Hypochondriasis. diagnostic issues and treatment.

Greeven, J.F.

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The long-term treatment effect of Cognitive Behavioral Therapy and Paroxetine in the treatment of hypochondriasis

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Abstract

Introduction: Hypochondriasis is a severe and chronic psychiatric condition. CBT and Paroxetine are effective short-term treatments. The present study investigated the natural course of hypochondriacal complaints after initial treatment with CBT and Paroxetine compared to a placebo and examined whether comorbidity, duration of complaints and benzodiazepine use predicted course.

Methods: A naturalistic follow-up period after a 16-week randomized controlled trial consisting of 112 subjects with DSM-IV hypochondriasis initially allocated to CBT (N = 40); Paroxetine (N = 37) and placebo (N = 35). Main outcome measure: Whiteley Index. Secondary outcome measures: SCL-90, BAS, MADRS. Sixty-eight subjects evenly distributed over the initial groups were administered a Life Chart Interview about their hypochondriacal complaints up to six years after treatment.

Results: Initial treatment with CBT and Paroxetine was significantly more effective than placebo in reducing hypochondriacal and comorbid anxious complaints on the short-term ($p < 0.001$). During the long-term follow-up, the superior effect of Paroxetine and CBT disappeared, because subjects initially assigned to placebo were treated with Paroxetine or CBT according to their preference and thus caught up the subjects initially treated with CBT or Paroxetine. Compared with initial treatment with placebo, less patients initially treated with CBT received treatment during the follow-up period ($p < 0.005$). About half of the patients recovered form hypochondriasis during the follow-up period.

Conclusion: CBT and Paroxetine are both effective treatments for hypochondriasis in the long term, but a subgroup does not fully benefit. Because of less use of mental health services, CBT should be preferred over Paroxetine.

Keywords: hypochondriasis, follow up, Cognitive Behavioral Therapy, Paroxetine, Placebo, Whiteley Index, Life Chart Interview

Introduction

Among the most common features of hypochondriasis are frequent visiting of general practitioners and demanding physical examinations for reassurance about the absence of a serious somatic condition. Besides contraindicative in terms of amelioration of hypochondriacal complaints (the reassurance is often of temporary nature), this overuse of healthcare services is also expensive. According to a study of Barsky among primary care subjects, the total outpatient costs of somatizers with high levels of health-related anxiety was approximately 22% higher than the costs of nonsomatizers in the year after being assessed (Barsky, Bates, Ettner & Horsky, 2001)

. Hypochondriasis has also been associated with marked impairments in physical and psychological functioning, work performance, and its course, when untreated, has been characterized as chronic (Barsky, Klerman, Cleary & Sarnie, 1993; Barsky et al., 2001). The above-mentioned stresses the importance of suitable and effective treatments on the short and long-term.

Because the hypochondriacal patients' conviction that he or she suffers from a medical instead of a psychological disorder, the mainstream opinion of hypochondriasis has been that of a difficult to treat disorder. This view has been changed gradually and substantially the last decade by several randomized controlled trials, which have shown that treatments with a cognitive behavioral orientation offer a credible rationale and useful techniques for improvement of hypochondriacal fears and behaviors. Amelioration of hypochondriacal complaints is maintained after a naturalistic follow-up period up to 12 months (Warwick, Clark, Cobb & Salkovskis, 1996; Clark et al., 1998; Visser & Bouman, 2001; Barsky & Ahern, 2004).

Besides Cognitive Behavior Therapy (CBT), evidence has been provided recently that treatment with SSRI's might be helpful in reducing hypochondriacal complaints on the short term. The first randomized controlled trial (RCT) with SSRI's in hypochondriasis, conducted by our group, showed that pooled CBT and Paroxetine were significantly superior to placebo, but did not differ significantly from each other (Greeven et al., 2007). Although these results are promising, follow-up data are indispensable to pass a final judgment about the relative efficacy of Paroxetine and CBT.

The present study is a continuation of the above-mentioned study of Greeven et al. (2007) and is, to the best of our knowledge, the first attempt to investigate the natural course of hypochondriacal complaints after initial treatment with CBT and Paroxetine compared to a placebo for hypochondriasis. Besides, we examined whether the course of hypochondriacal complaints can be predicted by severity of psychiatric

status, translated in the presence of comorbid diagnoses and duration of hypochondriacal complaints, and concomitant use of benzodiazepines. Moreover, use of mental health services during the follow-up period was investigated.

Methods

Participants

All subjects had participated in a 16-week RCT investigating the efficacy of CBT, Paroxetine as compared to placebo. Diagnosis and treatment took place at three psychiatric outpatient clinics in the Western region of the Netherlands.

We included subjects from age 18, meeting the DSM-III-R criteria for hypochondriasis (American Psychiatric Association, 1994) established by means of the SCID (First, Spitzer, Gibbon, & Williams, 1996). Excluded were subjects with comorbid psychotic disorders, substance-use disorders and organic mental disorders, pregnant and lactating women and subjects with severe medical illnesses. Concomitant use of antidepressants, mood stabilizers, antipsychotics and anticoagulants, an allergy for SSRI's and being in psychotherapy for hypochondriasis elsewhere were also exclusion criteria.

Hypochondriacal patients suffering from a comorbid mood disorder, anxiety disorder, and other somatoform disorders were included only when they indicated hypochondriasis to be the psychiatric disorder they suffered the most. Concomitant use of benzodiazepines was permitted

to a maximum of the equivalent of 30mg oxazepam, but only if subjects had been taking benzodiazepines for more than 3 months and were willing to keep use at a constant dosage for the duration of the trial.

The study received approval from the ethical committees of the participating medical centers and was conducted between January 1998 and August 2005. More information about the participants and the procedure can be found elsewhere (Greeven et al., 2007).

Study Design

Subjects meeting the inclusion criteria were asked informed consent and were randomized over the three conditions. All subjects were recruited from referrals by general practitioners and mental health agencies or through newspaper announcements.

