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Supported self-help to prevent relapse or recurrence of depression: Who benefits most?

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Short title: Supported self-help for recurrent depression: moderators

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1. Abstract

Objectives

To identify subgroups for whom supported self-help preventive cognitive therapy (S-PCT) is more (cost)effective than treatment as usual (TAU) in preventing relapse and recurrence of major depression.

Methods

We conducted a randomized controlled trial in which 248 remitted, recurrently depressed participants were randomized to S-PCT (n=124) or TAU (n=124). Clinical outcome was relapse or recurrence of major depressive disorder (SCID-I). We tested the potential moderating effects on relapse or recurrence of age, gender, education level, residual depressive symptoms, number of previous episodes, age of onset, antidepressant medication, somatization, and self-efficacy with logistic regression analyses adjusted for baseline values of depressive symptoms. We examined moderating effects on costs using linear regression analyses adjusted for baseline costs. A stratified cost-effectiveness analysis was performed to tease out differences in cost-effectiveness between subgroups.

Results

We found no moderating effect on relapse or recurrence for any of the potential moderators. For costs, the number of previous depressive episodes was identified as a moderator. At a willingness-to-pay of 16,000€, the probability that S-PCT was cost-effective compared to TAU was 95% for participants with 2-3 previous episodes and 11% for participants with ≥4 episodes.

Conclusions

S-PCT was effective in preventing relapse or recurrence of depressive disorders in a broad range of participants, but is more likely to be cost-effective in participants with 2-3 episodes than with ≥4 episodes. This indicates that S-PCT can best be offered to participants with fewer previous depressive episodes.

2. Introduction

Major depressive disorder is a leading cause of disability worldwide [1] and is associated with substantial societal costs as a result of increased health care utilization and productivity losses [2-3]. Its high disease burden is largely due to its recurrent nature. For instance, Mueller et al. (1999) found that 85% of recovered persons reported a recurrence during 15 years follow-up and that the risk of recurrence was increased by 18 % with each additional episode [4].

Interventions aimed at the prevention of relapse or recurrence might reduce the burden of depressive disorders by approximately 50% [5]. Both antidepressants and several psychological treatments, such as Preventive Cognitive Therapy (PCT) and mindfulness-based cognitive therapy (MBCT), are effective in the prevention of relapse or recurrences of depressive disorders [6-8]. However, people may find long-term use of antidepressants unattractive and non-adherence to continuation and maintenance of antidepressants for recurrent depression is high [9-10]. As for psychological treatment, psychologists may be less available in the primary care setting or people do not want to engage in therapeutic sessions when they are not experiencing many symptoms at that moment [9]. Therefore, offering a preventive psychological treatment, such as Preventive Cognitive Therapy (PCT) in a supported self-help format would be a major step forwards. PCT is an adapted version of Cognitive Therapy for acute depression [11] and aims to prevent relapse and recurrence by focusing on changing negative thoughts and dysfunctional attitudes. The Parade study examined whether PCT in a supported self-help format (S-PCT) was cost-effective in comparison with treatment as usual (TAU) to prevent relapse or recurrence of depressive disorders [12]. The study showed that S-PCT significantly reduced relapse and recurrence rates by 14% after twelve months and that €13,515 should be invested to prevent one relapse or recurrence in the S-PCT group in comparison with the TAU group [13-14].

It is, however, not yet clear whether subgroups can be identified that respond particularly well to supported self-help for recurrent depression. Distinguishing characteristics of persons that benefited most could help target the use of this supported self-help PCT. In this study we examined for which subgroups of remitted, recurrently depressed persons S-PCT was a (cost)effective addition as compared to treatment as usual (TAU) in preventing relapse and recurrence of depressive disorders.

3. Materials and methods

Design

We performed a pragmatic randomized controlled trial (n = 248) with two parallel groups: S-PCT plus TAU (n = 124) compared to TAU alone (n = 124). Participants with at least two episodes of depression who were at that time remitted were recruited in primary care practices and specialized mental health care institutions in the Netherlands and were observed for twelve months. The design and (cost)effectiveness results of this study have been described elsewhere [12-14].

