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Effects up to 20-Year Follow-Up of Preventive Cognitive Therapy in Adults Remitted from Recurrent Depression: The DELTA Study

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Keywords
Depression · Major depressive disorder · Relapse · Recurrence · Prevention

Abstract

Introduction: Major depressive disorder (MDD) is common, and recurrence rates are high. Preventive Cognitive Therapy (PCT), has been shown to prolong time to recurrence and reduce risk of recurrence(s) over 2–10 years in patients with recurrent depression. ***Objective:*** The aim of the study was to examine the effectiveness of PCT over 20 years on time to first recurrence, cumulative proportion of first recurrences, percentage of depression-free time, mean severity of recurrences, and the number of recurrences within a patient. ***Methods:*** Adults remitted from recurrent MDD were randomized to PCT or Treatment As Usual (TAU). Clinical outcomes were assessed using the SCID over 20 years. We used Cox regression analyses, Kaplan-Meier analyses, ANOVA, and negative binomial regression and tested for interaction with the number of previous episodes. ***Results:*** There was a significant interaction effect for number of previous episodes with treatment condition on time to first recurrence (Wald[1, $n = 172$] = 8.840, $p = 0.003$). For participants with more than 3 previous episodes, the mean time to recurrence was 4.8 years for PCT versus 1.6 years for TAU; the cumulative proportion of first recurrences was 87.5% for PCT and 100% for TAU. For participants with more than 3 previous episodes, exploratory analyses suggest that PCT had 53% less recurrences and percentage of depression-free time was significantly higher compared to TAU. There were no significant effects on mean severity. ***Conclusions:*** Up to 20 years, for MDD patients with more than 3 previous episodes, those who received PCT had significantly longer time to a first recurrence and lower recurrence risk and may have less recurrences and more depression-free time compared to TAU. This suggests long term protective effects of PCT up to 20-years.

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Introduction

Major depressive disorder (MDD) is one of the most common mental health disorders worldwide [1]. Recurrence rates are high and appear to increase with subsequent episodes [2, 3]. Recurrence prevention is therefore an important treatment target.

Numerous meta-analyses have shown that psychological interventions protect against recurrence [4–8] and are equally effective as long-term use of antidepressants [9–11]. When both are combined, the protective effect is superior to antidepressants only [9, 10, 12].

In the DELTA study, the effectiveness of such a psychological recurrence prevention intervention, preventive cognitive therapy (PCT) for adults with recurrent MDD, was studied [13–15]. Compared to treatment as usual (TAU), randomization to PCT resulted in a significant protective effect on time to a first recurrence that intensified with an increasing number of previous MDD episodes before entering the DELTA study, over 2-year, 5.5-year, and up to 10-year follow-up [13–15]. Further, at 2 years and 10 years, there was a significant protective effect on the mean severity of recurrences [13, 15]; at 2 years, there was a significant protective effect on the number of recurrences within a patient [14]; and at 10 years, there was a significant protective effect on cumulative proportion of first recurrences [15], all dependent on the number of previous episodes within a patient. Over follow-up time, the interaction effects with number of previous episodes were less pronounced [13–15]. In subsequent randomized controlled trials (RCTs), protective effects of PCT have also been found over several months [16–18] up to 1–2 years [19–27]. However, follow-up periods for PCT have been limited to 10 years maximum (the DELTA study) [15], and long term follow-up periods for other psychological interventions were no longer than 6 years maximum [28, 29]. Thus, follow-up studies on psychological interventions show promise in terms of recurrence prevention, although effects beyond 6–10 years remain unknown.

Therefore, the objective of the current study was to examine the effects of PCT over 20 years. In line with previous findings from the DELTA study, we expect that the effects of PCT intensify with a higher number of previous episodes.

Materials and Methods

Participants

This is a follow-up of the DELTA study [13–15]. Inclusion criteria at entry were age of ≥18 years, remission from MDD for at least 10 weeks and at most 2 years, ≥2 previous MDD episodes in the last 5 years, and a Hamilton Rating Scale for Depression (HRSD) [30] score of ≤10. Exclusion criteria were organic brain damage, alcohol/drug misuse, psychotic disorder, current or previous mania/hypomania, predominant anxiety disorder, recent ECT, and recent/current cognitive therapy at the start of the study/current psychotherapy (>2 times a month). Participants were recruited at psychiatric centers and through media from February to September 2000.