Therapists had ample experience in the use of CBT for the treatment of hypochondriasis, and had received training in the use of CBT for this purpose. CBT was based on the treatment protocol used by Visser and Bouman (2001) and consisted of the application of techniques which were especially suitable for hypochondriasis (such as cognitive restructuring, behavioral experiments and exposure). The treatment consisted of anywhere from 6 to 16 individual sessions, depending on speed of recovery. To monitor treatment progress and the psychotherapists' treatment integrity, all sessions were audiotaped.

Medication was administered double-blinded and prescribed by 5 experienced psychiatrists. Subjects started with a daily dosage of 10 mg of Paroxetine in the first week. During the second week the dosage was

increased to 20 mg per day. Following that, the dosage increased weekly in increments of 20 mg per day to a maximum dosage of 60 mg per day. The succes of this procedure was demonstrated by Oosterbaan, van Balkom, van Boeijen, de Meij, and van Dyck (2001). Where subjects began suffering from intolerable side-effects, the daily dose was decreased to 40 mg, or to 20 mg. During the 16-week treatment period, subjects were scheduled for twelve medication control visits lasting twenty minutes each. The psychiatrists were not allowed to resort to any formal psychotherapeutic intervention (such as cognitive restructuring). Besides, they were required to use a written manual to record the perceived effect of the medication, the prescribed dose, adverse events (scored on the Fawcett side-effect scale (1987)), concomitant illnesses and concomitant medication, including benzodiazepine use, between the visits. Paroxetine blood samples were taken in week 16 to verify subject compliance.

After this sixteen week period, subjects in the Paroxetine and placebo conditions were informed to which group they had been allocated. In addition, with all subjects an evaluation session was held in which advantages (i.e. decrease of hypochondriacal symptoms) and disadvantages (i.e. adverse events) of the treatment received was discussed with them. Based on this evaluation, cognitive behavioral therapists or psychiatrists made a new treatment plan together with the subjects. Those treated with placebo were treated with Paroxetine (open) or CBT according to their preference. Responders in the Paroxetine and CBT conditions were allowed to continue their treatment, when necessary. Responders to Paroxetine who wanted to stop their medication were tapered off and received relapse prevention according to clinical guidelines. CBT non-responders were

offered open treatment with Paroxetine, while Paroxetine non-responders were offered treatment with CBT. Partially improved subjects were offered combination treatment in order to gain further improvement. Furthermore, after the RCT, subjects were allowed to seek treatment for their hypochondriacal complaints elsewhere.

Measurements for evaluating treatment efficacy took place at pretest, posttest and at 1, 5 and 13 month follow-up. After a period up to six years after the end of the initial RCT subjects were contacted again. Both treatment completers and treatment dropouts from the RCT were sent a letter inviting them to be interviewed about the course of their hypochondriacal complaints after the conclusion of the acute treatment phase. Subjects who were not interested could return a form within two weeks. After that period subjects who had not returned the form were contacted by telephone by the first author who informed them about the aims and procedures and asked them to participate. If subjects consented they were invited for a personal interview at one of the three psychiatric outpatient clinics involved. In case they declined to come to the clinic a telephone interview was conducted. Telephone interviews are acceptable to subjects if face-to-face interviews are impossible for any reasons, and research supports the validity of structured telephone interviews for gathering information by telephone from mental health subjects about anxiety and depression (Kobak et al., 1997; Rohde, Lewinsohn, & Seeley, 1997). The first author performed the interview. After completing the interview subjects were offered a check of 15 euros.

Assessment

We used the 4-point Likert scale version of the Whiteley Index as the primary outcome measure. The Whiteley Index is a 14-item self-report questionnaire designed to assess the core features of hypochondriasis (Pilowsky, 1967; Speckens, Spinhoven, Sloekers, & Bolk, 1996). Secondary outcome measures were the Symptom Checklist SCL-90, a multi-dimensional measure of psychopathology (Arindell & Ettema, 1986). Furthermore, independent raters assessed global psychopathology, using the Comprehensive Psychopathological Rating Scale (CPRS) (Goekoop, Knoppert-van der Klein, Hoeksema, & Klinkhamer, 1991; Goekoop, Knoppert-van der Klein, Hoeksema, & Zwinderman, 1994). We used the following subscales: the Montgomery Åsberg Depression Rating Scale (MADRS) and the Brief Anxiety Scale (BAS). All outcome measures have good psychometric properties.

Predictor variables were (1) initial group membership (CBT, Paroxetine or placebo); (2) number of comorbid diagnoses (established using the SCID) (First et al., 1996), duration of hypochondriacal complaints and (4) comorbid benzodiazepine use, which were all assessed at pretest. We chose to include number of comorbid diagnoses and duration of hypochondriacal complaints as predictors because severity of psychiatric status at pretest has been associated with treatment efficacy (Kellner, 1983; Hiller, Leibbrand, Rief & Fichter, 2002). Benzodiazepine use was added as a predictor because several treatment studies on panic disorder, social phobia and hypochondriasis found that benzodiazepine use negatively affected

treatment outcome (van Balkom, Lange, van Dyck, de Beurs & Koele, 1996; Fava, Connti et al., 2001; Fava, Ruini, et al., 2001).

The course of hypochondriacal complaints up to 6 years after completing the RCT was assessed by means of the Life Chart Interview (LCI) (Lyketsos, Nestadt, Cwi & Heithoff, 1994). The LCI draws from the literature on autobiographical memory which shows that accuracy of memories is quite good, until at least 6 years prior to recall, when linked to highly salient personal memory cues (like holidays, birthdays, et cetera). Therefore, before ascertaining the course of psychopathology memory cues are obtained to enhance recall. A crucial aspect of the LCI's design is the time interval in which psychopathology is being assessed. Exploration of the reliability of memories revealed that a period of one year generated memories that were in 75% agreement with a retest one week later (Lyketsos et al., 1994). Thus, with the LCI it was assessed year by year after the RCT whether subjects had suffered from hypochondriacal complaints.

