

Prevention of panic attacks and panic disorder in  
chronic obstructive pulmonary disease

Nicole Livermore<sup>1</sup>, Louise Sharpe<sup>2</sup>, David McKenzie<sup>3</sup>

<sup>1</sup>Department of Liaison Psychiatry, Prince of Wales Hospital, Sydney, Australia, and School of Psychology, University of Sydney, Sydney, Australia; <sup>2</sup>Department of Psychology, University of Sydney, Sydney, Australia; <sup>3</sup>Department of Respiratory Medicine, Prince of Wales Hospital, Sydney, Australia, and Faculty of Medicine, University of New South Wales, Sydney, Australia.

Address for correspondence: Nicole Livermore B.Sc.(Hons), M.Psychol., Department of Liaison Psychiatry, Prince of Wales Hospital, Barker St., Randwick 2034 NSW Australia, E-mail: [nlivermore@sesiahs.health.nsw.gov.au](mailto:nlivermore@sesiahs.health.nsw.gov.au) Fax: 61 2 9382 2177. Phone: 61 2 9382 2731.

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## **ABSTRACT**

This study examined whether cognitive behavioural therapy (CBT) could prevent the development or worsening of panic-spectrum psychopathology and anxiety symptoms in chronic obstructive pulmonary disease (COPD).

Forty-one patients with COPD, who had undergone pulmonary rehabilitation, were randomised to either a 4 session CBT intervention condition ( $n = 21$ ) or a routine care condition ( $n = 20$ ). Assessments were at baseline, post-intervention, and at 6, 12 and 18 months follow-ups. Primary outcomes were the rates of panic attacks, panic disorder, and anxiety symptoms. Secondary outcomes were depressive symptoms, catastrophic cognitions about breathing difficulties, disease-specific quality of life and hospital admission rates.

There were no significant differences between the groups on outcome measures at baseline. By the 18 month follow-up assessment, 12 (60%) routine care group participants had experienced at least one panic attack in the previous 6 months, with 2 of these (17%) being diagnosed with panic disorder, while no CBT group participants experienced any panic attacks during the follow-up phase. There were also significant reductions in anxiety symptoms and catastrophic cognitions in the CBT group at all three follow-ups, and a lower number of hospital admissions between 6 and 12 month follow-ups.

The study provides evidence that a brief, specifically targeted CBT intervention can treat panic attacks in COPD patients, and prevent the development and worsening of panic-spectrum psychopathology and anxiety symptoms.

## **INTRODUCTION**

Symptoms of anxiety are common in chronic obstructive pulmonary disease (COPD) and predict worse quality of life and functional level [1]. Many patients with COPD experience panic attacks, which are episodes of intense anxiety accompanied by symptoms of physical arousal [2]. To be diagnosed with panic disorder, patients must experience recurrent panic attacks, anticipatory anxiety about future attacks, and some unexpected and unpredictable attacks (not always in situations inevitably causing dyspnoea in COPD) [2]. The prevalence of panic disorder in COPD has been estimated as up to 10 times greater than the population prevalence of 1.5–3.5% [2, 3].

This high prevalence of panic attacks and panic disorder in COPD is predicted by the cognitive model of panic anxiety [4]. In this model, panic attacks occur in healthy individuals when ambiguous physical sensations like shortness of breath are interpreted in a catastrophic way, such as indicating imminent asphyxia or death. Signs and symptoms of increased physical arousal follow, leading to an escalating cycle that results in panic. In COPD, worsening dyspnoea during physical activity is the defining symptom of an eventually fatal illness. It is easy to understand how vulnerable individuals with COPD, even early in the disease's course, may overestimate the immediate threat exertional dyspnoea presents and enter the cycle of panic. Anxious and depressive symptoms have been found to worsen over time in COPD patients, and this psychological deterioration has been only weakly correlated with decline in lung function [5]. In addition to affecting quality of life and functional level, anxiety and depression in COPD lead to increased reporting of medical symptoms, increased use of health services, and up

to double the health-related costs of patients with COPD alone [6]. Hence, treating anxiety in COPD patients, and so preventing panic disorder, is likely to improve patients' level of functioning and decrease costs. Cognitive behaviour therapy (CBT) is the treatment of choice for panic disorder in physically healthy adults [7, 8]. Evidence is increasing that CBT produces its effects on panic attacks and panic disorder by decreasing catastrophic beliefs about ambiguous physical sensations [9, 10].

