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Research report

Enduring effects of Preventive Cognitive Therapy in adults remitted from recurrent depression: A 10 year follow-up of a randomized controlled trial

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ABSTRACT

Background: Prevention of recurrence is a challenge in the management of major depressive disorder (MDD). The long-term effects of Preventive Cognitive Therapy (PCT) in preventing recurrence in MDD are not known.

Methods: A RCT comparing the addition of PCT to Treatment As Usual (TAU), versus TAU including patients with recurrent depression who were in remission at entry ($N=172$). PCT consisted of eight weekly group sessions. TAU involved standard treatment. Primary outcome is time to first recurrence of a depressive episode as assessed by blinded interviewers over 10 years based on DSM-IV-TR criteria.

Results: Also over 10 years, the protective effect of PCT was dependent on the number of previous episodes a patient experienced. The protective effect intensified with the number of previous depressive episodes (Cox regression; $p=.004$, Hazard ratio=.576, 95% CI=.396–.837) and is mainly established within the first half of the 10 year follow-up period. For patients with more than three previous episodes (52% of the sample), PCT significantly increased the median survival time (713.0 days) versus patients that received TAU (205.0 days). No enduring effects were found on secondary outcomes.

Limitations: Dropout rates were relatively high for secondary outcomes, but relatively low for the primary outcome. Results were comparable after multiple imputation.

Conclusions: PCT in remitted patients with multiple prior episodes has long-term preventive effects on time to recurrence. To reduce recurrence rates, booster sessions might be necessary. A personalized medicine approach might be necessary to reduce recurrence rates even further.

1. Introduction

Major depressive disorder (MDD) (Kessler et al., 2005; Kupfer et al., 2012) has a highly recurrent nature and it contributes largely to disability worldwide (Mathers and Loncar, 2006; Mathers and Lopez, 2006). Prevention of recurrence[1] is the most important challenge in the management of MDD. Patients suffering from a first depressive episode have a 40–60% chance to experience recurrence and after three episodes, this risk is as high as 90% (Moffitt et al., 2010; Eaton et al., 2008; Solomon et al., 2000).

The most used preventive strategy to reduce recurrence after remission is continued use of antidepressants (AD) for a number of years (Geddes et al., 2003; Kaymaz et al., 2008; Hansen et al., 2008; Glue et al., 2010). Reported reduction of the risk of recurrence compared to placebo are odds ratios ranging from 0.12 to 0.35 (Geddes et al., 2003; Kaymaz et al., 2008; Hansen et al., 2008; Glue et al., 2010). Treatment with ADs during the acute phase only, does not have an enduring effect in preventing recurrence (Geddes

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[1] The term recurrence is used for both relapse and recurrence throughout the manuscript.

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et al., 2003; Kaymaz et al., 2008; Hansen et al., 2008; Glue et al., 2010; Vittengl et al., 2007; Guidi et al., 2010; Oestergaard and Møldrup, 2011; Imel et al., 2008; Pigott et al., 2010). Unfortunately, in most pharmacological continuation studies, follow-up was restricted to one-year. So until now it is unclear how long patients should continue ADs. Moreover, especially recurrently depressed patients, for whom long-term AD use is recommended (American Psychiatric Association, 2010; National Institute for Health and Clinical Excellence, 2010), experience less protection from ADs (OR=0.37 for recurrence in recurrently depressed patients, OR=0.12 for recurrence in single episode patients) (Kaymaz et al., 2008). That is, with increasing number of episodes, patients develop a relative resistance against the protective effect of AD (Kaymaz et al., 2008).

In contrast to acute phase AD treatment, acute phase cognitive therapy (CT) has enduring preventive effects, as demonstrated in several meta-analyses, e.g. Vittengl et al. (2007), Guidi et al. (2010), Cuijpers et al. (2013). However, most depressed patients that receive help are treated with ADs instead of CT (Olfson and Marcus, 2009).