For the present study we used an answering format as adapted by Lyketsos et al. (1994). We questioned the frequency of hypochondriacal thoughts and fears on a 10-point Likert scale varying from "a few times a day" (1) to "never" (10) over periods of a year to gather nuanced information about the severity of the complaints after treatment. Besides, we asked about the severity of hypochondriacal thoughts and fears labeled in terms of personal suffering on a 5-point Likert scale varying from "my hypochondriacal thoughts and fears do not trouble me at all" (1) to "my hypochondriacal thoughts and fears trouble me a lot" (5).

In addition, at the interview subjects were asked year by year after the RCT whether they had received treatment (medication, CBT or other

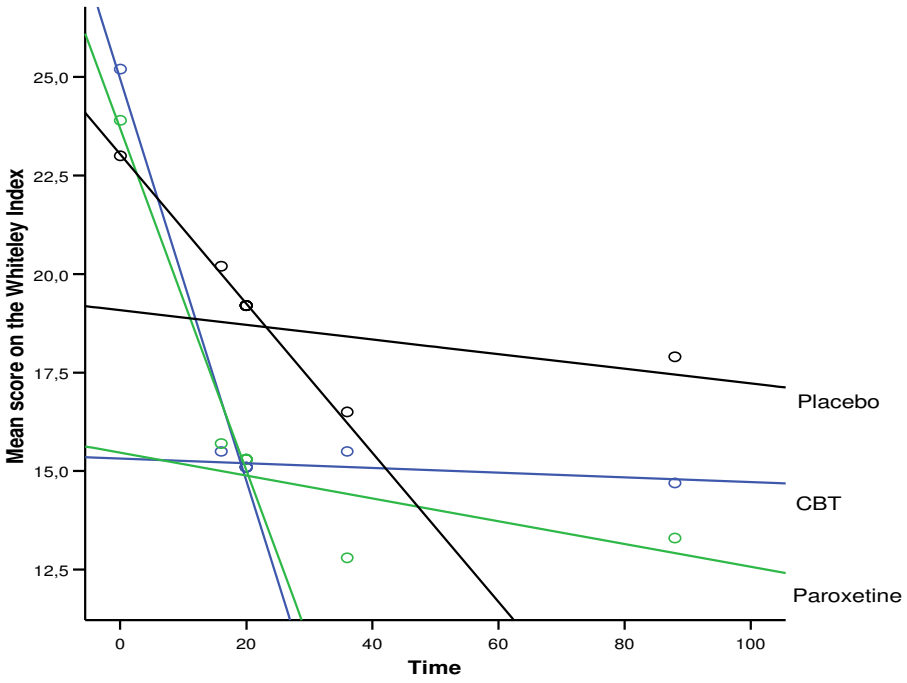
forms of psychotherapy, the combination or other kinds of treatment) for their hypochondriacal complaints during the follow-up period.

Statistical analysis

Random coefficient regression models (RCRMs) were used to examine the contribution of the various predictor variables on the course of the Whiteley Index, the SCL-90, the BAS and the MADRS. Time was measured as follows; pretest, posttest, 1-month follow-up, 5-months follow-up and 13-months follow-up.

After visual inspection of the data (see figure 1), we decided that two corresponding trajectories in two different linear models would describe the data better than a (non)-linear trend over the five time points for each experimental group and each outcome measure. The first model covered the first three measurements: pretest, posttest, 1-month follow-up (immediate effect). The second model used the measurements of 1-month follow-up, 5-month follow-up and 13-month follow-up (maintenance effect).

Figure 1: Linear models of the immediate and the maintenance trajectories



In the model for the first trajectory, intercept and slope can be referred to as average pretreatment score and average improvement rate. In the second model they can be referred to as average follow-up 1 score and average change rate. Both models contained variance components estimating the amount of variation of individual (linear) trends around these average lines. The data-analytic approach to examine the research questions was the same for both trajectories.

We used the model with time as the only predictor as the baseline model. To examine the effect of treatment group on change in hypochondriacal symptoms, we converted initial treatment group to three

separate dummy variables. Each dummy variable had two categories coded as zero (0) and one (1). Because we were only interested in predicting variables explaining change in hypochondriacal symptoms, we chose to include just the predictors interacting with time into the model). First, we incorporated time* CBT and time*Paroxetine interaction to the baseline model and used the time* placebo interaction as the reference category. A $\chi 2$ likelihood-ratio was used to test to see if this model had a significantly better fit than the baseline model. Subsequently, to investigate the effect of number of comorbid diagnoses, duration of hypochondriacal complaints and benzodiazepine use on amelioration of hypochondriacal symptoms, immediately as well as during the follow-up period, we added these predictors and their interaction with time separately to the model containing the time*CBT and the time*Paroxetine interactions. The variables showing a significant weight were retained for the final model. This model was simplified using likelihood-ratio tests ($\chi 2$, derived from deviance values) and tests for separate fixed effects. Variance components were tested using the same likelihood-ratio tests. The significance of the regression coefficients was assessed by using the z-statistic (two-tailed with alpha set at 0.05. We decided to describe only the models and the results of the primary outcome measure extensively, since the results were approximately the same for all outcome measures (see below).

RCRMs were fitted using the multilevel analysis software package MLwiN 2.02 (Rasbash et al., 2002). For all other data analyses the SPSS 11.1 package was used.

Kaplan Meier survival analysis was used to detect the year of recovery and the year use of mental health care services was stopped during the follow-up period.