The results of several controlled trials using self-report questionnaires have indicated that CBT can decrease anxiety symptoms in patients with COPD, but the effects of CBT on panic attacks and the development of panic disorder in COPD have not been assessed [11-15]. Intervening early with individuals at risk of panic disorder can prevent the personal and economic effects of the disorder becoming entrenched [16]. In the current study, we therefore evaluated a brief CBT intervention specifically directed at panic-related anxiety in COPD. The hypothesis was that CBT would be more effective than routine care, which included pulmonary rehabilitation, in preventing the development and/or worsening of panic-spectrum psychopathology and anxiety symptoms in patients with COPD, over an 18 month period.

## **METHODS**

### **Study subjects**

The study was conducted at a teaching hospital in Sydney, Australia. The trial was approved by the University and Hospital Ethics Committees, and all subjects gave written consent. Ninety-six consecutive COPD patients who met the study's inclusion criteria

were identified in the respiratory medicine department's outpatient clinics, or inpatient ward, and invited to participate. Fifty-two (54%) volunteered. This recruitment rate was similar to the 55% reported by Kunik and colleagues [17]. Baseline assessments were delayed until at least one month after any hospital admission for an infective exacerbation of COPD. All subjects had a diagnosis of moderate to severe COPD [forced expiratory volume in the first second ( $FEV_1$ ) post-bronchodilator  $<60\%$  predicted and  $FEV_1$ /forced vital capacity (FVC)  $<0.7$ ], corresponding to GOLD stages II or III [18]. They were receiving ongoing outpatient treatment in the respiratory medicine department, where they had also attended an integrated, comprehensive outpatient pulmonary rehabilitation programme. The possible confounding factor of pulmonary rehabilitation attendance, which has been associated with short-term reductions in questionnaire measured symptoms of anxiety and depression, was thus controlled for [19]. All subjects were being treated with a combination LABA/inhaled corticosteroid and a long acting anti-cholinergic. None was on high dose oral corticosteroids. Exclusion criteria were lack of English literacy (due to the requirement for completion of standardised questionnaires unavailable in other languages), and the presence of any other serious physical illness or psychiatric disorder, including panic disorder. Individuals with panic disorder were excluded because of the study's preventative focus, and because an extended psychological intervention was considered necessary for such patients [20]. At initial assessment, the Panic Disorder and Agoraphobia sections of the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) were administered, along with relevant questionnaires [21-24]. Eleven individuals were then found ineligible for the study: 9 (17%) were diagnosed with panic disorder and 2 (4%) were diagnosed with major

depression. The prevalence of panic attacks (19%,  $n=10/52$ ) and panic disorder (17%,  $n=9/52$ ) at initial assessment were within the ranges expected [3].

## **Procedure**

### *Assignment*

We used the Excel Bernoulli Function to generate a random sequence of numbers, with a 50% chance of each of the two groups occurring. Randomisation was linked to subject numbers and was concealed until after the baseline assessment was completed. Twenty-one participants were randomised to the CBT group and 20 to the routine care group (fig. 1).

### *Assessments*

Measures were administered at baseline, post-intervention (5–6 weeks later) and at 6, 12 and 18 month follow-up assessments. Pulmonary function tests ( $FEV_1$  and FVC) were carried out at baseline by trained laboratory scientists.

### *CBT Intervention*

The standardised CBT intervention comprised 4, individually administered, one hour sessions. These weekly outpatient sessions commenced within 2 weeks after baseline assessment. The patient manual for the intervention was developed by the first author (NL), an experienced clinical psychologist who also administered the intervention. The manual included strategies effective for the prevention and treatment of panic disorder in younger adults [25]. Adaptations were required for an elderly population with COPD [20, 26-28]. Components of the intervention therefore included: psycho-education about CBT, the effects of the stress response on breathing, and the cycle of panic anxiety in

COPD; training in cognitive challenging of unhelpful cognitions; training in “pursed lip breathing”; reinforcement of activity planning and “pacing”; the development of a personalised “good coping plan”; and problem-solving to address any barriers to good coping. The patient manual is available from the first author.