Screening potential participants was done using the telephone versions of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR Axis I (SCID-I) [31] and the HRSD. Inter-rater agreement was good-excellent (Kappa 0.77) [13]. Participants who met inclusion criteria were randomized to PCT or TAU. Randomization was executed by an independent research associate using random permutated blocks stratified by study location and type of aftercare (family physician, psychiatric center, or no aftercare). Further, computer-generated cards with concealed assignment codes and consecutively numbered and sealed envelopes were used.

Participants were invited for 2-, 3-, 5.5-, 10-, and 20-year follow-up assessments. At each follow-up time-point, all participants included at the previous time-point were invited to participate. Written informed consent was obtained for all participants, and the study protocols were approved by the Medical Research Ethics Committee of the Academic Medical Center.

Treatment

PCT was administered at weekly 2-h group sessions during the 8-week period. Each group consisted of seven to twelve participants. Treatment was administered according to a manual [13, 32, 44] and focused on (1) identifying and challenging dysfunctional attitudes and schemas using cognitive techniques that elicit positive affect [33, 34]; (2) training specific recall of positive experiences and feelings; and (3) formulating an individual recurrence prevention plan. Participants learned to enhance specific memories of positive experiences and formulate concrete prevention strategies. Therapists were psychologists who were fully trained in cognitive therapy and received 16 h of PCT training. Sessions were audiotaped and evaluated by assessors using a checklist of interventions, and if applicable, adherence issues were resolved prior to the next session. TAU consisted of standard treatment (including no treatment, pharmacotherapy, psychotherapy, and counseling).

Outcomes

Time to MDD recurrence; cumulative proportion of first recurrences; percentage of depression-free time; mean severity of recurrences (low <6; moderate 6–7; severe 8–9 symptoms); and number of recurrences within a patient over 20 years were assessed using the SCID I (at baseline, 3, 12, 24, 36, 66, and 120 months) [31] and SCID for DSM-5 syndrome disorders (SCID-5-S, 251–272 months) [35] and LIFE interviews. The reemergence of symptoms up to a point where a patient met MDD criteria again after 2 months since remission from a previous episode was considered a recurrence. The reemergence of symptoms within 2 months since remission from a previous episode was considered as one and the same prolonged MDD episode. Inter-rater agreement between the assessors up to 10 years was excellent (Kappa 0.94) [15]. At 20 years, all participants were assessed by one assessor. All assessors were trained psychologists or research assistants, blind to treatment allocation in line with recommendations for trials of psychological interventions [36]. Participants were instructed *not* to reveal allocation information.

Statistical Methods

The overall cumulative incidence of recurrence over 20 years was calculated using the Kaplan-Meier method. The number of recurrences over this period had to be estimated by extrapolation because not all participants had complete follow-up. This was done by multiplying the mean number of recurrences per year for each individual by 20 under the assumption that the recurrence rate remained unaltered after the last follow-up of the participant.

The effect of PCT on time to MDD recurrence was examined using Cox regression with time to recurrence or censoring as the dependent variable, and treatment condition, number of previous episodes, and their interaction as independent variables. We tested for effects of 2 or 3 previous episodes versus more than 3 previous episodes, in line with the 5.5- and 10-year follow-up [14, 15].

We performed a modified intent-to-treat analysis including all participants, except for those who dropped out directly after randomization ($n = 15$). We additionally performed a completers' analysis including participants that received ≥5 PCT sessions. The cumulative proportion of first recurrences was quantified and graphically presented using the Kaplan-Meier method according to treatment condition and number of previous episodes.

Percentage of depression-free time over 20 years at risk was assessed using analysis of variance (ANOVA) with treatment condition (PCT vs. TAU) and number of previous episodes (2 or 3 vs. more than 3) and their interaction as independent variables. We used depression-free time in days as a percentage of follow-up duration in days within a patient.