A shift in the treatment of mood disorders is the notion of sequential combinations, such as starting psychotherapy after remission on pharmacotherapy (Kupfer et al., 2012). A sequential approach in which brief preventive CT (including Mindfulness based CT) is started after recovery on other treatment (including AD treatment) is indeed effective in preventing recurrence. Most studies, including ours, indicate that CT is especially effective for patient with (Moffitt et al., 2010; Eaton et al., 2008; Solomon et al., 2000) or more previous episodes (Vittengl et al., 2007; Guidi et al., 2010; Olfson et al., 2009; Stangieret al., 2013; Bockting et al., 2005, 2009). We found in an RCT that adding PCT to TAU versus TAU resulted in a significant protective effect that intensified with an increasing number of previous episodes over 2 and 5,5 year follow-up (Bockting et al., 2009, 2005). However, follow-up periods were mostly restricted to 1–2 years with only two other studies having a 5–6 years follow-up (Bockting et al., 2009; Fava et al., 2004). To date, true long-term effects are yet unknown.

To our knowledge this is the first study that examines effects over 10 years after an eight session group therapy, i.e. Preventive Cognitive Therapy (PCT) wtihin a randomized controlled trial. We compared PCT and Treatment As Usual (TAU) to TAU only, in remitted recurrently depressed patients at entry that received various types of acute treatment (Bockting et al., 2009, 2005). In line with previous studies (Vittengl et al., 2007), e.g. Piet and Hougaard (2011), Jarrett et al. (2001), Stangier et al. (2013), we expect that the effect of PCT intensifies with increasing number of previous episodes experienced. The present paper reports on the endurance of the effects after receiving an 8 session PCT compared to controls in preventing recurrence with a 10-year follow-up.

2. Methods

2.1. Patients

To be eligible, patients had to meet the following criteria:

(a) at least two Major Depressive Episodes (MDEs) in the previous five years, according to the DSM-IV criteria, assessed with the Structured Clinical Interview for DSM-IV (SCID and LIFE interview (First et al., 1996)); (b) being in remission according to DSM-IV criteria, for at least ten weeks and no longer than two years; (c) a score of less than 10 on the Hamilton Rating Scale for Depression (Hamilton, 1960).

Exclusion criteria were organic brain damage, alcohol or drug misuse, a psychotic disorder, current mania/hypomania or a history of bipolar I/II disorder, predominant anxiety disorder, recent

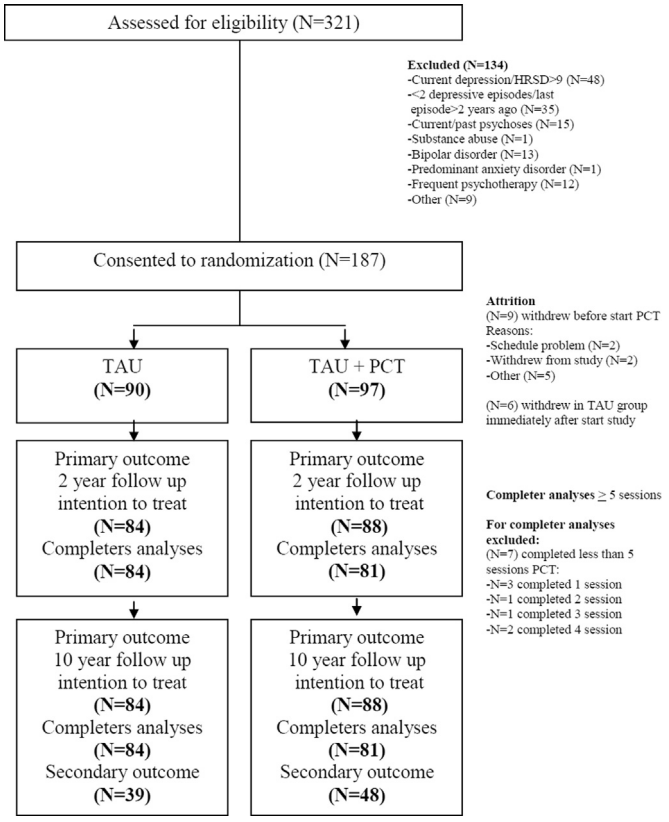

Fig. 1. Flow diagram of patients' process over the 10 year follow-up.