## **Measures**

### *Demographics*

Age, education, occupation before retirement, years since diagnosis of COPD, cigarette smoking history, body mass index, number of days per week when alcohol was consumed, number of alcoholic drinks consumed on these days, incidence of home O<sub>2</sub> use, FEV<sub>1</sub> post bronchodilator, FVC post bronchodilator, and FEV<sub>1</sub>/FVC ratio post bronchodilator were recorded.

### *Measures for assessing primary and secondary outcome variables*

The study’s primary outcome variables were rates of panic attacks and panic disorder, and anxiety symptomatology. Panic attacks and panic disorder were diagnosed with the ADIS-IV, the gold standard clinical interview for diagnosing anxiety disorders [21]. Although panic disorder is more difficult to diagnose when comorbid with respiratory disease, it is identifiable, as mentioned above, when patients have anticipatory anxiety about future panic attacks, and experience some unpredictable attacks not solely precipitated by unavoidable triggers for dyspnoea in COPD (such as physical exertion or infective exacerbations of the disease) [2]. The first author carried out the assessments and intervention, so ADIS-IV interviews were recorded to decrease any possible influence of experimenter bias. Inter-rater reliability was assessed by having another

clinical psychologist, blind to treatment condition, listen to a randomly selected 20% ( $n = 40$ ) of all recordings ( $n = 205$ ). Diagnostic agreement between the two raters for these interviews was 100%. The other primary outcome variable, anxiety symptomatology, was assessed using the anxiety subscale of the Hospital Anxiety Depression Scale (HADS), a 14 item questionnaire with good validity and reliability [22].

Four secondary outcome variables were investigated. Depressive symptoms were measured using the depression subscale of the HADS [22]. The Interpretation of Breathing Problems Questionnaire (IPBQ) was included as a measure of illness-specific catastrophic cognitions in patients with COPD [23]. The St. George's Respiratory Questionnaire (SGRQ) was used to assess quality of life [24]. Data on the number of COPD-related admissions for each participant was obtained from the hospital's database.

### **Sample size**

As this was the first study to investigate the efficacy of a specific CBT intervention in preventing panic-spectrum psychopathology in COPD, it was difficult to determine the effect size to use as a basis for predicting power. Power calculations, based on between group differences in anxiety scores at post intervention (effect size = 0.53) in a previous CBT study, indicated that a sample of 52 (26 in each group) would allow detection of changes at 5% significance with a power of over 95% for anxiety [14]. However, the study from which this effect size was drawn used a generic CBT programme. We expected larger effect sizes for the primary outcome variables (rates of panic attacks/panic disorder, and anxiety symptomatology as measured by the HADS) from a more

directly focused CBT approach for panic-spectrum psychopathology, anticipating that our total sample size of 41 would provide sufficient power to detect differences between groups on these variables.

### **Statistical analysis**

SPSS 12.0 (SPSS, Chicago, Il) was used for all analyses. Baseline differences between the groups were investigated using one-way analyses of variance (ANOVAs). It was planned to include any variable found to differ significantly between the groups as a covariate. A series of mixed model 2 (Group: CBT vs. routine care) x 2 (Time: Pre- vs. post-intervention/follow-up) analyses of covariance (ANCOVAs) were conducted. Only interaction effects, testing differences in changes in the two groups' results over time, are reported. Chi square tests were used to compare the incidence of panic attacks at each assessment. The Mann-Whitney test was used to compare the number of hospital admissions, as these were not normally distributed. Completer and intention to treat analyses were carried out, with no substantive difference in the pattern of results. Results of the intention to treat analysis are reported here. Statistical significance was defined as  $p < 0.05$ .

## **RESULTS**

### **Baseline Differences**

There were no significant differences at baseline assessment between CBT and routine care participants on number of males and females, age, years since diagnosis, cigarette smoking status, body mass index, home O<sub>2</sub> status, FEV<sub>1</sub> post bronchodilator, FVC post

bronchodilator, or FEV<sub>1</sub>/FVC ratio post bronchodilator (table 1). They did not differ on number of alcoholic drinks per day, but did differ on number of days per week on which some alcohol was consumed (table 1). We therefore controlled for the latter variable in subsequent analyses. All participants were Caucasian and retired (primarily from blue collar employment). Only one participant in each condition had completed high school, and one in each condition had English as a second language. There were no differences between the CBT and routine care groups at baseline on any of the study's outcome measures (table 1).

