseline (difference in mean=0.602, 95%CI 0.115 to 1.089).

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 (IRR=0.71, 95%CI 0.52 to 0.97). The risk-difference (RD) between the TAU-group and the S-PCT group was 14% (95%CI 2-24) which corresponds to a number-needed-to-treat (NNT) of 8 (Table 2).
### Table 2. Primary outcome and secondary outcomes (ITT analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>S-PCT</th>
<th>TAU</th>
<th>IRR* (95% CI)</th>
<th>RD** (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse or recurrence after 12 months</td>
<td>44/124 (35.5%)</td>
<td>62/124 (50.0%)</td>
<td>0.71</td>
<td>0.52;0.97</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>S-PCT mean (SD)</th>
<th>TAU mean (SD)</th>
<th>mean difference (95% CI) ***</th>
<th>Z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms (QIDS-sr)</td>
<td>9.6 (4.8)</td>
<td>8.9 (5.0)</td>
<td>-2.18 (-3.09;-1.27)</td>
<td>-4.70 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (SF-12, mental)</td>
<td>53.6 (12.2)</td>
<td>53.5 (11.6)</td>
<td>0.67 (-1.33;2.67)</td>
<td>0.65 0.513</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (SF-12, physical)</td>
<td>59.4 (11.4)</td>
<td>57.6 (11.7)</td>
<td>1.05 (-0.81;2.91)</td>
<td>1.10 0.270</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (EQ-5D)</td>
<td>0.77 (0.21)</td>
<td>0.78 (0.20)</td>
<td>0.04 (0.004;0.08)</td>
<td>2.18 0.029</td>
<td></td>
</tr>
<tr>
<td>Anxiety (4-DSQ)</td>
<td>3.2 (3.9)</td>
<td>3.2 (4.3)</td>
<td>-0.05 (-0.68;0.59)</td>
<td>-0.14 0.887</td>
<td></td>
</tr>
<tr>
<td>Distress (4-DSQ)</td>
<td>13.0 (7.6)</td>
<td>12.7 (8.0)</td>
<td>-0.21 (-1.81;1.39)</td>
<td>-0.26 0.798</td>
<td></td>
</tr>
<tr>
<td>Somatisation (4-DSQ)</td>
<td>8.1 (5.5)</td>
<td>8.9 (5.7)</td>
<td>0.38 (-0.64;1.39)</td>
<td>0.73 0.464</td>
<td></td>
</tr>
<tr>
<td>Self-efficacy (GSES)</td>
<td>28.6 (5.9)</td>
<td>28.3 (6.2)</td>
<td>-0.68 (-1.91;0.55)</td>
<td>-1.08 0.280</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence Interval; EQ-5D, Five Dimensional EuroQol; GSES, General Self Efficacy Scale; ITT, Intention-to-treat analysis; IRR, Incidence rate ratio; NNT, number needed to treat; QIDS-sr, Quick Inventory of Depressive Symptoms self-report; RD, Risk Difference; S-PCT, supported self-help preventive cognitive therapy; 4-DSQ, Four Dimensional Symptom Questionnaire; SF-12, 12-Item Short Form Health Survey

* 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 at baseline
**P=0.025; RD is the percentage risk difference in recurrence rate between S-PCT and TAU over the 12 months follow-up period
*** Scores were adjusted for baseline level of the outcome and estimated with linear mixed modeling
Secondary outcomes
Depressive symptom scores in the intervention group decreased significantly compared to TAU over 12 months (-2.18 QIDS-sr points; 95%CI-3.09 to -1.27). Quality of life (EQ-5D) improved significantly (0.04 EQ-5D points; 95%CI 0.004 to 0.08) but not on the SF-12. No significant effects were found on any of the other secondary outcomes (Table 2).

Adherence to the intervention
Seven participants did not start the supported self-help. Two participants dropped out after the first contact, and 5 participants dropped out after the first S-PCT meeting. 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 labelled as “completers”. At baseline, completers experienced more depressive symptoms (mean difference = 2.22, 95%CI 0.010 to 4.35), more distress (mean difference = 3.46, 95%CI 0.02 to 6.90) and a lower quality of life (EQ5D) (mean difference = -0.11, 95%CI 0.02 to 0.20) than non-completers.

The self-help was led by a primary care mental health nurse (31.5%) or by a non-specialised psychologist (68.5%). The first contact was organised face-to-face (40.3%) or by telephone (59.1%). The mean amount of time spent per phone-call per participant by the counsellor was 13.8 minutes (sd=5.42), totalling a mean of 110.2 minutes of attention per participant per treatment. According to the checklist of the counsellors, in 6% of all contacts the participant had not read the literature belonging to that week’s module. Reasons for not reading literature were (more than one 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 (5), physical illness (5), intervention does not meet expectations (2), other (2).