ECT, recent CT or receiving CT at the start of the study, or current psychotherapy with a frequency of more than two sessions a month (see Fig. 1).

Patients were recruited from February 2000 through September 2000 at psychiatric centers (31% of the patients) and through media announcements (69% of the patients). Written informed consent was obtained prior to randomization. Approval of the Institutional Review Board of the Academic Medical Center of the University of Amsterdam (AMC) was obtained and the trial was conducted in compliance with the Declaration of Helsinki (World Medical Association, 2000).

Patients were screened on inclusion and exclusion criteria with telephone versions of the Structured Clinical Interview for DSM-IV (SCID (First et al., 1996)) and the Hamilton Rating Scale for Depression (HDRS). Kappa for inter-rater agreement between the interviewers (psychologist/resident in psychiatry/research assistants) regarding inclusion or exclusion criteria as based on audiotaped interviews, was 0.77 (good/excellent agreement). Patients meeting the inclusion criteria were randomly allocated to (a) Treatment As Usual (TAU), or (b) Treatment As Usual+Preventive Cognitive Therapy (TAU+PCT). Randomization was organized and administered by an independent research associate using random permutated blocks and was stratified by study location and type of aftercare (family physician, psychiatric center, or no aftercare). Consecutively numbered, sealed envelopes contained computer-generated cards with concealed assignment codes. For follow-up assessments after 2 years, patients were sent an information letter after 3, 5.5 and 10 years. We were not allowed to contact patients that did not respond to this letter for ethical reasons.

2.2. Treatment

Preventive Cognitive Therapy (PCT). PCT involved eight weekly of

two-hour group sessions (7–12 members). We used a closed format and treatment manual was used (Bockting et al., 2009; Beck et al., 1979). The PCT focused on identification of dysfunctional attitudes and schemas (World Medical Association, 2000) and teaching patients to challenge these, enhancing specific memories of positive experiences and formulating specific prevention strategies (Bockting et al., 2009; Beck et al., 1979). The PCT was delivered by nine psychologists fully trained in CT who had received 16 h of specific training (Bockting et al., 2005). To maintain treatment integrity all sessions were audiotaped and evaluated by our assessors using a checklist of all particular interventions. Any adherence issues were resolved prior to the subsequent session (2 adherences issues were detected and resolved).

Treatment As Usual (TAU). This treatment involved"naturalistic' care, i.e. standard treatment (including no treatment). There were no restrictions on the use of pharmacotherapy. During the first 2 years (Bockting et al., 2008), information on AD use (type and dosage) and other psychological treatment (number of counseling or psychotherapy sessions) was collected every 3 months with the Trimbos/IMTA Self Report Questionnaire for Costs Associated with Psychiatric Illness (TIC-P (Hakkaart-van Roijen et al., 2002)).

2.3. Outcome

The primary outcome was time to first recurrence, assessed with the SCID-I and LIFE interview (First et al., 1996). At six follow-up points (at 3, 12, 24, 36, 66 and 120 months), current and past depressive episodes were checked. To maintain the assessors' blindness to treatment condition, we instructed participants not to reveal this information to the interviewers. Kappa for inter-rater agreement on recurrence between the interviewers and a supervising psychiatrist over the follow-up period ranged from 0.94 to 0.96, indicating high agreement.

Secondary outcomes were cumulative proportion of first recurrence, mean severity of recurrences (SCID based: low <6; moderate; 6–7, severe; 8–9 symptoms), and number of recurrences at risk over 10 years (SCID based).

