TREATMENT OF ANXIETY AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Contents

Abstract

Coexisting anxiety in Chronic Obstructive Pulmonary Disease (COPD) patients affects patients' symptoms, psychological status and healthcare costs. Prior to this thesis, the evidence for various interventions for management of anxiety in COPD was limited. The work described in this thesis examined pharmacological and psychological interventions for the treatment of anxiety in COPD through systematic reviews and a randomised placebo-controlled trial. Paroxetine was found to reduce anxiety symptoms and COPD-related hospital admissions. However, several medication-related side effects were observed. Overall, cognitive behavioural therapy has proven to be more effective for controlling anxiety in COPD patients and advocacy is required for its incorporation in management guidelines.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time. I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

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Signed…… Date ……04/12/2018……

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Abbreviations

BAI	Becks Anxiety Inventory
BDI	Becks Depression Inventory
CI	Confidence Interval
CRF	Case Report Form
COPD	Chronic Obstructive Pulmonary Disease
DOI	Digital Object Identifier
GAD	Generalised Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
MD	Mean Difference
Mgs	Milligrams
PAC	Paroxetine for Anxiety in Chronic obstructive pulmonary disease
PIS	Patient Information Sheet
RCT	Randomised Controlled Trial
SMD	Standardised Mean Difference
SSRI	Selective Serotonin Re-uptake Inhibitor
TSANZ	Thoracic Society of Australia and New Zealand

Peer-reviewed journal publications

1. Usmani ZA, Carson-Chahhoud KV, Esterman AJ, Smith BJ. Systematic meta-analysis of pharmacological and psychological interventions for the treatment of anxiety in patients with chronic obstructive pulmonary disease. Arch Psychol. 2018;2(7):1–16.
2. Usmani ZA, Carson KV, Esterman AJ, Smith BJ. A randomized placebo-controlled trial of paroxetine for the management of anxiety in chronic obstructive pulmonary disease (PAC study). J Multidiscip Healthc. 2018;11:287–93.
3. Usmani ZA, Carson KV, Cheng JN, Esterman AJ, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2017;3. DOI: 10.1002/14651858.CD010673.pub2 (2017 impact factor 6.754)
4. Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Protocol). Cochrane Database Syst Rev. 2013;7. DOI: 10.1002/14651858.CD010673 (2017 impact factor 6.754)

Presentations

Oral conference presentations

1. Usmani ZA, Carson KV, Esterman AJ, Smith BJ. A Meta-analysis of pharmacological & psychological interventions for treatment of anxiety in COPD. Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, April 2016, Perth, Australia.
2. Usmani ZA, Carson KV, Esterman AJ, Karen Heslop, Anthony DeSoyza, Smith BJ. Psychological interventions for treatment of anxiety in COPD: A Cochrane review. Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting, March 2015, Gold Coast, Australia.

Other (non-conference) invited oral presentations

3. Usmani ZA, Carson KV, Esterman AJ, Smith BJ. Paroxetine for treatment of anxiety in COPD. The Queen Elizabeth Hospital, Department of Respiratory Medicine, August 2017, Adelaide.

Chapter 1. Introduction

1.1 Description of COPD

Chronic obstructive pulmonary disease (COPD), a complex and progressive disease, is characterised by inflammation of the airways and destruction of pulmonary tissue resulting in airway limitation. It is associated with an abnormal inflammatory response by the lungs to noxious particles or gases [1] and, subsequently, is a major cause of mortality, illness and high levels of disability, particularly in the elderly [2, 3]. Symptoms vary from mild shortness of breath to disabling breathlessness with minimal exertion. Spirometry is the essential test to confirm the diagnosis and establish the staging of COPD. In the presence of FEV1/FVC of < 0.7, the percentage of predicted FEV1 is used to determine the severity of airflow limitation [1]. The following standards apply:

- GOLD 1: Mild (FEV1 ≥ 80% predicted)
- GOLD 2: Moderate (50% predicted ≤ FEV1 < 80% predicted)
- GOLD 3: Severe (30% predicted ≤ FEV1 < 50% predicted).
- GOLD 4: Very severe (FEV1 < 30% predicted).

Although other diseases have demonstrated a decline in mortality in recent years, COPD is reported to be the only leading cause of death that is increasing in prevalence [4]. In 2000, chronic lower respiratory tract disease was the fourth leading cause of death in Australia behind cancer, ischaemic heart disease and stroke, accounting for 5,962 deaths [5]. Research suggests that by 2020, COPD will become the third leading cause of death in Australians [6]. The Australian Lung Foundation estimates that 2.1 million Australians have some form of COPD [7, 8] and by 2050 this figure will more than double to 4.5 million [7]. Of those with COPD, 1.2 million Australians have COPD in stages II–IV, stages at which symptoms already affect their daily lives [7, 9].

1.2 Burden and effect of anxiety in COPD

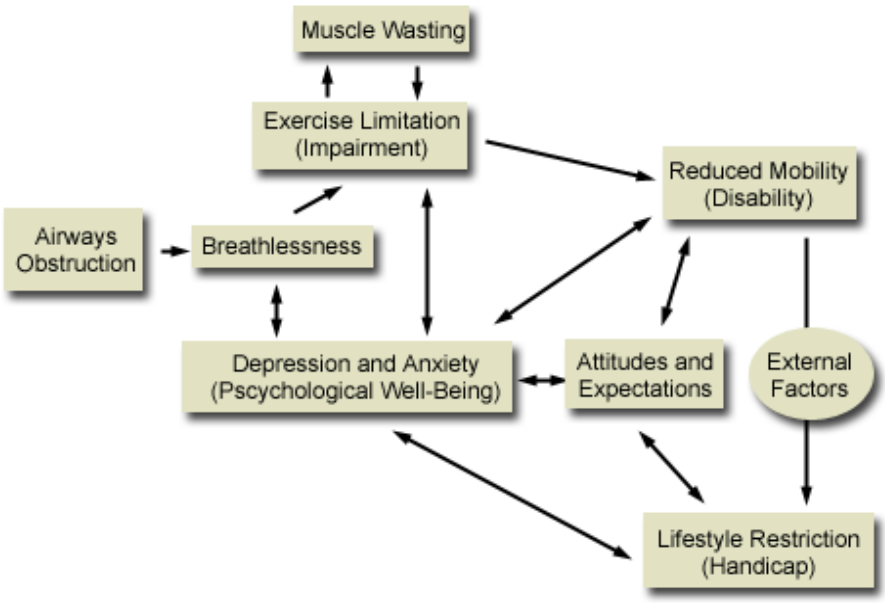
Anxiety and depression often co-exist in patients with COPD. Frequently, they are untreated or under-treated [10]. Generalised anxiety disorder (GAD) is characterised by excessive and persistent worrying that is difficult to control, which causes significant distress or impairment and occurs on most days for at least six months. The lifetime prevalence of GAD among patients with COPD is between 10 to 15.8 per cent [11]. The most likely lifetime prevalence for GAD in the general population is five per cent, using nationally recognised criterion [12]. This suggests that anxiety is two to three times more common in people with COPD. The presence of anxiety in patients with COPD has been associated with worsening quality of life [13], self-management [14], exercise performance [3],

increased medical symptom reporting [15], illness exacerbations [3] and hospitalisations [16], length of hospital stay [17], mortality [2] and healthcare costs [15].

1.3 Why anxiety in people with COPD is of particular concern

Various models can be used to explain increased levels of anxiety and panic disorder in people with COPD [18, 19]. One model explains this relationship as exaggerated misinterpretation of ambiguous bodily sensations (such as shortness of breath and rapid heart rate), which increase arousal, creating a positive feedback loop that results in a panic attack [20]. A crucial difference between physically healthy people and those with COPD is that in the latter, breathing—the most basic physical function necessary for life—is objectively threatened. The increase in breathlessness, which leads to inactivity, physical de- conditioning and exercise limitations, results in further inactivity, social isolation and the fear of dyspnoea and depression [21, 22]. Importantly, the effect of anxiety and depression on health-related outcomes will remain after adjusting for potential compounding factors, such as general health status, comorbidities and disease severity [11]. There is evidence to argue that the presence of anxiety and depression is more strongly related to functional status and hospital bed usage than the severity of COPD itself [23]. The relationship between dyspnoea and psychological symptoms has been expressed diagrammatically (see Figure 1).

Figure 1: The relationship between dyspnoea and psychological symptoms



Source: Jones PW, Quality of life measurement for patients with diseases of the airways. Thorax. 1991;46:676–682

1.4 Management of anxiety in COPD

Management strategies for the treatment of anxiety disorders in people with COPD include pharmacological and non-pharmacological or psychological interventions.

Despite the documented effect of anxiety and depression in patients with COPD, the literature surrounding pharmacological treatments is limited and lacks statistical significance, as published in the recent Cochrane review [24] and literature review [25]. These reviews for anxiety and depression in COPD patients highlight a significant gap in the evidence to support pharmacological intervention. Alarmingly, pharmacological treatments are commonly prescribed to patients for treating anxiety in COPD, regardless of the lack of supporting evidence for, not only efficacy, but also safety. It was discovered that, despite the significance of the problem, it was not possible to draw conclusions for treatment due to the sub-optimal quality of the trials. Moreover, no indicators exist to guide clinicians regarding likely treatment responses for pharmacotherapy.

Psychological therapies are intentional interpersonal relationships used by trained psychotherapists to aid people who have problems of living, with an aim to increase the individual's wellbeing [26]. Psychological therapies may be performed by practitioners with a number of different qualifications, including psychologists, marriage and family therapists, occupational therapists, licensed clinical social workers, counsellors, psychiatric nurses, psychotherapists, trained general nurses, psychoanalysts and psychiatrists.

The mode of delivery for these therapies may comprise individual, group or family (including couple) therapy, performed by a healthcare professional. Psychological therapies are not usually used in clinical practice for the management of anxiety in COPD patients. Although there are many randomised controlled trials addressing the efficacy of psychological interventions for this group of patients [27]**,** there is a lack of systematic meta-analysis to summarise the effect and efficacy of these interventions.

1.5 Outline for research

To determine the most effective intervention for management of anxiety in COPD patients, three studies were conducted.

The first study was to conduct a systematic meta-analysis according to the Cochrane methodology for assessing efficacy of psychological interventions for management of anxiety in COPD patients and the effect of this treatment on quality of life.

The second study was to conduct a randomised double-blind placebo-controlled trial to assess efficacy and safety of a selective serotonin re-uptake inhibitor (SSRI), paroxetine, for treatment of anxiety in COPD and its effect on patient quality of life and hospital utilisation. Pharmacotherapy, particularly SSRIs, have been widely used in clinical practice to treat depression and anxiety [24]. In the recently published meta-analysis, a small clinical improvement was identified that favoured SSRIs over placebo for controlling anxiety. Little or no difference was found for other classes of medications [24]. Unlike other SSRIs, paroxetine is indicated for treatment of depression and anxiety [28, 29]. The effectiveness of paroxetine in end stage COPD has been investigated in a small number of subjects (n = 8 on paroxetine and n = 7 on placebo), suggesting a possible overall benefit in significant depression [22]. Another 2005 trial of paroxetine in patients with COPD and comorbid depression demonstrated significant improvements in depression scores, walking distance and quality of life at three months [30]. However, this study was underpowered (total n = 28), with the authors concluding that a larger double-blind study with a longer treatment period was necessary. As such, a case can be made that a well-powered randomised controlled trial (RCT) is required to investigate the efficacy and safety of paroxetine for patients with co-existing anxiety and COPD.

The third study was to conduct an overarching systematic review comparing evidence for pharmacological (including data from the RCT) and psychological interventions. This review was required to inform clinical practice improvement decision making. This would facilitate practical improvements for quality of life and health status among COPD patients.

In line with these studies, the layout of this thesis includes an overview of aims and hypotheses in Chapter 2, followed by four peer-reviewed publications presenting results, preceded by a summary page. Finally, a discussion and conclusion consolidate this evidence in the context of implications for practice, policy and future research.

Chapter 2. Overview of aims and hypotheses

A summary of the aims/hypotheses for each manuscript presented in this thesis are listed below.

Psychological interventions for the treatment of anxiety in COPD (Chapters 3 and 4)

The aim of the Cochrane systematic meta-analysis is to evaluate the effectiveness of psychological interventions for the management of anxiety in COPD patients.

Randomised controlled trial of paroxetine for the treatment of anxiety in COPD (Chapter 5)

This study employed the hypothesis that subjects recruited from public hospitals with COPD and clinically significant anxiety who are given paroxetine 20mgs daily for four months will:

*(**Hypothesis 1: principal hypothesis**):* have a significant reduction in anxiety symptoms compared to the placebo at the four month follow-up,

*(**Hypothesis 2**):* will result in improved quality of life and exercise capacity and;

(Hypothesis 3): these improvements will be associated with a reduction in hospital bed utilisation.

Meta-analysis of pharmacological and psychological interventions for the management of anxiety in COPD (Chapter 6)

This publication combines pharmacological and psychological intervention into one meta-analysis to determine if one has superior efficacy. Publication in this format may be of greater relevance to public policy and clinical practice initiatives.

Chapter 3. Psychological therapies for the treatment of anxiety disorders in COPD (Protocol)

Literature review and meta-analysis

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Cochrane Database of Systematic Reviews 2013; Issue 7: 1–14

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Statement of authorship

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Publication details: Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Protocol). *Cochrane Database of Systematic Reviews.* 2013; July 31 (7) DOI: 10.1002/14651858.CD010673 (2015 impact factor 6.22)

Author contributions:

By signing the Statement of Authorship, each author certifies their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	Zafar Usmani		
Contribution to the paper	Invited to write the protocol, researched the content, prepared the protocol, wrote the first draft, jointly developed the arguments and structure for the protocol, made critical revisions and approved final version. Overall contribution towards the project, manuscript and publication 85%.		
Signature		**Date**	23 August 2018

Name of co-author	Kristin Carson		
Contribution to the paper	Invited to write the protocol, researched the content, assisted in preparing the protocol, jointly developed the arguments and structure for the protocol, assisted in making revisions and approved final version.		
Signature		**Date**	24 August 2018

Name of co-author	Karen Heslop		
Contribution to the paper	Contributed towards the research of contents, assisted in the first draft, jointly developed the arguments and structure for the protocol, made critical revisions and approved final version.		
Signature	Karen Heslop-Marshall	**Date**	28 August 2018

Name of co-author	Adrian Esterman		
Contribution to the paper	Analysed the feasibility of the protocol, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		**Date**	27 August 2018

Name of co-author	Anthony De Soyza		
Contribution to the paper	Analysed the feasibility of the protocol, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		**Date**	27 August 2018

Name of co-author	Brian Smith		
Contribution to the paper	Analysed the feasibility of the protocol, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		**Date**	27 August 2018

This publication has described the protocol for conducting the systematic review to assess the efficacy of psychological interventions for management of anxiety in COPD.

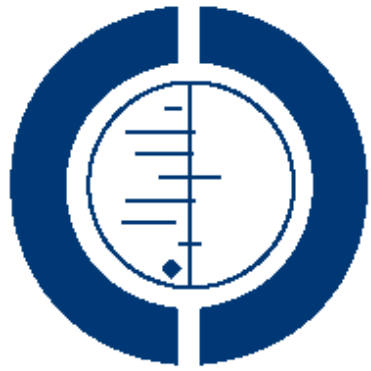
In line with recommendations for the *Cochrane Database of Systematic Reviews*, a pre-specified protocol was established underpinning the conduct of a methodologically rigorous systematic review.

Within this protocol, methodology is discussed. All RCTs that have assessed the efficacy of psychological intervention for patients with clinical anxiety and formally diagnosed COPD will be included. The primary outcome was change in anxiety scores. The secondary outcomes were quality of life, exercise capacity, dyspnoea scores, hospital length of stay and spirometry. The quality of the included studies was assessed using various domains for assessment of risk of bias including randomisation, sequence generation, reporting bias and other bias.

It has been mentioned that the Cochrane specialised registers and other national and international registers were used to search citations. The assessment of studies was conducted by two independent reviewers and any conflicts were resolved by discussion with a third reviewer. Data collection and risk of bias assessment were performed in a similar manner. The extracted data were pooled and presented in meta-analysis using a random effects model.

Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Protocol)

Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ



This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 7

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TABLE OF CONTENTS

[Intervention Protocol]

Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of psychological therapies for the treatment of anxiety disorders in patients with chronic obstructive pulmonary disease.disorders.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) consists primarily of chronic bronchitis and emphysema, conditions which are characterised by the inflammation of airways and the destruction of pulmonary tissues. The diagnosis of COPD is based on the documentation of a post bronchodilator forced expiratory volume1/forced vital capacity (FEV1/FVC) less than 70% (Rabe 2007). Anxiety disorder is a generalised term for a myriad of abnormal and pathological fear and anxiety states, including generalised anxiety disorder (GAD), panic disorder (PD), agoraphobia, neurocirculatory asthenia, obsessive-compulsive disorder (OCD), and phobic

Evidence suggests that there is an increased prevalence of anxiety disorders in patients with COPD (Maurer 2008). The lifetime prevalence of GAD in particular amongst patients with COPD is estimated at between 10% and 15.8% (Brenes 2003). GAD is defined as excessive anxiety which lasts for at least six months. Individuals must also experience three or more of the following symptoms: difficulty in concentrating; fatigue after little exertion; sleep disturbance; a sensation of being 'keyed up' (nervous or anxious); irritability or muscle tension, or both (Diagnostic and Statistical Manual (DSM) IV criteria) (APA 1994). Rates of anxiety symptoms in patients with COPD range from 13% to 51% and are higher than the rates in patients with heart failure, cancer, and other medical conditions (Brenes 2003).COPD is associated with a higher risk of anxiety, and once anxiety develops among patients with COPD it is related to poor health outcomes, including in terms of exercise tolerance, quality of life and COPD exacerbations (Eisner 2010). By compromising health status, mood disor-

ders lead to increased risk of hospitalisation and re-hospitalisation (Gudmundsson 2005) and hence also increase direct and indirect costs to the health system.

Various models could be considered to explain increased levels of anxiety and panic in patients with COPD (Ley 1985; Perna 2004). One of the models (Clark 1986) explains this relationship as catastrophic misinterpretations of ambiguous bodily sensations (such as shortness of breath, rapid heart rate) which increase arousal, creating a positive feedback loop that results in a panic attack. A crucial difference between physically healthy people and those with COPD is that in the latter, breathing, the most basic of all physical functions necessary for life, is objectively threatened (as measured by tests of lung function) and subjectively difficult. Dyspnoea (shortness of breath) can be an unpleasant and potentially frightening experience at any time, and, as the key symptom of an eventually fatal illness like COPD, it is an ambiguous sensation open to catastrophic interpretation, leading to increased levels of anxiety and panic in people with COPD (Livermore 2010).

Description of the intervention

Management strategies for the treatment of anxiety disorders in people with COPD include both pharmacological and non-pharmacological interventions. Evidence that pharmacological thera- pies (anti-anxiety and/or antidepressant medications) provide statistically or clinically significant benefits for this group of patients is limited (Usmani 2011). Psychological therapies include cognitive and/or behavioural therapies, psychodynamic psychother- apy, interpersonal psychotherapy, non-directive therapy, support therapy and counselling (Rose 2002; Davison 2003). Psycholog- ical therapies are intentional interpersonal relationships used by trained psychotherapists to aid patients with problems of living, with an aim of increasing the individual's well-being. Psychological therapies may also be performed by practitioners with a number of different qualifications, including psychologists, marriage and family therapists, occupational therapists, licensed clinical social workers, counsellors, psychiatric nurses, psychoanalysts, and psychiatrists.The mode of delivery for these therapies comprise individual, group or family (including couple) therapy, performed by a healthcare professional.

How the intervention might work

Because COPD is an irreversible condition, treatment recommendations are aimed at improving quality of life (Norweg 2005). Current evidence examining quality of life suggests a reduction in satisfaction above and beyond what should be expected by COPD disease severity or co-morbid medical illnesses (Coventry 2007), indicating that psychological status plays an intrinsic role in overall well-being. A recent study examining the impact of anxiety on the lives of patients with COPD found that patients felt isolated and would avoid social occasions and usual daily activities (Willgoss 2011). As a result, therapies targeting the reduction of psychological stressors should be expected to improve quality of life (Ries 1995; Rose 2002; Baraniak 2011).

Psychological therapies are often based on the assumption that psychological outcomes such as anxiety are linked with physical manifestations of COPD, for example dyspnoea, which can precipitate episodes of anxiety (Wu 2004). It has been hypothesised that a patient's fear and misinterpretation of bodily experiences from dyspnoea and hyperventilation cause a panic reaction (Nutt 1999). Alternatively, underlying psychological distress can contribute to an increased risk of symptom exacerbations, particularly those treated in the patient's own environment (Laurin 2011). As such, patients with anxiety and panic disorders interpret threats as more dangerous due to a higher awareness of cues such as dyspnoea and tachycardia (Mikkelsen 2004).

A psychological therapy, cognitive-behaviour therapy (CBT), aims to identify and correct dysfunctional emotions, behaviours and cognitions through a goal-oriented, systematic procedure (Rose 2002; Kaplan 2009). In the case of COPD patients, CBT may be a means of managing concurrent anxiety and depression. While not in itself improving an individual's medical condition, CBT may serve to increase perceived self-efficacy and motivate patients to manage their physical condition, thereby improving quality of life (Kunik 2001). Moreover, the learning about oneself that occurs in various forms of psychological therapy may in itself influence the structure and function of brain (Kandel 1998) or may have a significant impact on serotonin metabolism (Viinamaki 1998). 'Third wave CBT' applies to behavioural psychological therapies that integrate mindfulness and acceptance of unwanted thoughts and feelings with a behavioural understanding of emotional suffering, to elicit change in thinking process. Behavioural therapy includes methods that focus on behaviours, not the thoughts and feelings that might be causing them. The behavioural approach to therapy assumes that behaviour that is associated with psychological problems develops through the same processes of learning that affect the development of other behaviours. Psychodynamic therapy focuses on unconscious processes as they are manifested in patients' present behaviour. Hence by making the unconscious aspects of their life a part of their present experience, psychodynamic therapy helps people understand how their behaviour and mood are affected by unconscious feelings. Humanistic psychotherapy emphasises human uniqueness, positive qualities, and individual potential. It works by emphasising one's capacity to make informed and rational choices and develop to one's maximum potential. Integrative therapies are approaches that combine components of different psychological therapy models.