The mean severity of all recurrences was assessed using ANOVA. We corrected for differences in follow-up time and compared the mean severity of recurrence in the ANOVA analyses in four groups based on the model described above (PCT vs. TAU; 2 or 3 previous episodes vs. more than 3 previous episodes).

To explore the association of the number of MDD recurrences with treatment conditions, we used negative binomial regression. Results were expressed as incidence rate ratios (IRR) with 95% confidence intervals. The IRR indicates the relative reduction in recurrence rate within patients. We stratified according to the number of previous episodes (2 or 3 previous episodes vs. more than 3 previous episodes) and assessed potential interaction with treatment. Analyses were conducted separately over 20 years, the first 10 years, and the second 10 years.

Only participants who were followed-up for the full 20 years were included in the analyses on percentage of depression-free time, mean severity of recurrences, and number of recurrences within a patient. Furthermore, only participants who had at least one recurrence were included in the analysis on mean severity of recurrences. Analyses limited to the 20-year follow-up sample were considered explorative due to the small sample size and consequently low statistical power. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 25 for Windows.

Results

Participant Flow and Participant Characteristics

Figure 1 shows the participant flow throughout the trial. Participants that dropped out immediately after randomization ($n = 15$) were younger than the intention-to-treat sample [13]. Non-completers ($n = 7$) were younger and had lower scores on the Dysfunctional Attitude Scale [13]. The number of participants included at 2 years was $n = 165$; at 3 years, $n = 155$; at 5.5 years, $n = 138$; at 10 years, $n = 87$; and at 20 years, $n = 38$. At 10 years, $n = 10/87$ participants were still at risk for a first recurrence. Out of these 10 participants, 20-year follow-up data were available for 6 only. At 20 years, 1 out of these 6 participants (17%) was found to have had a first recurrence after 10 years. Table 1 provides an overview of participant characteristics of the intention-to-treat samples and 20-year follow-up samples. The 20-year follow-up sample randomized to TAU consisted of relatively more females and participants with a slightly higher level of education compared to the other samples. The 20-year follow-up sample randomized to PCT consisted of relatively more participants with more than 3 previous episodes compared to the other samples. Samples were comparable on other characteristics.

Recurrence

The overall cumulative incidence of recurrence was 91.7% over 20 years. We estimated that most participants experienced more than 5 recurrences. Based on our extrapolations, in the PCT condition, 17% experienced no recurrence; 2% had 1 recurrence, 26% had 2–5 recurrences, and 55% had >5 recurrences. In the TAU condition, 14% experienced no recurrence; 3% had 1 recurrence, 28% had 2–5 recurrences, and 55% had >5 recurrences ($n = 166$; $n = 6$ had follow-up time that was too short to experience ≥1 recurrence and were therefore excluded from these calculations).

Effectiveness of Preventive Cognitive Therapy

Time to Recurrence

Cox regression analyses showed that there was a significant interaction effect for number of previous episodes with treatment condition at 20-year follow-up: Wald(1, $n = 172$) = 8.840, $p = 0.003$, hazard ratio = 0.567, 95% CI = 0.391–0.824. A model with treatment condition only showed no significant effect. Results were closely similar for the completers group: interaction effect for number of previous episodes with treatment condition: Wald(1, $n = 165$) = 9.306, $p = 0.002$, hazard ratio = 0.547, 95% CI = 0.371–0.806.

We used dichotomization of participants based on the number of previous episodes: 2 or 3 previous episodes versus more than 3 previous episodes, based on former findings [14, 15]. This model revealed a significant treatment condition by previous episodes interaction effect: Wald(1, $n = 172$) = 6.625, $p = 0.010$, hazard ratio = 0.419,