Participants

Participants were eligible for participation if they: 1) were more than 18 years old, 2) had experienced at least two previous depressive episodes, and 3) were remitted according to a Structured Clinical Interview for DSM-IV (SCID-I) [15] with a trained interviewer. Their most recent, remitted depressive episode should have been longer than eight weeks, but not longer than five years ago. Having residual, subclinical depressive symptoms was not an exclusion criterion. Exclusion criteria were severe cognitive impairment; history of mania, hypomania or psychosis; current alcohol or drug-related abuse or dependence as the principal diagnosis; insufficient mastery of the Dutch language. Eligibility criteria were checked in patient medical records and during the SCID-I interview which took place by phone.

Intervention

S-PCT is a supported self-help treatment based on PCT [16-17], an adapted version of cognitive therapy for acute depression [11]. PCT aims to help remitted participants with a history of depression in preventing relapse and recurrence. Participants have to work through a self-help book with background literature and assignments, consisting of eight weekly modules. S-PCT starts with the identification of negative thoughts and dysfunctional attitudes. Next, the focus of S-PCT is directed on changing these attitudes by using various cognitive techniques such as identification of positive attitudes and enhancing specific memories of positive experiences. In the last modules of S-PCT, the participant formulates specific relapse and recurrence prevention strategies in a personal prevention plan. Counselors, i.e. certified mental health nurses and psychologists, supported the participants during weekly telephone calls (max. 15 minutes). The counselor aimed to evaluate progress and understanding and not to engage actively in a therapeutic relationship.

Treatment as usual

In both conditions, TAU included routine treatment according to the Dutch clinical guidelines [18-19]. These guidelines recommend continuation of antidepressant medication, preventive psychological treatment, or both, depending on the level of dysfunctioning and distress, psychiatric or somatic co-morbidity, and preferences of the participant. In both groups, there were no restrictions on TAU and TAU could also consist of no treatment.

Recruitment of participants and treatment allocation

Medical records of 22 primary care practices and four specialized mental health care institutions were screened for possibly eligible participants. This led to the identification of 5.489 persons, who received a short information letter and a screening questionnaire. Responding persons who were eligible according to the global screening questionnaire received detailed study information and an informed consent form. Once participants had provided informed consent, they received the SCID-I interview over the phone to assess eligibility criteria in detail. If participants met the criteria, they were randomly assigned to S-PCT plus TAU (n = 124) or TAU alone (n = 124) using a blockwise randomization scheme. Randomization was stratified according to the number of previous episodes (two or three previous episodes versus four or more episodes).

Measurements

Clinical outcome

Relapse or recurrence, our primary outcome, was defined as meeting DSM-IV criteria for a major depressive episode [20], as measured by the SCID-I interview at six and twelve months follow-up.

Cost outcomes

Costs were assessed from a societal perspective, including costs of the S-PCT intervention (bottom-up approach), health care utilization, and productivity losses (human capital approach). Health care utilization and productivity costs were measured using the Trimbos and iMTA self-report questionnaire for Costs associated with Psychiatric Illnesses (TiC-P) [21] at three, six, nine and twelve months of follow-up. Valuation of health care utilization and lost productivity was done according to Dutch guidelines [22].

Effect moderators

We hypothesized that participants at higher risk for relapse or recurrence would benefit the most from PCT. Several risk factors for relapse or recurrence of depression may predict treatment

response, particularly the number of depressive episodes and residual depressive symptoms [23-25]. We included these factors as effect moderators.

Sociodemographic characteristics

Age, gender, and education level (low versus high education) were assessed by means of a self-report questionnaire at baseline. We expected that a higher education level is associated with a better treatment response [26-27]. High education level was defined as a bachelor's or master's degree, whereas low education was defined as any education below a bachelor's or master's degree.

Clinical and psychosocial characteristics

The number of previous depressive episodes and the level of initial residual depressive symptoms are strongly associated with an increased risk of relapse or recurrence [24, 28]. The level of residual depressive symptoms was measured with the QIDS-sr [29]. The number of previous depressive episodes was assessed in a self-report questionnaire and dichotomized to two or three episodes versus four or more episodes.

Second, a younger age of onset of the first episode may be associated with a poorer prognosis regarding the course of depression but the evidence is still inconclusive (24, 30]. Due to its putative association with relapse or recurrence of depressive disorders, age of onset (self-report) was considered as a potential effect moderator.

Third, the use of antidepressant medication may influence treatment response positively and was measured at baseline (TiC-P, dichotomous), over the past three months [31].