2.4. Statistical methods

In view of previous findings (Vittengl et al., 2007; Guidi et al., 2010; Bockting et al., 2009, 2005), we expected the effect of PCT to be moderated by the number of previous depressive episodes. To detect time to first recurrence, we used a Cox regression with time to recurrence as the dependent variable and treatment condition, number of previous episodes, and the treatment condition by number of previous episodes interaction as independent variables. To assess the effect of number of previous episodes on survival the fitted proportional hazard model was used to estimate survival stratified on number of previous episodes. All patients of whom we have data after randomization were included in the analysis (15 patients dropped out immediately after randomization). To check for selection bias, analyses were repeated after multiple imputation of all patients, including these 15 patients. Additionally, we did a completers analysis including all patients that received ≥ 5 PCT-sessions.

The confounding or modifying effect of the stratification variables, site and type of treatment, on the treatment effect parameter was assessed. As no effect of site or type of treatment on the effect of treatment condition on recurrence was observed, further analyses were performed without these stratification variables.

In secondary analyses we examined the effects of treatment condition on cumulative proportion of first recurrences (Kaplan Meier), mean severity over all recurrences, and the number of recurrences at risk over 10 years (by correcting for differences in follow-up time of patients) comparing four groups based (ANOVA) on the above described model.

3. Results

Patient flow through the trial is displayed in Fig. 1. A total of 321 potential participants were contacted. We excluded patients for the following reasons: current depression/HRSD >9, fewer than two depressive episodes/last episode more than 2 years ago, current or past psychoses, substance abuse, bipolar disorder, predominant anxiety disorder, current and frequent psychotherapy and other reasons (e.g. time investment). All remaining 187 patients fulfilled the inclusion criteria, and consented to randomization. For the intention-to-treat analyses we included 172 patients after excluding 15 patients that dropped out immediately after randomization (PCT: $n=9$, TAU: $n=6$). These dropouts were slightly younger than the intention-to-treat group $t(170)=-2.25$, $p=0.03$ (drop out: $M=38.9$, $SD=10.6$, intention-to-treat group: $M=44.8$, $SD=9.5$), but comparable on all other characteristics. Additionally, the effect of PCT after multiple imputation of these 15 immediate drop-outs was analyzed.

For the 'completers' analyses we excluded another 7 patients of the PCT group because they attended fewer than five sessions. When these patients were compared with patients who attended at least five sessions ($n=81$), two significant differences emerged. 'Non-completers' were younger, $t(170)=-2.85$, $p=0.005$ (<5 sessions: $M=36.9$, $SD=8.7$, ≥ 5 sessions: $M=46.6$, $SD=8.7$), and had a lower score on the Dysfunctional Attitude Scale (Bockting et al., 2009), $t(170)=-2.01$, $p=0.048$ (<5 sessions: mean 97, $SD=21.2$, ≥ 5 sessions: $M=121.4$, $SD=29.1$). At 10 year follow-up we had data of the secondary outcomes on mean severity and number of recurrences of 87 patients (TAU: $N=39$, PCT: $N=48$). Data on severity and number of recurrences over time were respectively 2 years: $N=165$, 3 years: $N=155$; 5.5 years: $N=138$; 10 years: $N=87$.

Characteristics of the intention-to-treat group ($n=172$) are summarized in Table 1. Both groups were comparable on each of the variables (all p's >0.10), except for number of previous episodes, $\chi^2(1, N=172)=4.43$, $p=0.04$ (PCT 77/88 had more than two previous episodes versus TAU 63/84), subjective experience of daily hassles (Bockting et al., 2005), $t(170)=2.27$, $p=0.03$ (PCT $M=3.5$, $SD=1.0$, TAU $M=3.8$, $SD=0.8$) and experience of negative

Table 1
Characteristics of the intention-to-treat sample ($n=172$).