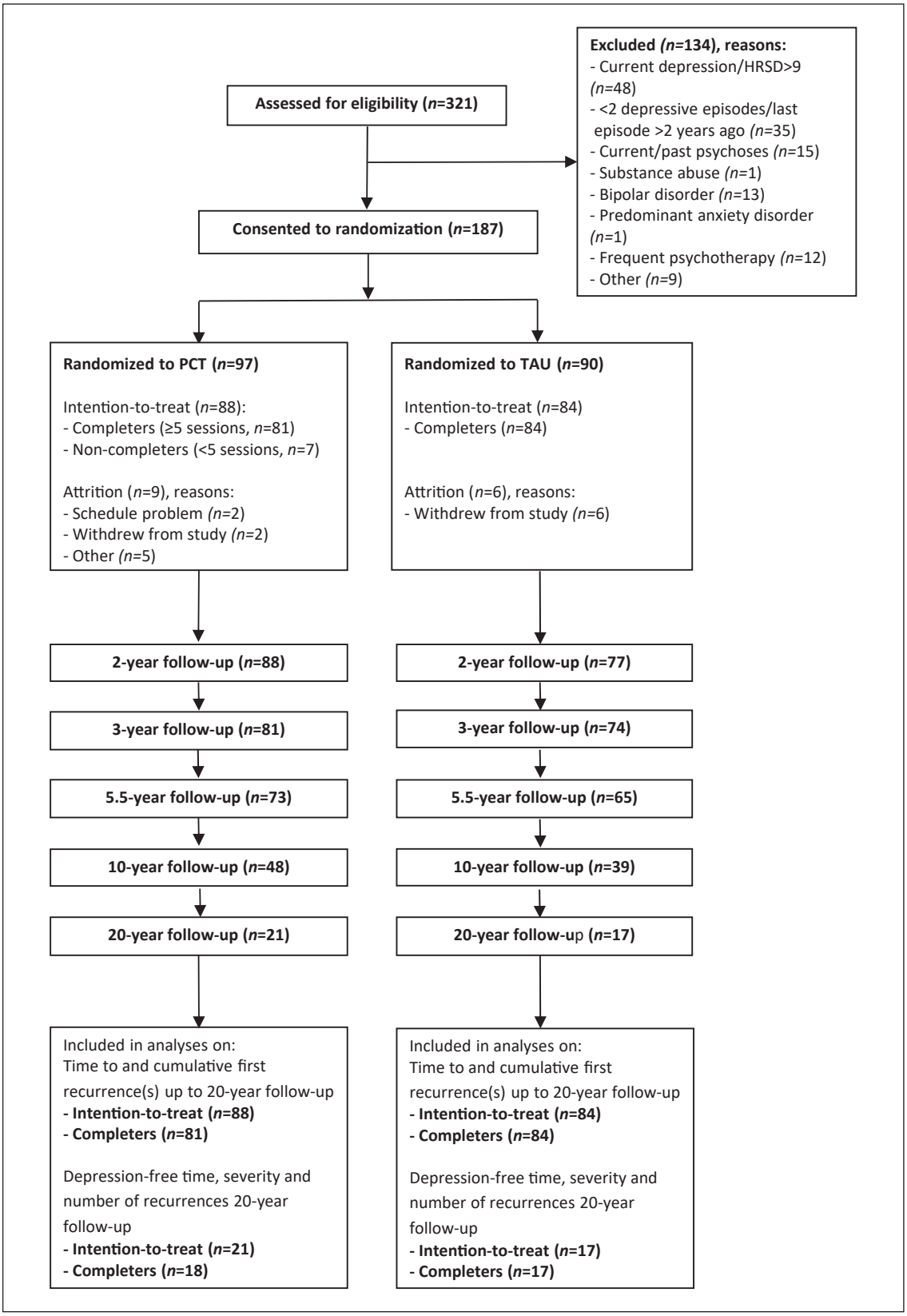

Fig. 1. Flow diagram of participants over 20-year follow-up.