**TABLE 1.** Characteristics of study subjects

	Intervention (n=21)	Routine care (n=20)	p value
Female (n, %)	12 (57)	11 (55)	0.89
Age (yrs)	73.2 (6.4)	73.5 (8.1)	0.91
Yrs since COPD diagnosis (n)	6.5 (4.9)	6.4 (5.6)	0.96
Current smoking (n, %)	3 (14)	2 (10)	0.68
Body mass index (kg/m <sup>2</sup> )	25.7 (4.3)	26.2 (5.3)	0.80
Days alcohol consumed each week (n)	2.5 (1.5)	3.4 (1.1)	0.04*
Number of standard drinks (n)	0.4 (0.9)	0.2 (0.4)	0.28
On home O <sub>2</sub> therapy (n, %)	4 (19)	5 (25)	0.65
FEV <sub>1</sub> post bronchodilator (% pred)	57.0 (25.1)	51.1(15.0)	0.11
FVC post bronchodilator (% pred)	88.5 (16.8)	80.3 (12.9)	0.10
FEV <sub>1</sub> /FVC ratio post bronchodilator	0.67( 0.2)	0.62 (0.17)	0.37
COPD admissions in 6 months prior (n, %)	13 (62)	14 (70)	0.60
At least one panic attack in month prior (n, %)	4 (20)	6 (30)	0.48
HADS anxiety subscale score	5.2 (2.9)	5.9 (2.7)	0.45
HADS depression subscale score	3.9 (2.1)	4.1 (2.8)	0.55
IBPQ score	7.0 (4.3)	8.2 (4.8)	0.44
SGRQ score	40.3 (15.1)	47.9 (17.9)	0.15

Values presented as mean (standard deviation), unless otherwise stated. FEV<sub>1</sub>: Forced expiratory volume in one second, percentage of predicted for age; FVC: Forced vital capacity, percentage of predicted for age; HADS: Hospital Anxiety Depression Scale; IBPQ: Interpretation of Breathing Problems Questionnaire; SGRQ: St. George's Respiratory Questionnaire. \*p<0.05 on analysis of variance.

### **Primary outcomes**

Although there were no differences between the groups on the ADIS-IV at baseline assessment ( $p=0.48$ ), there were significant differences post-intervention ( $p=0.003$ ), and at 6 ( $p<0.001$ ), 12 ( $p<0.001$ ), and 18 ( $p<0.001$ ) month follow-ups in the proportion who had experienced at least one panic attack since the previous assessment (fig. 2). Twenty per cent ( $n=4$ ) of participants in the CBT and 30% ( $n=6$ ) in the routine care group had experienced at least one panic attack in the month prior to baseline assessment. However, all CBT group participants were asymptomatic post-intervention, and remained so over the 18 month follow-up period. No further cases of panic attacks developed in the CBT group. In the routine care group, 35% of participants had experienced at least one panic attack by post-intervention, and 60% by 18 month follow-up. Two of the 12 routine care group participants who had experienced at least one panic attack by 18 month follow-up met criteria for panic disorder, one with and one without agoraphobia. This result represents an absolute risk reduction provided by the CBT intervention of 43%, indicating that 3 patients needed to be treated to prevent one case of panic attacks developing during the 18 month follow-up period (95% CI  $>1.5<5.9$ ).

On the HADS's anxiety subscale, there was no significant time by group interaction post-intervention ( $p=0.22$ ) (fig. 3a). However, there were significant time by group interactions at 6 ( $p=0.006$ ), 12 ( $p=0.008$ ), and 18 ( $p=0.001$ ) month follow-ups, favouring the CBT group. At each follow-up, mean anxiety scores for the CBT group were in the non-clinical range, while mean scores for the routine care group were above the cut-off score ( $>7$ ) for possible clinically significant anxiety [22]. Only 5% ( $n=1$ ) of CBT

participants, compared to 45% ( $n=9$ ) of routine care participants had scores above this cut-off at 18 month follow-up.