Why it is important to do this review

Anxiety disorders in people with COPD have been shown to increase disability and impair functional status, resulting in an overall

reduction in their quality of life (Beck 1988; Weaver 1997). Importantly, the impact of anxiety on these outcomes was shown after adjusting for other potential confounders such as general health status, other medical conditions and COPD severity (Brenes 2003). Kim 2000 reported that anxiety and depression were more strongly related to functional status than the severity of COPD. Co-morbid anxiety in an elderly population with COPD has been suggested as a significant predictor of the frequency of hospital admissions (Yohannes 2000). A recent study has shown that among patients with COPD, anxiety is related to poorer health outcomes including worse submaximal exercise performance, greater risk of self-reported functional limitations and a higher longitudinal risk of COPD exacerbations (Eisner 2010). However, the evidence for treatment of anxiety disorders in COPD is limited, and there are limited data to support the efficacy of medication-only treatments (Borson 1998). The results of a Cochrane review evaluating the effects of pharmacological interventions for anxiety in patients with COPD are inconclusive (Usmani 2011). A feasibility study of antidepressants in this population suggested poor acceptance of antidepressants for various reasons including side-effects and reluctance to take 'yet another medication' (Yohannes 2001). Furthermore the association between anxiety/panic and dyspnoea/COPD had been explained by various psychological theories (Clark 1986; Livermore 2010). It is important therefore, to evaluate psycho- logical therapies for the alleviation of these symptoms in patients with COPD.

In light of the health burden caused by psychological disorders and the limited evidence supporting treatment options, this review is one of four linked Cochrane reviews that will assess the effects of pharmacological and psychological therapies for the treatment of anxiety and depression in patients with COPD, one of which has already been published (Usmani 2011) and two of which are in progress (Usmani 2013a, Usmani 2013b).

OBJECTIVES

To assess the effects of psychological therapies for the treatment of anxiety disorders in patients with chronic obstructive pulmonary disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cross-over trials and cluster randomised trials.

Types of participants

Participants will be adults over 40 years of age (as it is very unlikely that people less than 40 years old have clinically-significant COPD (GOLD 2013)) of either sex and of any ethnicity, diagnosed with COPD and a recognised anxiety disorder or anxiety symptoms.

The COPD diagnosis needs to have been made by a medical professional clinically, or by GOLD (Global initiative for chronic Obstructive Lung Disease) criteria, or both (FEV1/FVC < 0.70).

The anxiety disorder (e.g. generalised anxiety disorder (GAD), panic disorder (PD), agoraphobia, neurocirculatory asthenia, obsessive-compulsive disorder (OCD), phobic disorders) needs be defined using established diagnostic criteria e.g. DSM criteria (APA 1994), and anxiety symptoms identified using a formal psychological instrument e.g. Beck Anxiety Inventory (BAI) (Beck 1961; BAI 1993) at the time of recruitment to the trial.

We will include participants with co-morbid mental health disorders. Anxiety need not be the primary mental health disorder for included participants as long as they had formally diagnosed or symptomatic anxiety (as diagnosed or assessed by a formal criteria or a validated tool).

We will exclude studies that only assess psychological therapies for the treatment of depression in patients with COPD, as these will be covered by a separate review.

Types of interventions

We will include studies assessing any form of psychological therapy for the treatment of anxiety disorders in people with COPD where this is compared with either no intervention or education only. We will include studies in which the psychological therapy is delivered in combination with another intervention (co-intervention) only if there is a comparison group that received the co-intervention alone.

Experimental interventions:

- Cognitive behavioural therapy (CBT) (e.g. problem solving, rational emotive therapy)
- Third Wave CBT (i.e. acceptance and commitment therapy, compassionate mind training, functional analytic psychotherapy, mindfulness-based cognitive therapy, behavioural activation, metacognitive therapy and dialectical behavioural therapy)
- Behavioural therapy (e.g. behaviour modification, assertiveness training)
- Psychodynamic therapy (e.g. insight-oriented therapy, group psychotherapy)
- Humanistic therapy (e.g. expressive therapy, supportive therapy)
- Integrative therapy (e.g. cognitive analytical therapy).

Comparators:

- No intervention (i.e. waiting list and usual care)
- Education only (education (written or oral), such as provision of information about physical and mental health issues

during a medical consultation or during a visit with a nurse where no formal counselling or psychological therapy was provided)

- Co-intervention (only if the same co-intervention was used in the intervention arm of the study). The co-interventions included will be pharmacotherapy and pulmonary rehabilitation.

Types of outcome measures

Primary outcomes

1. Change in anxiety symptoms as measured by a standardised or validated anxiety measure e.g. State-Trait Anxiety Inventory (STAI) (Spielberger 1970), the Hospital Anxiety and Depres- sion Scale (HADS) (HADS 1983) and the Beck Anxiety Inventory(BAI) (Beck 1961; BAI 1993). These scales generate a total score which will be recorded for all pair-wise comparisons as short-term follow up data (up to and including six months) and/or long term follow-up data (greater than six months).
2. Adverse events

Secondary outcomes

Each of the secondary outcomes will be assessed based on a validated assessment scale. The secondary outcomes measured will include:

3. Change in quality of life e.g. the St George's respiratory questionnaire (SGRQ) (Jones 1991). Generic, validated quality of life measures will also be included
4. Difference in exercise tolerance e.g. the six-minute walk test (Butland 1982)
5. Change in dyspnoea scores e.g. the Borg scale (Borg 1982)
6. Change in length of stay or readmission rate
7. Change in forced expiratory volume in one second (FEV1)

Timing of outcome assessment

Time frames will be defined as short-term (up to three months), medium-term (three to six months) and long-term follow up (more than six months).

Search methods for identification of studies

Electronic searches

Cochrane Specialised Registers

CCDAN Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK; a references register and a studies-based register. The CCDANCTR-References Register contains over 28,000 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Coordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from national and international trials registers via the World Health Organisation's trials portal (ICTRP), drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found on the Group'swebsite.

The CCDANCTR (Studies and References Registers) will be searched using the following terms:

(anxi* or *phobi* or PTSD or post-trauma* or posttrauma or "post trauma*" or "combat disorder" or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*)

AND

((obstruct* and (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or emphysema or (chronic* and bronchiti*))

CARG Register

The Cochrane Airways Group's Specialised Register is also derived from systematic searches of bibliographic databases including: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details).

All records in the CARG Specialised Register coded as 'COPD' will be searched using terms for 'Anxiety Disorders' as listed above. An additional search of CENTRAL and PsycINFO will be conducted to ensure no record has been missed from these databases in the creation of the CCDANCTR and CARG Specialised Registers (Appendix 1).

National and international trials registers

Complementary searches will be conducted on the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov.

Searching other resources

We will handsearch reference lists of retrieved, relevant articles to identify any other potentially-relevant articles. We will contact authors of potentially-included studies for raw data or unpublished data if required.

Data collection and analysis

Selection of studies

All citations generated from the search strategies will be independently assessed by two of three review authors (KC, ZU, KH) to determine whether they satisfy the Criteria for considering studies for this review, through screening of the title, abstract and descriptors. Studies identified as potentially relevant will have full text articles retrieved and examined for final inclusion by two of three independent authors as above. Disagreements will be resolved through discussion and by a third party if necessary (BS or AD).

Data extraction and management

The following data will be extracted using a standardised and piloted data extraction form by two independent review authors (a combination of ZU, KC and KH), for each included study. Any discrepancies will be resolved by discussion between the authors and if needed, a third party (BS or AD).

Study eligibility

Study design, population group and description of psychological therapy.

Participants

Number of participants, age, gender distribution, ethnicity and co-morbidities.

Interventions

Description of intervention, duration, intensity, who it was delivered by.

Main comparisons

1. Psychological therapies versus no intervention.
2. Psychological therapies versus education.
3. Psychological therapies and co-intervention versus co-intervention alone.

These comparisons will be stratified according to psychological therapy, however, an overall pooled estimate for intervention effectiveness will not be performed for all psychological therapies in each of these comparisons, i.e. sub-totals only will be used in the analyses.

Assessment of risk of bias in included studies

The risk of bias for all the included studies will be assessed by two independent review authors using a domain-based evaluation. Risk of bias will be assessed as 'Low risk of bias', 'High risk of bias' and 'Unclear risk of bias' as per the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, table 8.5.c (Higgins 2011). Conflicts in the assessment will be resolved either by consensus or by referring to a third party. The domains evaluated will be:

Sequence generation

Methods considered adequate include: random number table, computer random number generator, coin toss, shuffling cards or envelopes, throwing dice and drawing lots (Higgins 2011).

Allocation concealment

Methods considered adequate include: central allocation (phone, web, pharmacy), sequentially-numbered identical drug contain- ers and serially-numbered sealed and opaque envelopes (Higgins 2011).

Blinding (of participants)

Blinding will be considered adequate if: trial authors mention that participants were blinded to the intervention, although for psychological therapies this will be unlikely due to the difficulties associated with delivery of communication-based interventions (Higgins 2011).

Blinding (of outcome assessors)

Blinding will be considered adequate if: authors mention that outcome assessors were blinded to sequence allocation (Higgins 2011).

Incomplete outcome data

Risk of bias due to incomplete outcome data will be assessed on the grounds of whether the incomplete outcome data were adequately addressed or not, as per the Cochrane Handbook section 8.12 (Higgins 2011).

Selective outcome reporting

Studies will be considered to be at low risk of bias if a protocol is available and all pre-specified outcomes are reported in the pre-specified way, or in the absence of a protocol, if all expected outcomes are reported (and as per recommendations in table 8.5.c, Higgins 2011).

Other bias

Studies will be considered at a low risk of other bias if they were conducted in such a way as to ensure no other influencing factors that could potentially affect the outcome were evident. Examples of other biases include: extreme baseline imbalances for participants or outcomes, contamination of the intervention or control group, and selective recruitment of study participants.
The results of the 'Risk of bias' assessment will be presented in a 'Risk of bias' table and described narratively within the results of the review.

Measures of treatment effect

Continuous data

Available data will be summarised by either mean differences (MD) or standardised mean differences (SMD) where appropriate, using mean values and standard deviations. We will consult a statistician for additional support if required (AE).

Dichotomous data

For dichotomous data we will calculate odds ratios with 95% confidence intervals. Data will be presented as either final values (post-intervention) or as change from baseline if raw data from the trialists cannot be retrieved.

Unit of analysis issues

Cluster-randomised trials

Cluster randomised controlled trials, i.e. trials in which outcomes relate to individual subjects whilst allocation to the intervention is by hospital, clinic or practitioner, may introduce unit of analysis errors. Using statistical methods which assume for example that all patients' chances of benefit are independent, ignores the possible similarity between outcomes for patients seen by the same provider. This may underestimate standard errors and give misleadingly narrow confidence intervals, leading to the possibility of a type 1 error (Altman 1997). For cluster randomised studies, analysis will be performed at the level of individuals whilst accounting for the clustering in the data using a random-effects model for pooled meta-analysis as recommended in the *Cochrane Handbook* (chapter 16.3.3) (Higgins 2011) and checked by a statistician (AE). For those studies which do not adjust for clustering, the actual sample size will be replaced with the effective sample size (ESS), calculated using a rho = 0.02 as per Campbell 2000.

Cross-over trials

Data from cross-over studies will be extracted for the first phase only (pre-cross-over), due to the potential for a significant carry-over effect for psychological therapies.

Studies with multiple treatment groups

Multi-arm trials will be included provided there is an intervention arm with any of the interventions mentioned in the experimental group above and a control arm with any of comparators mentioned above. In the case of multi-arm trials we will include each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparators. However, if the intervention groups are deemed similar enough to be pooled, the groups will be combined using appropriate formulae in the *Cochrane Handbook* (table 7.7.a for continuous data and chapter 16.5.4 for dichotomous data, (Higgins 2011)).

Dealing with missing data

We will evaluate missing information regarding participants on an available case-analysis basis as described in chapter 16.2.2 of the *Cochrane Handbook* (Higgins 2011). Where statistics essential for analysis are missing (e.g. group means and standard deviations (SDs) for both groups not reported) and cannot be calculated from other data, we will attempt to contact the study authors to obtain the data. We will consider that any loss of participants that would occur before the baseline measurements are performed would not affect the eventual outcome data of the study. Any losses after the baseline measurements are taken may affect trial validity. For drop outs at the initial phase of a trial (by the end of the second week of intervention/placebo administration), we will not include their data and for these studies we will use the final data from the completers only. For participants who drop out after the second week or with unclear drop out time, we will use the last observation carried forward (LOCF), providing we can obtain raw data. If we are unsuccessful, we will report the missing data under 'other' sources of bias in the 'Risk of bias' tables and discuss the details in the text.

Assessment of heterogeneity

We expect this review to have some heterogeneity, contributed by factors such as baseline severity of anxiety, severity of underlying COPD, time of measurement of results and varying measuring tools used to assess outcomes. The Chi^2 and I^2 statistics (Higgins

2011) will be used to quantify inconsistency across studies in combination with visual inspection of the data for differences between studies (e.g. types of interventions, participants etc.) Thresholds for the interpretation of the I^2 statistic can be misleading, since the importance of inconsistency depends on several factors (Higgins 2011). These include magnitude and direction of the effect and strength of the evidence for heterogeneity, for example the P value from the Chi^2 test, or a confidence interval for I^2. For the purpose of this review, we will consider an I^2 statistic representing substantial or considerable heterogeneity for further investigation through subgroup analyses to examine possible causes, as per chapter 9.5.2 of the *Cochrane Handbook* (Higgins 2011). The overlapping bands for the I^2 statistic are:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Providing there are more than ten included studies, we will assess potential reporting biases using a funnel plot. Asymmetry in the plot might be attributed to publication bias, but may well be due to true heterogeneity or a poor methodological design. In case of asymmetry, contour lines may be included corresponding to perceived milestones of statistical significance (P = 0.01, 0.05, 0.1 etc.) to funnel plots, which may help to differentiate between asymmetry due to publication bias from that due to other factors (Higgins 2011). No additional formal testing for funnel plot asymmetry will be performed. If there are fewer than ten studies, the reporting biases will be extrapolated within the 'other bias' section in the 'Risk of bias' tables.

Data synthesis

The extracted data will be pooled in meta-analyses using the random-effects model to allow for expected heterogeneity (due to expected differences in the interventions and populations). All included studies will be assessed for inclusion in the primary analyses, and a sensitivity analysis will be performed for studies which are at an unclear or high risk of bias for sequence generation and allocation concealment, and for studies involving participants who have significant co-morbidities e.g. dementia or severe heart failure. We will perform separate meta-analyses for intervention subgroups as defined under Subgroup analysis and investigation of heterogeneity. For trials reporting data at more than one point in time, we will extract data from the final follow-up period reported by trialists. Data will be analysed using Review Manager (RevMan) 5.2 software (RevMan 2012).

Subgroup analysis and investigation of heterogeneity

We expect that the included studies will be heterogeneous due to multiple factors including baseline severity of anxiety, severity of underlying COPD, duration of intervention and multiple mea- suring tools assessing the same outcome. As such, we have pre- specified subgroups to investigate this heterogeneity to reduce the likelihood of spurious findings, first by limiting the number of subgroups investigated and second by preventing knowledge of the studies' results influencing which subgroups are analysed (Higgins 2011). These contributing factors were identified as relevant in our previous completed review for pharmacological interventions for anxiety in COPD (Usmani 2011). We will describe all included studies in table and narrative form reporting on study design, pop- ulation, intervention characteristics and outcome measures.

We will perform subgroup analyses for the above-mentioned psychological therapies according to:

1. duration of intervention (e.g. 0 to 3 months, 3 to 6 months, > 6 months); and
2. severity of anxiety symptoms (i.e. mild, moderate and severe).

These subgroups will permit an examination into the possible causes of heterogeneity, however their primary objective is to extrapolate data for the purposes of forming hypotheses.

Sensitivity analysis

We will conduct sensitivity analysis to examine the effects of methodological decisions taken throughout the review process, particularly in regard to the inclusion criteria. We will test the validity and robustness of the findings by removing studies based on the following criteria:

1. Inadequate sequence generation;
2. Inadequate allocation concealment;
3. Significant attrition of the study population (20% or higher attrition);
4. Studies on populations with significant co-morbidities;
5. Cluster randomised trials;
6. Cross-over studies;
7. Studies containing data imputed by the review authors.

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Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Additional Search Strategies (CENTRAL and PsycINFO):

CENTRAL search strategy:

#1. MeSH descriptor LUNG DISEASES, OBSTRUCTIVE, this term only
#2. MeSH descriptor PULMONARY DISEASE, CHRONIC OBSTRUCTIVE explode all trees
#3. emphysema*
#4. chronic* near/3 bronchiti*
#5. (obstruct*) near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#6. COPD
#7. COAD
#8. COBD
#9. AECB
#10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11. MeSH descriptor ANXIETY, this term only
#12. MeSH descriptor ANXIETY DISORDERS explode all trees
#13. MeSH descriptor ANXIETY, SEPARATION, this term only
#14. MeSH descriptor PANIC, this term only
#15. MeSH descriptor OBSESSIVE BEHAVIOR explode all trees
#16. MeSH descriptor COMPULSIVE BEHAVIOR explode all trees
#17. MeSH descriptor STRESS, PSYCHOLOGICAL explode all trees
#18. MeSH descriptor NEUROTIC DISORDERS, this term only
#19. (anxiety or phobi* or agoraphobi* or claustrophobi* or PTSD or post-trauma* or posttrauma or (post NEXT trauma*) or (combat NEXT disorder) or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*)
#20. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21. (#10 and #20)

OVID PsycINFO search strategy:

1. Lung Disorders/
2. Pulmonary Emphysema/

3. (chronic* adj3 bronchiti*).mp.
4. emphysema*.mp.
5. (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9
11. exp Anxiety/
12. exp Anxiety Disorders/
13. exp Phobias/
14. exp Neurosis/
15. exp Stress/
16. exp Trauma/
17. Emotional Trauma/
18. Panic Attack/ or Panic/ or Panic Disorder/
19. (anxiety or phobi* or agoraphobi* or claustrophobi* or PTSD or post-trauma* or posttrauma or post trauma* or combat disorder or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*).mp.
20. or/11-19
21. treatment effectiveness evaluation.sh.
22. clinical trials.sh.
23. mental health program evaluation.sh.
24. placebo.sh.
25. placebo*.ti,ab.
26. randomly.ab.
27. randomi#ed.ti,ab.
28. trial*.ti,ab.
29. ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).mp.
30. (control* adj3 (trial* or study or studies or group*)).ti,ab.
31. "2000".md.
32. factorial*.ti,ab.
33. allocat*.ti,ab.
34. assign*.ti,ab.
35. volunteer*.ti,ab.
36. (crossover$ or cross over*).ti,ab.
37. (quasi adj (experimental or random*)).mp.
38. or/21-37
39. (10 and 20 and 38

CONTRIBUTIONS OF AUTHORS

Protocol prepared by Zafar A Usmani, Kristin V Carson and Karen Heslop with feedback provided by Adrian J Easterman, Anthony De Soyza and Brian J Smith.

DECLARATIONS OF INTEREST

Dr De Soyza has received no fees nor grants that relate to anxiety and depression management in COPD. He has received fees for speaker meetings or consultancy work on management of COPD airways disease management from a variety of commercial companies. He has also received financial support from multiple partners in th past to attend national congresses/ symposia and has also had cofunding offers towards a multicentre bronchiectasis grant.

Karen Heslop has received fees for speaker meetings or consultancy work on management of COPD airways disease management from a variety of commercial companies and has received a NIHR Fellowship grant to undertake a RCT of CBT in COPD.

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Chapter 4. Psychological therapies for the treatment of anxiety disorders in COPD (Review)

Literature review and meta-analysis

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Signature		**Date**	27 August 2018

In the previous chapter, the protocol and methods for the planned systematic review and meta-analyses were defined to assess the efficacy of psychological intervention for management of anxiety in COPD patients. In this chapter, the findings after meta-analysing the RCT are reported, which were available up to August 2015, to assess the management of anxiety in the COPD population.

The objective of this systematic review and meta-analysis was to examine the effects of psychological therapies for the treatment of anxiety disorders in people with COPD. This analysis is important in the context of public policy and clinical practice, as the prevalence of anxiety among the COPD cohort is exceptionally high. Therefore, consolidation of this evidence in a well-regarded policy journal, such as the *Cochrane Database of Systematic Reviews*, will provide evidence for use by policy-makers, clinicians and consumers.

Three prospective RCTs were identified for inclusion in this review (319 participants were available to assess the primary outcome of anxiety). All three studies assessed cognitive behavioural therapy plus co-intervention versus co-intervention alone. Due to the small number of included studies identified and the low quality of the evidence, it is difficult to draw any meaningful and reliable conclusions. However, some evidence of improvement in anxiety over three to 12 months was observed, as measured by the Beck Anxiety Inventory, with psychological therapies performing better than the co-intervention comparator arm (mean difference [MD] –4.41 points, 95% confidence interval [CI] –8.28 to –0.53; P = 0.03). We were unable to find a reference for minimal clinical important difference for BAI in COPD patients. However, there was substantial heterogeneity between the studies (I2 = 62%), which limited the ability to draw reliable conclusions. No adverse events were reported.

Given the limitations around the quality of evidence identified, there is a need for methodologically rigorous RCTs that evaluate interventions for management of anxiety in COPD. This was observed in the 'Cochrane Review of Pharmacological Interventions for the Treatment of Anxiety in COPD' (Appendix 1). In an attempt to address this evidence gap, a multi-centre placebo-controlled trial of paroxetine was undertaken for management of anxiety in COPD. This is presented in Chapter 5.

Cochrane Library

Cochrane Database of Systematic Reviews

Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Review)

Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ

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TABLE OF CONTENTS

[Intervention Review]

Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) (commonly referred to as chronic bronchitis and emphysema) is a chronic lung condition characterised by the inflammation of airways and irreversible destruction of pulmonary tissue leading to progressively worsening dyspnoea. It is a leading international cause of disability and death in adults. Evidence suggests that there is an increased prevalence of anxiety disorders in people with COPD. The severity of anxiety has been shown to correlate with the severity of COPD, however anxiety can occur with all stages of COPD severity. Coexisting anxiety and COPD contribute to poor health outcomes in terms of exercise tolerance, quality of life and COPD exacerbations. The evidence for treatment of anxiety disorders in this population is limited, with a paucity of evidence to support the efficacy of medication-only treatments. It is therefore important to evaluate psychological therapies for the alleviation of these symptoms in people with COPD.

