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A RANDOMIZED, CONTROLLED TRIAL OF MEDICATION AND COGNITIVE BEHAVIOR THERAPY FOR HYPOCHONDRIASIS

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Abstract

Objective—Prior studies of hypochondriasis demonstrate benefit for pharmacotherapy and for cognitive-behavioral therapy (CBT). This study examines whether joint treatment offers additional benefit.

Method—195 patients with DSM-IV hypochondriasis were randomly assigned to one of 4 treatments – placebo, fluoxetine, CBT, or joint treatment with both fluoxetine and CBT. Evaluations assessed hypochondriasis, other psychopathology, adverse events, functional status, and quality of life. The primary analysis assessed outcome at week 24 among the intent-to-treat sample, with responders defined as having a 25% or greater improvement over baseline on both the Whiteley Index and the H-YBOCS-M. The Cochran-Armitage Trend test assessed the hypothesized pattern of response: joint treatment > CBT or fluoxetine treatment > placebo treatment.

Results—The response rate was greater with combined therapy than either fluoxetine or CBT alone; all three were more effective than placebo. Responder rates for each active treatment were not significantly different compared to placebo. Secondary analyses of the Whiteley Index as a continuous measure revealed that, compared to placebo, fluoxetine (but not CBT) was significantly more effective at week 24 in reducing hypochondriasis and had a significantly faster rate of improvement over 24 weeks. The fluoxetine group also had significantly less anxiety and an improved quality of life compared to placebo. Drop-out rates did not differ between groups and treatment emergent adverse events were evenly distributed.

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Disclosure

The authors report no competing financial interests.

Conclusions—This study supports the safety, tolerance, and efficacy of fluoxetine for hypochondriasis. Joint treatment provided a small incremental benefit. Because approximately 50% of patients did not respond to the study treatments, new or more intensive approaches are needed.

[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00339079) Identifier: NCT00339079

Hypochondriasis is a common, distressing, disabling and costly psychiatric disorder (1). These patients have greatly elevated rates of medical care utilization and the associated functional impairment is comparable to several major psychiatric disorders and chronic medical conditions (2–6)

Effective treatments have been developed. Cognitive-behavioral therapy (CBT) has been shown to reduce hypochondriacal symptoms, with effect sizes ranging from small to large (7–11). Other psychotherapies or adaptations of CBT are also beneficial in hypochondriasis, including exposure therapy (10), mindfulness-based CBT (12–14), acceptance and commitment therapy (11), attention training (15), and internet-based CBT (16). A more limited literature exists on the efficacy of pharmacotherapy. Two randomized, placebo-controlled trials (17, 18) demonstrated the benefit of a serotonin reuptake-inhibitor (SSRI). One study compared CBT and paroxetine, finding that the two modalities were similar in treatment effect (18). We are unaware of other, large-scale controlled trials comparing or combining the two treatment modalities. The current study is one of the largest treatment studies of hypochondriasis, and the first to assess joint therapy.

The primary aims were to determine the efficacy of pharmacotherapy and CBT individually and together in joint treatment. We hypothesized there would be a pattern of efficacy such that joint treatment would be superior to each of the single modalities, and that each of these in turn would be superior to placebo.

METHOD

Study design and procedure

This 24-week, randomized, controlled trial for adults with DSM-IV hypochondriasis (19) compared four treatment conditions: fluoxetine plus medication-management;; placebo plus medication-management; CBT; and joint treatment with fluoxetine and CBT. The study was conducted at the Brigham and Women's Hospital in Boston and the New York State Psychiatric Institute. All data were pooled, managed, and analyzed at the New York site.

Participants were screened by telephone and then completed an in-person evaluation, a structured diagnostic interview for hypochondriasis, and a medical evaluation. Eligible subjects returned for a baseline research battery, following which treatment condition was assigned. The baseline research battery was re-administered by the same independent evaluators at 6, 12, and 24 weeks (the study endpoint). At 12 weeks, subjects with less than minimal improvement (defined as less than 15% improvement over baseline on the H-YBOCS-M (20)) were removed from the protocol and offered alternative treatment.

Study Participants

Subjects were recruited through advertisements and professional referrals between 2004 and 2009. The target sample size was 264. Because we enrolled only 7% of screened individuals (Figure 1) and because fiscal constraints prevented extension of the study duration, our final sample size was 195.