### **Secondary outcomes**

There were significant time by group interactions on the IPBQ at 6 ( $p=0.012$ ), 12 ( $p=0.001$ ), and 18 ( $p=0.002$ ) month follow-ups, again favouring the CBT group (fig. 3b). There were no significant interactions on the HADS's depression subscale at any follow-up ( $p>0.11$ ) (fig. 3c). Similarly, there were no significant interactions on the SGRQ ( $p>0.40$ ). There was a significant difference in the number of hospital admissions for exacerbations of COPD between the 6 and 12 month follow-ups, with 4 admissions for the CBT and 9 for the routine care group ( $p=0.04$ ). Differences in admission numbers at other time points (between post-intervention and 6 month follow-up there were 2 for the CBT and 7 for the routine care group, and between 12 and 18 month follow-ups 3 for the CBT and 5 for the routine care group) were not significant ( $p>0.23$ ).

### **DISCUSSION**

Our findings support the hypothesis that CBT is more efficacious than routine care in preventing the development or worsening of panic-spectrum psychopathology in COPD patients. At the 18 month follow-up, 60% ( $n=12$ ) of routine care participants had experienced at least one panic attack in the previous 6 months, with 17% ( $n=2$ ) of those meeting criteria for panic disorder. In contrast, no-one in the CBT group had experienced a panic attack during the intervention or follow-up period, even though at baseline 4 patients had experienced at least one panic attack in the previous month. This result

indicates that CBT had a treatment effect, as well as a preventative impact. The number needed to treat analysis provided further evidence of the intervention's usefulness, with approximately one case of panic attacks prevented for every 3 patients treated over an 18 month follow-up period. There was also a decrease in anxiety symptoms, as measured by the HADS, over time in the CBT group, in contrast to a mean increase in symptoms to a level of possible clinical significance in the routine care group. Nearly half (45%) of the routine care group had anxiety scores in either the clinical or possible clinical ranges at 18 months follow-up. Further, the CBT group had significantly fewer COPD-related hospital admissions between the 6 and 12 month follow-ups. The results suggest that this brief CBT intervention had a specific impact on panic-related anxiety. The only treatment effect on secondary outcome questionnaires was found for the IPBQ, which assesses the degree to which individuals with COPD interpret potentially anxiety-provoking scenarios in a catastrophic way. This outcome corresponds with the central roles of both the catastrophic interpretation of ambiguous physical sensations such as dyspnoea in the cognitive model of panic anxiety, and of changes in catastrophic interpretations in mediating the effects of CBT for panic symptoms [4, 9, 10, 20].

Five previous controlled trials have provided evidence that CBT can decrease anxiety symptoms in COPD patients who have not been selected on the basis of existing psychopathology [11-15]. However, in all five studies anxiety symptoms were measured solely by self-report questionnaire, and only one of the studies included a follow-up assessment (at three months) [12]. Kunik and colleagues recently conducted a randomised controlled trial of a group CBT intervention for selected COPD patients with

moderate to severe anxiety and/or depressive symptoms, as measured by questionnaire [17]. At baseline, 38% of subjects were diagnosed with unspecified anxiety disorders, but diagnostic status after treatment was not reported. Patients receiving CBT showed similar, clinically significant improvements, maintained over 10 months, to those receiving only COPD education: Mean scores for both groups on the questionnaire measures of anxiety and depressive symptoms decreased from the “moderate” to the “mild” range. Reasons for the negative results of the study include the possibilities that the control intervention had an anxiety-reducing effect and that the CBT intervention was too general in content to fully address the symptoms of individuals with clinical anxiety and/or depression [17]. The current study is the first to focus on formally diagnosed panic-spectrum psychopathology in COPD. It is also the first psychological treatment study to include a follow-up period longer than 10 months [17].

Although the findings of the current study are encouraging, there are limitations to be noted. The first of these is sample size. With such a relatively small sample, there may be some concerns about statistical stability. The sample size may also limit extrapolation of the results to the entire population of patients with COPD. It is additionally possible that some of the null findings in secondary outcome variables were due to insufficient statistical power. However, effect sizes for secondary outcome questionnaires other than the IPBQ were small, with the largest (0.29) being observed for the HADS depression subscale. Any changes in these secondary outcome questionnaires are therefore unlikely to be clinically significant. The intervention studied here particularly targeted panic-spectrum psychopathology. For other psychological problems, such as depressive

disorders, a different intervention would be appropriate. A further limitation of the study was that neither the assessor nor participants were blind to treatment condition. To decrease any potential effects of experimenter bias, a fully structured diagnostic interview was administered. Further, we checked inter-rater reliability with a blind assessor on a 20% sub-sample of all interviews ( $n = 40/205$ ), where 100% concordance was achieved. The consistency of results between self-report, diagnostic interview, and hospital admission data also decreases the likelihood that experimenter bias could account for the results.