Fourth, somatization increases the risk of recurrence [32] and negatively affects the prognosis of depressive disorders [33]. Somatization can be defined as "the tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them" [34]. We measured somatization at baseline by the Four-Dimensional Symptom Questionnaire (4DSQ) somatization scale [35]. The 4DSQ operationalizes somatization as a high number and frequency of physical symptoms. Experiencing some physical symptoms unaccounted for by pathological findings is a common phenomenon, while experiencing multiple (unexplained) physical symptoms from different organ systems implies probably somatization [35-36]. The 4DSQ somatization scale consists of 16 symptoms (e.g. during the past week did you suffer from dizziness; painful muscles; headache), which are scored on a 5-point Likert scale (0-32).

Lastly, we hypothesized that self-efficacy is positively associated with better treatment response. Self-efficacy refers to the belief in one's competence to cope with a broad range of stressful or

challenging demands and the perceived ability to produce a desired action [37]. Above-average levels of self-efficacy are protective for the onset of depressive disorders [38] and may be related to a lower risk of relapse or recurrence of depressive disorders [24]. Self-efficacy was measured with the General Self-Efficacy Scale (GSES) [39] at baseline. The ten items are scored on a 4-point scale, yielding a total score of 10-40.

Statistical analyses

Clinical moderators

We applied logistic regression analyses to identify subgroups with particularly good responses to S-PCT regarding relapse or recurrence, using interaction terms of randomization status and baseline characteristics, adjusted for residual depressive symptoms at baseline (QIDS-sr). All interaction terms were tested separately for statistical significance ($p < .10$, two-tailed). After that, we performed subgroup analyses (logistic regression analyses) for all statistically significant moderators.

Cost moderators

Moderators of total costs over twelve months follow-up were tested using linear regression analyses, adjusted for total costs in the three months before baseline. The same set of putative moderators was evaluated as mentioned above. Again, we conducted subgroup analyses for the statistically significant moderators ($p < .10$, two-tailed) identified in the moderation analyses. In these subgroup analyses, we dichotomized the continuous variables based on clinical cut-offs (QIDS-sr, 4DSQ) or median split (age, age of onset, self-efficacy).

Cost-effectiveness analyses

Lastly, we performed cost-effectiveness analyses, stratified for subgroups of the statistically significant clinical and cost moderators. To create subgroups, we dichotomized continuous variables based on clinical cut-offs or median split. Cost-effectiveness acceptability curves (CEAC) show the probability that S-PCT is cost-effective in comparison with TAU for a range of monetary values society is willing to pay (WTP) to gain one unit of effect (i.e. to prevent one relapse or recurrence). We estimated the CEACs by non-parametric bootstrapping with 5000 replications and adjusted for residual depressive symptoms at baseline (QIDS-sr) and total costs in the three months before baseline (TiC-P).

Missing data

Complete data for the twelve months observation period were collected from 95/124 participants (77%) in the S-PCT group and 93/124 participants (75%) in the control group ($\chi^2(1) = 0.088$, $p = .77$).

We imputed the missing data on costs and outcome using multiple imputations by chained equations (MICE) [40]. Ten complete datasets were needed to reach a loss of efficiency that was smaller than 5% [41]. We performed the analyses in each of the ten data sets and pooled the results.

All analyses were performed with STATA version 14, based on the intention-to-treat principle (ITT).

4. Results

Baseline characteristics

Baseline characteristics of the study sample are shown in Table 1. Participants experienced mild levels of residual depressive symptoms at baseline, defined as a QIDS-sr score of less than 11.

Clinical moderators

During the twelve month observation period, 44/124 (35.5%) participants in the S-PCT group compared to 62/124 (50.0%) participants in the TAU group reported a new relapse of recurrence, resulting in a risk difference of 14% (95%CI = 2 to 24, $t(167.7)=-2.25$, $p=.025$) [13]. In the moderation analyses (Table 2), no statistically significant moderators of treatment outcome in terms of relapse or recurrence of a depressive disorder were identified.