All subjects provided written informed consent; the same protocol was approved by the Institutional Review Boards at both participating institutions. Inclusion criteria were: 1) outpatients age 21-75; 2) DSM-IV hypochondriasis rated at least “moderate” in severity; and 3) if a comorbid psychiatric disorder was present, hypochondriasis was earlier in onset, was judged to be the more severe disorder and was the predominant source of distress. Exclusion criteria were: 1) psychoactive medication use in the preceding two weeks; 2) presence of an unstable medical illness; 3) lactation, pregnancy, or women of child-bearing age not using contraception; 4) current medication that might be unsafe to combine with fluoxetine; 5) any current comorbid DSM-IV psychiatric disorder rated as severe when assessed with the Mini International Neuropsychiatric Interview Plus (MINI) (21); 6) any comorbid psychiatric disorder causing marked functional impairment or which might compromise treatment adherence (e.g. substance abuse/dependence; antisocial personality disorder); 7) a history of psychosis or bipolar disorder; 8) current suicidality or a suicide attempt in prior 6 months; and 9) symptom contingent litigation or disability/worker’s compensation proceedings.

Treatment Conditions and Therapists

CBT was delivered via a scripted manual used in prior work(8). Six, in-person, 60-minute weekly sessions were followed by 2 biweekly and then 3 monthly booster sessions, delivered by Master’s or PhD level therapists with prior CBT experience. The treatment emphasized psychoeducation, reformulation of dysfunctional assumptions about symptoms, modification of confirmatory bias, reduction of maladaptive sick role behaviors, identification of situations that exacerbated health anxiety, and reduction of bodily hypervigilance. Exposure therapy was not a treatment component.

Medication (fluoxetine or placebo) was prescribed by experienced psychiatrists on a similar schedule to that of the CBT, but for 20-30 minutes. The medication-management was manualized and reviewed clinical status, medication compliance, side effects, and intervening illnesses or medications. No cognitive, behavioral, or other psychotherapeutic interventions were allowed. The medication was administered on a fixed-flexible dosing regimen, beginning at 10 mg daily and increasing as tolerated and needed to 80 mg/day; both patient preference and clinician judgment guided dose escalation.

Individuals in the joint therapy group saw both a CBT therapist and a psychiatrist. All providers participated in regular, conjoint telephone conferences to review cases and ensure treatment fidelity across sites.

Randomization, Masking, and Quality Control Procedures

Participants were stratified into those with and without comorbid major depression or dysthymia. Each group was then randomized to treatment group using a computer-generated

random sequence. The psychiatrists, CBT therapists, and independent evaluators remained blinded to treatment assignment. To assess maintenance of masking within the fluoxetine and the placebo groups, participants were asked to guess treatment assignment at weeks 12 and 24.

Treatment fidelity was ensured by regularly scheduled supervision sessions provided separately for CBT (by AJB and DKA) and for medication (by BAF). Treatment fidelity was rated by blind audit by experienced clinicians using randomly selected audio recordings of treatment sessions; the rating scale for fidelity was adapted from prior studies. Good to excellent treatment fidelity by both the CBT clinicians and the psychopharmacologists was demonstrated. The integrity of the independent evaluator ratings was maintained through periodic sessions in which all evaluators rated sample subjects; the intra-class correlation coefficient for independent evaluators across both sites was 0.98.

Variables

DSM-IV hypochondriasis was diagnosed with the Structured Diagnostic Interview for Hypochondriasis (SDIH) (22) and severity was assessed with the Heightened Illness Concern Severity Scale (1). Hypochondriacal symptoms were assessed with the Whiteley Index (23, 24) and the H-YBOCS-M (20). The Whiteley Index is a 14-item self-report questionnaire whose sensitivity to change, validity, internal consistency, and test-retest reliability have been demonstrated (23–25). The H-YBOCS-M is a well-standardized, sensitive, and reliable semi-structured interview rating of hypochondriacal thoughts, behaviors, avoidance, and insight (20). Somatization was assessed with the Patient Health Questionnaire-15 (26).

To identify responders, a composite variable of hypochondriacal symptoms was created using both self-report (Whiteley) and independent evaluator (H-YBOCS-M) ratings.