These limitations notwithstanding, there are several strengths of the study. This is the first trial with COPD patients to specifically address panic-spectrum psychopathology, and the first to formally measure diagnostic status for panic attacks and panic disorder at all assessment points. Subject retention was excellent, with 100% of those randomised completing the post-intervention assessment and 78% completing the study. The CBT intervention was sufficiently brief to be offered to all patients who had attended pulmonary rehabilitation, but sufficiently long for relevant skills to be practiced. The intervention responds to the recent call by Bourbeau and van der Palen for further programmes to help COPD patients self-manage their care as effectively as possible [29]. The follow-up period was longer than in previous studies, and the effects of the intervention were maintained. The trial provides the first evidence that untreated panic attacks in COPD do not spontaneously remit, and are a risk factor for panic disorder [30]. Pollack and Smoller have proposed that when an anxiety disorder develops comorbidly with a respiratory disease (as in nearly 40% of Kunik and colleagues' subjects), treatment

of the anxiety disorder may be more prolonged and difficult [31, 17, 20]. Interventions such as the current one may help to prevent the high costs of entrenched panic disorder for patients and for health services [6].

If we had provided CBT only to COPD patients with existing high anxiety, we would have missed some patients who went on to develop panic-spectrum psychopathology [5]. We therefore suggest that this type of brief, CBT self-management intervention should be routinely made available to all COPD patients, perhaps as a component of pulmonary rehabilitation programmes. Doing so could normalise contact with a mental health professional for elderly patients who may otherwise resist such contact [32]. Using a “stepped care” approach, it could prepare the ground for treatment of psychological disorders when necessary for some patients, while simultaneously decreasing the likelihood of panic-spectrum psychopathology developing in others [30, 33, 34].

A full cost benefit analysis was beyond the scope of the study. However, hospitalisation is the major contributor to health care costs in COPD [35]. For the period between the 6 and 12 month follow-ups, with an average admission length of 7 days at a cost to the health service of AUD800 per day, the direct hospitalisation cost for the CBT group was approximately \$22,400 and the routine care group \$50,400. The total cost of the clinical psychologist’s time with all 21 patients was \$3,650. We calculated an admission rate of 0.19 (4/21) for the CBT group and 0.45 (9/20) for the routine care group for this 6 month period. For a pool of 500 patients (a typical case load for a large referral centre) over a 12 month period, the admission costs would be \$1,064,000 versus \$2,520,000, a difference

of \$1,456,000 at a cost for the clinical psychologist's time of about \$87,000. The net saving of \$1,369,000 suggests that brief, preventative CBT interventions may decrease the burden of COPD not only to patients and carers but to health care systems, adding to any decrease achieved by integrated, comprehensive pulmonary rehabilitation [36].

In conclusion, the results of this study indicate that brief, specifically targeted CBT can treat panic attacks in COPD patients, and prevent the development or worsening of panic-spectrum psychopathology and anxiety symptoms. The intervention was also associated with a decrease in hospital admissions. Larger scale prevention trials are warranted by the current findings, the high prevalence of panic disorder in COPD, and the high individual and social costs when panic disorder develops.