Cost moderators

The mean difference in total societal costs over 12 months was €2,114 (95%CI= -112 to 4261), after adjusting for baseline costs [14]. In moderation analyses, we found that the number of previous episodes was a moderator of total costs during twelve months follow-up (Table 2). Subgroup analyses showed that total costs were statistically significantly higher in the S-PCT group compared to the TAU group (€ 4451 [95%CI = 1083 to 7819], $p = .010$) for participants with four of more previous episodes. Total costs were not significantly different in the S-PCT group compared to the TAU group for participants with two or three previous episodes (€ -85, 95%CI = -3273 to 3103, $p = .958$). The other interaction terms were not statistically significant.

Cost-effectiveness analyses stratified for moderators

The cost-effectiveness acceptability curve stratified for the number of previous depressive episodes is displayed in Figure 1. In the main analysis using the full population, the probability that S-PCT was cost-effective compared to TAU was 95% at a WTP of 40,000 €/patient with relapse or recurrence prevented. At a WTP of 40,000€, the probability that S-PCT was cost-effective in comparison with TAU was 99% for participants with two or three previous depressive episodes and 59% for four or more episodes.

Moreover, at a probability of 95% of S-PCT being cost-effective compared to TAU in persons with two to three depressive episodes, the WTP should be 16000€/patient with relapse or recurrence prevented. Using the same WTP of 16000€, the probability that S-PCT is cost-effective was 61% in the full population and 11% in persons with four or more episodes.

As the number of previous episodes moderated costs and cost-effectiveness, we also assessed (post-hoc) the effectiveness of S-PCT on preventing relapse and recurrence in stratified regression analyses for participants with two to three episodes compared to participants with four or more episodes. In these additional analyses, we found a statistically significant effect of S-PCT on relapse or recurrence for participants with two to three episodes (OR = 0.35, 95%CI = 0.15 to 0.83, p = .017) but a statistically non-significant effect of S-PCT for participants with four or more depressive episodes (OR = 0.61, 95%CI = 0.29 to 1.29, p = .198).

5. Discussion

Main results

This study aimed to identify subgroups for which a supported self-help intervention for recurrent depression (S-PCT) is more (cost)effective in preventing relapse and recurrence of depressive disorders. We found no moderating effect on relapse or recurrence for any of the potential moderators and, therefore, no subgroups were identified for which S-PCT was particularly effective. Besides, we found that participants with four or more previous depressive episodes receiving S-PCT reported higher total costs during follow-up compared to TAU, whereas this difference was not statistically significant in participants with less than four episodes. As a result, the cost-effectiveness acceptability curves (CEAC) indicated that S-PCT is more likely to be cost-effective in preventing relapse or recurrence in participants with two or three episodes than with four or more episodes.

Interpretation of findings, in the context of the literature

We hypothesized that participants at higher risk of relapse or recurrence, for instance participants with many previous depressive episodes or a high level of residual symptoms, would benefit the most from S-PCT. This was not confirmed by the results of the moderation analyses. Although a high number of previous depressive episodes is one of the most important risk factors of relapse and recurrence of depressive disorders [23], it did not moderate treatment effect in our study, only costs during follow-up. In contrast to our study, other studies found that PCT in group therapy format was particularly effective in preventing relapse or recurrence for persons with four [42] to five [43] or more previous depressive episodes. For instance, Bockting et al. (2006) found that the number of previous episodes predicted relapse or recurrence in the TAU group but not in the PCT group, which

indicates that PCT neutralizes the influence of this important risk factor [43]. An explanation for our deviant results may be that we studied PCT in a less intensive format, namely supported self-help, compared to group-based PCT in these other studies.

In our study, we found that participants with four or more previous episodes in the S-PCT group reported higher total costs during follow-up compared to TAU, while we found no difference between the S-PCT and TAU groups for participants with two or three previous episodes. The higher costs in the S-PCT group cannot fully be explained by the costs of the intervention itself. Additional analyses showed that these higher costs largely stem from costs due to lost productivity. As a consequence of the higher costs and smaller effect, S-PCT is less likely to be cost-effective in preventing relapse or recurrence compared to TAU for participants with four or more depressive episodes than two to three episodes. This finding did not meet our expectations as we hypothesized that S-PCT would have a higher probability to be cost-effective as compared to TAU in participants with a higher risk of relapse or recurrence. To our best knowledge, no other relapse or recurrence studies have examined moderators of costs or have stratified the cost-effectiveness for different subgroups.