Objectives

To assess the effects of psychological therapies for the treatment of anxiety disorders in people with chronic obstructive pulmonary disease.

Search methods

We searched the specialised registers of two Cochrane Review Groups: Cochrane Common Mental Disorders (CCMD) and Cochrane Airways (CAG) (to 14 August 2015). The specialised registers include reports of relevant randomised controlled trials from The Cochrane Library, MEDLINE, Embase, and PsycINFO. We carried out complementary searches on PsycINFO and CENTRAL to ensure no studies had been missed. We applied no date or language restrictions.

Selection criteria

We considered all randomised controlled trials (RCTs), cluster-randomised trials and cross-over trials of psychological therapies for people (aged over 40 years) with COPD and coexisting anxiety disorders (as confirmed by recognised diagnostic criteria or a validated measurement scale), where this was compared with either no intervention or education only. We included studies in which the psychological therapy was delivered in combination with another intervention (co-intervention) only if there was a comparison group that received the co-intervention alone.

Data collection and analysis

Two review authors independently screened citations to identify studies for inclusion and extracted data into a pilot-tested standardised template. We resolved any conflicts that arose through discussion. We contacted authors of included studies to obtain missing or raw data. We performed meta-analyses using the fixed-effect model and, if we found substantial heterogeneity, we reanalysed the data using the random-effects model.

Main results

We identified three prospective RCTs for inclusion in this review (319 participants available to assess the primary outcome of anxiety). The studies included people from the outpatient setting, with the majority of participants being male. All three studies assessed psychological therapy (cognitive behavioural therapy) plus co-intervention versus co-intervention alone. We assessed the quality of evidence contributing to all outcomes as low due to small sample sizes and substantial heterogeneity in the analyses. Two of the three studies had prespecified protocols available for comparison between prespecified methodology and outcomes reported within the final publications.

We observed some evidence of improvement in anxiety over 3 to 12 months, as measured by the Beck Anxiety Inventory (range from 0 to 63 points), with psychological therapies performing better than the co-intervention comparator arm (mean difference (MD) -4.41 points, 95% confidence interval (CI) -8.28 to -0.53; P = 0.03). There was however, substantial heterogeneity between the studies (I^2 = 62%), which limited the ability to draw reliable conclusions. No adverse events were reported.

Authors' conclusions

We found only low-quality evidence for the efficacy of psychological therapies among people with COPD with anxiety. Based on the small number of included studies identified and the low quality of the evidence, it is difficult to draw any meaningful and reliable conclusions. No adverse events or harms of psychotherapy intervention were reported.

A limitation of this review is that all three included studies recruited participants with both anxiety and depression, not just anxiety, which may confound the results. We downgraded the quality of evidence in the 'Summary of findings' table primarily due to the small sample size of included trials. Larger RCTs evaluating psychological interventions with a minimum 12-month follow-up period are needed to assess long-term efficacy.

PLAIN LANGUAGE SUMMARY

Psychotherapy for treatment of anxiety in chronic obstructive pulmonary disease (chronic bronchitis and emphysema)

Why is this review important?

Chronic obstructive pulmonary disease (COPD) is commonly referred to as emphysema and chronic bronchitis. People with COPD are more likely to have anxiety disorders compared with the general population. Symptoms of anxiety affect various aspects of daily life, including quality of life and the ability to perform physical activities. Psychological therapies are used as part of clinical practice to treat these symptoms, however, there is little evidence to support these techniques.

Who will be interested in this review?

Health professionals and people with emphysema and underlying anxiety and panic.

What questions does this review aim to answer?

What is the current evidence on psychological therapies for anxiety in people with COPD and coexisting anxiety?

Which studies were included in the review?

Randomised controlled trials (research trials in which participants are allocated according to a random sequence either to the intervention to be tested or to a comparator intervention).

What does the evidence from the review tell us?

This systematic review found three studies with a total of 319 participants with COPD and coexisting anxiety. All three studies assessed psychotherapy (CBT) with a co-intervention, versus the co-intervention alone. There was limited evidence showing some improvements

in reduced levels of anxiety and improved quality of life in the psychotherapy group. It is important to note that the overall quality of the evidence was low and hence further research is needed to increase our confidence in this effect. A limitation of this review is that all three included studies recruited participants with both anxiety and depression, not just anxiety, which may confound the results.

What should happen next?

Further research is needed to establish whether this therapy will reduce hospital admissions and length of hospital stays, as this was not assessed in the current evidence base. Larger studies of longer duration need to be conducted. There are at least two more clinical trials currently ongoing for this question. Once they are published, the evidence from them could increase or decrease our confidence in the findings of this review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Psychological therapies for anxiety for people with COPD

Patient or population: people with COPD
Settings: hospital and home
Intervention: psychological therapies plus co-interventions for anxiety
Comparators: co-intervention alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Psychological therapies for anxiety				
Anxiety Becks Anxiety Inventory. Scale from: 0 to 63. Follow-up: 3-12 months	The mean anxiety in the control groups was **15.51**	The mean anxiety in the intervention groups was **4.41 lower** (8.28 to 0.53 lower)		319 (3 studies)	⊕⊕◯◯ **low**[1,2]	Beneficial findings were observed in favour of the psychological therapy group (p= 0.03), with levels of anxiety half that of the control population by final follow-up (Gillis 1995)
Adverse events	**Study population**		Not estimable	0 (0)	See comment	No studies reported on adverse events
	See comment	See comment				
	Moderate					

Quality of life - physical composite SGRQ and SF36 Follow-up: 6-12 months	The mean quality of life - physical composite in the control groups was **45.08**	The mean quality of life - physical composite in the intervention groups was **0.40 standard deviations lower** (0.88 lower to 0.08 higher)		289 (2 studies)	⊕⊕◯◯ **low**[1,3]	Two studies reported on quality of life with one study (Kunik 2008) reporting both SF36 and CRQ. Meta-analysis occurred only for SF36 composite scores with SGRQ, as no totals were available for CRQ. Subgroup analyses separating short-term (0 to 3 months; SMD -0.22, 95%CI -0.45 to 0.01; P = 0.06) and long-term follow-up (6 to 12 months; SMD -0.30, 95% CI -0.53 to -0.06; P = 0.01) resulted in better treatment outcomes long-term
Quality of life - emotional composite SGRQ and SF36 Follow-up: 6-12 months	The mean quality of life - emotional composite in the control groups was **52.3**	The mean quality of life - emotional composite in the intervention groups was **0.30 standard deviations lower** (1.03 lower to 0.44 higher)		289 (2 studies)	⊕⊕◯◯ **low**[1,3]	Two studies reported on quality of life with one study (Kunik 2008) reporting both SF36 and CRQ. We only meta-analysed SF36 composite scores with SGRQ as no totals were available for CRQ. Subgroup analyses separating short-term (0 to 3 months; (SMD 0.05, 95% CI -0.18 to 0.28) and long-term follow-up (6 to 12 months; (SMD

					-0.09, 95% CI -0.32 to 0.14) resulted in better treatment outcomes long-term
Exercise capacity 6MWD Follow-up: 3-12 months	The mean exercise capacity in the control groups was **839**	The mean exercise capacity in the intervention groups was **2.78 lower** (58.49 lower to 52.94 higher)		268 (2 studies)	⊕⊕◯◯ **low**[1,4]	The Kunik 2008 study which examined 6MWD at 8 weeks (post-intervention) and again at 12 months' follow-up with a difference in favour of the control arm at 12 months (P = 0.05). However, authors reported that group means at beginning of the follow-up period were not equal (P < 0.01), contributing to the spurious finding

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
6MWD: six minute walking distance; **CI:** confidence interval; CRQ: Chronic Respiratory Questionnaire; SF36: Short Form 36; SGRQ: Saint George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1]Substantial heterogeneity as identified via the I-squared statistic and visual inspection of the data.
[2]Two of the three studies have sample sizes lower than the prespecified optimal sample size, study participants were predominantly men across all three studies and most subjects had comorbid anxiety and depression, therefore imprecision was downgraded by one point.
[3]Both studies had sample sizes lower than the prespecified optimal sample size.
[4]Wide confidence intervals around effect estimate.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a chronic lung condition characterised by the inflammation of airways and irreversible destruction of pulmonary tissue leading to progressively worsening dyspnoea and is a leading international cause of disability and death in adults (Kerstjens 2001). COPD is a preventable and treatable disease with some significant extrapulmonary effects. Its pulmonary component is characterised by airflow limitation that is not fully reversible (GOLD 2013). The diagnosis of COPD is based on the person's history, evaluation of risk factors and relevant investigations, including pulmonary function testing and chest imaging. Spirometry will typically show a post bronchodilator forced expiratory volume 1/forced vital capacity (FEV1/FVC) less than 70% (Rabe 2007). Anxiety disorder is a generalised term for a myriad of abnormal and pathological fear and anxiety states, including generalised anxiety disorder (GAD), panic disorder (PD), agoraphobia, neurocirculatory asthenia, obsessive-compulsive disorder (OCD), and phobic disorders. GAD is defined as excessive anxiety which lasts for at least six months. Individuals must also experience three or more of the following symptoms: difficulty in concentrating; fatigue after little exertion; sleep disturbance; a sensation of being 'keyed up' (nervous or anxious); irritability or muscle tension, or both (Diagnostic and Statistical Manual (DSM) IV criteria) (APA 1994). Other anxiety symptoms can include increased behavioural and psychological symptoms of distress (Suh 2013) and fears (Breland 2015), which is of particular importance as disease-specific fears can have an impact on disability (Keil 2014).

Evidence suggests that there is an increased prevalence of anxiety disorders in people with COPD (Maurer 2008). Moreover, the severity of anxiety has been shown to correlate with the severity of smoking as a coping strategy for anxiety management (Royal College of Physcians). Several risk factors have been identified that contribute to anxiety amongst people with COPD, including being employed, less education, lack of contentment with family support, living with family and friends, comorbid hypertension and depression, and having 10 or more exacerbations per year (Tan 2013). Indeed, co-morbid depression is known to be a strong predictor of anxiety (DiNicola 2013), which confounds anxiety symptoms making treatment more difficult (Atlantis 2013). By compromising health status, mood disorders lead to increased risk of hospitalisation and re-hospitalisation (Gudmundsson 2005) and hence also increase direct and indirect costs to the health system. Various models could be considered to explain increased levels of anxiety and panic in people with COPD (Ley 1985; Perna 2004). One model explains this relationship as catastrophic misinterpretations of ambiguous bodily sensations (such as shortness of breath, rapid heart rate) which increase arousal, creating a positive feedback loop that results in a panic attack (Clark 1986). A crucial difference between physically healthy people and those with COPD is that in the latter, breathing, the most basic of all physical functions necessary for life, is objectively threatened (as measured by tests of lung function) and subjectively difficult. Dyspnoea (shortness of breath) can be an unpleasant and potentially frightening experience at any time, and, as the key symptom of an eventually fatal illness like COPD, it is an ambiguous sensation open to catastrophic interpretation, leading to increased levels of anxiety and panic in people with COPD (Livermore 2010b).

of COPD and the presence of lower Pa@ (partial pressure of oxygen in the blood, an indicator of severity of COPD)(Elassal 2014). Other studies suggest that anxiety can occur at any stage of COPD (Kim 2000; Heslop-Marshall 2014. Studies have suggested prevalence rates for anxiety disorders of 28%-36% in people with COPD (Di Marco 2006; Yohannnes 2006). The lifetime prevalence of GAD in particular amongst people with COPD is estimated at between 10% and 15.8% (Brenes 2003). The prevalence of panic disorder in the COPD population is estimated to be ten times higher than the general population (Smoller 1996; Smoler 1999). Rates of anxiety symptoms in people with COPD range from 13% to 51% and are higher than the rates in people with heart failure, cancer, and other medical conditions (Brenes 2003). COPD is associated with a higher risk of anxiety, and co morbid COPD and anxiety is related to poor health outcomes in terms of exercise tolerance, quality of life, COPD exacerbations (Eisner 2010), inappropriate use of medications and persistence

Description of the intervention

Management strategies for the treatment of anxiety disorders in people with COPD include both pharmacological and non-pharmacological interventions. Evidence that pharmacological therapies (anti-anxiety or antidepressant medications, or both) provide statistically or clinically significant benefits for this group of patients is limited (Usmani 2011). Psychological therapies include cognitive or behavioural therapies, or both, psychodynamic psychotherapy, interpersonal psychotherapy, non-directive therapy, support therapy and counselling (Rose 2002; Davison 2003). Psychological therapies are intentional interpersonal relationships used by trained psychotherapists to aid people with problems of living, with an aim of increasing the individual's well-being. Psychological therapies may also be performed by practitioners with a number of different qualifications, including psychologists, marriage and family therapists, occupational therapists, licensed clinical social workers, counsellors, psychiatric nurses, psychotherapists, trained general nurses, psychoanalysts, and psychiatrists. The mode of delivery for these therapies may comprise individual, group or family (including couple) therapy, performed by a healthcare professional.

How the intervention might work

Because COPD is an irreversible condition, treatment recommendations are aimed at improving quality of life (Norweg 2005). Current evidence examining quality of life suggests a reduction in satisfaction above and beyond what should be expected by COPD disease severity or co-morbid medical illnesses (Coventry 2007), indicating that psychological status plays an intrinsic role in overall well-being. A recent study examining the impact of anxiety on the lives of people with COPD found that they felt isolated and would avoid social occasions and usual daily activities (Willgoss 2011). As a result, therapies targeting the reduction of psychological stressors should be expected to improve quality of life (Ries 1995; Rose 2002; Baraniak 2011).

Psychological therapies are often based on the assumption that psychological outcomes such as anxiety are linked with physical manifestations of COPD, for example dyspnoea, which can precipitate episodes of anxiety (Wu 2004). It has been hypothesised that a person's fear and misinterpretation of bodily experiences from dyspnoea and hyperventilation may cause a panic reaction (Nutt 1999). Alternatively, underlying psychological distress can contribute to an increased risk of symptom exacerbations, particularly those treated in the person's own environment (Laurin 2011). As such, people with anxiety and panic disorders interpret threats as more dangerous due to a higher awareness of cues such as dyspnoea and tachycardia (Mikkelsen 2004).

A psychological therapy, cognitive-behaviour therapy (CBT), aims to identify and correct dysfunctional emotions, behaviours and cognitions through a goal-orientated, systematic procedure (Rose 2002; Kaplan 2009). In the case of people with COPD, CBT may be a means of managing concurrent anxiety and depression. While not in itself improving an individual's medical condition, CBT may serve to increase perceived self-efficacy and motivate people to manage their physical condition, thereby improving quality of life (Kunik 2001). Moreover, the learning about oneself that occurs in various forms of psychological therapy may in itself influence the structure and function of the brain (Kandel 1998) or may have a significant impact on serotonin metabolism (Viinamaki 1998). 'Third wave CBT' applies to behavioural psychological therapies that integrate mindfulness and acceptance of unwanted thoughts and feelings with a behavioural understanding of emotional suffering, to elicit change in thinking process. Behavioural therapy includes methods that focus on behaviours, not the thoughts and feelings that might be causing them. The behavioural approach to therapy assumes that behaviour that is associated with psychological problems develops through the same processes of learning that affect the development of other behaviours. Psychodynamic therapy focuses on unconscious processes as they are manifested in people's present behaviour. Hence by making the unconscious aspects of their life a part of their present experience, psychodynamic therapy helps people understand how their behaviour and mood are affected by unconscious feelings. Humanistic psychotherapy emphasises human uniqueness, positive qualities, and individual potential. It works by emphasising one's capacity to make informed and rational choices and develop to one's maximum potential. Integrative therapies are approaches that combine components of different psychological therapy models.

Why it is important to do this review

Anxiety disorders in people with COPD have been shown to increase disability and impair functional status, resulting in an overall reduction in their quality of life (Beck 1988; Weaver 1997). Importantly, the impact of anxiety on these outcomes was shown after adjusting for other potential confounders such as general health status, other medical conditions and COPD severity (Brenes 2003). Kim 2000 reported that anxiety and depression were more strongly related to functional status than the severity of COPD. Screening data from a large randomised controlled trial in the UK showed anxiety was common in COPD and was not correlated with COPD severity (Heslop-Marshall 2014). Co-morbid anxiety in an elderly population with COPD has been suggested as a signif- icant predictor of the frequency of hospital admissions (Yohannes 2000). A recent study has shown that among people with COPD, anxiety is related to poorer health outcomes including worse sub- maximal exercise performance, greater risk of self-reported func- tional limitations and a higher longitudinal risk of COPD exacerbations (Eisner 2010).

The evidence for treatment of anxiety disorders in COPD is limited, and there are limited data to support the efficacy of medication-only treatments (Borson 1998). The results of a Cochrane Review evaluating the effects of pharmacological interventions for anxiety in people with COPD are inconclusive (Usmani 2011). A feasibility study of antidepressants in this population suggested poor acceptance of antidepressants for various reasons including side-effects and reluctance to take "yet another medication" (Yohannes 2001). Furthermore the association between anxiety/panic and dyspnoea/COPD had been explained by various psychological theories (Clark 1986; Livermore 2010b). It is important therefore, to evaluate psychological therapies for the alleviation of these symptoms in people with COPD.

In light of the health burden caused by psychological disorders and the limited evidence supporting treatment options, this review is one of four linked Cochrane Reviews that assess the effects of pharmacological and psychological therapies for the treatment of anxiety and depression in people with COPD, one of which has already been published (Usmani 2011).

OBJECTIVES

To assess the effects of psychological therapies for the treatment of anxiety disorders in people with chronic obstructive pulmonary disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cross-over trials and cluster-randomised trials.

Types of participants

Participants were adults over 40 years of age (as clinically significant COPD is generally seen in people more than 40 years of age (GOLD 2013)) of either gender and of any ethnicity, diagnosed with COPD and a recognised anxiety disorder or anxiety symptom(s).

The COPD diagnosis needed to have been made objectively, for example, according to GOLD (Global initiative for chronic Obstructive Lung Disease) criteria, or similar criteria (e.g. FEV1/FVC less than 0.70).

The anxiety disorder (e.g. generalised anxiety disorder (GAD), panic disorder (PD), agoraphobia, neurocirculatory asthenia, obsessive-compulsive disorder (OCD), phobic disorders) needed be defined either using established diagnostic criteria, for example, DSM criteria (APA 1994) or anxiety symptoms identified using a formal psychological instrument, for example, Beck Anxiety Inventory (BAI) (Beck 1961; BAI 1993) or Hospital Anxiety & Depression Scale (Zigmond 1983) at the time of recruitment to the trial.

We included participants with co-morbid mental health disorders. Anxiety did not need to be the primary mental health disorder for included participants as long as they had formally diagnosed or symptomatic anxiety (as diagnosed or assessed by a formal criteria or a validated tool).

We excluded studies that only assessed psychological therapies for the treatment of depression in people with COPD, as these will be covered by a separate review.

Types of interventions

We included studies assessing any form of psychological therapy for the treatment of anxiety disorders in people with COPD where this was compared with either no intervention or education only. Studies in which the psychological therapy was delivered in combination with another intervention (co-intervention) were included only if there was a comparison group that received the co-intervention alone.

Experimental interventions:

- Cognitive behavioural therapy (CBT) (e.g. problem solving, rational emotive therapy)
- Third Wave CBT (i.e. acceptance and commitment therapy, compassionate mind training, functional analytic psychotherapy, mindfulness-based cognitive therapy, behavioural activation, meta-cognitive therapy and dialectical behavioural therapy)
- Behavioural therapy (e.g. behaviour modification, assertiveness training)
- Psychodynamic therapy (e.g. insight-oriented therapy, group psychotherapy)
- Humanistic therapy (e.g. expressive therapy, supportive therapy)
- Integrative therapy (e.g. cognitive analytical therapy)

Comparators:

- No intervention (i.e. waiting list and usual care)
- Education only (education (written or oral), such as provision of information about physical and mental health issues during a medical consultation or during a visit with a nurse where no formal counselling or psychological therapy was provided)
- Co-intervention (only if the same co-intervention was used in the intervention arm of the study). The co-interventions considered were pharmacotherapy and pulmonary rehabilitation.

Types of outcome measures

Primary outcomes

- Change in anxiety symptoms as measured by a standardised or validated anxiety measure, for example, State-Trait Anxiety Inventory (STAI) (Spielberger 1970), the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983) and the Beck Anxiety Inventory (BAI) (Beck 1961; BAI 1993). These scales generated a total score which were recorded for all pair-wise comparisons as short-term follow up data (up to and including six months) or long term follow-up data (greater than six months), or both.
- Adverse events

Secondary outcomes

Each of the secondary outcomes were assessed based on a validated assessment scale. The secondary outcomes measured included:

- Change in quality of life, for example, the St George's respiratory questionnaire (SGRQ) (Jones 1991). Generic, validated quality-of-life measures were also considered
- Difference in exercise tolerance, for example, the six-minute walk test (Butland 1982)
- Change in dyspnoea scores, for example, the Borg scale (Borg 1982)
- Change in length of stay or readmission rate
- Change in forced expiratory volume in one second (FEV1)

Timing of outcome assessment

Time frames were defined as short-term (up to three months), medium-term (three to six months) and long-term follow-up

(more than six months). The primary time point used in the 'Summary of findings' table is the longest reported follow-up by each included study. The range of follow-ups for each outcome is described in the 'Summary of findings' table and in the Results section of the review.

Search methods for identification of studies

Electronic searches

Cochrane Specialised Registers

Cochrane Common Mental Disorders Register (CCMDCTR)

Cochrane Common Mental Disorders maintains a specialised register of RCTs, the CCMDCTR. This register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with more than 50% of reference records tagged to c. 12,500 individually PICO-coded study records. Reports of trials for inclusion in the register are collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and review-specific searches of additional databases. Reports of trials are also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) can be found on the Group's website with an example of the core MEDLINE search displayed in Appendix 1.