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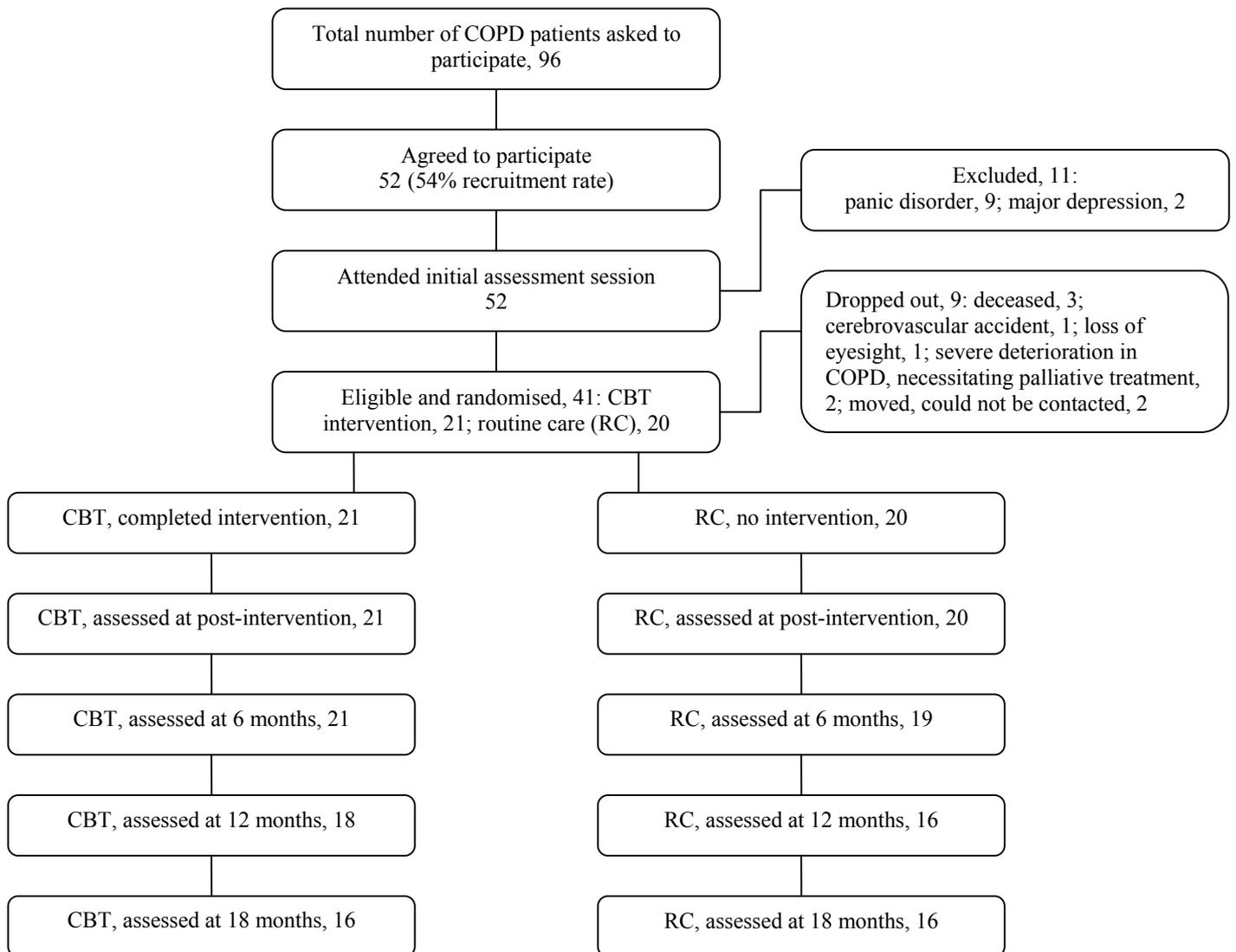
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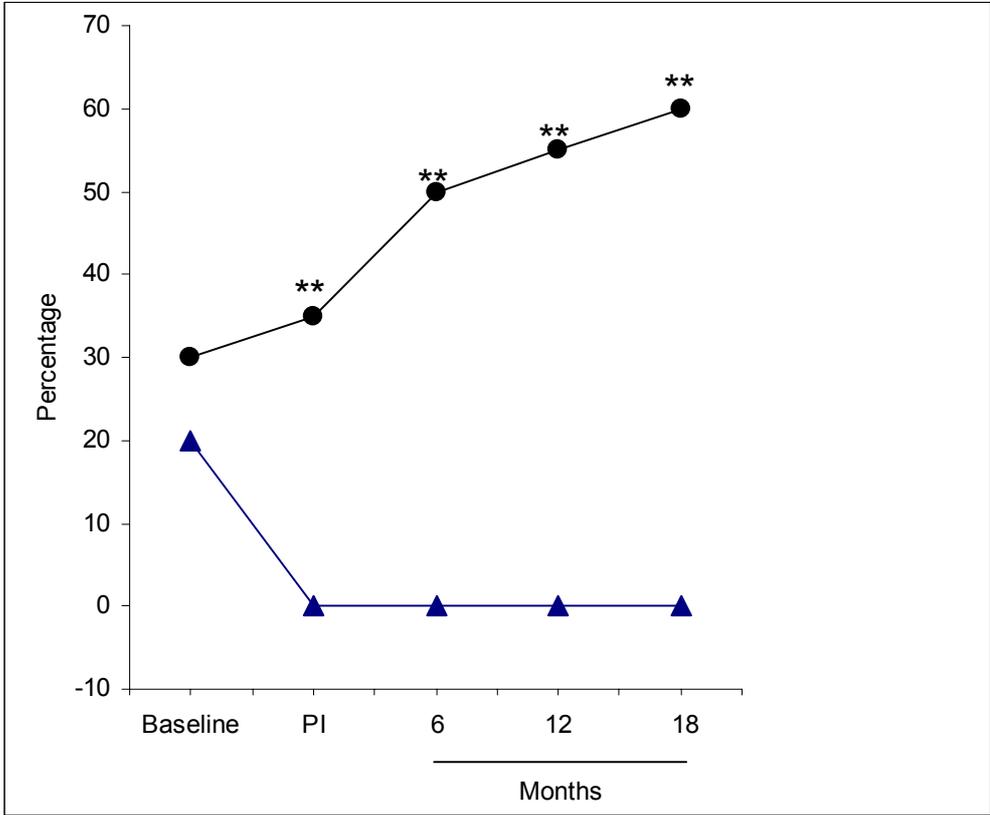
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**FIGURE 1.** Numbers/attrition of participants from enrolment to 18 month follow-up.