Subjects who had clinically significant less hypochondriacal complaints as assessed with the Whiteley Index after 16 weeks of treatment, the so-called responders (as determined on the basis of the criteria of Jacobson and Truax (1991)), were used to lay down a standard of recovery on the basis of the LCI interview. These authors suggest that subjects can be considered to have improved when they shift from a dysfunctional distribution to a functional one, and the reliable change scores exceed measurement error (calculated by dividing the difference between the pre-test and post-test scores by the standard error of the measurement). The average frequency of hypochondriacal complaints (at most thrice a month) combined with the average trouble these complaints gave (at most a considerable amount of trouble) during the first year of the follow-up period was used as a cut-off for recovery. All subjects scoring on or below this cut-off were considered recovered, while those above the cut-off score were considered to still suffer from hypochondriacal complaints. Because survival analysis does not allow for such precision we had to treat those subjects who relapsed after a symptom-free period the same as those who were still suffering from hypochondriasis. Both subjects not recovering during the follow-up period as well as subjects who relapsed after a symptom-free period were defined as censored cases, because the follow period ended before recovery.

To investigate whether active treatment by means of CBT or Paroxetine predicted recovery or use of mental health care services during

the follow-up period compared to placebo, we conducted a Cox regression analysis. We decided to treat those subjects who started a new treatment during the follow-up period the same as those subjects who continued treatment after finishing the RCT. So subjects *still* or *again* in therapy after finishing the RCT were considered as censored cases. Because the categorical predictor has three levels we included this variable using dummy variables with the placebo group as the reference group.

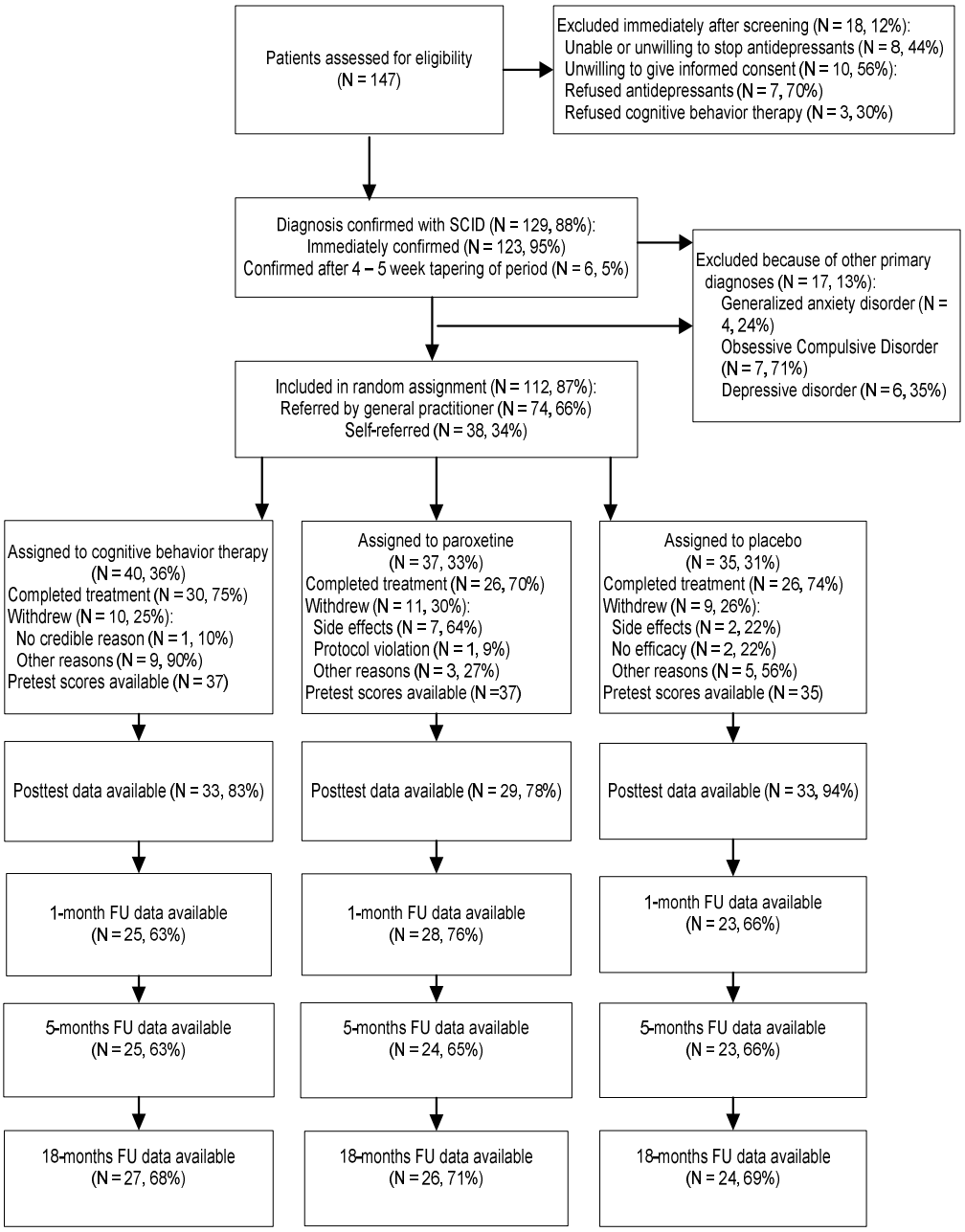
Because we were mainly interested in the natural course of hypochondriacal symptoms after initial treatment with CBT or Paroxetine, we choose to maintain the original formation of treatment group in Kaplan Meier and Cox Regression analysis. This implied that although some subjects in the Paroxetine group received CBT and vice versa, the CBT group consisted only of subjects randomly allocated to the original CBT group of the RCT. The same holds for the placebo group; although a large percentage of those in the former placebo group choose to be treated for their hypochondriacal complaints, we decided to adhere to the original formulation.

Results

Participants

The number of dropouts during active treatment was evenly distributed over the three conditions. Dropouts did not differ in initial severity from treatment completers. For reasons for dropping out and an overview of subjects flow through the trial see figure 2.