CCMD's Information Specialist cross-searched the CCMDCTR-Refs and CCMDCTR-Studies registers (to 14 August 2015) using the following terms:

(anxi* or *phobi* or PTSD or post-trauma* or posttrauma or "post trauma*" or "combat disorder" or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*)

AND

((obstruct* and (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or emphysema or (chronic* and bronchiti*))

Cochrane Airways' Register (CAGR)

Cochrane Airways' Specialised Register is also derived from systematic searches of bibliographic databases including: the Cochrane Central Register of Controlled Trials (CENTRAL; in the Cochrane Library), MEDLINE, Embase, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (details of the CAGR can be found on the Group's website).

Cochrane Airways' Information Specialist searched CAGR records coded as 'COPD' for 'Anxiety Disorders' as listed above (14 August 2015).

An additional search of CENTRAL and PsycINFO was conducted at this time, to ensure no records had been missed from these databases in the creation of the CCMDCTR and CAGR (Specialised Registers) (Appendix 2).

Searching the CAGR, CENTRAL and PsycINFO did not retrieve any additional studies beyond those identified by the CCMDCTR, so in 2015 we decided to conduct update searches on the CCMDCTR alone.

National and international trials registers

Complementary searches were conducted on the World Health Organization International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov.

Searching other resources

We handsearched reference lists of retrieved, relevant articles to identify any other potentially relevant articles. We contacted authors of potentially-included studies for raw data or unpublished data where required.

Data collection and analysis

Selection of studies

Two of three review authors (either KC, ZU or KHM) independently assessed all citations generated from the search strategies to determine whether they satisfied the Criteria for considering studies for this review, through screening of the title, abstract and descriptors. Two of three review authors, as above, retrieved and independently examined the full texts of studies identified as potentially relevant for final inclusion. We resolved disagreements through discussion and by involving a third party if necessary (BS or AD).

Data extraction and management

Two independent review authors (a combination of ZU, KC and KHM) extracted the following data using a standardised and piloted data extraction form, for each included study. The review authors resolved any discrepancies by discussion between themselves and if needed, a third party (BS or AD).

Study eligibility

Study design, population group and description of psychological therapy.

Participants

Number of participants, age, gender distribution, ethnicity and co-morbidities.

Interventions

Description of intervention, duration, intensity, who it was delivered by.

Main comparisons

Comparison 1: Psychological therapies versus no intervention
Comparison 2: Psychological therapies versus education
Comparison 3: Psychological therapies and co-intervention versus co-intervention alone
We stratified these comparisons according to psychological therapy, however, we did not perform an overall pooled estimate for intervention effectiveness for all the psychological therapies in each of these comparisons, that is, we used sub-totals only in the analyses.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for all the included studies using the Cochrane tool for assessing risk of bias, which is a domain-based evaluation (Higgins 2011a). We assessed risk of bias as 'Low risk of bias', 'High risk of bias' and 'Unclear risk of bias' as per the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, table 8.5.c (Higgins 2011a). We resolved any conflicts in the assessment either by consensus or by referring to a third party. The domains we evaluated were:

Sequence generation

Methods considered adequate included: random number table, computer random-number generator, coin toss, shuffling cards or envelopes, throwing dice and drawing lots.

Allocation concealment

Methods considered adequate included: central allocation (phone, web, pharmacy), sequentially-numbered identical drug containers and serially-numbered sealed and opaque envelopes.

Blinding (of participants)

We considered blinding adequate if: trial authors mentioned that participants were blinded to the intervention, although for psychological therapies this was unlikely due to the difficulties associated with delivery of communication-based interventions.

Blinding (of outcome assessors)

We considered blinding adequate if: authors mentioned that outcome assessors were blinded to sequence allocation.

Incomplete outcome data

We assessed risk of bias due to incomplete outcome data on the grounds of whether the incomplete outcome data were adequately addressed or not, as per the *Cochrane Handbook for Systematic Reviews of Interventions* section 8.12.

Selective outcome reporting

We considered studies to be at low risk of bias if a protocol was available and all prespecified outcomes were reported in the prespecified way, or in the absence of a protocol, if all expected outcomes were reported (and as per recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, table 8.5.c.

Other bias

We considered studies at a low risk of other bias if they were conducted in such a way as to ensure no other influencing factors that could potentially affect the outcome were evident. Examples of other biases included: extreme baseline imbalances for participants or outcomes, contamination of the intervention or control group, and selective recruitment of study participants.
We have presented the results of the 'Risk of bias' assessment in a 'Risk of bias' table and described them narratively within the results of the review.

Measures of treatment effect

Continuous data

We summarised available data by either mean differences (MD) or standardised mean differences (SMD) where appropriate, using mean values and standard deviations. We consulted a statistician for additional support where required (AE) (Deeks 2011).

Dichotomous data

Had dichotomous data been presented we would have calculated odds ratios with 95% confidence intervals. We would have presented data as either final values (post-intervention) or as change from baseline, if we had not been able to retrieve raw data from the trialists (Deeks 2011).

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised controlled trials, that is, trials in which outcomes relate to individual participants, whilst allocation to the intervention is by hospital, clinic or practitioner, may introduce unit of analysis errors. Using statistical methods that assume, for example, that all participants' chances of benefit are independent, ignores the possible similarity between outcomes for participants seen by the same provider. This may underestimate standard errors and give misleadingly narrow confidence intervals, leading to the possibility of a type 1 error (Altman 1997). For cluster-randomised studies, we performed analyses at the level of individuals, whilst accounting for the clustering in the data using a random-effects model for pooled meta-analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 16.3.3) (Higgins 2011b) (checked by a statistician (AE)). For those studies that did not adjust for clustering, we replaced the actual sample size with the effective sample size (ESS), calculated using a rho = 0.02 (as per Campbell 2000).

Cross-over trials

We extracted data from cross-over studies for the first phase only (pre-cross-over), due to the potential for a significant carry-over effect for psychological therapies.

Studies with multiple treatment groups

We considered multi-arm trials for inclusions provided that there was an intervention arm with any of the interventions men- tioned in the experimental group above and a control arm with any of the comparators mentioned above. In the case of multi- arm trials we included each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparators. However, in cases where the intervention groups were deemed similar enough to be pooled, we combined the groups using appropriate formulae in the *Cochrane Handbook for Systematic Reviews of Interventions* (table 7.7.a for continuous data (Higgins 2011c) and chapter 16.5.4 for dichotomous data, (Higgins 2011b)).

Dealing with missing data

We evaluated missing information regarding participants on an available case-analysis basis as described in chapter 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Had there been statistics essential for analysis missing (e.g. group means and standard deviations (SDs) for both groups not reported) that could not be calculated from other data, we would have attempted to contact the study authors to obtain the data. Any loss of participants that occurred before the baseline measurements were performed would not have affected the eventual outcome data of the study. Any losses after the baseline measurements were taken may have affected trial validity. For dropouts at the initial phase of a trial (by the end of the second week of intervention/placebo administration), we did not include their data and for these studies we used the final data from the completers only. For participants who dropped out after the second week or with unclear dropout time, we used the last observation carried forward (LOCF) as presented in the publications, or had the data been missing we would have obtained raw data. Had we been unsuccessful in obtaining this raw data, we would have reported the missing data under 'other' sources of bias in the 'Risk of bias' tables and discussed the details in the text.

Assessment of heterogeneity

We expected this review to have some heterogeneity, with factors such as baseline severity of anxiety, severity of underlying COPD or consistency of diagnostic thresholds for COPD, or both, time of measurement of results and varying measuring tools used to assess outcomes contributing. We used the Chi^2 (Deeks 2011) and I^2 statistics (Higgins 2003) to quantify inconsistency across studies in combination with visual inspection of the data for differences between studies (e.g. types of interventions, participants etc.). Thresholds for the interpretation of the I^2 statistic can be misleading, since the importance of inconsistency depends on several factors (Deeks 2011). These include magnitude and direction of the effect and strength of the evidence for heterogeneity, for example the P value from the Chi^2 test, or a confidence interval for I^2. For the purpose of this review, we considered an I^2 statistic representing substantial or considerable heterogeneity for further investigation through subgroup analyses to examine possible causes, as per chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). The overlapping bands for the I^2 statistic are:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Since there were fewer than 10 studies, where we identified reporting biases we extrapolated them within the 'other bias' section in the 'Risk of bias' tables. If in future versions of this review we include more than 10 studies in any analysis, we will assess potential reporting biases using a funnel plot. Asymmetry in the plot might be attributed to publication bias, but may well be due to true heterogeneity or a poor methodological design. In case of asymmetry, contour lines may be included corresponding to perceived milestones of statistical significance (P = 0.01, 0.05, 0.1 etc.) to funnel plots, which may help to differentiate between asymmetry due to publication bias from that due to other factors (Sterne 2011).

Data synthesis

We pooled the extracted data in meta-analyses using the random-effects model to allow for expected heterogeneity (due to expected differences in the interventions and populations). We assessed all the included studies for inclusion in the primary analyses, and performed a sensitivity analysis for studies which were at an unclear or high risk of bias for sequence generation and allocation concealment, and for studies involving participants who had significant co-morbidities, for example, dementia or severe heart failure. We performed separate meta-analyses for intervention subgroups as defined under Subgroup analysis and investigation of heterogeneity (Deeks 2011). For trials reporting data at more than one point in time, we extracted data from the final follow-up period reported by trialists. We analysed data using Review Manager 5 (RevMan 5) software (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We have prespecified subgroups to investigate this heterogeneity to reduce the likelihood of spurious findings, first by limiting the number of subgroups investigated and second by preventing knowledge of the studies' results influencing which subgroups are analysed (Deeks 2011). These contributing factors were identified as relevant in our previous completed review for pharmacological interventions for anxiety in COPD (Usmani 2011). We have described all included studies in table and narrative form reporting on study design, population, intervention characteristics and outcome measures.

We performed subgroup analyses for the above-mentioned psychological therapies according to:

- duration of intervention (e.g. 0 to 3 months, 3 to 6 months, > 6 months); and
- severity of anxiety symptoms (i.e. mild, moderate and severe accepting the study authors' definition of this).

These subgroups permit an examination into the possible causes of heterogeneity, however their primary objective is to extrapolate data for the purposes of forming hypotheses.

Sensitivity analysis

Had there been sufficient data we would have conducted a sensitivity analysis to examine the effects of methodological decisions taken throughout the review process, particularly in regard to the inclusion criteria (Deeks 2011). We would have tested the validity and robustness of the findings by removing studies based on the following criteria:

- inadequate sequence generation;
- inadequate allocation concealment;
- significant attrition of the study population (20% or higher attrition);
- studies on populations with significant co-morbidities;
- cluster-randomised trials;
- cross-over studies;
- studies containing data imputed by the review authors.

'Summary of findings' table

As there were only three included studies in this review, the 'Summary of findings' table was limited only to the data reported under comparison 3 (psychological interventions and co-interventions versus co-interventions alone). Follow-up periods presented in the 'Summary of findings' table relate to the final follow-up reported in each study for every outcome measure (range of follow-up is specified in the 'Summary of findings' table). We used only published data to populate information in the 'Summary of findings' table. We used the GRADE approach to assess the quality of evidence (GRADE 2013). The source of all information used in the table is from the publications only. The first four outcomes listed above under Types of outcome measures are the same outcomes used in the 'Summary of findings' table (Schünemann 2011).

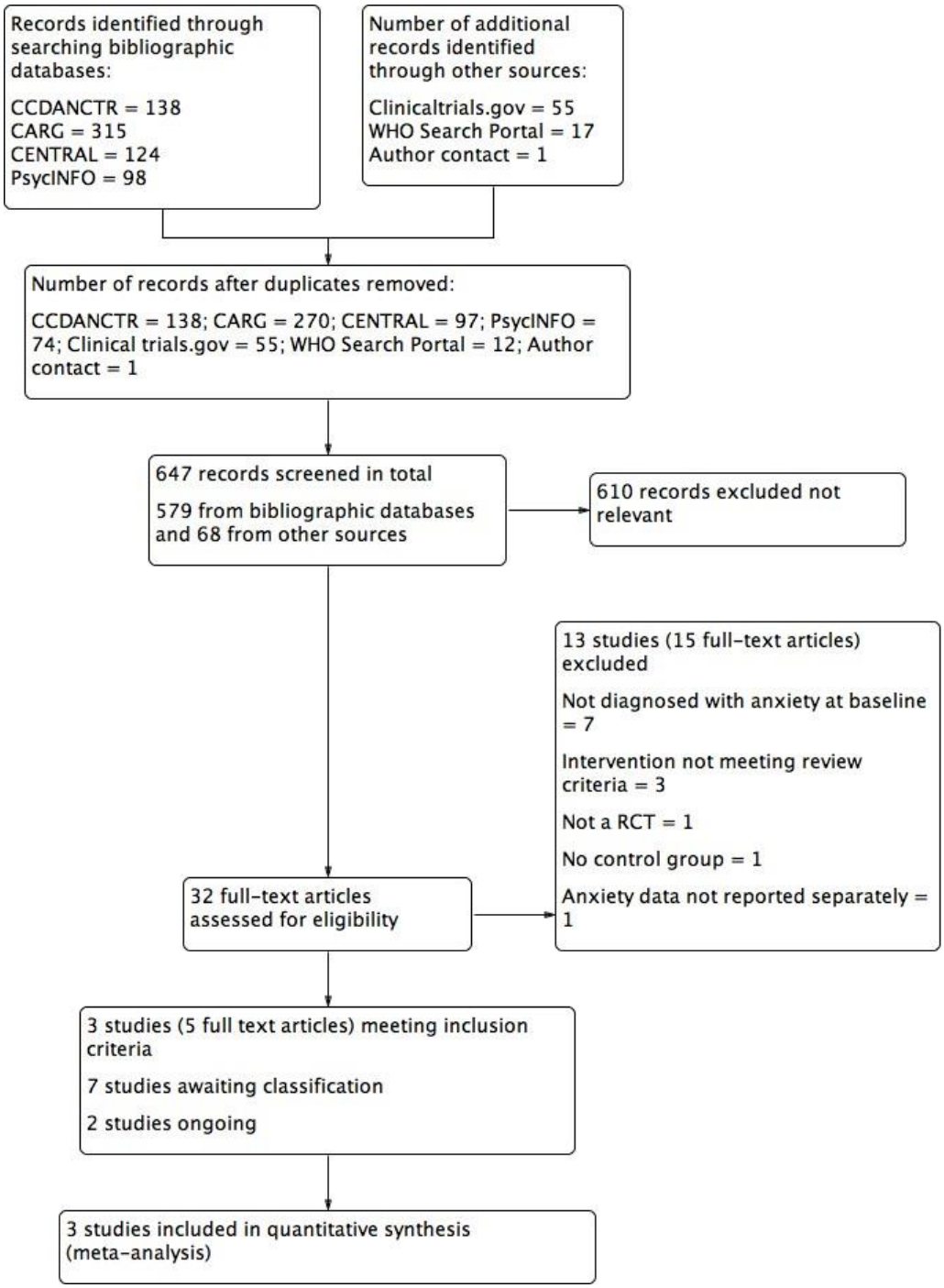
RESULTS

Description of studies

Results of the search

We identified a total of 675 records from searching Cochrane specialised registers and bibliographic databases (to 14th of Aug 2015) with 579 short-listed once duplicates were removed. We retrieved an additional 72 records from screening clinical trials registries and identified one citation via author contact. This resulted in a total of 647 records screened and 32 full-text articles (including online protocols) identified as potentially eligible. From these, we included three studies (five full-text articles) in the final qualitative and quantitative analyses. Seven studies are awaiting classification and two were ongoing at the time of review completion (Figure 1).

Figure 1. Study flow diagram



Included studies

We included three studies in this review, with the following characteristics (see also Characteristics of included studies).

Design

All three studies were single-centre, parallel RCTs coming from Brazil (de Godoy 2003), Norway (Hynninen 2010) and the USA (Kunik 2008).

Sample sizes

Each study reported difficulties with sample size, two being unable to meet the target recruitment number (Kunik 2008; Hynninen 2010) and the third (de Godoy 2003) not reporting a prespecified sample size calculation. Samples sizes ranged from n = 30 in de Godoy 2003, n = 51 in Hynninen 2010 and the largest being n = 238 in Kunik 2008.

Setting

Specific settings for psychological therapies were not described in detail, however two studies did report group settings for intervention delivery with an average of five participants in each session for the Hynninen 2010 study and up to 10 participants in each session for the Kunik 2008 study, whilst the setting for de Godoy 2003 was unclear. Participants of the Kunik 2008 study were recruited from a Veterans Affairs hospital, whilst the Hynninen 2010 study used outpatients from a University hospital and de Godoy 2003 recruited from a pulmonary rehabilitation clinic.

Participants

All three studies recruited people with diagnosed COPD and anxiety using a validated tool. Although all studies recruited participants from the hospital setting, two studies (Kunik 2008; Hynninen 2010) also used external advertisements/flyers to attract participants into the study. The male to female ratio in the Hynninen 2010 study was similar, however there were more men recruited into both the de Godoy 2003 study (22 men and 8 women) and the Kunik 2008 study (226 men and 9 women). Only the Kunik 2008 study reported on participant ethnicity with 192 white, seven Hispanic and 38 black participants recruited. Of the 256 eligible participants for the Kunik 2008 study, 238 were randomised but only 181 attended their first session (24% attrition before the intervention commenced).

Interventions and comparators

de Godoy 2003 used psychotherapy in addition to exercise, physiotherapy and education in comparison to exercise, physiotherapy and education alone. Hynninen 2010 and Kunik 2008 both employed Cognitive and Behavioural Therapy (CBT) in addition to co-interventions of telephone counselling and group discussions for each study respectively. The control population of the Hynninen 2010 study used an enhanced standard care programme for COPD with regular telephone contacts whilst the Kunik 2008 control group received COPD education. Although we defined the control of the Kunik 2008 study to be a co-intervention, it could also have been considered as an education-only intervention. However, due to the small number of included studies in this review (three studies) we classified all studies as co-interventions, which also facilitated meta-analysis and interpretation of results.

Outcomes

All three studies measured anxiety using the Beck Anxiety Inventory (BAI). A number of secondary outcomes were also assessed including depression, quality of life, exercise capacity and service utilisation.

Excluded studies

We excluded 13 of the potentially eligible studies (15 full-text articles) from the review due to no diagnosis of anxiety at baseline (n = 7; Aubuchon 1990; Blake 1990; Gift 1992; Livermore 2010a; Williams 2011; Doyle 2013; Blumenthal 2014), the intervention not meeting the criteria for inclusion as defined in the protocol (n = 3) due to being either an intervention of progressive muscle relaxation without a psychological intervention (Lolak 2008), or due to being a multi-component intervention (Pommer 2012; Yang 2015), and we excluded the remaining three studies because they were not randomised (Cully 2007), did not have a control group (de Godoy 2005) or did not report anxiety data separately (Lamers 2010). See Characteristics of excluded studies.

Ongoing studies

We identified seven studies as ongoing at the time of review completion. See Characteristics of ongoing studies for individual trial details. We identified all the studies through either published protocols in manuscript format or via online clinical trials registries. It is unclear if all inclusion/exclusion criteria as outlined in the protocol of this review will be met for each study due to the limitations in reported data. One study is reported to use mindfulness-based cognitive therapy (Farver-Vestergaard 2014), whilst the remaining six studies specifically report the use of CBT.

Studies awaiting classification

We classified two studies as 'awaiting classification'. One study was a Chinese paper that could not be translated in time for inclusion in this review (Shao 2003). Fifty-four people with COPD were randomised to a behavioural therapy with psychological and somatic components or usual care, however, it is unclear if the presence of baseline anxiety was an inclusion criteria or if people with COPD were formally diagnosed as per the requirements for inclusion within this review (see Characteristics of studies awaiting classification). For the other study (Livermore 2015) there is a question surrounding baseline anxiety scores for individual participants to determine eligibility of subjects for this review. We will continue to attempt to contact the study authors and, if no response has been received by the time of the next update, this study will be moved to the excluded category.