Strengths and limitations

One of the strengths of this study is that we used data from an RCT to evaluate the (cost) effectiveness of S-PCT for recurrent depression in comparison with TAU. A second strength is that participants with recurrent depression were included without restrictions on treatment as usual and antidepressant use, which has a positive impact on the generalizability of our results. The results should be interpreted in the light of some limitations. First, the Parade study was primarily designed and powered to assess the (cost)effectiveness of S-PCT in preventing relapse or recurrence of depressive disorders and not to conduct moderation analyses. As a result, the power to detect all relevant moderators may have been insufficient [44]. Second, the number of previous depressive episodes and age of onset were assessed retrospectively in a self-report questionnaire. A structured interview to assess the course of psychopathology, such as the Life Chart Interview [45], would perhaps have been more appropriate. In addition, the number of previous episodes was dichotomized. These limitations might have contributed to our finding that the number of previous episodes did not moderate the treatment effect in terms of relapse or recurrence of depressive disorders. However, in the randomization procedure we stratified for number of depressive episodes to ensure equal number of participants in these subgroups among treatment groups [44, 46]. Third, due to the type of intervention, participants and counselors were not blinded. This may have introduced bias. Fourth, in both the S-PCT and TAU group, there were no restrictions to TAU.

Although the lack of restrictions may result in better generalizability to the real world, we cannot rule out that participants in the TAU group received treatment for recurrent depression, comparable to S-PCT. Lastly, previous studies have identified patient characteristics that may be relevant for treatment response, such as stressful life events, daily hassles, coping style, cortisol levels and childhood abuse [43, 47]. However, these characteristics were not assessed in our study and we were not able to include these putative moderators in our analyses.

Implications for practice and future research

Our findings showed no moderation effects for certain groups, in terms of effectiveness in preventing relapse or recurrence of depressive disorders. S-PCT may thus be offered to various types of patients. Furthermore, we found that S-PCT is more likely to be cost-effective in preventing relapse or recurrence compared to TAU for participants with two or three previous depressive episodes than four or more episodes. This indicates that S-PCT may best be offered to persons with few previous depressive episodes.

Future studies could investigate which type of psychological intervention is most appropriate for whom. Various psychological interventions to prevent relapse or recurrence were compared to treatment as usual and antidepressant medication in a meta-analysis by Biesheuvel-Leliefeld et al. (2015) [7]. They conclude that cognitive therapy, interpersonal therapy and mindfulness based cognitive therapy are equally effective in preventing relapse and recurrence compared to TAU. However, they did not assess the differential effectiveness in subgroups of participants. Also, additional research could compare the effectiveness of psychological interventions in various delivery modes (e.g. PCT offered in group sessions versus supported self-help), as well as examining which delivery mode is most suitable for which persons. For instance, self-help PCT may be more appropriate for persons with a lower risk of relapse or recurrence (i.e. few previous depressive episodes), while for high risk groups (i.e. many previous episodes) more intensive interventions may be required that also focus on restoring role functioning, besides reducing the actual risk of relapse or recurrence, as depressive disorders affect many aspects of life, even after recovery, and costs due to productivity losses are especially high in this group.

Conclusion

Our results imply that supported self-help PCT is effective in preventing relapse or recurrence of depressive disorders in a broad range of persons. However, S-PCT is more likely to be cost-effective in preventing relapse and recurrence in persons with two or three depressive episodes than with four or more episodes.

8. Statements

8.1 Acknowledgements

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8.2 Statement of Ethics

The study is registered in the Dutch Trial Register, www.trialregister.nl, under NTR3001. The Medical Ethics Committee of the VU University Medical Center Amsterdam approved the study protocol (2011/285). All participants provided written informed consent.

8.3 Disclosure statement

The authors have no conflicts of interest to declare**.**

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8.5 Author Contributions

KBL, DvS, HvM, and HvdH contributed to the design of the Parade-study. SDK, JvdW, and JB contributed to the analytic strategy. SDK performed the analyses and drafted this paper, which was added to and modified by KBL, JvdW, DvS, JB, HvM, and HvdH. All authors read and approved the final manuscript.

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10. Legends

Table 1 Baseline characteristics of the study sample (N = 248), according to randomization group [13]

Table 2 Moderation analyses for relapse or recurrence and costs during twelve months follow-up (n = 248)

Figure 1 Cost-effectiveness acceptability curve, stratified for number of previous depressive episodes