Current DSM-IV axis I psychiatric disorders were assessed with the Mini International Neuropsychiatric Interview Plus (MINI) (21). Anxiety symptoms were assessed with the self-report Spielberger State-Trait anxiety inventory (STAI) (27) and depressive symptoms with the Beck Depression Inventory-II (BDI-II) (28).

Perceived quality of life was assessed with the self-report Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q) (29). Functional impairment was assessed with the self-report Sickness Impact Profile (30).

The physical examination, structured medical history, and screening laboratory test results were reviewed to rate aggregate medical morbidity using the Cumulative Illness Rating Scale (CIRS) (31).

Side effects were assessed by the treating clinician using the SAFTEE (32), which rates each of 28 symptoms for distress and functional impairment (none, mild, moderate, severe). Symptoms were judged “treatment emergent” if ratings between major evaluations went from: a) none to moderate or severe; or b) mild to severe.

Data Analysis

The primary outcome was the dichotomous composite variable of treatment response, defined by the double-requirement of improvement of at least 25% over baseline scores on both the Whiteley Index and the H-YBOCS-M. The primary data analysis compared treatment groups with respect to proportion of responders (an omnibus test of the composite variable). A pattern of efficacy with respect to response/non-response was evaluated using the Cochran-Armitage trend test. Our a priori hypothesis was that the improvement of the joint treatment over the single treatments is half the improvement of the single treatments over placebo treatment. The planned sample size of 264 was estimated to have 80% power with a 2-sided $\alpha=0.05$.

The composite variable was also analyzed by logistic regression and modeled using independent predictors: treatment condition, baseline H-YBOCS-M, baseline Whiteley, and site. The analysis used an adjusted model (treatment and covariates), contrasts for each treatment group were tested against the placebo, and odds ratios were calculated. An intent-to-treat design was employed, using the last observation carried forward for subjects who dropped out before week 24. For treatment drop-outs who initiated an alternative treatment before week 24, the last independent evaluation prior to the new treatment was used.

Secondary analyses of the Whiteley Index and the H-YBOCS-M total score as continuous measures were conducted on the intent-to-treat sample comparing the treatment groups with respect to the severity of symptoms at treatment end (adjusting for baseline severity); we anticipated that the performance of each of the active treatment groups on these measures would exceed that of the placebo group. These two measures of hypochondriasis at week 24 were highly correlated ($r=0.72$, $p<0.0001$).

Generalized Linear Models were used to analyze all continuous outcomes at week 24. It was necessary to log transform the continuous outcome measures. The description of predictors for each outcome and their relationships are described in Table 2. Cohen's d was used to estimate effect size. All apriori secondary analyses were exploratory for the purpose of hypothesis generation.

Secondary outcome analyses of the dichotomous composite variable were conducted on the "completer sample" – i.e., those who returned for week 24 ratings and had not undergone an alternative treatment. Exploratory analysis using higher improvement thresholds (30%, 40%, and 50%) to define responders on the H-YBOCS-M and Whiteley Index was also conducted on the intent-to-treat sample (Table 3).

Dose differences at week 12 and week 24 were tested between the fluoxetine group and joint treatment group using the nonparametric Wilcoxon Two-Sample Test, and dose at week 24 was explored as a predictor of the Whiteley outcome. Number of CBT sessions was explored as a continuous predictor of the Whiteley outcome at week 12 using the CBT and the joint treatment groups; week 12 was chosen given its temporal proximity to the intensive CBT. Number-needed-to-treat was calculated for each treatment group. .

The analysis of the longitudinal assessments, measuring severity of symptoms in different domains, was based on longitudinal mixed effects models (MEM) which accommodate data repeatedly measured at not necessarily equal time intervals. *PROC MIXED in SAS®* was used for the MEM analysis.

All statistical tests were two-tailed with an alpha significance level of 5%, unless otherwise stated.

RESULTS

Screening and Enrollment

2686 volunteers were screened by telephone. Of these, 365 were invited for in-person intake interview and 195 were enrolled and randomized; the primary reasons for exclusion are listed in Figure 1.

Sociodemographic and Clinical Characteristics

The sample composition is presented in Table 1. The treatment groups did not differ significantly in sociodemographic and clinical characteristics, except that the New York site had a significantly higher proportion of Hispanics and of patients with depression and with obsessive compulsive disorder. The analyses of primary and secondary outcomes controlled for site differences.