Risk of bias in included studies

For details of the risk of bias judgements for each study, see Characteristics of included studies. We have presented a graphical representation of the overall risk of bias in included studies in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

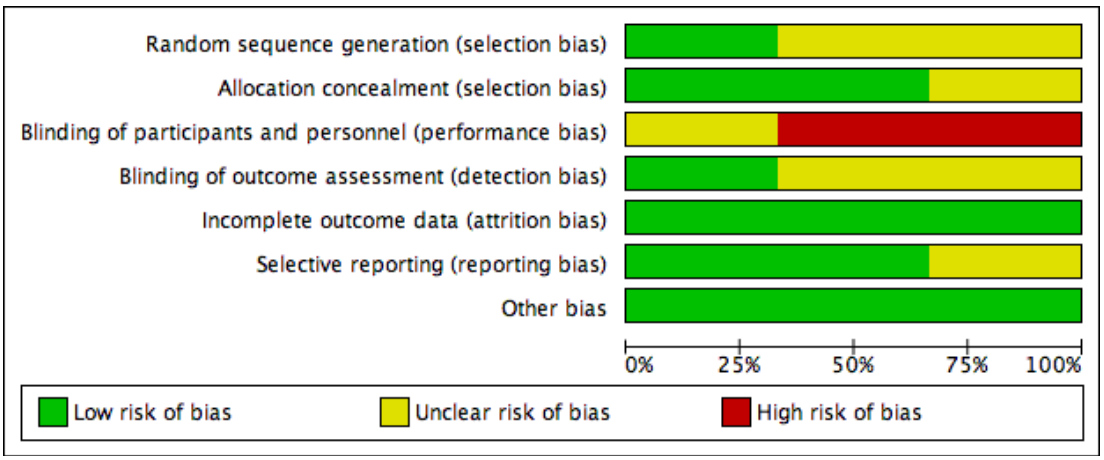
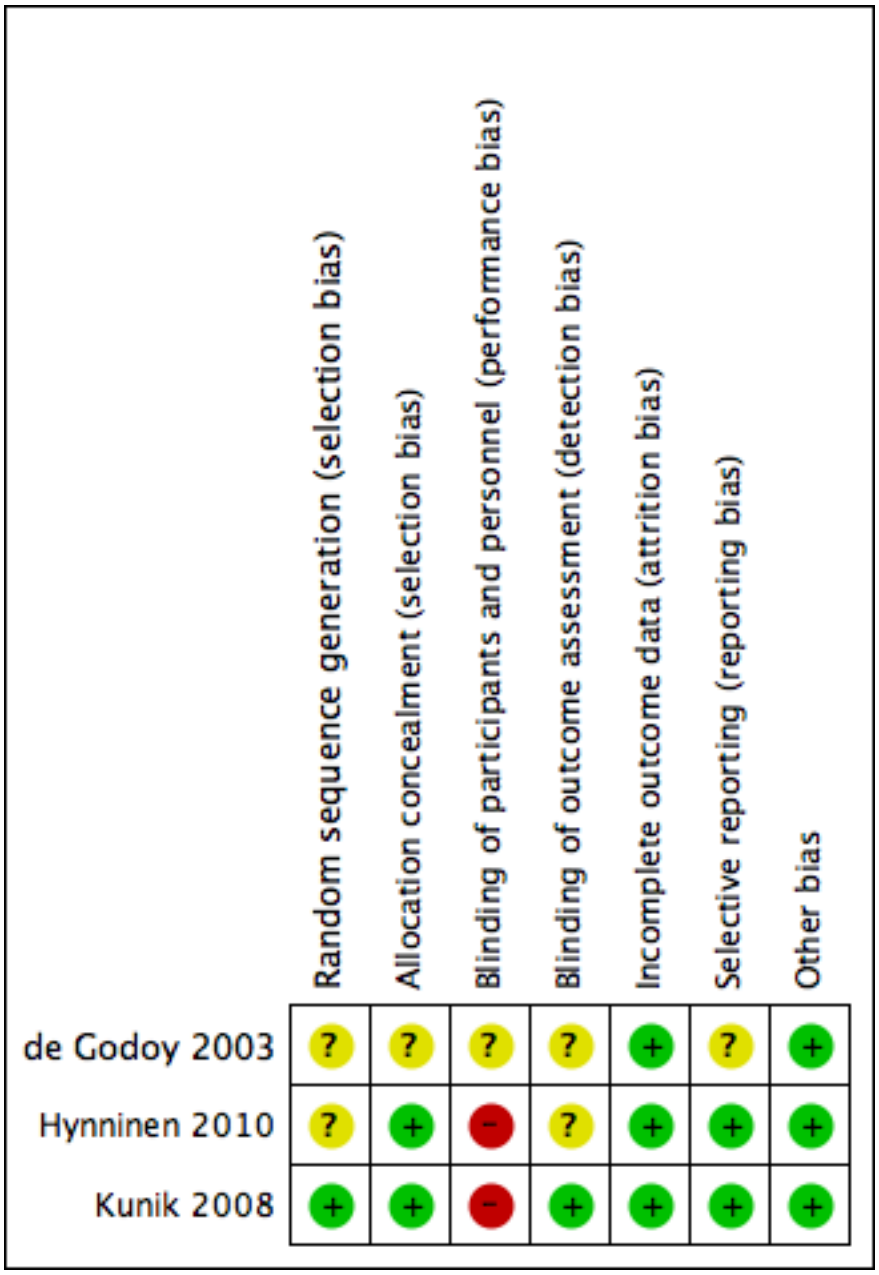


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Sequence generation (selection bias)

Only one study adequately reported on method of sequence generation (Kunik 2008) using a computer program with blocks to provide appropriately equal numbers per class of COPD. The instructor assigned treatment to the code initially through flipping a coin. The two remaining studies reported randomisation as occurring, however, they did not describe their methods in detail.

Allocation

Two studies sufficiently reported allocation concealment using an external statistician to provide treatment codes to the study co-ordinator once sufficient numbers of participants for two classes had been recruited (Kunik 2008) and by using numbered containers that were identical in appearance for the two groups (Hynninen 2010). The de Godoy 2003 study did not report any details of allocation concealment.

Blinding

Blinding of participants and personnel (performance bias)

Blinding to psychological therapies can be challenging unless an active comparator arm, for example, education or sham interventions is included. Two studies did not blind participants or personnel to the treatment allocation, whilst the third study (de Godoy 2003) reported that group 1 was blinded in relation to the activities of group 2 and vice versa.

Blinding of outcome assessors (detection bias)

Outcome assessor blinding was unclear in two studies and assessed to be a low risk of bias in the Kunik 2008 study as authors reported that study personnel performing assessments were blinded to treatment condition.

Incomplete outcome data

All three studies had a low risk of bias for incomplete outcome data as they used intention-to-treat analyses. Moreover, any missing data were reported to be accounted for in the analyses.

Selective reporting

Selective reporting was a low risk in two studies due to the availability of prespecified published protocols, allowing adequate comparison of prespecified outcomes and those reported in the publications. We assessed the de Godoy 2003 study as having an unclear risk of bias due to the inability to review a prespecified protocol.

Other potential sources of bias

Had there been a sufficient number of studies to properly assess reporting bias, we would have assessed potential reporting biases using a funnel plot. Asymmetry in the plot may have been attributed to publication bias, but may well be due to true heterogeneity or a poor methodological design. In case of asymmetry, contour lines would have been included corresponding to perceived milestones of statistical significance (P = 0.01, 0.05, 0.1 etc.) to funnel plots, which may have helped to differentiate between asymmetry due to publication bias from that due to other factors (Higgins 2011a). No additional formal testing for funnel plot asymmetry would have been performed.

Although we defined the control of the Kunik 2008 study to be a co-intervention, it could also have been considered as an education-only intervention. However, due to the small number of included studies in this review (three studies) we pooled all studies together to facilitate meta-analysis.

Effects of interventions

See: **Summary of findings for the main comparison** Psychological therapies for anxiety for people with COPD

Comparison 1: Psychological therapies versus no intervention

There were no data for this comparison.

Comparison 2: Psychological therapies versus education

There were no data for this comparison.

Comparison 3: Psychological therapies and co-intervention versus co-intervention alone

Three studies including 319 participants contributed data to this comparison. See also: Summary of findings for the main comparison.

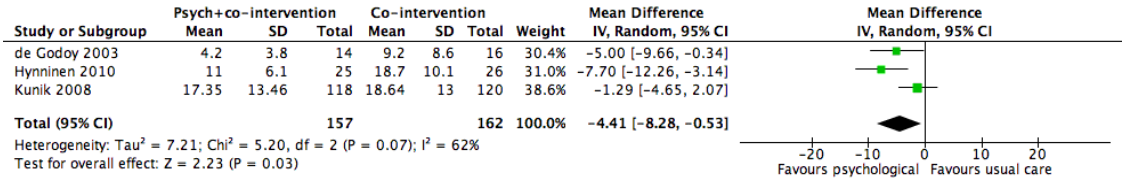
Primary outcomes

Change in anxiety symptoms

Psychological therapies were observed to be more effective for the treatment of anxiety compared with co-interventions or usual care (mean difference (MD) -4.41, 95% confidence interval (CI) -8.28 to -0.53; participants = 319; I^2 = 62%; P = 0.03; Analysis 1.1; Figure 4). However, there was substantial heterogeneity (I^2

= 62%), which limits the reliability of the findings. In the study by de Godoy 2003 the psychotherapy group started with a BAI score of 12.9 ± 6.9, whilst the control population was 10.9 ± 9.8. Authors reported a change from baseline in the intervention arm (P < 0.001), though no change was observed from baseline to follow-up in the control group (9.2 ± 8.6; P = 0.15).

Figure 4. Forest plot of comparison 1: Psychological therapies versus co-intervention, outcome: 1.1 Anxiety



Adverse events

No adverse events were reported for any of the included studies.

Secondary outcomes

Change in quality of life

Two studies with 289 participants reported quality of life through use of three different tools, being SGRQ, SF36 and CRQ. Psychological interventions were observed to be more effective compared to the control population for the combination of SGRQ and the physical composite of SF36 (standardised mean difference (SMD) -0.40, 95% CI -0.88 to -0.08; participants = 289; studies = 2; I^2 = 61%; P = 0.10). No evidence of any effect was observed for SGRQ and the emotional composite of SF36 (SMD -0.30, 95% CI -1.03 to 0.44; participants = 289; studies = 2; I^2= 82%); Analysis 1.2). Of note substantial heterogeneity was observed in these analyses. Alongside SF36, CRQ was also reported in the Kunik 2008 study with only one of the eight categories producing results in favour of the CBT group for general health (end of treatment eight-week score: intervention arm mean 34.14 ± 28.53 and control arm mean 37.76 ± 27.74; P = 0.05).

Difference in exercise tolerance

Compared with the control, there was no significant difference in the number of steps taken as measured by the Six Minute Walking Distance (6MWD) when engaged in psychological therapies: (MD -2.78, 95% CI -58.49 to 52.94, participants = 268; studies = 2; I^2 = 80%; Analysis 1.3). The Kunik 2008 study, which was included in the meta-analysis, examined 6MWD at eight weeks' (post-intervention) and again at 12 months' follow-up with a difference in favour of the control arm at 12 months (P = 0.05). However, the study authors reported that group means at the beginning of the follow-up period were not equal (P < 0.01), contributing to the spurious finding.

Exercise capacity in the psychotherapy group of the de Godoy 2003 study improved almost twice as much from baseline as the control population (P = 0.11). The study authors reported that it may have been the improvement in physical functioning that facilitated improvement in the psychological variables, rather than the psychotherapy itself.).

Change in dyspnoea scores

Only one study (Kunik 2008) reported dyspnoea via CRQ, with an improvement in the CBT group over that of control at eight-week end-of-treatment follow-up (intervention group mean 3.36 ± 1.64; control group mean 3.51 ± 1.59; P = 0.02).

Change in length of stay or readmission rate

No studies provided data specifically on length of stay or hospital readmission rates. However the Kunik 2008 study did indirectly examine this by tracking the number of treatment visits pre and post study. No differences were observed for the ratio of pre treatment to post treatment between groups for outpatient visits, hospital admissions, mental health visits and emergency visits per month, per participant.

Change in forced expiratory volume in one second (FEV1)

No studies reported on FEV1. Whilst FEV1 is helpful to note the severity of COPD, as with most interventions few if any other therapies, including pharmacotherapies significantly improve FEV1 in COPD.

Subgroup analyses

We carried out subgroup analyses for duration of follow-up due to multiple follow-up periods reported in the Kunik 2008 study (eight weeks, i.e. post treatment, and 12 months) and the Hynninen 2010 study (seven weeks and six months). In both anxiety and quality-of-life outcomes, results became better (favoured intervention more) with longer follow-up compared to immediately post treatment. In the case of anxiety, short-term (0 to 3 month follow-up) benefits were seen in favour of the intervention arm with a MD of -3.86; 95% CI of -6.63 to -1.10 and P = 0.006 (I^2 = 19%), whilst these findings were not maintained long-term (6 to 12 months; MD -4.30 with 95% CI of -10.57 to 1.97 and P = 0.18; I^2 = 80%; Analysis 2.1). We did not note any evidence of an effect for exercise capacity (Analysis 2.2) or quality of life (Analysis 2.3, Analysis 2.4), even after sub group analyses.

DISCUSSION

Summary of main results

Based on the small number of included studies within this review (only three), it is difficult to draw any meaningful and reliable conclusions. Some evidence of improvement in anxiety was observed with a benefit in favour of the psychological therapy arm, however, the presence of substantial heterogeneity and low quality of the evidence limits the reliability of these findings. Six-minute walking distance was analysed in two of the three included studies, producing no evidence of any effect. As such there is insufficient information to draw reliable conclusions about whether psychological therapies are beneficial for people with COPD with anxiety (see Summary of findings for the main comparison).

Of note however, sub-group analyses for duration of follow-up for both anxiety and quality of life indicate the potential for greater benefits in favour of the psychological intervention given more time (in the presence of wider confidence intervals due to small number of relevant studies). Although intervention treatment lasted for similar periods of time (eight weeks and seven weeks for the Kunik 2008 and Hynninen 2010 studies respectively), participants within both studies did better at long-term follow-up in comparison to immediately post-intervention. This suggests that psychological interventions may take longer to work than during the treatment phase alone.

Overall completeness and applicability of evidence

A limitation of this review is that all three included studies recruited participants with both anxiety and depression, not just anxiety, which may confound the results, as presence of co-morbid depression may have over estimated or under estimated the effect of intervention in different participants (based on different levels of severity of anxiety and depression), the details of which are out of the scope of this review. Also important to note is that the majority of the participants of this review were men. From the prespecified outcomes identified as being important for this review, none of the three included studies included as an outcome either adverse events or objective markers of lung disease, such as FEV1. Length of stay and readmission rate was also not effectively evaluated in any of the three studies. Considering the small number of included studies and limited reporting for each of the outcomes, the overall completeness and applicability of evidence is poor. As such, findings from this review should be interpreted with caution and the questions posed in this review remain unanswered.

Quality of the evidence

The quality of evidence in this review overall was low, with two of the three studies having prespecified protocols available for comparison to methods, and outcomes reported on within the final publications. Although all studies reported that randomisation occurred, only one provided a description of the methods for sequence generation. Allocation concealment was adequately reported in two studies whilst the third was unclear.

Consistency

Substantial heterogeneity was identified in all meta-analyses across studies, suggesting the possibility of these being true differences in the underlying treatment effect. However, as we only included three studies, it is difficult effectively to examine consistency. As such, the quality of results was downgraded due to inconsistency.

Indirectness

Due to the small number of included studies and broad classification of psychological therapies, it is likely that this review contains indirectness through varying interventions, comparators, populations and even outcomes and the use of different reporting tools.

Imprecision

Imprecision was identified particularly when examining exercise capacity with the presence of wide confidence intervals around the treatment effect. This is of particular concern when there are few studies with few participants attempting to determine the results of

a particular outcome. As such the quality of the 6MWD outcome was downgraded due to imprecision.

Publication bias

It is difficult to determine the presence of publication bias and systematic underestimation or overestimation of the underlying beneficial or harmful effect due to inclusion of only three studies. Screening of online clinical trial registries allows identification of studies regardless of a positive or negative effect for the treatment, which may reduce the possibility of publication bias. The identification of six ongoing studies and one awaiting classification is reassuring, however, there is the possibility of negative studies being missed before publication of protocols became mandatory.

Potential biases in the review process

As the three studies identified for inclusion within the review were from three different countries and different healthcare settings, it is difficult to determine the extent to which the results can be generalised. In particular, all three studies reported issues with either prespecified sample sizes not being met (Kunik 2008; Hynninen 2010) or a small sample limiting the ability to draw reliable conclusions from the results (de Godoy 2003, in which there was no mention of sample size calculations). Authors in the Hynninen 2010 trial reported that, due to the low sample size of their study, it was possible that significant differences had not been detected when they existed. They also reported that it may have been possible to detect a difference on anxiety symptoms due to age if a larger sample size had been achieved. Low recruitment numbers in the Kunik 2008 study was reported to be due to difficulties often occurring with recruitment of Veteran Affairs' patients due to greater prevalence of physical and mental health problems. Authors of the de Godoy 2003 study suggested that, due to the relatively small sample size, the conclusions from their study should only be considered as tentative.

An additional limitation relates to risk of bias categories deemed to be unclear by review authors, as we did not contact individual study authors for clarification or to obtain further information.

Agreements and disagreements with other studies or reviews

Meta-analyses attempting to examine the impact of psychological interventions for anxiety in people with COPD have consistently identified a lack of methodologically rigorous evidence to support treatment efficacy (Rose 2002; Mikkelsen 2004; Baraniak 2011), resulting in the inability to draw reliable conclusions. A 2014 overview examining the prevalence, impact and management of depression and anxiety in COPD also found that the quality of evidence underpinning treatment varied considerably (Panagioti 2014). The authors found that interventions that included pulmonary rehabilitation with or without psychological components improved symptoms of depression and anxiety in COPD. They considered cognitive and behavioural therapy and, though treatment effects were small, they concluded that this type of therapy could potentially lead to greater benefits in anxiety for people with COPD if embedded in multi-disciplinary collaborative frameworks. Another systematic review and meta-analysis of complex interventions for depression and anxiety in COPD identified 28 studies for inclusion (Coventry 2013). Subgroup analyses identified small but non-significant effects on self-reported anxiety symptoms post-treatment for cognitive and behavioural interventions (SMD -0.17; 95% CI -0.35 to 0.01; 7 studies) and relaxation (SMD -0.18; 95% CI -0.67 to 0.30; 3 studies), but observed no evidence of any effect for self-management education (SMD -0.00; 95% CI -0.17 to 0.16; 5 studies). This review observed an improvement with the intervention for multi-component exercise training, though the sample included substantial heterogeneity (SMD -0.47; 95% CI -0.66 to -0.28; P = 0.002; 14 studies; I^2 = 63.3%; Coventry 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the small number of included studies identified for inclusion within this review (only three), it is difficult to draw any meaningful and reliable conclusions. All three included studies recruited participants with both anxiety and depression, not just anxiety (which may confound the results) and compared psychotherapy with co-intervention versus co-intervention alone. Some evidence of improvement in anxiety was observed in the psychological therapy arm, however, the low quality of the evidence and presence of substantial heterogeneity limits our ability to draw any conclusions from these findings.

Implications for research

There is a need for further research trials to evaluate the role of psychotherapy for anxiety in people with chronic obstructive pulmonary disease (COPD) using a population with anxiety symptoms and COPD. Given problems with sample size, participant selection and only one type of psychotherapy in current studies, future researchers might need to consider multi-centre studies with different modalities of psychotherapy other than cognitive behavioural therapy. New research should also assess adverse events, the effect on hospital admissions, length of stay and long-term effects on quality of life produced by psychotherapy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

de Godoy 2003

Methods	Country: Brazil Design: a blinded prospective RCT Multicentre?: no Funders of the trial: supported by the Universidade de Caxias do Sul (BPC level II grant) Duration of trial: October 1999-May 2001 Duration of participation: 12-week programme
Participants	Population description: people with COPD treated at a pulmonary rehabilitation clinic in Brazil; participant's COPD was stratified according to the Brazilian Society of Pulmonology and Tisiology guidelines into 3 severity levels: mild, moderate and severe Setting: all participants were referred from the University's Department of Respiratory Diseases to the Pulmonary Rehabilitation Clinic Inclusion criteria: diagnosis of COPD (corroborated by clinical history, physical examination, spirometry, chest plain films, thoracic computer tomography or both and pulse oximetry Exclusion criteria: physical incapacity to perform the proposed protocol; refusal to participate in the pulmonary rehabilitation programme; lack of adherence to the pulmonary rehabilitation programme due to illness of more than 2 weeks' duration Method of participant recruitment: pulmonary rehabilitation clinic patients Total number randomised: 30 participants Withdrawals and exclusions: no withdrawals mentioned Age: mean age 60.33 Sex: 22 men and 8 women Race/ethnicity: not stated
Interventions	**Intervention** Number randomised to group: 14 Details of the interventions: • 12 psychotherapy sessions including sessions of psychotherapy which addressed the patient's psychosocial needs and included his/her social, marital, work, health, and interpersonal philosophy and habits; cognitive therapy and logotherapy techniques were used during these sessions Intervention intensity: 12-week treatment programme with 12 psychotherapy sessions in addition to co-interventions of 24 physiotherapy sessions, 24 physical exercise sessions and 3 educational sessions Mode of delivery: unclear if intervention was delivered in group settings or to individuals **Co-interventions**: • 24 sessions of exercise (arm and leg exercises, aerobic condition with a treadmill, and flexibility training • 24 sessions of physiotherapy (diaphragmatic breathing, sputum clearance, bending forward postures, pursed-lip breathing, postural drainage, chest percussion, vibration, directed cough and forced expiratory technique was used) • 3 education sessions (including compliance, coping with illness, stress management, anatomy and physiology of the lungs, relaxation and energy-saving

	techniques, drug actions, side effects and technique for administration, good nutrition, use of oxygen, environmental control, intimacy and sexuality, the doctor-patient relationship, smoking cessation, benefits of exercise **Comparison** Comparison name: reported as 'Group 2' in the paper Number randomised to group: 16 Details of the interventions: • 24 sessions of exercise (arm and leg exercises, aerobic condition with a treadmill, and flexibility training) • 24 sessions of physiotherapy (diaphragmatic breathing, sputum clearance, bending forward postures, pursed-lip breathing, postural drainage, chest percussion, vibration, directed cough and forced expiratory technique was used) • 3 education sessions (including compliance, coping with illness, stress management, anatomy and physiology of the lungs, relaxation and energy-saving techniques, drug actions, side effects and technique for administration, good nutrition, use of oxygen, environmental control, intimacy and sexuality, the doctor-patient relationship, smoking cessation, benefits of exercise Intervention intensity: 12-week treatment programme with 24 physiotherapy sessions, 24 physical exercise sessions and 3 educational sessions Mode of delivery: unclear if intervention was delivered in group settings or to individuals
Outcomes	Outcomes collected: BAI, BDI and 6MWD Time points measured: baseline and post-intervention Person collecting time point: not specified Outcome measures validated?: yes for all three Missing data addressed?: not reported
Notes	Note: no mention of a sample size calculation is made but authors do report the "relatively small sample size" as a limitation of the study Funding: Supported by the Universidade de Caxias do Sul (BPC level II grant); No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified "patients were randomised into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Group 1 was blinded in relation to the activities of Group 2 and vice versa

de Godoy 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for choosing not to participate prior to randomisation (n = 6 participants) and attrition post recruitment (n = 3 intervention participants) were reported for all participants
Selective reporting (reporting bias)	Unclear risk	Insuffient information due to lack of prespecified study protocol
Other bias	Low risk	No other biases identified

Hynninen 2010

Methods	Country: Norway Design: prospective RCT Multicentre?: no Funders of the trial: no funding sources mentioned Duration of trial: participants were enrolled over a period of 1.5 years; no other information provided Duration of participation: 8 months from baseline
Participants	Population description: people with COPD who answered positively to at least 2 of the 5 anxiety and depression questions from the PRIME-MD questionnaire Setting: participants in both groups attended the pulmonary clinic at baseline and 2 and 8 months later for spirometry, self-report measures and provision of Actigraph device for sleep registration Inclusion criteria: COPD diagnosis confirmed with post -bronchodilator spirometry FEV1 < 80% predicted and ratio < 0.7, aged 40 years or over, had BAI scores > 15 and/or BDI-II > 13, not participating in other psychological interventions e.g. pulmonary rehabilitation, no cognitive impairment (MMSE score > 23) and no severe psychiatric disorders as per DSMIV Exclusion criteria: as per inclusion criteria Method of participant recruitment: consecutive eligible patients who were interested in participating in the study were recruited from an outpatient clinic at the Haukeland University Hospital, Bergen, Norway or were recruited via a newspaper advertisement Total number randomised: 51 participants Withdrawals and exclusions: intervention arm: 2 discontinued intervention; control arm: 2 could not be contacted and 1 died Age: intervention group: mean 59.3 years; control group: mean 62.6 years Sex: intervention group: 11 women, 14 men; control group: 15 women, 11 men Race/ethnicity: not reported