Characteristics	**Preventive Cognitive Therapy ($n=88$)**	**Treatment As Usual ($n=84$)**
Sex, female (%)	73	74
White (%)	98	99
Age (yr; mean ± SD)	45.9 ± 9.1	43.4 ± 9.8
Years of education (mean ± SD)	14.1 ± 2.5	14.4 ± 2.6
Marital status (%)		
Single	19	29
Married/cohabiting	59	57
Divorced/widowed	22	12
Type of current treatment (%)		
Family doctor	32	25
Psychiatric help	29	33
No treatment	39	42
Antidepressant medication at entry (%)	52	50
HRSD-17 score (mean ± SD)	3.8 ± 2.8	3.7 ± 2.9
Previous episodes		
>2 previous episodes (%)	88	75
Median previous episodes ± IQR	4 ± (3–7)	3 ± (2–6)
Age of first onset (yr; mean ± SD)	28.7 ± 12.6	28.1 ± 12.5

life events before their sixteenth year, $\chi^2(1, N=172)=6.74$, $p=0.01$ (PCT 84/88 experienced negative life events versus TAU 70/84). In both the intention-to-treat analyses and completers-analyses none of these variables had a confounding effect on the relation between treatment and outcome (Bockting et al., 2009).

3.1. Recurrence

Overall the cumulative recurrence was 90.3% of at least one recurrence over 10 years follow-up period. Most patients experienced more than 1 recurrence (for PCT, 13% experienced 1 recurrence, 9% 2–5 recurrences 36% and 26% >5 recurrences; for TAU, 9% experienced 1, 2–5 recurrence 50% and 24% >5 recurrences).

3.2. Effectiveness

As expected and previously reported (Bockting et al., 2009, 2005), difference in outcome was dependent on the number of previous depressive episodes. A Cox regression analyses (intention-to-treat), with treatment condition, previous episodes and their interaction as predictors, revealed a significant previous episodes by treatment condition interaction at 10-year follow-up, Wald(1, $N=172$)=8.366, $p=0.004$, Hazard ratio=0.576, 95% CI=0.396–0.837, for treatment condition in this model; Wald(1, $N=172$)=0.851, $p=0.356$, Hazard ratio=1.302, 95% CI=0.743–2.279; for number of previous episodes effect in this model; Wald (1, $N=172$)=15.498, $p=<0.001$, Hazard ratio=1.679, 95% CI=1.297–2.174. A model with the main treatment effect showed a non significant difference (Wald(1, $N=172$)=2.785, $p=0.095$, Hazard ratio=0.755, 95% CI=0.543–1.050).

After multiple imputation of the data including the 15 patients (8%) that dropped out immediately after randomization, results were closely similar ($n=187$, for interaction with previous episodes effect Wald(1)=17.961, $p=0.003$, Hazard ratio=0.567, 95% CI: 0.389–0.827). Results were also closely similar for the completers-group (attended ≥ 5 sessions PCT, $n=165$; for interaction treatment condition with previous episodes effect, Wald(1)=8.366, $p=0.004$, Hazard ratio=0.576, 95% CI: 0.396–0.837).

Fig. 2 shows the hazard rates for TAU and PCT patients conditional on their number of previous depressive episodes (TAU patients with 2 previous depressive episodes as reference group). For TAU patients their hazard increased (i.e. their survival prospect decreased) with the number of previous episodes (intention-to-treat) for 10 year follow-up. For patients in the PCT group, the effect of the number of previous episodes is neutralized (the hazard rate line is almost parallel to the *X*-axis). In line with our 2 year and 5.5 year follow-up findings, the protective effect of PCT increases with the number of previous depressive episodes. As Fig. 2 shows the 10 years and 5 years lines diverge a bit more than the 2 years lines.