Primary Outcomes

Cochran-Armitage Trend Analysis—The hypothesized pattern of response was significant ($p=.036$), revealing an increasing linear trend in the response rates: placebo group (29.55%), individual active treatment groups (41.84%), and joint treatment group (47.17%). See Figure 2.

Categorical Responder Analyses (Tables 2 and 3)—In the logistic regression analysis predicting treatment response/nonresponse, neither the main effect of treatment nor the pairwise contrasts were significant. The number-needed-to-treat was 6 for the joint treatment group, 7 for the fluoxetine group, and 10 for the CBT group.

Secondary Analyses

Continuous Measure Analyses (Table 2)—Using the Whiteley Index score, treatment group was significant overall ($p=.049$). The pairwise contrasts revealed that fluoxetine treatment was more effective than placebo treatment ($p=.016$, a small to moderate effect size of 0.36) while the contrast between joint treatment and placebo treatment disclosed a similar but non-significant trend ($p=.090$, small effect size of 0.18). At week 24, patients in the fluoxetine group had 16% lower Whiteley scores than patients in the placebo group, and patients in the joint treatment group had 11% lower Whiteley scores than patients in the placebo group. Using the H-YBOCS-M score, neither treatment assignment overall nor pairwise contrasts was significant. CBT was not more effective than placebo treatment as assessed by change on either the Whiteley Index or the H-YBOCS-M.

The percentage of responders among the 123 week 24 completers revealed a similar pattern to the intent-to-treat analysis, although the fluoxetine group had the most responders (26/32, 81.3%) compared to the joint treatment group (23/37, 62.2%), the CBT group (15/29, 51.7%), and the placebo group (11/25, 44.0%). Longitudinal course of treatment response was examined using the hypochondriasis measures at baseline and weeks 6, 12, and 24. On the Whiteley Index, a significantly faster rate of decline of symptoms was noted over 24 weeks for patients treated with fluoxetine compared to placebo ($p=.043$). No significant difference in rate of decline was noted for the joint versus placebo treatment or for CBT versus placebo treatment. On the H-YBOCS-M, compared to placebo treatment, none of the active treatment groups showed a faster rate of decline over time.

Anxiety scores at 24 weeks showed a trend toward difference across treatment groups in the regression analysis ($p=.064$) (Table 2). Pairwise contrasts showed significant differences favoring fluoxetine versus placebo treatment ($p=.031$) and joint versus placebo treatment ($p=.047$). Patients receiving fluoxetine had 16% lower anxiety scores than patients receiving placebo treatment, and patients receiving joint treatment had 14% lower anxiety scores than those receiving placebo treatment. In the regression models for depression, functional impairment and somatization, treatment group was not significant, nor were any pairwise contrasts versus the placebo group.

In the analysis of quality of life, treatment group was not significant, but pair-wise contrasts indicated the fluoxetine versus placebo group contrast was significant ($p=.029$). Notably, patients given fluoxetine had 11% higher quality of life scores compared to patients given placebo.

Alternative Thresholds for Treatment Response

The exploratory intent-to-treat analyses using progressively more stringent criteria for treatment response at week 24 (Table 3) revealed a wider separation between active and placebo treatments when greater improvement was required. When 40% or 50% improvement over baseline was required, the fluoxetine group had the highest percentage of responders.

Dose, Adherence, and Treatment Response

At week 24, the mean fluoxetine dose was 40 mg in the fluoxetine group and 30.9 mg in the joint treatment group, a non-significant difference. The mean percentage improvement over baseline on the Whiteley Index was significantly greater for those receiving doses ≥ 40 mg than for those receiving <40 mg (37.2% for high dose ($n=34$) vs 24.5% for low dose ($n=63$) ($p=.015$)). Similar analyses with H-YBOCS-M were not significant.

All 6 sessions of CBT were completed by 31 of 53 patients in the joint group and by 35 of 53 patients in the CBT group. The number of sessions attended was significantly related to the week 12 Whiteley Index score in the CBT alone and JOINT groups ($p<.0001$).

Dropouts by Treatment (Figure 1)

Of the 195 enrolled, 147 had week 12 assessments and 123 had week 24 assessments. There was no significant difference in the percentage of patients who dropped treatment before week 12 across the 4 conditions.