Treatment as usual
Medication use (all types of medication including ADM) data for all 12 months were available for 74% of the participants (92/124) in the S-PCT group and 74% of the participants (92/124) in the TAU group. During this period, 62% (57/92) of the participants in the S-PCT group received medication at any 3-month measurement versus 63% (58/92) participants in the TAU group ($\chi^2=0.23$, df=1, $P=0.8$). Data on mental health care use were available for 85% of the participants (105/124) in the S-PCT group and 81% of the participants (100/124) in the TAU group. In the S-PCT group 43% received additional counselling from a psychiatrist/psychologist/psychotherapist versus 40% of the participants in the TAU group ($\chi^2=0.172$, df=1, $P=0.678$).
Per protocol analysis
The per protocol (PP) analysis included only those participants who completed at least 80% (5 modules) of the intervention (81%; 101/124 participants). The results were roughly similar. 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 (incidence rate ratio=0.68, 95%CI 0.50 to 0.93, risk difference=15%, 95%CI 4 to 25, NNT=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 and 0.04; 95%CI 0.003 to 0.81, respectively).

Table 3. Changes in primary and secondary outcome measures (PP-analysis)

<table>
<thead>
<tr>
<th></th>
<th>IRR* (95% CI)</th>
<th>RD** (95%CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Relapse or recurrence</td>
<td>0.68 (0.50-0.93)</td>
<td>15% (4;25)</td>
<td>7</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
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<tr>
<td>Depressive symptoms (QIDS-sr)</td>
<td>-2.31 (-3.26;-1.37)</td>
<td>-4.81 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (SF-12, mental)</td>
<td>0.44 (-1.62;2.50)</td>
<td>0.42 0.675</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (SF-12, physical)</td>
<td>0.89 (-1.01;2.80)</td>
<td>0.92 0.359</td>
<td></td>
</tr>
<tr>
<td>Health related quality of life (EQ-5D)</td>
<td>0.04 (0.003;0.81)</td>
<td>2.10 0.036</td>
<td></td>
</tr>
<tr>
<td>Anxiety (4-DSQ)</td>
<td>-0.05 (-0.71;0.60)</td>
<td>-0.16 0.872</td>
<td></td>
</tr>
<tr>
<td>Distress (4DSQ)</td>
<td>-0.25 (-1.90;1.41)</td>
<td>-0.29 0.769</td>
<td></td>
</tr>
<tr>
<td>Somatisation (4-DSQ)</td>
<td>0.42 (-0.63;1.48)</td>
<td>0.79 0.432</td>
<td></td>
</tr>
<tr>
<td>Self-efficacy (GSES)</td>
<td>-0.57 (-1.81;0.67)</td>
<td>-0.91 0.36</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence Interval; EQ-5D, Five Dimensional EuroQol; GSES, General Self Efficacy Scale; ITT, Intention-to-treat analysis; IRR, Incidence rate ratio; NNT, number needed to treat; QIDS-sr, Quick Inventory of depressive Symptoms self-report; RD, Risk Difference; S-PCT, supported self-help preventive cognitive therapy; 4-DSQ, Four Dimensional Symptom Questionnaire; SF-12, 12-Item Short Form Health Survey

*p=0.017; scores were adjusted for depressive symptoms at baseline

**p= 0.011; RD is the percentage risk difference in recurrence rate between S-PCT and TAU over the 12 months follow-up period

***Scores were adjusted for baseline level of the outcome and estimated with linear mixed modeling
Chapter 6

DISCUSSION

Main findings
In this study, we evaluated the real-life effectiveness of a supported self-help preventive Cognitive Therapy (S-PCT) in primary care, in remitted patients with a history of depression. Our analyses showed that S-PCT statistically significantly reduced relapse and recurrence over 12 months with 14% (95%CI 2 to 24) compared to usual care.

Public health significance
Major depressive disorder (MDD) is a prevalent mental disorder and is associated with a high risk of relapse and recurrence. MDD is frequently associated with incomplete remission between episodes and is considered to be among the most disabling illnesses, negatively affecting many aspects of life. Largely due to this recurrent nature, the economic consequences of MDD are substantial. Due to budget- and time restraints, health care systems have difficulties addressing the demand for care and treatment of people experiencing full-blown mental health problems and can only avert a fraction of the total disease burden that is attributable to mental disorders. Our prevention trial showed that no less than 50% of the participants who received usual care recurred within 12 months. This emphasizes the vulnerability of this patient group and underlines that a preventive, low-cost, accessible minimal intervention, offered in primary care is much needed.