Interventions	**Intervention** Number randomised to group: 25 (23 received allocated intervention) Details of the interventions: • psychoeducation awareness (how COPD may affect psychological well-being, patterns of anxiety and depression adding to the burden of lung disease) • relaxation (using breathing techniques and postural changes for relaxation and coping with physical symptoms) • cognitive therapy (identifying unhelpful thoughts and explore more functional patterns of thought) • behavioural therapy (identify depressive, passive behaviours and replace them with activities that are pleasant/increase mastery; • fear-based exposure (replace avoidance with graded exposure to increase tolerance) • sleep skills management (learn about sleep hygiene and use skills); CBT was undertaken in the Department of Clinical psychology. The group session was facilitated by two masters-level psychology students; The sessions were videotaped and a specialist in clinical psychology monitored the students' competence Intervention intensity: 7 weekly 2-h sessions Mode of delivery: group sessions (4-6 participants, 5 on average) **Co-interventions** • Participants were phoned 1 and 3 months after post-treatment assessments and encouraged to maintain behavioural changes instigated in therapy **Comparison** Comparison name: Enhanced Standard care for COPD Number randomised to group: 26 (23 received allocated intervention) Details of the interventions: • standard COPD care plus telephone contact every 2 weeks in the intervention period of seven weeks; • the same student therapists conducted the phone calls Intervention intensity: phone calls every 2 weeks for intervention period; Calls lasted 5-10 min Mode of delivery: telephone **Co-interventions** • participants were phoned 1 and 3 months after post-treatment assessments and encouraged to maintain behavioural changes instigated in therapy
Outcomes	Outcomes collected: BAI, BDI, SGRQ, PSQI, Actigraphy (objective measure of sleep efficiency) and CSQ Time points measured: baseline, 2 and 8 months (or baseline, post treatment and six months post treatment) Person collecting time point: not reported Outcome measures validated?: yes for all Missing data addressed?: yes, ITT analysis used and authors report that missing data at one measurement point did not prevent including the individual in the analysis
Notes	Note: the target sample size identified as being necessary in the power analysis (33 in each arm) was not reached by the end of the study period (25 in the intervention arm and 26 in the control arm) Funding: no mention of funding or financial support for this work

Hynninen 2010 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation reported however methods not described
Allocation concealment (selection bias)	Low risk	Allocation concealment was implemented using numbered containers that were identical in appearance for the two groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor therapists were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition reported in participant flow chart. Missing outcome data at one measurement point did not preclude analysis as mixed models with random effect was used for analysis; Intention-to-treat analysis occurred
Selective reporting (reporting bias)	Low risk	Prespecified protocol available and no selective reporting identified
Other bias	Low risk	No other biases identified

Kunik 2008

Methods	Country: USA Design: prospective RCT Multicentre?: no Funders of the trial: grant from Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development; Houston Centre for Quality Care and Utilization Studies and South Central Medical Illness Research, Education and Clinic Center, Department of Veterans Affairs Duration of trial: 11 July 2002-30 April 2005 Duration of participation: 12 months' follow-up from baseline
Participants	Population description: people with a chronic breathing disorder (COPD) who had moderate anxiety symptoms and/or depression and were receiving care at the Michael E DeBakey VA Medical Centre (MEDVAMC) within the year before the study Setting: participants were from the Michael E DeBakey VA Medical Center in Houston, Texas, USA and community members meeting the criteria outside of the medical centre

	Inclusion criteria: diagnosis of COPD confirmed with spirometry (ratio < 70 and FEV1 < 70; according to ATS 1991); moderate anxiety (BAI ≥ 16) and/or depression (BDI > 14); and treatment by primary care or provider or pulmonologist Exclusion criteria: cognitive disorder or evidence of score of 23 or less on MMSE, a psychotic disorder and people with psychotic and non-nicotine substance use disorders Method of participant recruitment: people on administrative database from the Michael DeBakey Medical Center (MEDVAMC) were targeted for recruitment and screened, in addition to other methods including flyers and advertisements Total number randomised: 238 Withdrawals and exclusions: 69 participants dropped out following randomisation(because of the following reasons: medical 2, no time 6,transportation 6,no interest 49, no information 46) Age: Mean 66.3 + 10.2 years Sex: 226 men and 9 women in total Race/ethnicity: white n = 192, Hispanic n = 7 and black n = 38
Interventions	**Intervention** Number randomised to group: 118 (89 attended at least one CBT session) Details of the interventions: • education and awareness training focused on anxiety, depression and associated physiological, cognitive and behavioural symptoms (session 1) • relaxation training (session 2) • increasing pleasurable activity and decreasing anxiety-related avoidance (session 2-3) • cognitive therapy - alternative thoughts, encouraging self statements and thought stopping (session 4-5) • problem-solving techniques (session 6) • sleep management skills (session 7) • skills review and maintenance of gains (session 8) Intervention intensity: eight 1-h sessions Mode of delivery: group CBT (up to 10 participants each session) **Co-interventions** • Group discussion **Comparison** Comparison name: COPD Education Number randomised to group: 120 (92 received the education intervention) Details of the interventions: • COPD education 45 min sessions with similar frequency to CBT group; • Topics included: breathing strategies, airways management, physiology of lung disease, use of oxygen, avoidance of environmental irritants, nutrition, exercise, smoking cessation and end-of-life planning Intervention intensity: eight 45-min lectures and 15-min discussions (to control for contact time) Mode of delivery: group sessions **Co-interventions**: • Group discussion
Outcomes	Outcomes collected: CRQ, SF36, BAI, BDI, 6MWD and service use determined by number of hospitalisations, outpatient, mental health and emergency room visits

	Time points measured: 1 month, 2 months, 4 months, 8 months and 12 months Person collecting time point: not reported Outcome measures validated?: yes, with the exception of service use outcomes Missing data addressed?: Yes, ITT analysis used and authors reported that missing data at one measurement point did not prevent including the individual in the analysis
Notes	Note: of 256 eligible participants, 238 were randomised but only 181 attended their first session. Study authors reported that retention in research studies at that particular facility could often be challenging with patients treated at Veteran Affairs facilities having more physical and mental health problems than the average US citizen. Also, the sample size calculation in the statistical analysis section stated that 120 participants per group would be required yet this n-value was not met Funding: study supported by grant No IIR 00-097 from the Department of Veterans Affairs, Veteran Health Administration, Health Services Research and Development, Washington DC and in part by Houston Center for Quality of Care and Utilization Studies, Office of Research and Development; and the South Central Mental Illness Research, Education and Clinical Center, Department of Veteran Affairs

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list occurred via computer program (SAS) with blocks to provide appropriately equal numbers per class of COPD; instructor assigned treatment to the code initially by flip of coin
Allocation concealment (selection bias)	Low risk	The statistician provided randomisation numbers and treatment codes to the study co-ordinator when sufficient participants for two classes had completed the baseline assessment and consented to participate; the instructor assigned the treatment to the code initially by flipping a coin
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and staff performing the intervention were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study personnel performing assessments were blinded to treatment condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for in regression analyses; reasons for participants' exclusion (pre-enrolment) and attrition of participants post recruitment are reported in detail within the subject flowchart; reasons for

Kunik 2008 (*Continued*)

		exclusion reported
Selective reporting (reporting bias)	Low risk	Pre-specified protocol available and no selective reporting identified
Other bias	Low risk	No other biases identified

6MWD: Six Minute Walking Distance
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
COPD: chronic obstructive pulmonary disease
CRQ: Chronic Respiratory Questionnaire
CSQ: client satisfaction questionnaire
DSMIV: Diagnostic and Statistical Manual of Mental Disorders (4th Ed)
FEV1: forced expiratory volume in 1 second
ITT: intention-to-treat
MMSE: Mini-Mental State Examination
PRIME-MD: Primary Care Evaluation of Mental Disorders
PSQI: Pittsburgh Sleep Quality Index
RCT: randomised controlled trial
SGRQ: Saint George's Respiratory Questionnaire
SF36: Medical Outcomes Survey Short Form 36

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aubuchon 1990	Participants not diagnosed with anxiety at baseline
Blake 1990	Participants not diagnosed with anxiety at baseline (diagnosed with stress) and not COPD-specific
Blumenthal 2014	Participants not diagnosed with anxiety at baseline
Cully 2007	Not a RCT as defined for this review
de Godoy 2005	No adequate control group: co-intervention in groups 1 and 3 was an exercise regimen, which was not a prespecified co-intervention for this review
Doyle 2013	Participants not diagnosed with anxiety at baseline. No intervention arm
Gift 1992	Participants not diagnosed with anxiety at baseline
Lamers 2010	Anxiety data not reported separately

(*Continued*)

Livermore 2010a	Participants not diagnosed with anxiety at baseline and mean HADS scores are with normal range
Lolak 2008	Progressive muscle relaxation, not psychological intervention
Pommer 2012	Multi-component intervention, more than just a psychological intervention
Williams 2011	Participants not diagnosed with anxiety at baseline
Yang 2015	Multi-component intervention, more than just a psychological intervention

COPD: chronic obstructive pulmonary disease
HADS: Hospital Anxiety and Depression Scale
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bove 2015

Methods	Parallel RCT
Participants	N = 66 subjects with severe COPD and associated anxiety randomised Exclusion criteria: HADS-A (anxiety) subscale score of < 8, a psychiatric diagnosis, pulmonary cancer or involvement in a different interventional trial
Interventions	Single psycho-educative session in the participant's home in combination with a telephone booster session; intervention based on a manual, with theoretical foundation in CBT and psychoeducation Usual care comparator
Outcomes	Primary outcomes: HADS-A (anxiety) and HADS-D (depression) Secondary outcomes: CRQ and SGRQ for quality of life and mastery of dyspnoea
Notes	Part of a PhD project

Cully 2012

Methods	Parallel RCT
Participants	N= 320 participants with patient-reported functional limitations associated with COPD, and/or heart failure, with clinically significant symptoms of anxiety and/or depression Exclusion criteria: clinical factors e.g. ongoing psychotherapy, concurrent speciality mental healthcare and patient factors e.g. cognitive, bipolar, psychotic or substance abuse disorders
Interventions	Brief manualised CBT delivered by clinicians in comparison to usual care Intervention group: 6 weekly treatment sessions and 2 brief (10-15-min) telephone booster sessions within a 4-month time frame of the ACCESS

Cully 2012 (*Continued*)

	Intervention: core modules focus on increasing awareness and controlling physical and emotional symptoms and subsequently producing skills aligning with their most pressing needs; therapists used a structured manual yet could also tailor the intervention with the participant based on their needs; participant workbook also provided Control group: usual care with feedback about their depression and anxiety
Outcomes	Participant outcomes: depression, anxiety and physical health functioning Implementation outcomes: participant engagement, adherence and clinician brief CBT adoption and fidelity
Notes	

Farver-Vestergaard 2014

Methods	Double-blind RCT
Participants	Estimated n = 120 participants with severe to very severe COPD, motivated to participate in pulmonary rehabilitation and with sufficient mobility to attend pulmonary rehabilitation Exclusion criteria: certain co-morbidities (e.g. unstable coronary complications, psychiatric illness), severe cognitive disability (e.g. dementia) and inability to speak Danish
Interventions	Mindfulness-based cognitive therapy + pulmonary rehabilitation compared to pulmonary rehabilitation only Intervention group: 8-week manual-based programme developed by Segal, Williams and Teasdale (2013) adjusted to the COPD population; programme delivered as an add-on to an 8-week standardised rehabilitation programme consisting of physical exercise and COPD-specific patient education Control group: 8-week standardised rehabilitation programme consisting of physical exercise and COPD-specific patient education
Outcomes	Primary outcomes: quality of life (CAT), anxiety and depression (HADS), and BODE index Secondary outcomes: physical activity (measured by accelerometry), inflammation and oxidative stress (measured by gene expression profiling)
Notes	

Heslop 2013

Methods	Parallel RCT
Participants	N = 312 participants with a confirmed diagnosis of COPD (FVC/FEV1 ratio < 70%, (NICE 2010); including mild-moderate (FEV1 > 50% predicted) and severe-very severe (< 50% predicted)), probable anxiety defined by HADSA > 8, willing to participate and provide informed consent, agreed to attend minimum of 2 and maximum of 6 CBT sessions Exclusion criteria: people with HADS-A scores < 8, known psychosis or personality disorders, currently receiving psychological therapy including counselling or psychotherapy, unable to engage in CBT (due to cognitive impairment or dementia) and limited verbal and/or written communication problems
Interventions	Psychological treatment for anxiety and depression through CBT compared to self-help leaflets Intervention group: 2-6 sessions depending on participant need and progress as per HADS (usually involved 1 session of CBT every two weeks); components of CBT included developing a CBT formulation, psychoeducation about COPD with panic/depression, identifying/challenging negative or unhelpful thinking, identifying challenging

Heslop 2013 (*Continued*)

	negative or unhelpful behaviours, distraction, breathing control, relaxation, mindfulness, behavioural experiments and graded exposure Control group: self-help leaflets
Outcomes	Primary outcome: HADS (3 months) Secondary outcomes: HADS (6 and 12 months)
Notes	

Livermore 2015

Methods	RCT
Participants	People with moderate to severe COPD
Interventions	CBT (4 sessions) versus usual care
Outcomes	Dyspnea scores
Notes	We have tried to contact the study authors to get more information in regards to the baseline anxiety scores of the individual participants to assess the eligibility of some of the participants for this review. We will continue intermittent attempts at contact and if no response has been received by the time of the next update, this study will be moved to the excluded category

Phan 2015

Methods	Parallel, multi-arm RCT
Participants	N = 128 people attending the COPD outpatient community clinics in Perth, Western Australia were included if they had a diagnosis of COPD confirmed from medical records and screened positive for anxiety and depression Exclusion criteria: life expectancy of less than 6 months, were currently involved in another research study, had an illness exacerbation resulting in hospitalisation within the previous month, were not fluent in English, or were blind, deaf or diagnosed with dementia or Alzheimer's disease
Interventions	Six weeks of 2 formats of CBT, being group therapy (6-16 people in each group) versus a self-paced simulation-based learning resource (DVD) compared to usual care; group therapy consisted of 2 half-day sessions a fortnight apart and a 1-hour telephone booster session 4 weeks later; the sessions were semi-structured in nature and included both CBT global concepts and those that were specific to people with COPD; a manual was provided to participants for referral to CBT concepts; CBT included information about treatment rationale explaining the link between cognitions, behaviours and breathing, coping skills training, cognitive restructuring and the application and maintenance of learned coping skills; The self-paced simulation included 6 vignettes (participants were asked to watch one per week) approximately 10 min in length on CBT skills to cope with anxiety disorders and depression, a resource manual to guide participants through the video and a weekly phone call by a researcher to check if each vignette was watched, activities completed and if participants had any questions Usual care group was under the usual treating physician; telephone follow-up (or home visits for those with hearing difficulties) occurred at one week post-intervention completion, 3, 6, 9 and 12 months

Phan 2015 (*Continued*)

Outcomes	Primary outcomes: BAI and BDI Secondary outcomes: SGRQ, absolute FEV1, FEV1 % predicted, FVC
Notes	

Shao 2003

Methods	The aim of the study was to explore the effect of behavioral intervention on the quality of life among people with COPD during the remission period
Participants	54 people with COPD were randomly divided into intervention group and control group
Interventions	The 2 groups were treated with the same clinical therapy. The intervention group was also given a behavioral intervention that included psychological therapy with a somatic function and lifestyle intervention
Outcomes	All participants were evaluated with the Fang Zhong-Jun quality-of-life scale pretreatment, before discharge, 3 months and 1 year after discharge
Notes	Results: at 1 year follow-up, quality of life (measured as 'ability of daily life' and 'status of social activity'), psychological symptom of depression, and psychological symptom of anxiety in the intervention group (2.03 +/- 0.32, 2.29 +/- 0.77, 2.36 +/- 0.34, 2.07 +/- 0.25) were significantly lower than those in the control group (2.29 +/- 0.30, 2.39 +/- 0.41, 2.41 +/- 0.28, 2.16 +/- 0.51), ($t = 2.801, 2.914, P < 0.01$, $t = 2.250, 2.340, P < 0.05$)

ACCESS: Adjusting to Chronic Conditions Using Eucation, Support, and Skills
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
BODE: Body mass index, airflow Obstruction, Dyspnea and Exercise capacity
CAT: COPD Assessment Text
CBT: cognitive behavioural therapy
COPD: chronic obstructive pulmonary disease
CRQ: Chronic Respiratory Questionnaire
HADS-A: Hospital Anxiety and Depression Scale - Anxiety Subscale
HADS-D: Hospital Anxiety and Depression Scale - Depression Subscale
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
RCT: randomised controlled trial
SGRQ: Saint George's Respiratory Questionnaire

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12612000254897

Trial name or title	Telephone Cognitive Behavioural Therapy for the treatment of depression and anxiety associated with chronic obstructive pulmonary disease: a pragmatic randomised controlled trial
Methods	Parallel RCT
Participants	N = 140 participants over 45 years of age, with a HADS score of > 8 and a PHQ-9 score > 10, with a diagnosis of COPD, living in the community and able to speak English Exclusion criteria: people who commenced anti-depressants and/or anxiolytics in the past 3 months or have had a clinically significant change in this medication in the last 3 months and deafness
Interventions	Telephone administered Cognitive Behavioural Therapy (CBT) plus usual care Control population not specified Intervention group: starts with a face-to-face 50-min session at the outpatient clinic or participant's home followed by 8 scheduled weekly telephone calls for up to 30 min in length Intervention includes behavioural strategies such as behavioural activation, activity scheduling, relaxation training, exposure hierarchies and social skills training, as well as cognitive strategies, such as cognitive re-structuring, structured problem solving and behavioural experiments
Outcomes	Primary outcomes: BAI and PHQ-9 (depression scale) Secondary outcomes: costs of illness (including medical treatment, equipment and working hours), quality of life (AQoL-4D), client satisfaction, COPD assessment test, General Self-Efficacy scale, Working Alliance Inventory, acute hospitalisations, number of pulmonary rehabilitation attendances
Starting date	February 2012
Contact information	Colleen Doyle; +61 3 8387 2169; c.doyle@nari.unimelb.edu.au; National Ageing Research Institute 34-54 Poplar Rd Parkville Victoria 3052, Australia
Notes	

ACTRN12614000915651

Trial name or title	Randomised controlled trial of a brief telephone based cognitive behavioural therapy (CBT) for patients with chronic lung disease and anxiety and/or depression undergoing pulmonary rehabilitation to evaluate the effect on quality of life, symptoms of anxiety and depression, and exacerbation rate
Methods	Parallel RCT
Participants	N = 100 participants with chronic lung disease, undergoing pulmonary rehabilitation and clinical or sub-clinical anxiety or depression defined by GAI score ≥ 4/20, and/or GDS of ≥ 4/15 Exclusion criteria: inability to provide written informed consent, known psychotic disorder, cognitive impairment determined by MOCA score of < 25/30 and current enrolment in other interventional clinical trials that would potentially interfere with this study
Interventions	6 CBT sessions administered by psychology interns compared to usual care Intervention group: 6 CBT sessions divided into: 2 face-to-face individual sessions of 1 h each, within the

ACTRN12614000915651 (*Continued*)

	first 4 weeks of pulmonary rehabilitation; 4 phone sessions of 60 min each undertaken for counselling, each session will be fortnightly within the first 2 months after the face-to-face sessions; CBT intervention will be standardised following a manual written by the Prince Charles Hospital psychology department Control group: usual care comprised of medical treatment and pulmonary rehabilitation
Outcomes	Primary outcomes: symptoms of anxiety using GAI and depression using GDS Secondary outcomes: 6MWD, SGRQ, Asthma Quality-of-Life Questionnaire, Asthma Control Questionnaire, primary care and hospital health service utilisation, pulmonary rehabilitation attendance and participation assessment
Starting date	September 2014
Contact information	A/Prof Ian Yang; +61-7-31395050; Ian.Yang@health.qld.gov.au; The Prince Charles Hospital Rode Road Chermside, Postcode 4032 Queensland, Australia; and Dr Marsus I Pumar; +61 04 37739874; marsusicaro@gmail.com; The Prince Charles Hospital Rode Road Chermside, Postcode 4032 Queensland, Australia
Notes	

6MWD: Six Minute Walking Distance
BAI: Beck Anxiety Inventory
CBT: cognitive behavioural therapy
COPD: chronic obstructive pulmonary disorder
GAI: Geriatric Anxiety Inventory
GDS: Geriatric Depression scale
HADS: Hospital Anxiety and Depression Scale
MOCA: Montreal Cognitive Assessment (MOCA)
PHQ-9: Patient Health Questionnaire-9
SGRQ: Saint George's Respiratory Questionnaire

DATA AND ANALYSES

Comparison 1. Psychological therapies versus co-intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anxiety	3	319	Mean Difference (IV, Random, 95% CI)	-4.41 [-8.28, -0.53]
2 Quality of life	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 SGRQ and SF36 Physical composite	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.88, 0.08]
2.2 SGRQ and SF36 Emotional composite	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.03, 0.44]
3 Six minute walking distance	2	268	Mean Difference (IV, Fixed, 95% CI)	-2.78 [-58.49, 52.94]

Comparison 2. Duration of intervention sub-group analyses - psychological therapies versus co-intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anxiety	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short-term (0 to 3 months)	3	319	Mean Difference (IV, Random, 95% CI)	-3.86 [-6.63, -1.10]
1.2 Long term (6 to 12 months)	2	289	Mean Difference (IV, Random, 95% CI)	-4.30 [-10.57, 1.97]
2 Six minute walking distance	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Short-term (0 to 3 months)	2	268	Mean Difference (IV, Random, 95% CI)	29.35 [-30.13, 88.82]
2.2 Long-term (6 to 12 months)	2	268	Mean Difference (IV, Random, 95% CI)	-30.08 [-170.92, 110.77]
3 Quality of life - SGRQ and SF36 Physical composite	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Short-term (0 to 3 months)	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.73, 0.13]
3.2 Long-term (6 to 12 months)	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.88, 0.08]
4 Quality of life - SGRQ and SF36 Emotional composite	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Short-term (0 to 3 months)	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.93, 0.60]
4.2 Long-term (6 to 12 months)	2	289	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.03, 0.44]