Masking

Among the patients randomized to drug or placebo, there was no significant difference in the proportion of those who correctly guessed their treatment assignment at weeks 12 or 24. Among those who believed they were on active medication, twice as many in the fluoxetine group were responders compared to placebo at week 12 (54% vs 21%, $p=.088$) with a similar but smaller difference at week 24 (69% vs 50%). Using a higher threshold of 40% to define responders, among those who believed they were on active medication, the same responder pattern occurred at week 12 (46% fluoxetine treatment vs 21% placebo treatment) and week 24 (59% fluoxetine treatment vs 25% placebo treatment).

Adverse Events

There were no significant differences across groups in adverse events (Table 4).

DISCUSSION

In this study, our predicted pattern of response was supported (joint>active>placebo). Although the logistic regression analysis did not show a significant difference across groups, the continuous measures analyses of the hypochondriasis measures support the conclusion that fluoxetine was the primary treatment contributing to improvement. Compared to placebo, using the Whiteley Index, fluoxetine was significantly more effective and had a significantly faster rate of improvement, and higher doses appeared more effective than lower doses. The effect size and number-needed-to-treat were comparable to anti-depressant trials (33) and the responder rate of 44% was comparable to trials of SSRIs for Obsessive Compulsive Disorder (34) and Generalized Anxiety Disorder (35). Compared to placebo, fluoxetine also resulted in a significantly greater reduction in anxiety and improvement in quality of life. The improvement with fluoxetine could not be accounted for by improvement in depression alone, as the difference in depression scores over time was not significant. This suggests that pharmacotherapy had a relatively specific effect on hypochondriacal symptoms, and not simply a generalized effect on comorbid psychiatric disorders. Nor could the improvement with fluoxetine be due to unmasking, as no significant difference was noted in correct guessing between groups. Fluoxetine appeared to be well tolerated, as demonstrated by the absence of significant differences in treatment emergent adverse events or in drop-out rates across groups. In contrast to hypochondriasis, somatization did not improve in any of the treatment arms.

Although our predicted pattern of response was supported, joint treatment showed only a small incremental advantage over fluoxetine alone. With more stringent definitions of treatment response, the relative benefit of joint treatment diminished. Why? One possible explanation arises from the observation that the joint group had an end-of-study mean dose that was 10 mg/day lower than that of the fluoxetine group. Because improvement was

greater for those on higher dose of fluoxetine, we speculate that the joint group might have performed better had the fluoxetine dose been higher.

The 30% placebo responder rate, while comparable to that seen in studies of depression (36), was higher than the 25% predicted based on our prior studies (17), making treatment effects harder to demonstrate. Future studies may rectify this problem by increasing the magnitude of improvement required to define a responder. Had we used more stringent thresholds than 25% to define improvement (e.g., 30, 40, or 50%), the proportion of placebo responders would have dropped to 20%, 13% and 9% respectively. These higher thresholds would have yielded statistically significant differences in responder rates between active treatment and placebo and should be considered in future trials of hypochondriasis.

The weak results for CBT in this study are in contrast to those generally reported, where effect sizes (Hedge's g) average 0.95 immediately after treatment and 0.34 at longer-term follow-up (9). Factors that may have reduced CBT's efficacy include poor retention in treatment (only 2/3 of patients completed all 6 sessions), a relatively short course of therapy (6 sessions), and the absence of treatment components that emphasize exposure (both imaginal and in vivo) or adherence (motivational interviewing). The study most comparable to ours (18) revealed a responder rate on the Whiteley Index of 45% for CBT and 30% for paroxetine; our responder rates were slightly lower for CBT (40%) and higher for pharmacotherapy (44%). Similar to other studies of CBT (9), our data analysis revealed that the more sessions completed, the better the response. Although poor CBT retention may be the result of preferential dropout by patients who are doing poorly, it may also indicate that having the full course of acute treatment conferred a greater therapeutic benefit.

The Whiteley Index proved to be a more sensitive measure of change than the H-YBOCS-M. The Whiteley Index deals primarily with illness-related fears and beliefs rather than behaviors, and is similar to the obsession subscale of the H-YBOCS-M. The illness obsession subscale of the H-YBOCS-M is more sensitive to change than are its two behavior subscales (20). This difference may explain the greater sensitivity of the Whiteley Index compared to the H-YBOCS-M total score. These observations also suggest that CBT targeting avoidance and safety behaviors may yield a particularly beneficial impact, as demonstrated in a recent study (37).