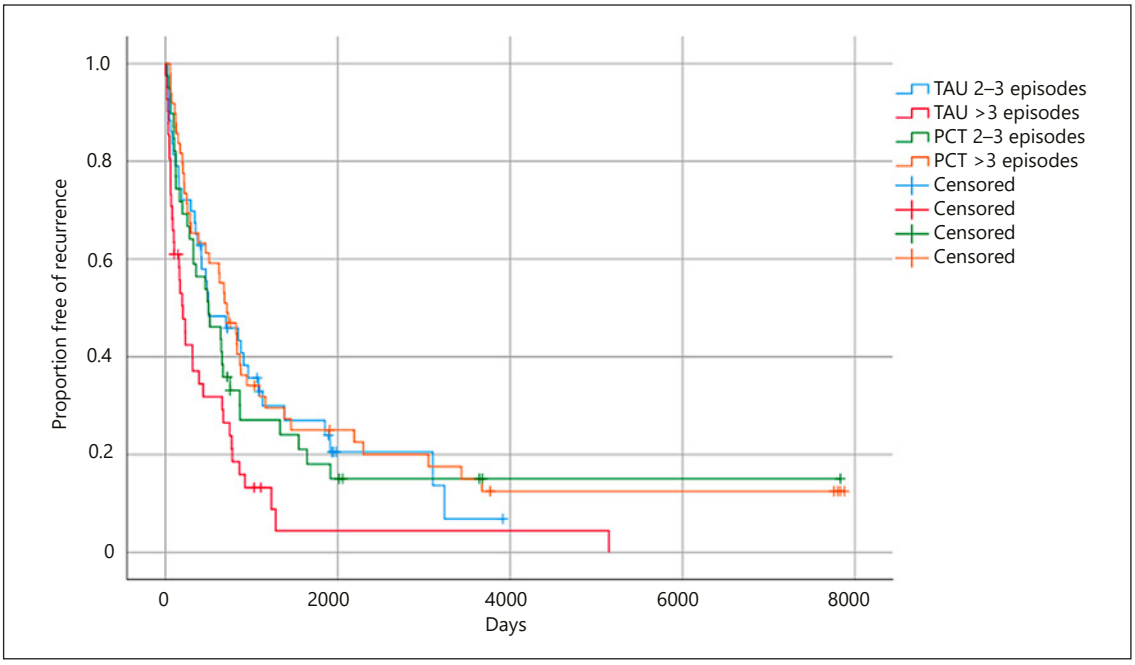

Fig. 2. Survival curves over 20 years. "Completers" completed ≥5 PCT sessions. TAU, treatment as usual; PCT, preventive cognitive therapy.

Table 1. Participant characteristics at start of the study

Characteristic	Intention-to-treat sample (n = 172)		20-year-follow-up sample (n = 38)	
	PCT (n = 88)	TAU (n = 84)	PCT (n = 21)	TAU (n = 17)
Sex, female, n (%)	64 (73)	62 (74)	14 (67)	16 (94)
Age, years (mean ± SD)	45.9±9.1	43.4±9.8	43.2±8.4	42.5±8.9
Education, n (%)				
Lower	33 (38)	22 (26)	8 (38)	3 (18)
Medium	25 (28)	30 (36)	6 (29)	7 (41)
Higher	30 (34)	32 (38)	7 (33)	7 (41)
HRSD-17 score (mean ± SD)	3.8±2.8	3.7±2.9	3.5±2.8	4.1±3.6
Previous episodes				
>3 previous episodes, n (%)	49 (56)	41 (49)	10 (71)	9 (53)
Previous episodes (median, IQR)	4 (3–6.8)	3 (2.3–6)	3 (2.5–5)	5 (3–8)
Age of first onset, years (mean ± SD)	28.7±12.6	28.1±12.5	28.9±13.5	26.1±11.7

TAU, treatment as usual; PCT, preventive cognitive therapy; HRSD, Hamilton Rating Scale for Depression; IQR, interquartile range 25th to 75th percentile. Examples of education levels: lower, up to prevocational secondary education; medium, upper secondary education, vocational training, middle management, and specialist education; higher, preparatory scientific education, associate degree programs, higher education bachelor programs, higher education master programs, and doctoral programs.

95% CI = 0.216–0.813. In this model, there was no significant effect for treatment condition: Wald(1, n = 172) = 0.163, p = 0.686, hazard ratio = 1.105, 95% CI = 0.681–1.792, and a significant effect for previous episodes: Wald(1, n = 172) = 7.972, p = 0.005, hazard ratio = 1.969, 95% CI = 1.230–3.153. The mean survival time in days for participants

with 2 or 3 previous episodes for PCT was 1,634.9, SE 443.3, 95% CI = 766.1–2,503.7 (median 502), and for TAU 1,160.6, SE 202.8, 95% CI = 763.1–1,558.1 (median 502). For participants with more than 3 previous episodes, the mean survival time for PCT was 1,748.5, SE 369.7, 95% CI = 1,023.9–2,473.2 (median 713) and for TAU 577.8, SE 195.0, 95% CI = 195.5–960.1 (median 205).