Analysis 1.1. Comparison 1 Psychological therapies versus co-intervention, Outcome 1 Anxiety.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 1 Psychological therapies versus co-intervention

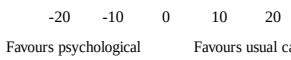
Outcome: 1 Anxiety

Study or subgroup	Psych+co-intervention N	Mean(SD)	Co-intervention N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
de Godoy 2003	14	4.2 (3.8)	16	9.2 (8.6)		30.4 %	-5.00 [-9.66, -0.34]
Hynninen 2010	25	11 (6.1)	26	18.7 (10.1)		31.0 %	-7.70 [-12.26, -3.14]
Kunik 2008	118	17.35 (13.46)	120	18.64 (13)		38.6 %	-1.29 [-4.65, 2.07]
Total (95% CI)	**157**		**162**			**100.0 %**	**-4.41 [-8.28, -0.53]**

Heterogeneity: $Tau^2 = 7.21$; $Chi^2 = 5.20$, df = 2 (P = 0.07); $I^2 = 62\%$

Test for overall effect: Z = 2.23 (P = 0.026)

Test for subgroup differences: Not applicable

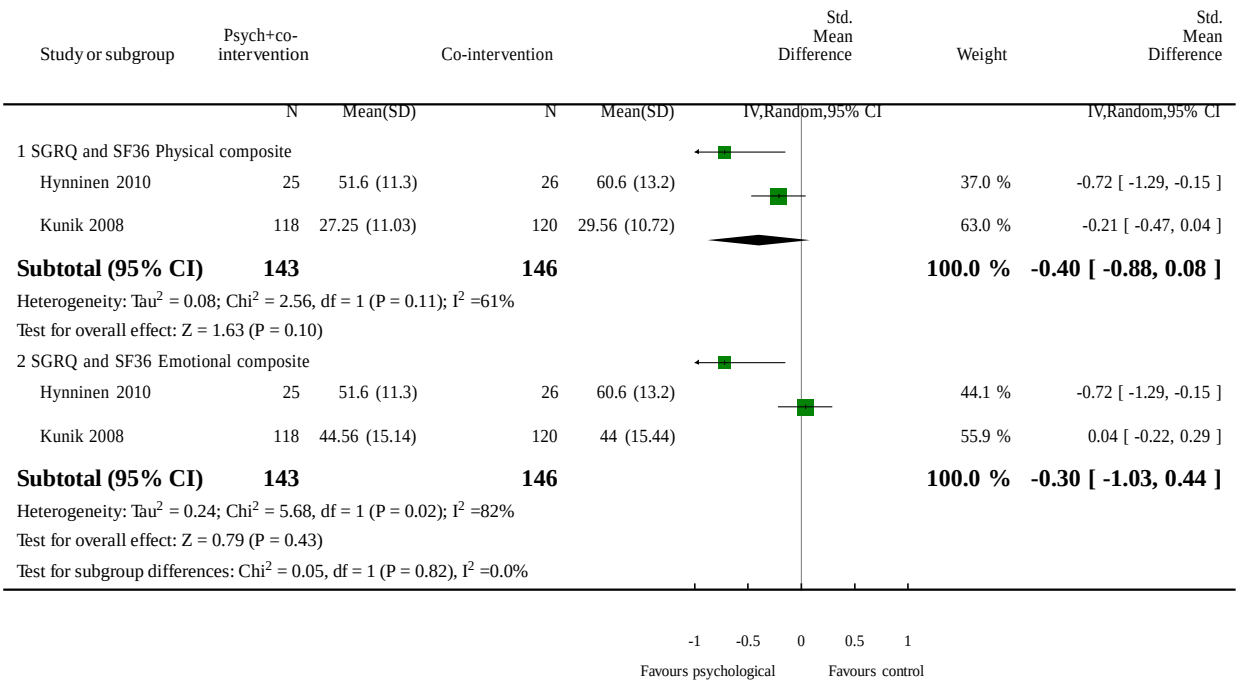


Analysis 1.2. Comparison 1 Psychological therapies versus co-intervention, Outcome 2 Quality of life.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 1 Psychological therapies versus co-intervention

Outcome: 2 Quality of life



Analysis 1.3. Comparison 1 Psychological therapies versus co-intervention, Outcome 3 Six minute walking distance.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 1 Psychological therapies versus co-intervention

Outcome: 3 Six minute walking distance

Study or subgroup	Psych+co-intervention N	Mean(SD)	Co-intervention N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
de Godoy 2003	14	506.1 (86.8)	16	470.8 (94.6)		73.6 %	35.30 [-29.63, 100.23]
Kunik 2008	118	1097.62 (447.14)	120	1206.69 (405.36)		26.4 %	-109.07 [-217.55, -0.59]
Total (95% CI)	**132**		**136**			**100.0 %**	**-2.78 [-58.49, 52.94]**

Heterogeneity: Chi^2 = 5.01, df = 1 (P = 0.03); I^2 =80%

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

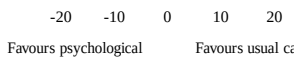
Analysis 2.1. Comparison 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention, Outcome 1 Anxiety.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention

Outcome: 1 Anxiety

Study or subgroup	Psych+co-intervention		Co-intervention		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Short-term (0 to 3 months)							
de Godoy 2003	14	4.2 (3.8)	16	9.2 (8.6)		29.3 %	-5.00 [-9.66, -0.34]
Hynninen 2010	25	12.7 (6.8)	26	18.7 (10)		29.1 %	-6.00 [-10.68, -1.32]
Kunik 2008	118	15.89 (14.87)	120	17.46 (14.54)		41.6 %	-1.57 [-5.31, 2.17]
Subtotal (95% CI)	**157**		**162**			**100.0 %**	**-3.86 [-6.63, -1.10]**
Heterogeneity: $Tau^2 = 1.16$; $Chi^2 = 2.47$, df = 2 (P = 0.29); $I^2 = 19\%$							
Test for overall effect: Z = 2.74 (P = 0.0062)							
2 Long term (6 to 12 months)							
Hynninen 2010	25	11 (6.1)	26	18.7 (10.1)		47.0 %	-7.70 [-12.26, -3.14]
Kunik 2008	118	17.35 (13.46)	120	18.64 (13)		53.0 %	-1.29 [-4.65, 2.07]
Subtotal (95% CI)	**143**		**146**			**100.0 %**	**-4.30 [-10.57, 1.97]**
Heterogeneity: $Tau^2 = 16.37$; $Chi^2 = 4.92$, df = 1 (P = 0.03); $I^2 = 80\%$							
Test for overall effect: Z = 1.34 (P = 0.18)							
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.90), $I^2 = 0.0\%$							

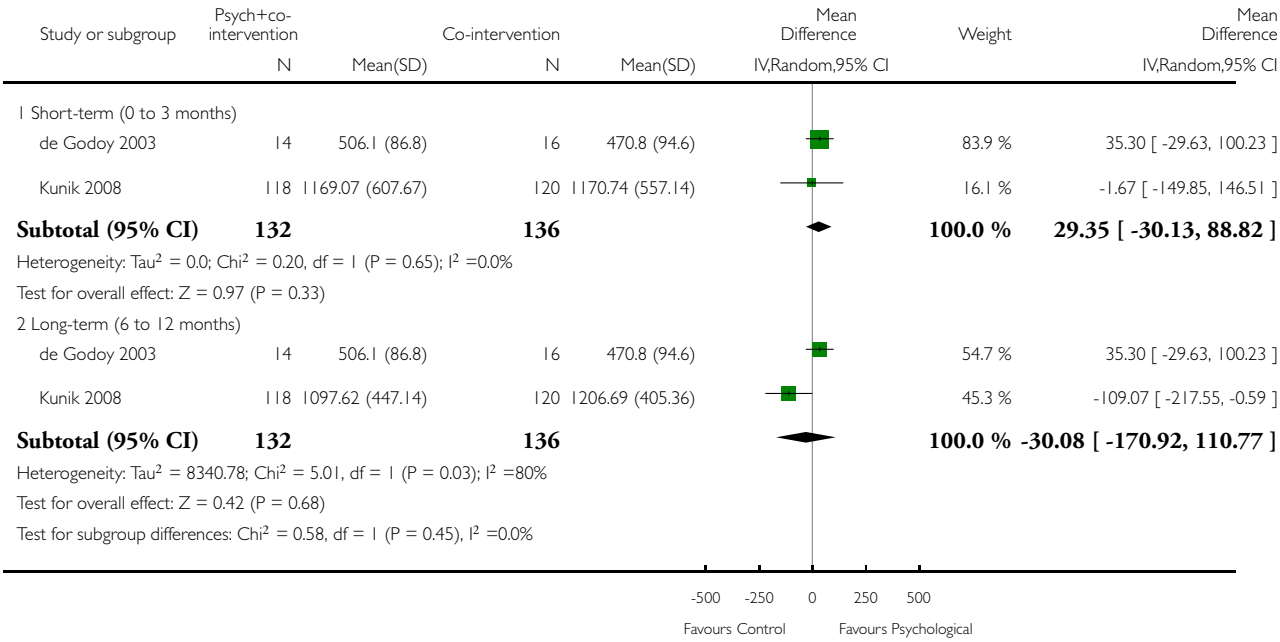


Analysis 2.2. Comparison 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention, Outcome 2 Six minute walking distance.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention

Outcome: 2 Six minute walking distance

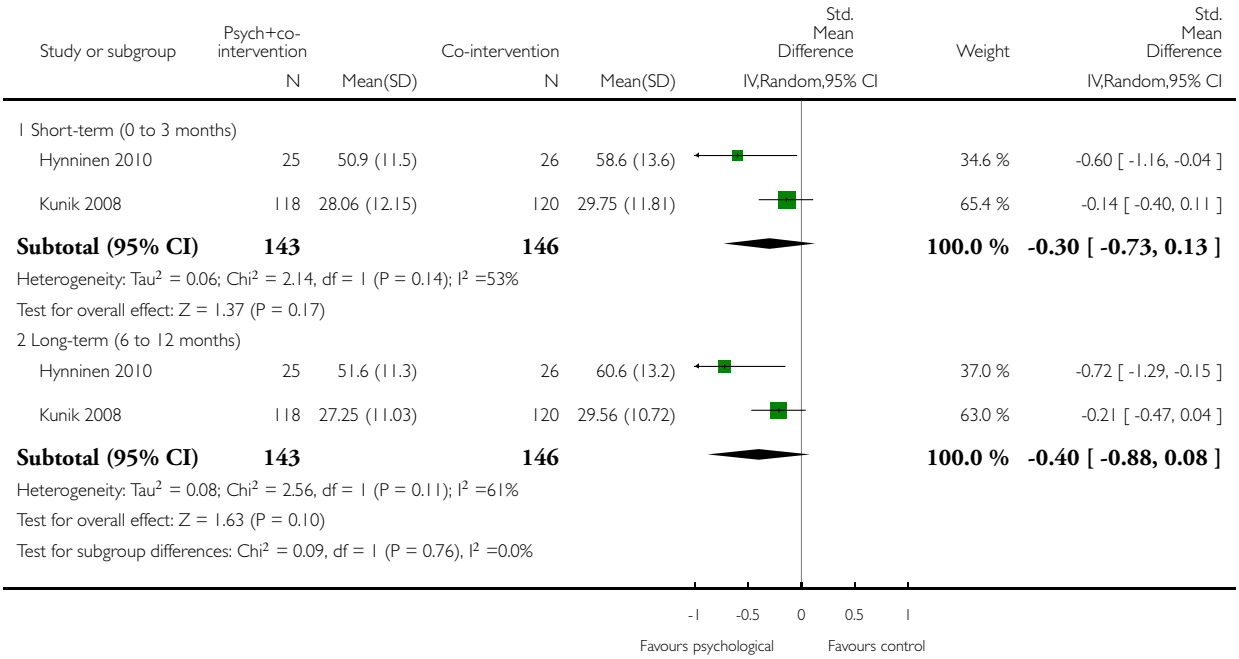


Analysis 2.3. Comparison 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention, Outcome 3 Quality of life - SGRQ and SF36 Physical composite.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention

Outcome: 3 Quality of life - SGRQ and SF36 Physical composite

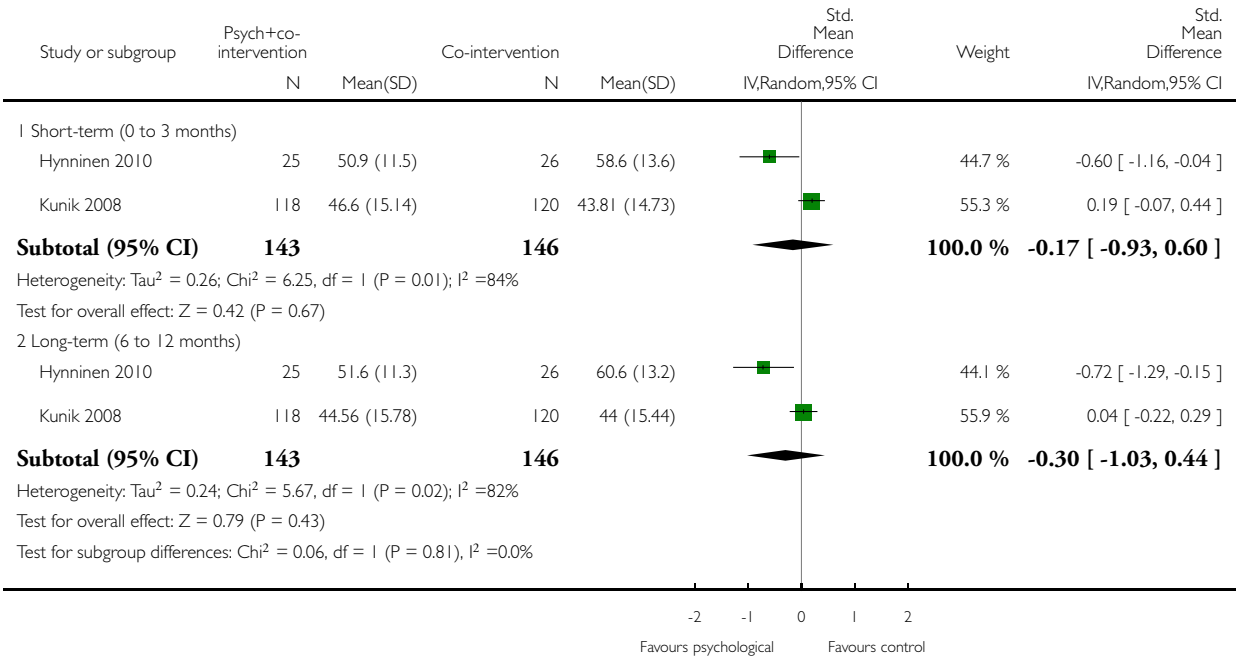


Analysis 2.4. Comparison 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention, Outcome 4 Quality of life - SGRQ and SF36 Emotional composite.

Review: Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease

Comparison: 2 Duration of intervention sub-group analyses - psychological therapies versus co-intervention

Outcome: 4 Quality of life - SGRQ and SF36 Emotional composite



APPENDICES

Appendix 1. CCMDCTR - core MEDLINE search

Core search strategy used to inform Cochrane Common Mental Disorders' specialised register: OVID Medline

A weekly search alert based on condition + RCT filter only

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety,

castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati# ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*

(controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records are screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.

Similar weekly search alerts are also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. Additional search strategies (CENTRAL and PsycINFO):

CENTRAL search strategy:

Issue 8, 2013, n=124

#1. MeSH descriptor LUNG DISEASES, OBSTRUCTIVE, this term only

#2. MeSH descriptor PULMONARY DISEASE, CHRONIC OBSTRUCTIVE explode all trees

#3. emphysema*

#4. chronic* near/3 bronchiti*

#5. (obstruct*) near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#6. (COPD or COAD or COBD or AECB)

#7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

#8. MeSH descriptor ANXIETY, this term only

#9. MeSH descriptor ANXIETY DISORDERS explode all trees

#10. MeSH descriptor ANXIETY, SEPARATION, this term only

#11. MeSH descriptor PANIC, this term only

#12. MeSH descriptor OBSESSIVE BEHAVIOR explode all trees

#13. MeSH descriptor COMPULSIVE BEHAVIOR explode all trees

#14. MeSH descriptor STRESS, PSYCHOLOGICAL explode all trees

#15. MeSH descriptor NEUROTIC DISORDERS, this term only

#16. (anxiety or phobi* or agoraphobi* or claustrophobi* or PTSD or post-trauma* or posttrauma or (post NEXT trauma*) or (combat NEXT disorder) or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*)

#17. (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18. (#7 and #17)

#19. (SR-DEPRESSN OR HS-DEPRESSN)
#20. (SR-AIRWAYS OR HS-AIRWAYS)
#21. #19 OR #20
#22. (#18 NOT #21)

OVID PsycINFO search strategy:

Searched 26 September 2013, n=98

1. Lung Disorders/
2. exp Chronic Obstructive Pulmonary Disease/
3. (chronic* adj3 bronchiti*).mp.
4. emphysema*.mp.
5. (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).mp.
6. (COPD or COAD or COBD or AECB).mp.
7. or/1-6
8. exp Anxiety/
9. exp Anxiety Disorders/
10. exp Phobias/
11. exp Neurosis/
12. exp Stress/
13. exp Trauma/
14. Panic Attack/ or Panic/ or Panic Disorder/
15. exp Fear/
16. (anxiety or phobi* or agoraphobi* or claustrophobi* or PTSD or post-trauma* or posttrauma or post trauma* or combat disorder or panic or OCD or obsess* or compulsi* or GAD or stress* or distress* or neurosis or neuroses or neurotic or psychoneuro*).mp.
17. or/8-16
18. treatment effectiveness evaluation.sh.
19. clinical trials.sh.
20. mental health program evaluation.sh.
21. placebo.sh.
22. placebo*.ti,ab.
23. randomly.ab.
24. randomi#ed.ti,ab.
25. trial*.ti,ab.
26. ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).mp.
27. (control* adj3 (trial* or study or studies or group*)).ti,ab.
28. "2000".md.
29. factorial*.ti,ab.
30. allocat*.ti,ab.
31. assign*.ti,ab.
32. volunteer*.ti,ab.
33. (crossover$ or cross over*).ti,ab.
34. (quasi adj (experimental or random*)).mp.
35. (((waitlist* or (wait* and list*)) and (control* or group)) or treatment as usual or TAU).ab.
36. or/18-35
37. (7 and 17 and 36)

CONTRIBUTIONS OF AUTHORS

Protocol prepared by Zafar A Usmani, Kristin V Carson and Karen Heslop-Marshall with feedback provided by Adrian J Easterman, Anthony De Soyza and Brian J Smith.

Data screened and extracted by ZU, KC and HM, data entry, analysis and manuscript preparation by ZU and KC with feedback on manuscript by AE, AD and BS.

DECLARATIONS OF INTEREST

Dr Zafar Usmani has previously received a grant from Cochrane Airways for his Cochrane Review. He has not received any other funding for his research related to the management of anxiety in people with COPD.

Kristin Carson has received travel grants from the Thoracic Society of Australia and New Zealand, Healthy Development Adelaide (associated with The University of Adelaide) and the Young Professionals Group (associated with SA Health) to attend national and international conferences. She has received financial support and grants from multiple organisations in the past year including the Australian and New Zealand School of Government, the National Health and Medical Research Council, Cancer Australia, the Thoracic Society of Australia and New Zealand and Seeley International, toward supporting several research initiatives unrelated to this particular Cochrane Review.

Karen Heslop-Marshall has received fees for speaker meetings or consultancy work on management of anxiety and depression in COPD from a variety of commercial companies and has received a NIHR Fellowship grant to undertake a RCT of CBT in COPD.

Dr De Soyza has received no fees nor grants that relate to anxiety and depression management in COPD. He has received fees for speaker meetings or consultancy work on management of COPD airways disease management from a variety of commercial companies. He has also received financial support from multiple partners in the past to attend national congresses/symposia and has also had co-funding offers towards a multi-centre bronchiectasis grant.

Professor Brian Smith has received grant funding in the past year from the Australian and New Zealand School of Government, the National Health and Medical Research Council, Cancer Australia, the Thoracic Society of Australia and New Zealand and Seeley International, toward supporting several research initiatives unrelated to this particular Cochrane Review.

SOURCES OF SUPPORT

Internal sources

- Respiratory Department - The Queen Elizabeth Hospital, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not conduct sensitivity analyses due to the small number of included studies reported within each meta-analysis.

Chapter 5. A randomised placebo-controlled trial of paroxetine for the management of anxiety in COPD (PAC study)

Zafar A Usmani[1, 2], Kristin V Carson-Chahhoud[1, 3], Adrian J Esterman[4,5], Brian J Smith[1, 2]

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Journal of Multidisciplinary Healthcare 2018; Issue 11: 287–93

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Statement of authorship

A randomized placebo-controlled trial of paroxetine for the management of anxiety in chronic obstructive pulmonary disease (PAC Study).

Publication status: Published.