The strengths of this study include its large sample size; the testing of joint treatment; the use of two different treatment sites; the rigorous diagnosis of DSM-IV hypochondriasis; a "responder" definition that was based on a composite of self-report and independent evaluator assessments; the precise assessment of medical morbidity; the stratification of randomization to balance the distribution of depressive symptoms across treatment groups; the inclusion of a placebo control arm; and the relatively long duration (24 weeks) of controlled follow-up. Although hypochondriasis was not retained as a diagnosis in DSM-5, the new diagnoses of Illness Anxiety Disorder and Somatic Symptom Disorder both retain health/illness anxiety as prominent features; therefore we anticipate that the results from this trial will be generalizable to many individuals with these DSM-5 diagnoses (38).

This study has limitations. First, generalizability is limited because community volunteers were used rather than patients from medical settings; the former might differ from the latter in having greater insight into the psychological nature of their condition. Second, the joint treatment, which required meeting with a psychiatrist and CBT therapist, may have been too burdensome and time consuming, as nearly a third of patients from the joint group chose to complete only one of the two treatments. Third, because our attrition rates were relatively high, the results need to be viewed with caution. This was partially a consequence of the study design which removed those patients from protocol treatment who were not at least minimally responsive at week 12. Fourth, in the continuous analysis, each of the two primary hypochondriasis measures was assessed individually. This enhanced the study's sensitivity to detect change, but also increased the number of comparisons, raising the risk of a false positive finding. Because these two hypochondriasis measures are highly correlated and because this was a secondary analysis, a Bonferroni correction was not conducted; the overall Type 1 error is less likely to be increased as otherwise would have been the case had the measures been unrelated. Fifth, because our medication strategy employed fixed-flexible dosing, many patients did not reach the target dose of 80 mg/day. Higher dosing has been associated with greater improvement in trials of Obsessive Compulsive Disorder and depression (39, 40) and was associated with more substantial improvement in this study. A future study using fixed dosing regimens would be better able to address this issue. Sixth, because our final sample size of 195 fell short of our target sample size of 264, our study was under-powered to detect smaller differences between groups. Our targeted sample size was not reached because we enrolled only 7% of screened individuals (see Figure 1), primarily due to other comorbidities, medication concerns, or not meeting criteria for hypochondriasis.

In conclusion, this study provides further evidence supporting the safety, tolerance, and efficacy of fluoxetine for hypochondriasis. However, this study also demonstrates that approximately 50% of patients continue to suffer with substantial hypochondriasis despite treatment, highlighting the limitations of both the pharmacologic and the cognitive-behavioral approaches used in this trial.

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Patient Perspectives

“Ms. A”, a 54-year-old former Broadway stage manager, presented with 18 months of recurrent fears of having undiagnosed brain or lung cancer, following the death of a close friend from lung cancer. Ms. A repeatedly visited her primary care doctor seeking extensive medical evaluations. Not reassured, she sought second and third medical opinions. She stopped socializing with friends to spend more time researching symptoms online. She avoided travel outside of New York City, as she feared being too distant from her doctors. She was randomized into the masked pill treatment, starting at 10 mg daily and titrated over six weeks to 60 mg daily. Ms. A noted a steady reduction in her health fears, with a new freedom to resist online symptom searches and a renewed desire to socialize with friends. She proudly announced she “graduated” from the study after having traveled over 300 miles away from home to see her sister. After the blind was broken, she opted to continue taking fluoxetine, feeling the treatment had made a major difference in her life.

“Mr. B”, a 42 year old investment banker, presented with 2 years of illness fears that started after his mother’s death from pulmonary hypertension. Although physically well, he was troubled by episodes of dyspnea, began to monitor his symptoms, consulted six different pulmonologists, and began having panic attacks and vivid nightmares of dying in a palliative care unit. After seeing an ad entitled, “Do people call you a hypochondriac?”, he enrolled and was randomized to Cognitive Behavioral Therapy (CBT). After several weeks of CBT, he reported that “things are beginning to get better”; he appreciated that CBT was goal-oriented and focused, that he learned breathing techniques to relax, and that his therapist was non-judgmental and helped him to confront his thoughts and challenge his assumptions, one at a time. At the end of the 24 weeks he reported, “I can now recognize negative patterns in my thinking; most of the time I am able to stop the downward spiral before it starts. CBT is not a quick fix, but it has given me back my sanity, my marriage, and my life”.