Cumulative Proportion of First Recurrences

Figure 2 shows the survival curves for participants with 2 or 3 previous episodes (Kaplan-Meier method) (PCT, $n = 39$: 84.9%; TAU, $n = 43$: 93.2% experienced a recurrence) and those with more than 3 previous episodes (PCT, $n = 49$: 87.5%; TAU, $n = 41$: 100% experienced a recurrence). Inspection of Figure 2 shows that the protective effect of PCT on time to recurrence and proportion of first recurrences was mainly established in the first 5 years after the intervention.

Percentage of Depression-Free Time

Data for 38 participants was available, who completed the full 20-year follow-up period. There was no significant effect of treatment condition ($F(1, 38) = 1.528$, MS = 299.978, $p = 0.224$). There was, however, a significant interaction of treatment condition by number of previous episodes (2–3 vs. more than 3) ($F(1, 38) = 4.852$, MS = 865.633, $p = 0.034$). There were no significant effects for the completers' sample ($n = 35$) (respectively, $F(1, 35) = 2.932$, MS = 463.369, $p = 0.096$ and $F(1, 35) = 3.601$, MS = 512.371, $p = 0.067$). For participants with 2 or 3 previous episodes, the mean percentage of depression-free time for PCT was 90.9, SE 4.0, 95% CI = 82.7–99.1; and for TAU, 95.1, SE 4.7, 95% CI = 85.5–104.7. For participants with more than 3 previous episodes, the mean percentage of depression-free time for PCT was 95.7, SE 4.2, 95% CI = 87.1–104.3; and for TAU, 80.7, SE 4.5, 95% CI = 71.7–89.8.

Severity

Concerning the mean severity of recurrences over 20 years, data was available for 33 out of 38 participants who experienced at least one recurrence. For mean severity of recurrences (ANOVA), no significant treatment condition by number of previous episodes (2–3 vs. more than 3) interaction was found ($F(1, 33) = 3.173$, MS = 0.986, $p = 0.085$). For participants with more than 3 previous episodes, the mean severity of recurrences was lower in PCT (mean 1.88, 95% CI: 1.41–2.34) compared to TAU (mean 2.28, 95% CI: 1.90–2.66). For participants with 2 or 3 previous episodes, the mean severity of recurrences was lower in TAU (mean 1.80, 95% CI: 1.40–2.21) compared to PCT (mean 2.11, 95% CI: 1.75–2.47).

Number of Recurrences

For analyses of the regression of the number of recurrences on treatment condition, data of 38 participants was available. Over 20 years, PCT had 23% (IRR = 0.767, CI: 0.375–1.569) less recurrences compared to TAU; over the first 10 years, PCT had 19% (IRR = 0.810, CI: 0.3887–1.690) less recurrences compared to TAU; and over the second 10 years, PCT had 37% (IRR = 0.630, CI: 0.244–1.623) less recurrences compared to TAU. For participants with more than 3 previous episodes, over 20 years, PCT had 53% (IRR = 0.473, CI: 0.166–1.342) less recurrences compared to TAU; over the first 10 years, PCT had 49% (IRR = 0.510, CI: 0.173–1.501) less recurrences compared to TAU; over the second 10 years, PCT had 64% (IRR = 0.360, CI: 0.083–1.563) less recurrences compared to TAU. For participants with 2 or 3 previous episodes, over 20 years, PCT had 3% (IRR = 1.030, CI: 0.377–2.817) more recurrences compared to TAU; over the first 10 years, PCT had 7% (IRR = 1.065, CI: 0.380–2.982) more recurrences compared to TAU; over the second 10 years, PCT had 9% (IRR = 0.909, CI: 0.247–3.341) less recurrences compared to TAU.