Figure 2: Flow of patients through the study



After a period of at most 6 years after the RCT, the LCI was administered to a subgroup (N = 68) of subjects. Subjects who were interviewed did not differ significantly from those who were not with respect to the severity of hypochondriacal complaints at post-test, but significantly less often dropped out of the RCT (12 of the 68 (18%)) than those who were not interviewed (18 of the 44 (41%)) (χ^2 = 7.371, df = 1, p = < 0.01). The percentage of interviewed subjects did not differ significantly across the three groups (CBT, N = 28 (41%); Paroxetine, N = 22 (32%); placebo, N = 18 (27%)). No significant differences in hypochondriacal complaints were found between participants telephoned (N = 11 (16%)) or interviewed face-to-face (N = 57 (84%)). Of the 44 patients who were not interviewed, 18 (41%) could not be traced; 6 (14%) reported severe somatic or psychiatric complaints; 3 (12%) would not be interviewed because they had no complaints at all and 17 (39%) declined because of other reasons.

Pretest characteristics the subjects

Demographic and psychiatric status variables of the sample and pretest scores are presented in table 1. As can be concluded from the pretest scores, our sample can be considered severely hypochondriacal, given a mean duration of 10 years (SD 7.8 years), 75% suffering from comorbid psychiatric diagnoses and 19% using benzodiazepines chronically. No significant differences were found between the three conditions. In addition, referral by a general practitioner or self-referral did not result in any differences on demographic and psychiatric status variables

Table 1. Pre-test Characteristics of all Subjects

Characteristics	CBT (N = 40)	Paroxetine (N = 37)	Placebo (N = 35)	All Subjects (N = 112)
Female sex	27 (67.5)	21 (56.8)	17 (48.6)	65 (58)
Mean age (yr)	41.3 ± 11.5	43.3 ± 10.8	39.2 ± 12.6	41.3 ± 11.7
Marital status,				
Married/Cohabiting	30 (75.0)	27 (73.0)	20 (57.1)	77 (68.5)
Unmarried	3 (7.5)	8 (21.6)	13 (37.1)	24 (21.4)
Divorced/Widowed	4 (10)	2 (5.4)	2 (5.7)	8 (7.1)
Unknown	3 (7.5)	0	0	3 (3)
High education	13 (32.5)	14 (37.8)	17 (48.6)	44 (39.3)
Co-morbid use of diazepam	5 (13)	6 (16)	10 (18)	21 (21)
Unknown	9 (23)	0	0	9 (8)
Hypochondriasis without co-morbid psychiatric diagnoses	7 (17.5)	11 (29.7)	10 (28.6)	28 (25.0)
Most frequently reported co-morbid psychiatric diagnoses				
Major Depressive Episode	11 (27.5)	6 (16.2)	6 (17.1)	23 (21.0)
Panic Disorder	18 (45.0)	15 (40.5)	12 (34.3)	45 (40.0)
Social Anxiety Disorder	9 (22.5)	3 (8.1)	5 (14.3)	17 (15.0)
Generalized Anxiety Disorder	9 (22.5)	9 (24.3)	10 (28.6)	28 (25.0)
Other Diagnoses	18 (40.0)	21(56.7)	18 (51.4)	57 (50.9)
Mean duration (years)	9.4 ± 8.0	11.2 ± 8.0	9.6 ± 7.7	10.0 ± 7.8
Most reported feared complaints,				
Palpitations	11 (27.5)	9 (24.3)	8 (22.9)	28 (25.0)
Chest pain	11 (27.5)	9 (24.3)	7 (20.0)	27 (24.1)
Headache	8 (20.0)	11 (29.7)	5 (14.3)	24 (21.4)

Immediate Effect – improvement rate

Of the possible 336 assessment points 280 (83%) responses were present in the data and used for analyses. The baseline model[2] for the immediate effect showed that the mean trajectory can be described by an average initial severity (β_0) of 23.99 (SE = 0.51) and a significant average decrease of hypochondriacal symptoms as assessed by the Whiteley Index over time (β_1 = - 0.39 (SE = 0.04)). The individual variation in initial severity (σ^2_{0j} = 21.24 (SE = 4.0)) and the individual variation in the improvement rate (σ^2_{1j} = 0.10 (SE = 0.02)) were large and significant. This model's deviance was 1703.131.

[2] Level 1 = repeated measures, time in months; level 2 = individual participant.

Model 0: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + u_{0j} + u_{1j}Months_{ij} + e_{ij}$

β_0 = 23.99 (SE = 0.51); β_1 = - 0.39 (SE = 0.04);

σ^2_{u0} = 21.24 (SE = 3.96); σ^2_{u1} = 0.10 (SE = 0.02)

σ^2_e = 6.98 (SE = 1.13); σ^2_{u0u1} = 0.01 (SE = 0.02)

Deviance: 1703.131 (280 of 336 cases in use)

Incorporation of treatment group showed that the mean trend of the Whiteley Index scores over the three time points was explained by treatment: both active treatment groups ameliorated significantly more than the placebo group. This model[3] had a significantly better fit than the baseline model ($\chi 2$ = 14.752, df = 2 =, p < 0 .001). Model 1 is extensively described in table 2.

None of the subsequently added predictors and their interaction with time to the model explained the mean trend of the Whiteley Index over the three time points.

Table 2. Two-level RCRM for immediate effect with treatment as a predictor (model 1)

	Model 1		
Fixed Effect	Estimate (β)	SE	z- statistic
Intercept (β_0)	24.0	0.51	47.1***
Months (β_1)	- 0.21	0.06	3.5***
CBT * Time	-0.31	0.08	3.9***
Paroxetine * Time	-0.23	0.08	2.9**
Variance components			
Level 1: residual (σ^2_e)	7.01	1.13	
Level 2: intercept (σ^2_{u0})	21.21	4.00	
Level 2: slope (σ^2_{u1})	-0.08	0.02	
Covariance (σ^2_{u0u1})	0.01	0.02	
Deviance (2*loglikelihood)	1688.379		

***p < 0.001, ** p < 0.005

[3] Model 1: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + \beta_2 CBT*Months_j + \beta_3 Paroxetine*Months_j + u_{oj} + u_{1j}Months_{ij} + \underline{e}_{ij}$

Deviance: 1688.379 (280 of 336 cases in use)

Repeating the analysis for the secondary outcome measures resulted in a slight advantage of CBT. Only CBT predicted a significant decrease in depressive (MADRS) and psychoneurotic symptoms (SCL-90) compared to the placebo. On the BAS, measuring anxiety, both active treatments were significantly more effective compared to the placebo. None of the other predictors was significant.