Figure 1.

*Cochran-Armitage Trend Test was significant ($P < .036$)

Figure 2.
Pattern of response across intervention groups

Table 1

Demographic and Clinical Characteristics

	Total (n=195)		Site		NYC (n=101)		Joint (n=53)		Fluoxetine (n=45)		CBT (n=53)		Placebo (n=44)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Demographics														
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Females	85	43.6	41	43.6	44	43.6	21	39.6	25	55.6	24	45.3	15	34.1
Hispanic	23	11.8	6	6.4*	17	16.8*	6	11.3	9	20.0	5	9.4	3	6.8
Single	120	61.5	57	60.6	63	62.4	25	47.2	32	71.1	35	66.0	28	63.6
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Age	39.7	14.3	39.4	14.9	40.0	13.8	40.0	14.3	43.1	15.9	39.2	13.7	36.4	12.9
Education	15.4	2.6	15.4	2.4	15.4	2.7	15.8	2.8	15.2	2.5	15.2	2.4	15.5	2.6
Clinical Variables														
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Major Depression	64	32.6	16	17.0 ⁺	48	47.5 ⁺	16	30.2	21	46.5	18	34.0	9	20.5
OCD	25	12.9	7	7.5*	18	18.0*	8	15.1	7	15.9	6	11.3	4	9.1
Panic	28	14.5	16	17.0	12	12.1	9	17.0	8	18.6	8	15.1	3	6.8
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Whiteley	49.5	9.7	48.2**	9.0	50.8**	10.1	49.9**	8.9	48.6**	10.1	52.0**	8.9	47.0**	10.4
H-YBOCS-M	35.7	11.3	35.3	11.1	36.0	11.5	36.8	11.9	34.0	11.1	36.4	11.5	35.5	10.7
PHQ-15	10.3	4.5	9.8	4.0	10.8	4.9	10.6	5.3	10.2	3.9	10.8	4.0	9.6	4.6
BDI	16.7	11.3	14.6*	10.6	18.6*	11.7	15.8**	11.3	18.7**	10.7	18.5**	12.2	13.4**	10.5
STAI	51.7	13.7	50.1	13.3	53.1	13.9	15.8	11.3	18.7	10.7	18.5	12.2	13.4	10.5
Medical Morbidity (CIRS)	1.91	2.1	1.87	1.76	1.94	2.38	2.08	2.15	1.8	1.82	1.79	1.67	1.95	2.74
SIP	0.18	0.15	0.17	0.15	0.20	0.15	0.17	0.15	0.21	0.15	0.21	0.16	0.15	0.14
Q-LES-Q	43.95	10.10	45.11	10.26	42.88	9.87	43.42	11.05	43.59	10.10	43.31	9.35	45.70	9.88

* p-value < .05;

** p-value < .10;

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[†]p-value <.0001.

Ranges for above scales: Whiteley Index (14-70), H-YBOCS-M (0-72), PHQ-15 (0-30), BDI-II (0-63), STAI (20-80), CIRS (0-44), SIP (weighted score 0-1), Q-LES-Q (14-70). For all of the above (except for the Q-LES-Q), higher scores indicate more pathology.