According to this model, the beneficial effect of PCT became statistically significant at more than three previous episodes. Dichotomization of the number of previous episodes in 2 or 3 episodes versus more than 3 previous episodes revealed at 10 year follow-up a significant treatment condition by previous episodes interaction effect, Wald(1 $N=172$)=6.090, $p=0.014$, Hazard ratio=0.434, 95% CI=0.223–0.842; for treatment condition effect; Wald(1 $N=172$)=0.178, $p=0.673$, Hazard ratio=1.110, 95% CI=0.684–1.800; for dichotomized number of previous episodes effect; Wald(1, $N=172$)=7.402, $p=0.007$, Hazard ratio=1.929, 95% CI=1.202– 3.097. The mean survival time for the group of patients with 2 or 3 episodes in PCT was 1020.0, SE 204.7 days, 95% CI=618.8–1421.0 (median 502.0) and for TAU 1160.6, SE 202.8 days, 95% CI=763.2–1558.1 (median 502.0). For patients with more than 3 episodes the mean survival time in PCT was 1255.2, SE 196.5 days, 95% CI=870.1–1640.3 (median 713.0) and for TAU 515.8, SE 140.1 days, 95% CI=241.3–790.4 (median 205.0).

Fig. 3 shows the survival curves comparing time to recurrence in the PCT group and the TAU group for patients with 2 or 3 previous episodes versus those with more than 3 previous episodes. This figure shows longer survival time over 10 years (maximum of 3.967 follow-up days) in favor of the PCT group with more than 3 previous episodes (Logrank; Bonferroni, 2 comparisons, $p<0.025$): in this group PCT did significantly reduce recurrence compared to TAU; $\chi^2(1, n=90)=9.783$, $p=0.001$. No difference was found for the 2–3 previous episode group ($\chi^2(1, n=82)=0.166$, $p=0.683$).

3.3. Secondary outcome

3.3.1. Cumulative proportion of recurrence

Fig. 3 shows the survival curves comparing cumulative recurrence in the PCT group and the TAU group for patients with 2 or 3 previous episodes (PCT, $n=39$; 84.9% versus TAU, $n=43$; 93.2%) versus those with more than 3 previous episodes (PCT, $n=49$; 88.7% versus TAU, $n=41$; 95.6%). Cumulative recurrence rates did not significantly differ between both PCT groups (respectively a

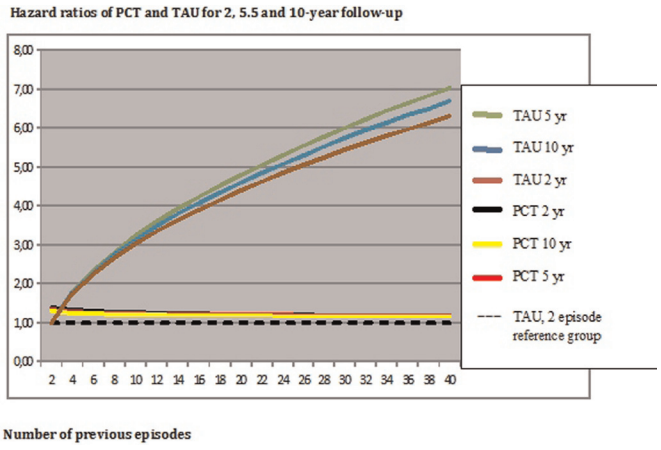

Fig. 2. Hazard ratios of Preventive Cognitive Therapy versus Treatment As Usual with the number of previous episodes (intention-to-treat, $N=172$) for 10-year follow-up.

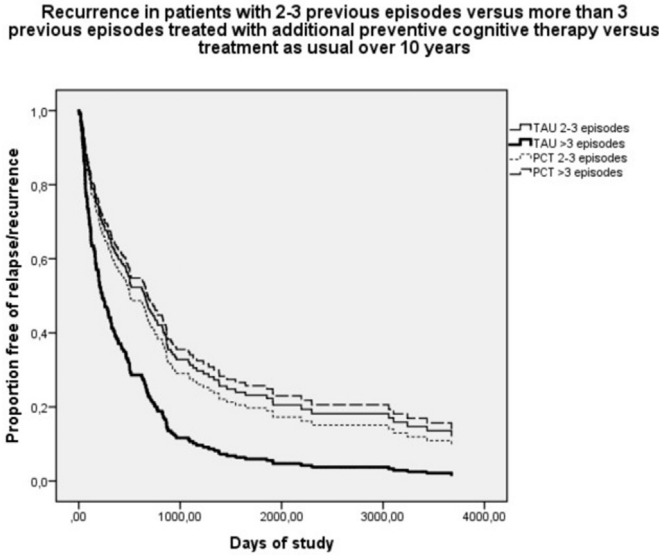

Fig. 3. Survival curves for patients with 2–3 previous episodes and patients with more than 3 previous episodes in the Treatment As Usual versus the Preventive Cognitive Therapy group over 10 year follow-up.