Maintenance Effect

Of the possible 336 assessment points, 225 (67%) responses were present in the data and used for analyses. The baseline model[4] for the maintenance effect showed that the average severity of hypochondriacal symptoms on the Whiteley Index at 1-month FU (FU 1) (β_0) was 16.93 (SE = 0.89) and that the average change, although still significant ($p < 0.005$), was much decreased compared to the first trajectory assessing the immediate effect (β_1 = - 0.03 (SE = 0.01)). The individual variation of the intercept (σ^2_{1j} = 0.004 (SE = 0.002)) and the variation in the slope (σ^2_{0j} = 47.16 (SE = 10.62) were both significant, indicating large variation in the hypochondriacal symptoms

[4] Level 1 = repeated measures, time in months; level 2 = individual participant.

Model 0: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + u_{0j} + u_{1j}*Months_j + e_{ij}$

β_0 = 16.93 (SE = 0.89); β_1 = - 0.03 (SE = 0.01);

σ^2_{u0} = 47.16 (SE = 10.62); σ^2_{u1} = -0.18 (SE = 0.12)

σ^2_e = 12.31 (SE = 2.19); σ^2_{u0u1} = 0.004 (SE = 0.002)

Deviance: 1442.434 (225 of 336 cases in use)

severity reached at follow-up 1 and in the individual improvement rate. The model's deviance was 1442.434.

In order to investigate whether initial treatment with Paroxetine or CBT still predicted amelioration during the follow-up period we incorporated treatment group in the model[5]. In contrast to the first trajectory, treatment group no longer significantly predicted reduction of hypochondriacal symptoms. This model did not have a significantly better fit than the baseline model ($\chi 2$ = 2.142, df = 2, p= ns).

We incorporated number of comorbid diagnoses, duration of hypochondriacal complaints, benzodiazepine use and their interaction with time separately to the baseline model to investigate whether they contributed to change. Incorporation of number of comorbid diagnoses resulted in model 2[6] that had a significantly better fit than the baseline

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[5] Model 1: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + \beta_2CBT*Months_j + \beta_3Paroxetine*Months_j + u_{oj} + u_{1j}*Months_j + \underline{e}_{ij}$

Deviance: 1440.292 (225 of 336 cases in use)

[6] Model 2: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + \beta_2Months*Number\ of\ Comorbid\ diagnoses_j + u_{1j}*Months_j + e_{0ij}$

β_0 = 16.83 (SE = 0.09); β_1 = - 0.07 (SE = 0.02); β_2 = 0.017 (SE = 0.007)

σ^2_{u0} = 46.75 (SE = 10.60); σ^2_{u1} = -0.23 (SE = 0.12)

σ^2_e = 12.38 (SE = 2.20); σ^2_{u0u1} = 0.004 (SE = 0.002)

Deviance: 1436.631 (225 of 336 cases in use)

model ($\chi 2$ = 5.661, df = 1, p < 0.05). Model 3[7] is an illustration of the model including duration of complaints ($\chi 2$ = 479.16, df = 1, p < 0.001). Incorporation of number of comorbid diagnoses and duration of hypochondriacal symptoms in one model resulted in a loss of significance influence for number of comorbid diagnoses.

Repeating the analysis exactly the same for the secondary outcome measures showed a significant reduction in anxious and depressive symptoms and a significant decelerating influence for number of comorbid diagnoses only.

Kaplan Meier Analyses

The Kaplan Meier curves showed that 32 subjects (47%) of all subjects recovered during the follow-up period of six years. Sixteen (57%) belonged to the initial CBT group, 9 (41%) to the initial Paroxetine and 7 subjects (39%) to the initial placebo group. The survival curve for each group during the follow-up period is presented in figure 3. The survival

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[7] Model 3: $WI_{ij} = \beta_{0ij}Constant + \beta_{1j}months_{ij} + \beta_2 Months*Duration\ of\ complaints_j + u_{1j}*Months_j + e_{0ij}$

β_0 = 16.98 (SE = 1.19); β_1 = - 0.05 (SE = 0.02); β_2 = 0.002 (SE = 0.001)

σ^2_{u0} = 56.89 (SE = 15.43); σ^2_{u1} = -0.43 (SE = 0.18)