Table 2

Primary and Secondary Outcomes

Outcome Measure and Covariates*	Treatment						Covariates					
	Overall effect of Treatment						Fluoxetine					
	X ² or F	df	p	X ² or T	df	p	X ² or T	df	p	X ² or T	df	p
Responders - Composite Variable	3.99	3	0.26	1.39	1	0.24	2.7	1	0.1	3.45	1	0.06
INTENT-TO-TREAT												
Site												
Baseline Whiteley											2.73	1 0.1
Baseline H-YBOCS-M											1.5	1 0.22
											2.65	1 0.1
H-YBOCS-M	1.67	3,189	0.17	1.09	189	0.28	-0.05	189	0.95	-1.05	189	0.28
INTENT-TO-TREAT												
Site												
Baseline H-YBOCS-M											4.77	1,189 0.1
											12.43	1,189 <.01
Whiteley	2.67	3,188	<.05	-0.38	188	0.7	-2.44	188	0.02	-1.71	188	0.09
INTENT-TO-TREAT												
Site												
Baseline Whiteley											2.23	1,188 0.03
											57.12	1,188 <.01
STAI Anxiety	2.49	3,112	0.06	-0.4	112	0.69	-2.18	112	0.03	-2.01	112	<.05
Baseline STAI											42.37	1,112 <.01
BDI-II Depression	1.2	3,112	0.31	-0.55	112	0.58	-1.36	112	0.18	-1.71	112	0.09
Baseline BDI											50.51	1,112 <.01
SIP Functional Status	0.56	3,112	0.64	-0.6	112	0.55	-1.08	112	0.28	-0.07	112	0.94
Baseline SIP											58.27	1,112 <.01
Q-LES-Q Quality of Life	1.72	3,110	0.17	1.02	110	0.31	2.21	110	0.03	1.55	110	0.12
Baseline Q-LES-Q											79.76	1,110 <.01
PHQ15 Somatization	0.18	3,110	0.91	-0.12	110	0.91	-0.61	110	0.54	-0.04	110	0.97

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Treatment		Covariates									
		Fluoxetine					Joint				
Outcome Measure and Covariates*		Overall effect of Treatment		CBT		p		df		p	
		X ² or F	df	X ² or T	df	X ² or T	df	X ² or T	df	X ² or F	p
Baseline PHQ15										41.78	1,110 < .01

* H-YBOCS-M (Hypochondriasis – Yale-Brown Obsessive Compulsive Scale – Modified); Whiteley (Whiteley Index of Hypochondriasis; STAI (Spielberger State-Trait Anxiety Inventory); BDI-II (Beck Depression Inventory-II); SIP (Sickness Impact Profile); Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form); PHQ-15 (Patient Health Questionnaire-15)

Table 3

Proportion of Responders (both H-YBOCS-M & Whiteley) in the Intent-To-Treat Sample

Varying Thresholds for % Improvement compared to baseline	Placebo		CBT		Fluoxetine		Joint	
	N	%	N	%	N	%	N	%
Protocol: 25%	13	29.55	21	39.62	29	44.44	25	47.17 ⁺
Alternative: 30% ¹	9	20.45	16	30.19	18	40.00 [*]	25	47.17 ^{**}
Alternative: 40% ²	6	13.64	12	22.64	17	37.78 [*]	16	30.19 ⁺
Alternative: 50% ³	4	9.09	3	5.66	12	26.67 [*]	10	18.87

⁺ p-value <.10;

^{*} p-value <.05;

^{**} p-value<.01

¹ A patient receiving joint therapy had 3.47 (95% CI: 1.40, 8.62) times the odds of being a respondent than a patient receiving placebo treatment.

¹ A patient receiving fluoxetine treatment had 2.59 (95% CI: 1.01, 6.67) times the odds of being a respondent than a patient receiving placebo treatment.

² A patient receiving fluoxetine treatment had 3.85 (95% CI: 1.35, 11.00) times the odds of being a respondent than a patient receiving placebo treatment.

³ A patient receiving fluoxetine treatment had 3.64 (95% CI: 1.07, 12.34) times the odds of being a respondent than a patient receiving placebo treatment.

Table 4

Serious and Treatment Emergent Adverse Events (TEAE) as assessed by SAFTEE^a

GROUP	N	# of Serious Adverse Events ^c	Week 12 compared to Baseline ^b		Week 24 compared to Baseline ^b	
			% Subjects with at least 1 TEAE	# TEAE per subject	% Subjects with at least 1 TEAE	# TEAE per Subject
Fluoxetine	45	0	22.2	1.1	8.9	2
Placebo	44	0	13.6	1.2	4.5	2
Joint	53	2	13.2	1.4	7.5	1
CBT	53	1	17	1.7	3.8	1.5

^aThere were no individual TEAE common to at least 5% of subjects in a group & possibly related to treatment

^bNo significant differences were noted in any of the group comparisons at week 12 or week 24

^cSuicidal thoughts occurred in 2 patients in joint treatment & gastrointestinal problems in 1 patient in CBT treatment.
There were no deaths or injury.