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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

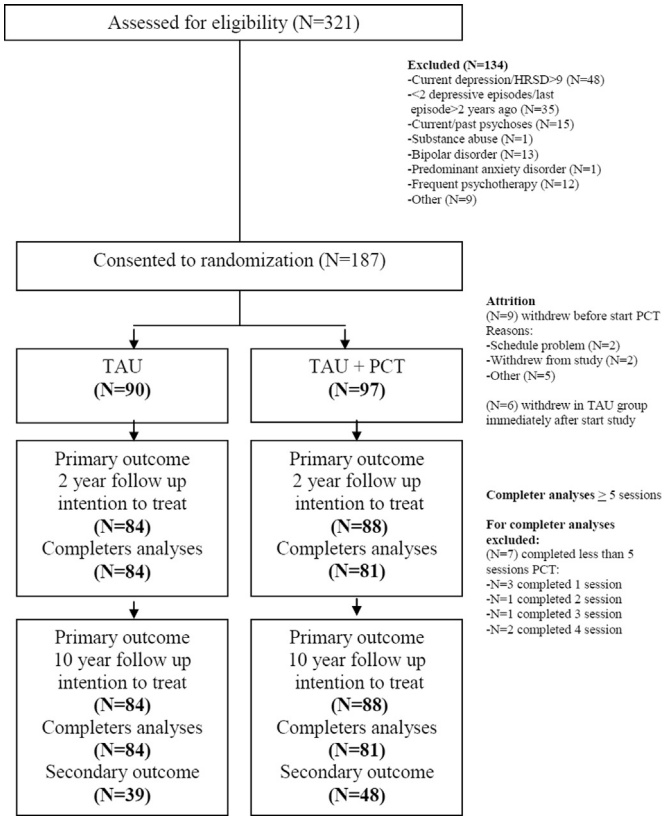

Fig. 1. Flow diagram of patients' process over the 10 year follow-up.

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