Results were closely similar for the completers group: over 20 years, PCT had 29% (IRR = 0.708, CI: 0.336–1.494) less recurrences compared to TAU; over the first 10 years, PCT had 28% (IRR = 0.716, CI: 0.332–1.547) less recurrences compared to TAU; and over the second 10 years, PCT had 32% (IRR = 0.682, CI: 0.258–1.806) less recurrences compared to TAU. For participants with more than 3 previous episodes, over 20 years, PCT had 65% (IRR = 0.350, CI: 0.116–1.058) less recurrences compared to TAU; over the first 10 years, PCT had 67% (IRR = 0.333, CI: 0.104–1.073) less recurrences compared to TAU; over the second 10 years, PCT had 60% (IRR = 0.400, CI: 0.091–1.762) less recurrences compared to TAU. For participants with 2 or 3 previous episodes, over 20 years, PCT had 6% (IRR = 1.062, CI: 0.371–3.035) more recurrences compared to TAU; over the first 10 years, PCT had 8% (IRR = 1.079, CI: 0.368–3.165) more recurrences compared to TAU; over the second 10 years, PCT and TAU had the same number of recurrences (IRR = 1.000, CI: 0.260–3.845).

Conclusion

This follow-up of a randomized controlled trial examined the long-term protective effects of a psychological intervention over 20 years in adults remitted from recurrent MDD. We found a significant effect of PCT on time to recurrence that intensified with an increasing number of previous episodes. For participants that received PCT, the

number of previous episodes was no longer a predictor of recurrence risk. For participants with more than 3 previous episodes, the mean time to recurrence was 4.8 years for the PCT group, whereas the mean time to recurrence was 1.6 years for the TAU group. The cumulative proportion of first recurrences was 87.5% for PCT and 100% for TAU. It should be noted, that the protective effect of PCT on time to recurrence and the cumulative proportion of first recurrences was mainly established in the first 5 years after the intervention. For participants with more than 3 previous episodes, exploratory analyses suggest that over 20 years, PCT had 53% less recurrences and the percentage of depression-free time was significantly higher compared to TAU.

In contrast to the beneficial effects over 10 years, we did not find significant effects on mean severity or number of recurrences over 20 years [15]. This might indicate that the protective effects on these outcomes decline after 10 years. However, the reduction in number of recurrences associated with PCT for participants with more than 3 previous episodes was larger in the second 10-year period (PCT had 64% less recurrences compared to TAU) compared to the first 10-year period (PCT had 49% less recurrences compared to TAU). We should be cautious to draw firm conclusions on either the decline or increase of protective effects after 10 years, given that the sample size for this comparison was small. Furthermore, although not significant, we found an indication that for participants with 2 or 3 previous episodes, mean severity was lower in TAU compared to PCT. This contrasts with more reliable findings of meta-analyses indicating no adverse effects of PCT and other psychological interventions aimed at recurrence prevention [4, 5, 9–11]. With regard to the percentage of depression-free time, there was a significant beneficial effect of PCT over a 20-year follow-up. In contrast, we have previously found no significant effect on the percentage of depression-free time over a 5.5-year follow-up [14]. A prolonged (20-year) follow-up period might be required in order for effects on this outcome to reach statistical significance.

Our finding of an increasing protective treatment effect with an increasing number of previous episodes, is in line with results from a recent individual participant data meta-analysis on preventive psychological interventions as compared to each other and TAU unpublished data by Breedvelt et al. [10], but contrast another meta-analyses that examined PCT and Mindfulness Based Cognitive Therapy as an alternative to continuation of antidepressants in terms of preventing recurrence. Although we found that PCT was effective for those with more than 3 previous episodes, others found that preventive psychological interventions were effective for those with more than 2 previous episodes (unpublished data by Breedvelt et al. [10]).