difference of 6.9% for the PCT-group with more than 3 episodes; $z=1.2450$ $p=0.213$ and 8.3% for the PCT-group with 2 or 3 previous episodes; $z=1.2029$ $p=0.229$). Inspection of the survival curves, reveals that the protective effect of PCT was established in the first half of the 10 year follow-up period.

Number of recurrences. The number of recurrences *within a patient* per 10 years at risk was calculated for the 166 patients ($N=6$ missing because follow-up time was too short to experience >1 recurrence). for multiple recurrences per 10 years at risk no significant interaction of treatment condition by number of previous episode (2–3 versus >3 episodes), was found ($F(1, 166)=2.350$, MS=0.240, $p=0.127$).

Severity. For the effect of PCT on mean severity of detected recurrences over the 10 years follow-up period, data of 87 patients were available of whom 77 patients experienced recurrences. for mean severity of recurrences (ANOVA) a significant treatment condition by number of previous episodes (2–3 versus >3 episodes) interaction was found ($F(1, 77)=5.847$, MS=1.184, $p=0.018$). for patients with more than 3 episodes, mean severity of recurrences was lower in the PCT group (mean 1.91, CI: 1.72–2.10) than in the TAU group (mean 2.18, CI: 1.97–2.40). for patients with 2 or 3 previous episodes mean severity of recurrences was lower in the TAU group (mean 1.94, CI: 1.73–2.15) than in the PCT group (mean 2.16 CI: 1.95–2.37).

4. Discussion

This is the first randomized controlled trial that examined long-term protective effects over 10 years of a brief Preventive Cognitive Therapy (PCT) in remitted patients at entry of the study with recurrent depression. In line with previous studies (Vittengl et al., 2007; Piet and Hougaard, 2011; Stangier et al., 2013; Bockting et al., 2009, 2005), the effect of PCT intensified with increasing number of previous episodes experienced. That is, the effect is larger in patients with more previous episodes. At 10 year follow-up, the group of patients with multiple previous depressive episodes that received PCT was still better off than the initial TAU group. That did not receive PCT The protective effect of the intervention was established mainly in the first half of the 10 years period. The median survival time for PCT patients with more than 3 previous episodes was significantly longer (713.0) than for TAU patients (205.0). The beneficial effect observed in the PCT group could not be attributed to other psychological treatments or use of AD within the first 2 years (Bockting et al., 2009, 2008). Although, we cannot rule out whether the beneficial effect of PCT after these first 2 years could be explained by an increase of use of mental health care.

To date there are no other prevention studies that examined the effect of sequential PCT over 10 years, though long-term effects of C(B)T over 6 years have been demonstrated in patients with residual symptoms (Fava et al., 2004, 1998). C(B)T during the acute depressed stage that was stopped after remission has been shown to have an enduring protective effect e.g. Vittengl et al. (2007), Guidi et al. (2010), Cuijpers et al. (2013), Hollon et al. (2005), Dobson et al. (2008). In partially remitted patients, protective effects of C(B)T over 3.5 years have been reported (Paykel et al., 2005).