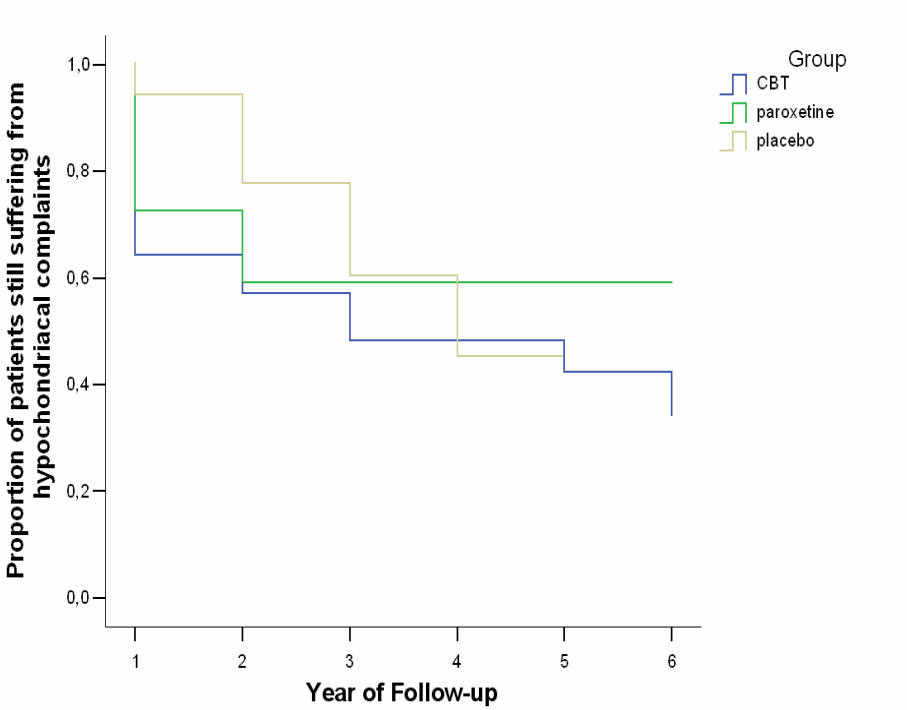
σ^2_e = 13.47 (SE = 2.91); σ^2_{u0u1} = 0.006 (SE = 0.003)

Deviance: 963.274 (148 of 336 cases in use)

distributions did not differ between the three groups (χ^2 = 1.26, df = 2, p = 0.53). Initial treatment group did not predict recovery (χ^2 = 1.029, df = 2, p = 0.60).

In the initial CBT group 3 subjects (11%) relapsed during the follow-up period. For the initial Paroxetine and the placebo group these numbers were respectively 3 (14%) and 1 (6%).

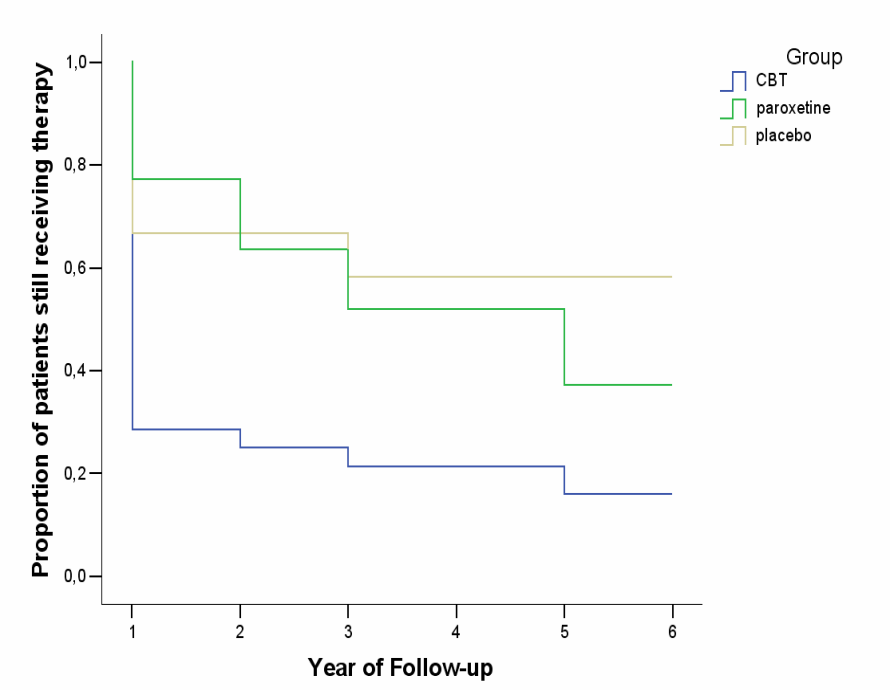
Figure 3: Course of hypochondriacal symptoms in the CBT, the Paroxetine and the placebo group



Interestingly, the survival analysis on use of mental health care services revealed significant differences in survival distributions of the

different initial treatment groups ($\chi^2 = 9.80$, df = 2, p = 0.007). Figure 4 shows this differential effect of initial treatment group.

Figure 4: Course of additional treatment in the CBT, the Paroxetine and the placebo group



Twenty-six subjects (38%) still received treatment when the follow-up period ended. Five subjects belonged to the initial CBT group (18%); 10 to the initial Paroxetine group (46%) and 11 to the initial placebo group (61%). Of the initial CBT group, 2 subjects used antidepressants, 1 received CBT and 2 received other kinds of treatment (e.g. haptonomy). Of the initial Paroxetine group, 7 subjects still took an antidepressant, two subjects received CBT and one subject received other kinds of treatment. Finally, in the initial placebo group 4 subjects took antidepressants, 3 subjects were in

psychotherapy and 4 subjects received other kinds of therapy. Initial treatment group predicted treatment during the follow-up period ($\chi^2 = 5.980$, df = 2, p = 0.05). In the initial CBT group 1 subject (4%) started with a new treatment during the follow-up period, in the initial Paroxetine and placebo groups these numbers were respectively 7 (32%) and 2 (18%).

Table 3 shows regression coefficients, degrees of freedom, p-values and odds ratios for each predictor. The greatest and significant contribution was by initial CBT; when compared to the reference group of initial placebo the odds of initial CBT subjects for not being in therapy anymore for their hypochondriacal complaints is 2.482 greater than the odds of subjects from the initial placebo group. The odds of initial Paroxetine subjects for not being in therapy anymore did not significantly differ from the odds of subjects from the initial placebo group (odds = 1.315).