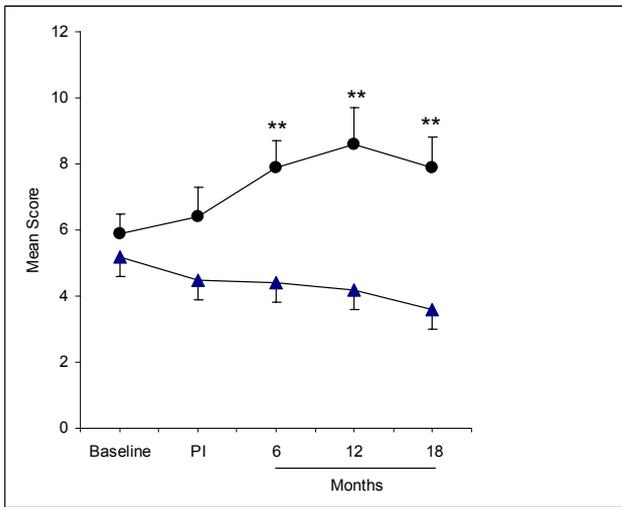


**FIGURE 2.** Percentage of subjects who had experienced at least one panic attack in the previous month (at baseline and post intervention) or previous 6 months (at 6, 12 and 18 month follow-ups) in the CBT group (▲) and the routine care group (●). Differences between the groups were significant at post-intervention and all follow-ups. \*\*:  $p < 0.01$ .

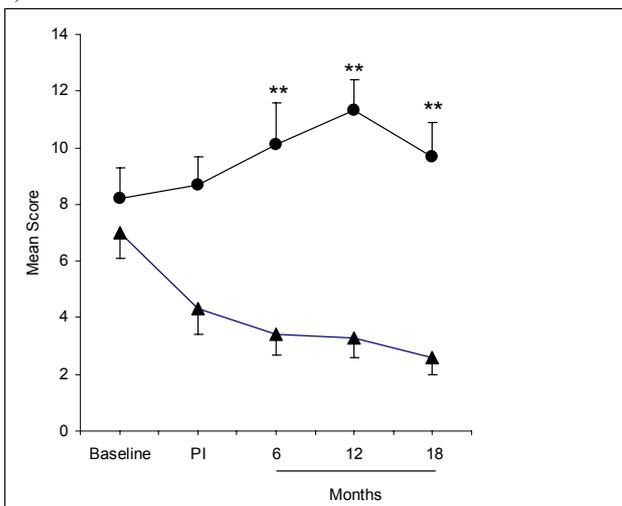


**FIGURE 3.** Mean scores at baseline, post-intervention, and 6, 12 and 18 month follow-ups for the CBT group (▲) and the routine care group (●) on a) the Hospital Anxiety Depression Scale's anxiety subscale b) the Interpretation of Breathing Problems Questionnaire c) the Hospital Anxiety Depression Scale's depression subscale. Data is presented as mean  $\pm$  standard error of the mean. Higher scores indicate worse symptomatology. \*\*:  $p < 0.01$ .

a)



b)



c)