Our randomised controlled trial is one of the first that supplies evidence that such an endeavour might be successful. Our study shows that the risk of relapse or recurrence decreases significantly by 14% (NNT=8) when targeting remitted patients with a history of depression. Yet, the incidence rate ratio of 0.71 that we found, was somewhat higher (i.e. less effective) than the IRR we found in our meta-analysis comparing psychological interventions to usual care (0.64). The most likely explanation for this is our short follow-up period of 12 months (52 weeks) in our trial, while the mean follow-up in the meta-analysis was 115 weeks. Time to recurrence might exceed 12 months, possibly implying that we have missed the interventions’ and TAUs’ impact on later recurrences. Also, on average, participants in our trial experienced a higher level of residual symptoms than participants in the studies that were included in the meta-analysis. Therefore, the a-priori chance of relapse or recurrence might have been higher in our trial. Besides, we chose to offer a bibliotherapeutical self-help intervention with minimal guidance by a counsellor. Though economically attractive, the format of this intervention may have been too light. A possible way to improve outcome is to differentiate between high risk- and ultra-high risk patient-groups; in ultra-high risk groups (including patients with multiple previous episodes and higher levels of residual symptoms as in our sample) a specific psychological intervention might be indicated such as face-to-face PCT and MBCT as several studies indicate.
for a relatively lower risk group (including patients with a single previous episode and lower levels of residual symptoms) a less specific minimal intervention such as self-help might be optimal. Finally, S-PCT should be offered at the right moment to gain maximum effects. In our trial, the intervention was offered to participants at a random moment during remission or recovery. However, our meta-analysis 20 shows that the preventive effect of a psychological intervention is usually higher when the prevention directly follows the acute phase.

To end with, the statistically significant increase in quality of life in favour of the S-PCT group, found with the EQ-5D, was low (0.004, 95% CI 0.004 to 0.08). Research has shown that the smallest change in utility scores for the EQ-5D that can be regarded as important is 0.074 68. Besides, the SF-12 showed no statistically significant change in quality of life. This implies that the improvement of quality of life, measured with the EQ-5D, should be interpreted with caution.

Implementation
The addition of S-PCT seems a strategy that can be relatively easily implemented into current longitudinal primary care systems. Paraprofessionals in primary care could act as case managers in a model for continued care for recurrent depression. Still, referral to a paraprofessional in primary care requires a careful and timely coordination between health care professionals.

Strengths and limitations
Our operationalization of depression and relapse or recurrence was based on a structured clinical interview (SCID-1). A further strength of this study is that our participants achieved remission on antidepressants, other psychotherapies, psychiatric help, counselling, 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 maximise external validity, which suggests good generalizability of the findings.

Our study also has limitations. First, as is common in studies on psychological interventions, it was not possible to blind participants to the condition to which they were assigned. Second, effects were considered over a time-span of one year. A longer follow-up is preferred because it is important to know whether the positive clinical effects will sustain over time. Previous results on longer term effects of PCT are promising; brief CT, started after remission from a depressive episode on diverse types of treatment in patients with multiple prior episodes, has long-term preventive effects for at least 5.5 to 10 years 32,69.
Chapter 6

Conclusions and further research
This is the first study to evaluate the effects of a supported self-help preventive cognitive therapy (S-PCT) compared to usual care in primary care, over 12 months in remitted patients with a history of depression. We found a significant difference in relapse or recurrence rate between the two groups, in favour of S-PCT. Also, the level of depressive symptoms and quality of life changed significantly in favour of the S-PCT group.

Suggestions for further research include an evaluation of S-PCT with a longer follow-up. Another research question is how to improve relapse and recurrence prevention strategies by finding out what works for whom and what type of guidance (e.g. frequency, intensity) works best. Also, it would be valuable to make a comparison of S-PCT with mobile, internet-based PCT and face-to-face PCT.

Acknowledgements
We are very grateful to all participants. We would also like to thank all recruitment sites for their efforts: GGZ NHN, GGZ Amstelmere, GGZ Zuiderpoort, GGZ Rivierduinen, de Bosgroep, and the participating general practitioners. We also thank all counsellors for their guidance. Finally, we are grateful to Evelien van Valen for her help.
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Effectiveness of supported self-help for recurrent depression


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