The increasing protective effect of PCT with increasing number of episodes is particularly important given the finding in a recent meta-analysis that AD has a decreasing protective effect, with an increasing number of episodes (Kaymaz et al., 2008). Currently, leading international guidelines suggest long-term use of ADs for recurrently depressed patients (Cuijpers et al., 2013; Olfson and Marcus, 2009). Rather than a relative resistance with increasing numbers of episodes, an increasing protective effect is found for sequential psychological interventions, including MBCT and CT (Vittengl et al., 2007; Guidi et al., 2010; Piet and Hougaard, 2011; Stangier et al., 2013; Bockting et al., 2009, 2005). These psychological interventions might be an alternative strategy for long-term use of ADs especially for this recurrent patient group, as first studies already indicate (Kuyken et al., 2008; Segal et al., 2010). However, large scale studies are needed to validate this positive effect of psychological interventions.

PCT seemed to have no significant protective effect for patients with two previous episodes, in line with most studies (Vittengl et al., 2007; Guidi et al., 2010; Piet and Hougaard, 2011; Stangier et al., 2013; Bockting et al., 2009, 2005). A recent study indicates that for patients with few episodes, psycho-education is equally effective as maintenance CT (Stangier et al., 2013). Alternatively, the lack of protective effect of PCT in patients with few episodes, may be due to the limited follow-up periods in these studies, that were no longer than two years (Beshai et al., 2011). In our study the apparent indication of the number of previous episodes seemed lower in our 10 year follow-up than in our 2 year follow-up (i.e. for 2 year: ≥ 5 episodes versus for 10-year: >3 episodes). However, these indications of the number of episodes in all conducted studies for these interventions to be beneficial should be interpreted with caution because of the modest sample size.

Although PCT increases time to recurrence, we found no effect on secondary outcomes, such as number of recurrences. The effect on these outcomes of this brief intervention might be restricted to a period of 2–5.5 years (Bockting et al., 2009, 2005), although we cannot rule out the possibility of a small-medium effect given the limited sample size and associated small statistical power as a consequence of relatively high drop-out rate for these secondary outcomes. In addition, the mean severity of recurrences was lower in patients with more than 3 episodes who received PCT, but a reversed effect was found for patients with 2 and 3 episodes. Moreover, the cumulative recurrence rate was still high over 10 years. This indicates that we need to improve preventive strategies. As the intervention under study consisted of eight weekly sessions, additional sessions might prolong protective effects. Alternatively, booster sessions might be needed to reinforce the effect (Beshai et al., 2011). Also, combining this intervention with new technologies (e.g. E-health) might enhance long-term effects (Bockting et al., 2011). There are some indications that internet-based CT is promising in preventing recurrence in persons with partially and remitted major depression (Holländare et al., 2011; Kok et al., 2015).

This study was designed to maximize external validity, which suggests good generalizability of the findings. Our patient group included patients remitted on treatment as typically provided in clinical practice, including ADs. However, a number of limitations should be acknowledged here. Although the beneficial effect observed in the PCT group could not be attributed to other psychological treatments or use of ADs over the first two year (Bockting et al., 2009), we cannot completely rule out that the increased use of these treatments explained the preventive effect of PCT, over the subsequent 8 years. Additionally, dropout rates were high, as is common in longitudinal studies, yet it needs to be mentioned that drop outs for the primary aim analysis was relatively low and results were comparable after multiple imputation. Additionally, the intervals between assessments increased over time (1–4.5 years) with potential recall difficulties for especially secondary outcomes.

Future studies are needed to examine whether long-term effects can be replicated. To reduce recurrence rates in MDD a personalized medicine approach using specific combined markers (Kupfer et al., 2012) might help us to determine what preventive strategy works for whom at what stage. In sum, this is the first study that indicates that a brief psychological intervention has long term protective effects over 10 years in patients with multiple

previous depressive episodes. Future studies should examine how the preventive effect every 4–5 years can be increased, for instance by booster sessions or by using E health and Apps.

Contributors

Authors CLHB, AHS, MWJK designed the study and wrote the protocol. Data was collected by CLHB, NHS. Authors CLHB, MWJK managed the literature searches and analyses. Authors CLHB, MWJK undertook the statistical analysis, and authors CLHB, NHS, MWJK, PHS and AHS wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

All authors have no conflicts of interest.

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