Table 3: Cox Regression Analysis of treatment group on treatment after finishing the RCT

Predictor	B	Wald	df	p-value	Odds Ratio
CBT	0.909	4.388	1	0.04	2.482
Paroxetine	0.274	0.331	1	0.57	1.315

Discussion

Our results indicate that CBT and Paroxetine are both effective treatments for hypochondriacal symptoms which is shown by both the self-report data and the Life Chart Interview. Directly after the RCT hypochondriacal symptoms decreased substantially and the effect was maintained after 13 month follow-up. During the 6 year follow-up period,

the significant difference between both active treatment groups and placebo disappeared because the subjects initially assigned to placebo were treated with Paroxetine or CBT according to their preference and thus caught up the subjects initially treated with CBT or Paroxetine. In the first year after finishing the RCT, 67% of the initial placebo group, 77% of the initial Paroxetine group and only 29% of the initial CBT group used mental health care services. Six years after conclusion of the RCT, these percentages were respectively 61%, 46% and 18%. Compared to the initial placebo group, initial CBT appeared to be a significant predictor for not being in therapy anymore. Although the analysis did not allow a separate comparison between CBT and Paroxetine, the percentages suggest that the difference between Paroxetine and placebo might be significant as well. Strikingly, of subjects in the initial Paroxetine group still receiving treatment, 70% still took an antidepressant during the 6-year follow up period compared to 40% in the initial CBT and 36% in the initial placebo group. The results show that subjects in the Paroxetine group might find it difficult to discontinue the use antidepressant medication in the long-term and are in line with those of studies on for the long-term treatment effect of obsessive compulsive disorder (van Oppen, van Dyck, van Balkom, & de Haan, 2006). In view of the interesting results with regard to use of mental health care services during follow-up, it is a pity that more detailed information about the type and duration of psychological treatments has not been collected, With regard to pharmacological treatment, more detailed information about the exact type and dosage would also have been valuable.

The percentages of subjects relapsing after therapy were relatively small: in the initial CBT group 11% relapsed during the follow-up period.

For the initial Paroxetine and the initial placebo group these numbers were respectively 14% and 6%.

Duration of hypochondriacal complaints and comorbid diagnoses did not predict amelioration on the short-term, which is promising because it suggests that treatment is effective, even in case of a severe psychiatric status. During the follow-up period, however, a longer duration of complaints had a decelerating (but not a stagnating) effect on amelioration.

Until now, few studies have investigated predictors of amelioration after treatment for hypochondriasis, and to our knowledge, only on the short-term. An early study of Kellner (1983) found that good treatment outcome was associated with illness of less than three years duration and absence of an additional diagnosis of a personality disorder. Another study of Hiller et al. (2002) found that treatment non-responders were characterized by a higher degree of pre-treatment hypochondriasis, more somatization symptoms and general psychopathology, more dysfunctional cognitions related to bodily functioning, higher levels of psychosocial impairments, and more utilization of the health care system as indicated by the number of hospital days and costs for inpatient treatments and medication. Severity of psychiatric status could be identified as a general denominator, predicting a decrease of treatment effect.

Concomitant use of benzodiazepines had no effect on change of hypochondriacal symptoms in the immediate, as well as in the follow-up phase. This finding is not consistent to our previous study about the short-term treatment effect of CBT and Paroxetine; here we found that not using benzodiazepines predicted clinically significant change (Greeven et al., 2007). We think the contradictory results with regard to benzodiazepine use

in our present and our former study can largely be explained by differences in methods, like (i) data-analysis (Random Coefficient models versus independent sample t-test) and (ii) number of assessments (three versus two). Therefore, we think more definitive conclusions about the role of benzodiazepine use can only be drawn when more treatment studies have investigated its role, using similar data-analytic approaches.

Several other remarks should be taken into account when interpreting the results. First, because of our relatively small, hierarchical structured sample size containing much missing data, we chose to analyze our data by means of random coefficient regression models, which are widespread recommended, and nowadays the state-of-the-art method to analyze repeated measures (van der Leeden, 1998). Despite its strengths, a disadvantage of this method is the inability to compare dummy variables in the regression model to each other. The same holds for the Cox regression. In our situation this implied that we could not compare the efficacy of CBT and Paroxetine to each other, but only to the placebo (that was the reference category). Other limitations of the Kaplan Meier and Cox regression analysis will be mentioned in the following. First, although we tried to calibrate our definition of recovery by combining the average frequency of hypochondriacal complaints with the average trouble these complaints gave of responders of the Greeven et al. (2007) study during the first year of the follow-up period, it remains an arbitrary definition. Second, the results could be compromised by the finding that we had more data to our disposal from those who completed the RCT than from those who dropped out. This might have led to an overestimation of the results. Third, because of the dichotomous character we were forced to make no distinction between

subjects still having hypochondriacal complaints/receiving treatment and subjects having recurrent hypochondriacal complaints/treatment. The fact that we have no data about gradual change during the six year follow-up is related to this limitation. Finally, the sample size during the 6 year follow-up period was also small; obliging us to be careful with interpretation of the results.

Although the results seem in general promising, thorough inspection of the data and its connected limitations oblige us to be only moderately enthusiastic about treatment results. Subjects do ameliorate after treatment, but the percentage of subjects still having substantial hypochondriacal complaints is 53% after approximately 6 years of follow-up; full recovery after treatment for the majority of subjects seems therefore hard to reach.

Strikingly, the percentage of subjects allocated to the initial Paroxetine group which ameliorates during the 6 year follow-up, reached a plateau 2 years after conclusion of the RCT. This finding implies a more chronic course of the complaints after this specific intervention. Since subjects initially treated with Paroxetine are also more likely to continue their treatment compared with subjects treated with initial CBT these results suggest that CBT should be preferred over Paroxetine. Other advantages of CBT seems it's specific focus on challenging and modifying faulty appraisals by means of cognitive techniques and behavioral experiments, which is not only very effective for decreasing hypochondriacal complaints but also for comorbid anxious and depressive symptoms. Furthermore, CBT seems to offer subjects valuable tools to handle hypochondriacal thoughts autonomously without additional professional help (Butler, Beck, Forman, & Chapman, 2005). Therefore, it

also could be a more cost-effective intervention than Paroxetine. For future research it would therefore be interesting to investigate cost-effectiveness of different interventions.