In our sample, 91.7% experienced at least one recurrence over 20 years. We estimated that most participants experienced more than 5 recurrences. Others that followed MDD patients for prolonged periods found recurrence rates of 64% over 10 years [37] and 85% over 15 years [38]. These studies included, however, patients with a first episode as well as patients with recurrent MDD, while we included patients with recurrent MDD only. This may explain the higher recurrence rates in our study. Moreover, these high recurrence rates emphasize the importance of recurrence prevention in clinical practice as well as to invest in research that aims to improve recurrence prevention interventions. It should be noted that the benefits of relapse prevention interventions could be smaller for MDD patients after a first episode compared to MDD patients after recurrent episodes because the control event rate is expected to be lower. This is also in line with our findings of an effect of PCT that is dependent on the number of previous episodes (more than 3).

With regard to the working mechanism of PCT, there is some evidence that PCT reduces the impact of daily stressors [39], which have been shown to predict recurrence in MDD [39–42]. A possible explanation for this is that the cognitive techniques in PCT improve one's ability to challenge and change negative thoughts and schemas when confronted with daily stressors and thus reduce subsequent negative feelings. In line with this finding, in the DELTA study sample, cortisol levels predicted time to recurrence in participants in the TAU condition, but not in participants in the PCT condition [39, 43].

A number of limitations should be taken into account. First, our estimations on the number of recurrences in the full intention-to-treat sample rest on the assumption that what we have observed with regard to the number of recurrences continued at the same pace for the remaining years after "loss to follow-up." This assumption does not necessarily have to be true. Therefore, these results should be interpreted keeping in mind that they are estimates; they do not represent observations. Second, analyses on time to first recurrence and cumulative proportion of first recurrences depended to a large extent on the first 10-year follow-up period, as the majority of participants (90.3%) had already experienced a first recurrence within these first 10 years. Third, it is possible that the beneficial effects of PCT could be (partially) attributed to differences in other treatments received as a consequence of receiving PCT in the first 8 weeks. Although, this was examined in the analyses at the first 2-year follow-up after receiving PCT, indicating that the

protective effect of PCT could not be explained by differences in the other treatment(s) received [13]. Fourth, dropout rates were high over the 20-year follow-up period, likely affecting the internal validity of this study due to attrition bias and limiting the statistical power of a subset of analyses. However, baseline clinical characteristic of the original intention-to-treat sample and the 20-year follow-up sample were largely comparable, indicating a limited potential for bias. Nevertheless, the analyses on percentage of depression-free time, mean severity of recurrences, and number of recurrences within a patient that were limited to the 20-year follow-up sample should be considered explorative due to the small sample size and consequent low statistical power. Fifth, the type of control condition (TAU) does not allow establishing whether any effects are specific to PCT, or a result of nonspecific factors such as attention received [36]. Finally, differential recall could have affected the accuracy of data.

In sum, up to 20 years, for MDD patients with more than 3 previous episodes, those who received PCT had significantly longer time to a first recurrence and lower recurrence risk and may have less recurrences and more depression-free time compared to TAU. Although a number of limitations preclude firm conclusions and the results of exploratory analyses in this paper cannot inform clinical decisions, our findings cautiously indicate long term protective effects of PCT up to 20 years. More long-term studies on recurrence prevention interventions are needed to examine their enduring effects. Future studies should investigate how preventive strategies for MDD can be enhanced in order to improve patient outcomes, including research on optimal timing points for repeating recurrence prevention interventions in order to achieve sustainable effects.

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Statement of Ethics

The protocols for this study were reviewed and approved by the Medical Research Ethics Committee of the Academic Medical Center/Amsterdam UMC, University of Amsterdam, approval numbers 99/223#99.17.740; 99/223#03.17.0245; 99/223#05.17.0939; 99/223#10.17.0611; 2020_283#B202134. Written informed consent was obtained from all participants at inclusion and at all follow-ups.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Author Claudi L. Bockting designed the original study, and Claudi L. Bockting, Amanda M. Legemaat, Huibert Burger, Gert J. Geurtsen, Marlies Brouwer, and Damiaan Denys designed the current follow-up study. Data collection was managed by Claudi L. Bockting and Amanda M. Legemaat. Authors Amanda M. Legemaat and Huibert Burger analyzed the data for the current manuscript, and Amanda M. Legemaat wrote the first draft of the manuscript. All the authors reviewed and revised the manuscript. The final manuscript was approved by all the authors.

Data Availability Statement

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available because they contain information that could compromise research participant privacy.

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