Publication details: Usmani ZA, Carson-Chahhoud KV, Eserman AJ, Smith BJ. A randomized placebo-controlled trial of paroxetine for the management of anxiety in chronic obstructive pulmonary disease (PAC Study). Journal of Multidisciplinary Healthcare 2018:11 287–293

Author contributions:

By signing the Statement of Authorship, each author certifies their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	Zafar Usmani		
Contribution to the paper	Developed protocol, organised ethics approval, organised case report forms, participant recruitment and outcome measures and monitoring, extracted the data, prepared the manuscript, wrote the first draft, contributed to writing the manuscript, agree with manuscripts results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version. Contribution towards the project, manuscript and publication 85%.		
Signature		**Date**	23 August 2018

Name of co-author	Kristin Carson		
Contribution to the paper	Assisted in developing protocol and ethics approval, organised case report forms, participant recruitment and outcome measures and monitoring, extracted the data, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version.		
Signature		**Date**	24 August 2018

Name of co-author	Adrian Esterman		
Contribution to the paper	Developed the statistical part of the protocol, analysed the data, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		**Date**	27 August 2018

Name of co-author	Brian Smith		
Contribution to the paper	Assisted in multisite ethics approval and recruitment, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		**Date**	27 August 2018

In the previous chapter, the findings of the Cochrane systematic meta-analysis evaluating psychological interventions for management of anxiety in COPD patients are presented. Our previous Cochrane review examined the evidence of pharmacological interventions for management of anxiety in COPD patients (Appendix 1). Combined, these two modes of treatment are used in clinical practice to treat anxiety. However, as identified in both reviews, the evidence base is not strong, with small numbers of included studies and poor methodological rigour in study designs to date. Despite available evidence, use of pharmacological and psychological interventions for treatment of anxiety in the context of COPD is ad hoc and poorly executed in the clinical setting. In an attempt to address this evidence gap, an RCT is proposed using SSRIs and paroxetine, compared to placebo across multiple hospitals in South Australia for patients with COPD. The patient case report form (Appendix 2), patient information sheet (Appendix 3), Human Research Ethics Committee approval (Appendix 4) and Ethics Committee approval for additional sites (Appendix 5) are available in the appendices.

As presented in the preceding chapter, the aim of this study was to assess the efficacy and safety of paroxetine (an SSRI) for management of anxiety in COPD and the effect of treatment on patients' quality of life and rate of hospitalisation. A double-blind RCT of patients with clinical anxiety (BAI > 15) and formally diagnosed COPD was conducted. Participants were allocated into groups that either received paroxetine 20mg or placebo pills daily, for four months. Differences in outcomes were assessed based on an intention-to-treat analysis using linear mixed effects models. 38 participants were recruited. 22 of them completed the trial. A clinically and statistically significant reduction was noted in anxiety symptoms after four months of treatment compared to the placebo (mean change/reduction of 11.9 units of Beck Anxiety Inventory (BAI) was noted in the intervention group, v. 3.16 units in the placebo group, $p = 0.007$). Clinically important improvement was noted in depression symptoms, with no statistically significant differences in walking distance or quality of life measure outcomes. The intervention group had less COPD-related admissions compared to the placebo group but experienced medication-related side effects. This is the first methodologically rigorous study in the world to assess the effect of paroxetine for anxiety among COPD patients. Given the effectiveness of treatment for anxiety, it could be considered for uptake in clinical practice. However, no benefits were reported on quality of life and a number of medication-related side effects were observed. As such, the role of paroxetine in the clinical context is limited.

Journal of Multidisciplinary Healthcare

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ORIGINAL RESEARCH

A randomized placebo-controlled trial of paroxetine for the management of anxiety in chronic obstructive pulmonary disease (PAC Study)

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Kristin V Carson-Chahhoud[1,3]
Adrian J Esterman[4,5]
Brian J Smith[1,2]

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Background: Despite the high prevalence of anxiety in COPD patients and its impact on quality of life, evidence to support the effectiveness of various anxiety treatment options is insufficient, leading to the need for further research in this field.

Aim: The aim of this study was to assess the efficacy and safety of paroxetine for the management of anxiety in COPD and the impact of treatment on patients' quality of life and rate of hospitalization.

Patients and methods: In a double-blind, randomized, controlled trial, COPD patients were allocated into groups that either received paroxetine 20 mg or placebo pills daily, for four months. Differences in outcomes were assessed based on an intention-to-treat analysis using linear mixed effects models. A chi-square test was used to compare the number of COPD-related admissions.

Results: Thirty-eight participants were recruited. Twenty-two of these completed the trial. A clinically and statistically significant reduction was noted in anxiety symptoms after four months of treatment compared to the placebo. Clinically important improvement was noted in depression symptoms, with no statistically significant differences in walking distance or quality-of-life measure outcomes. The intervention group had less COPD-related admissions compared to the placebo group but experienced medication-related side effects.

Conclusion: Treatment with paroxetine significantly improved anxiety levels, but this difference did not translate into improved quality of life at four months follow-up.

Keywords: anxiety, COPD, pharmacotherapy, paroxetine, BAI, emphysema

Introduction

COPD is one of the most common chronic medical conditions worldwide with a prevalence range of 7.8–19.7%.[1] Importantly, this estimate is predicted to double by 2050.[2] Anxiety and depression are common comorbidities of people with COPD, which are frequently undertreated or not treated at all.[3] Anxiety is two- to threefold more common in COPD patients (10–15.8%[4]) as compared to the general population, with a lifetime prevalence of 5%.[5]

There are various physiological and pathological mechanisms that could be responsible for the increased levels of anxiety and panic in people with COPD.[6,7] For example, COPD individuals frequently experience dyspnea and palpitations, which could be misinterpreted as serious or catastrophic events by the brain or body, leading to the creation of a positive feedback loop resulting in anxiety and panic.[8,9]

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Coexisting anxiety among people with COPD is commonly associated with a deterioration in quality of life,[10] self-management,[11] exercise performance,[12] and an increase in medical symptom reporting,[13] illness exacerbations,[12] hospitalizations,[14] length of hospital stay,[15] mortality,[16] and health care costs.[13] The impact of anxiety and depression on health-related outcomes in these individuals is independent of other confounding factors such as general health status, comorbidities, and disease severity.[4] It has even been reported that the functional status of COPD patients is more dependent on their emotional status as compared to the actual severity of COPD itself.[17,18]

In clinical practice, pharmacological therapies are usually used as first-line therapy to treat anxiety in people with COPD. However, there is limited evidence to support this practice within the COPD population.[19,20] There is currently a lack of randomized controlled trials to assess the effects of pharmacological interventions in people with COPD. The studies which are available have methodological limitations in terms of small sample size, large dropout rates, or a short follow-up period.[19,21]

Despite the lack of evidence, selective serotonin reuptake inhibitors (SSRIs) have been widely used in clinical practice for treating depression and anxiety in people with COPD. In our published Cochrane systematic review, we identified a potentially useful clinical improvement favoring the use of SSRIs over that of placebo for controlling anxiety in an underpowered study, while little or no difference was found for the other classes of medications.[21] Unlike other SSRIs, paroxetine is indicated for the treatment of both depression and anxiety,[22,23] which is of relevance in COPD sufferers. Another study of paroxetine in people with COPD and comorbid depression showed significant improvements in depressive symptoms, exercise capacity, and quality of life at three months follow-up.[24] However, this study was underpowered, and the authors concluded that a larger, double-blind trial with a relatively longer treatment period was indicated. As such, a case can be made that a study of robust design and appropriate power is warranted.

Our study tested the hypothesis that people with COPD and clinically significant anxiety, recruited from public hospitals, who are prescribed 20 mg of paroxetine (Pharmaceutical Packaging Professionals Pty Ltd., Port Melbourne, VIC, Australia) daily for 16 weeks will:

(Hypothesis 1: principle hypothesis) have a significant reduction in their anxiety symptoms measured by Beck Anxiety Inventory (BAI) as compared with the placebo at four months follow-up, and

(Hypothesis 2) will experience improved quality of life measured by Chronic Respiratory Questionnaire (CRQ), and exercise capacity measured by six-minute walk distance (6MWD), and

(Hypothesis 3) have reduced hospital visits.

Methods

Ethical approval

The trial was approved by the Human Research and Ethics Committee of The Queen Elizabeth Hospital, Adelaide, SA (HREC Ref # 2012012). The trial was registered with the Australian and New Zealand Clinical Trials Registry (Trial ID: ACTRN12613000458730) in April 2013, and participant recruitment began in June 2013.

Design

The trial was double blind, placebo controlled, with randomization to either:

1. paroxetine 20 mg daily (four-month course);
2. placebo tablets of identical appearance (four-month course).

Hospital sampling frame and recruitment

The sampling frame included four Adelaide Hospitals, The Queen Elizabeth Hospital (TQEH), Repatriation General Hospital (RGH), Flinders Medical Centre (FMC), and the Royal Adelaide Hospital (RAH), which collectively have more than 40,000 admissions per year. Of these, at least 4,000 admissions are for patients diagnosed with COPD.

Inclusion criteria

Patients who met the following criteria were included in the trial: adults over 40 years of age, diagnosed with any class of COPD of any severity (by a medical consultant or by Global initiative for chronic Obstructive Lung Disease [GOLD] criteria: post-bronchodilator forced expiratory volume in one second [FEV1]/forced vital capacity <0.70[25]), and recognized as having clinically significant anxiety, with a score of >15 as assessed using BAI.[26]

The BAI has been validated for use with older medical patients,[27] and the scale possesses strong psychometric properties related to internal consistency, validity, and test–retest reliability.[28] The BAI can be used to assess and establish a baseline anxiety level, as a diagnostic aid, and also as a post-treatment outcome measure.

The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Total

scores ranging from 0 to 7 are indicative of minimal anxiety, 8–15 of mild anxiety, 16–25 of moderate anxiety, and 26–63 of severe anxiety. However, it is worth noting that the BAI includes numerous somatic symptoms that may represent COPD rather than anxiety, so COPD patients with anxiety scores at the very mild end of the scale should be treated cautiously. A score of >15 was categorized as moderate or severe anxiety[28] and has been used in previous studies as the "cutoff" for anxiety in people with COPD;[17] hence, a BAI score of >15 was chosen to define clinical anxiety.

Exclusion criteria

Patients with any of the following criteria were excluded: current or recent (within a week) exacerbation of COPD; severe dementia or significant cognitive impairment, terminal cancer, or other concurrent significant psychological disease (e.g., schizophrenia or suicidal ideation); history of current or recent (within last two weeks) use of monoamine oxidase inhibitors; Prolonged QT interval (>440ms in males and >460ms in females) on ECG; current pregnancy or lactation; severe liver, kidney, cardiovascular, or locomotor disease; uncontrolled epilepsy or previous history of SSRI intolerance.

Randomization, allocation concealment, and blinding

All the participants were provided with written informed consent and signed the consent prior to being enrolled in the study. Randomization was accomplished by a random number generator computer software program, by an external researcher unrelated to the trial. Allocation concealment and blinding were maintained for patients, investigators, research/data collection staff, and outcome assessors by using an external pharmacy dispensing company to package the study medication as per the randomization schedule into identical containers, which were consecutively numbered. This medication was then dispensed by the hospital pharmacy as each new participant was recruited. However, if a subject experienced a serious adverse event, the treatment was ceased, and the code was broken by a research pharmacist unrelated to the trial, resulting in all trial staff remaining blinded.

Intervention delivery and monitoring

Research staff blinded to the treatment allocation commenced patients on 20 mg of paroxetine or an identical placebo pill during their first visit for baseline measurements. Patients were provided with contact details of research personnel for notification of adverse events. The medication was provided for 16 weeks with a weekly phone call for the first four weeks to identify and address any side effects or adverse events. This procedure is summarized in Figure 1.

Data collection

Baseline questionnaires

Patient demographic characteristics including age, gender, ethnicity, and marital and smoking status were collected. Details regarding the diagnosis and severity of COPD and other medical comorbidities were also documented, and a detailed note was made of all concomitant medications. Primary outcome of anxiety was measured using BAI. Secondary outcomes included depression measured using Beck Depression Inventory (BDI),[29] quality of life assessed via CRQ,[30] and dyspnea assessed using modified Medical Research Council dyspnea scale.[31,32] Smoking status, 6MWD, and spirometry were also documented.

Follow-up questionnaires

Weekly phone calls were made for the first four weeks to assess compliance and any intervening management, and for adverse events monitoring. The prespecified outcomes of anxiety, depression, quality of life, dyspnea score, 6MWD, spirometry, and hospital utilization were reassessed at four months during a face-to-face visit.

Withdrawal criteria

The withdrawal criteria included any clinically significant adverse event that was considered related to the study and patients' unwillingness to continue further with the trial.

Statistical analysis

Very few previous studies were available to guide the original power calculation. One study had shown an effect size of 1.0;[33] however, we chose a more conservative effect size estimate of 0.5, based on a linear mixed effects model with two time points, a power of 80%, a type 1 error of 0.05, and an expected correlation between baseline and four-month results of 0.4. This required a sample size of 50 patients in each study arm. However, after three years of an intense recruitment campaign, only 38 participants could be recruited and were randomized to either placebo or intervention group. An intention-to-treat analysis was conducted by the trial statistician to determine if significance was reached and the study could be discontinued. Linear mixed effects models were used to assess change score by group. The fixed factors consisted of group, time, and a group–time interaction term,

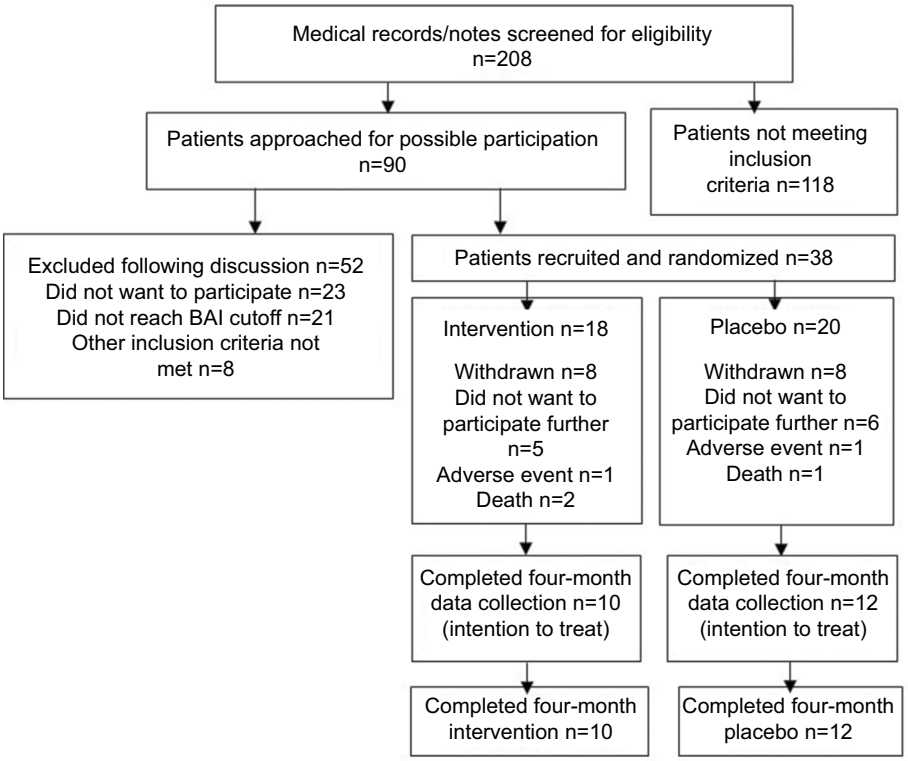

Figure 1 Flowchart of the study.
Abbreviation: BAI, Beck Anxiety Inventory.

the latter being the basis for a formal test of the intervention. A chi-square test was used to compare the number of COPD-related admissions by group.

Results

Participants

A total of 208 patients were screened for eligibility (Figure 1). More than half of these did not meet the prespecified inclusion criteria. Ninety patients were approached for enrollment, and more than half of these could not be included primarily due to a lack of interest for participation or because their BAI score was <15. Thirty-eight participants were enrolled during three years of recruitment.

Demographics for this population were similar between groups with no statistically or clinically significant differences observed (Table 1). Two participants in each group had past history of depression. The mean FEV1 in the intervention group was 44.7% versus mean FEV1 in placebo group of 35.8%, however, from a clinical perspective, both averages were within the range for severe COPD or GOLD stage III classification.

Eighteen participants were randomized to the intervention group, with eight of these lost to follow-up and therefore not available for the four-month questionnaire. Out of these eight patients, one suffered severe nausea and dizziness as a side effect of the intervention, two passed away for reasons unrelated to the trial, and five refused follow-ups for various

Table 1 Baseline demographic characteristics

Demographics	Intervention (n=18)	Placebo (n=20)
Age (years)	70.6 (9.0)	67.6 (7.7)
Males:females (n)	9:9	11:9
COPD severity (FEV1%)	44.7 (18.0)	35.8 (16.1)
BMI (kg/m^2)	25.7 (6.6)	28.5 (5.5)
Pulmonary rehabilitation: yes (n, %)	2 (11.1%)	3 (15.0%)
Ethnicity (n, %)		
Caucasian	18 (100%)	20 (100%)
Other	0	0
Educational attainment (n, %)		
High school or less	17 (94.4%)	18 (90%)
Some college	0	0
College degree or higher	1 (5.6%)	2 (10.0%)
Household income (n, %)		
Low income (≤$20kp.a.)	10 (55.6%)	12 (60.0%)
Medium income ($20–$50kp.a.)	4 (22.2%)	5 (25.0%)
Unknown income	4 (22.2%)	3 (15.0%)
Smoking status (n, %)		
Current smoker	6 (33.3%)	5 (33.3%)
Ex-smoker	18 (66.7%)	15 (66.7%)

Note: Data are presented as mean (standard deviation) unless otherwise specified.
Abbreviations: FEV1, forced expiratory volume in one second; BMI, body mass index; kp.a., thousand per annum.

reasons (two changed their mind and did not wish to continue, one developed other health priorities, one reported significant worsening of anxiety, and one experienced significant deterioration of health).

Twenty participants were randomized to the control group. Eight of these were lost to follow-up and were not available for the four-month questionnaire. Of these eight patients, one suffered severe headaches as a side effect of placebo, one passed away for reasons unrelated to the trial, and six refused follow-ups for various reasons (two changed their minds and did not wish to continue, two had general deterioration of health, one developed other health priorities, and one reported significant worsening of anxiety and did not wish to continue). No significant difference was noted in terms of COPD severity between the patients who completed the trial versus those who lost the follow-up in either of the groups.

Subsequently, data from 10 participants in the intervention and 12 participants in the placebo group were available for the intention-to-treat analysis. Of these subjects, seven in the intervention and six in the placebo group completed the entire course of 120 capsules. The number of capsules returned by the other participants was minimal and ranged between 4 and 17. However, it is expected that unintentional missed doses would not cause any significant clinical impact, particularly in the setting of proper randomization and blinding.

Treatment effect

For the primary outcome of anxiety (BAI), participants in the intervention group had a greater improvement after four months compared to the placebo group (Table 2). The difference was both statistically and clinically significant (p=0.007). Mean change (reduction) of 11.9 units of BAI was noted in the intervention group versus 3.16 units in the placebo group.

Clinically important improvement in the treatment group (with a mean change of 4.5 units of BDI) was noted for depression symptoms compared to the placebo group. Neither clinical nor statistical difference was noted for dyspnea, walking distance, or quality-of-life outcomes.

There were fewer COPD-related hospital admissions in the intervention group compared to the placebo group during the four-month treatment phase (1/10 and 6/12, respectively; p=0.050). However, this was based on a small number of admissions and shorter follow-up period. More side effects were reported in the intervention arm compared to the placebo arm (Table 3).

Discussion

COPD is one of the most common medical conditions worldwide, and comorbid anxiety is frequently seen in people suffering from COPD. Anxiety when associated with COPD also has a significant impact on patients' exercise capacity and quality of life. There is evidence that the rate of

Table 3 COPD-related hospital admissions and adverse events during treatment period

Side effects	Intervention	Placebo
Headache	1	1
Heart burn	1	0
Insomnia	1	0
Itch	0	1
Nausea	1	0
Stomach upset	1	0
Shakes	1	0
Tiredness	0	1
Vertigo	0	1
Total adverse events	6	4

Table 2 Outcome scores at baseline and follow-up with differences between groups

Outcome measured	Intervention (n=10)			Placebo (n=12)			p-value*
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Anxiety (BAI)	26.80 (7.4)	14.90 (8.8)	−11.9	25.25 (8.2)	22.09 (11.8)	−3.16	**0.007**
Depression (BDI)	16.20 (10.7)	11.70 (10.5)	−4.5	14.58 (8.2)	15.92 (10.6)	1.34	0.144
Dyspnea (mMRC dyspnea scale)	2.00 (1.2)	2.00 (1.2)	0.0	2.17 (1.1)	2.42 (0.9)	0.25	0.684
6MWD (m)	311.90 (132.9)	329.13 (115.7)	17.23	294.45 (115.7)	354.56 (62.0)	60.11	0.301
CRQ							
Dyspnea	3.62 (0.9)	3.80 (1.4)	0.18	3.50 (1.2)	3.48 (1.4)	−0.02	0.775
Fatigue	3.42 (1.0)	3.83 (1.3)	0.41	3.42 (1.4)	2.84 (0.7)	−0.58	0.089
Emotional	3.68 (1.2)	4.83 (1.1)	−1.55	3.76 (1.4)	4.19 (1.3)	0.43	0.196
Mastery	3.25 (1.3)	4.25 (1.3)	1.0	3.52 (1.7)	4.00 (0.8)	0.48	0.270

Notes: Data are presented as mean (standard deviation). *Based on the statistical significance of the group–time interaction term in the linear mixed effects model.
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; m, meters; mMRC, modified Medical Research Council; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire.

hospitalization is also increased among these patients, possibly due to noninfective presentations or primary presentations because of panic and then being found to have low oxygen saturation due to underlying COPD and admitted to hospital.

Despite the impact of psychological comorbidities, the major focus of clinical practice and research still focuses on improvement in lung function, rather than patients' emotional and psychological well-being.

As discussed above, previous trials for the pharmacological treatment of anxiety in people with COPD were of small sample size; hence, we decided to conduct a larger clinical trial. However, the difficulty we faced in terms of recruitment and retention of the participants has further confirmed the complex nature and management issue surrounding these patients and may explain the small sample size of previous trials.

This study has shown that a four-month course of paroxetine reduces anxiety levels in people with COPD compared to placebo, albeit based on a small sample size. It is important to note that anxiety and depression often coexist, and although not statistically significant, our study demonstrated a clinically significant improvement in depression scores for the treatment arm, measured by BDI. However, at four months, these improvements in anxiety and depression scores did not translate into improvement in exercise capacity or quality of life; a longer duration of treatment may be required to prompt this. Another possible explanation for this lack of effect on exercise capacity and quality of life could be that though the medication has calmed the patients, it has not modified their thought process and behavior, an effect which could be achieved by adding a psychological intervention. Both the study arms experienced similar rates of withdrawal; however, side effects of nausea, stomach upset, and shakes were more common in the treatment group; these are common and expected side effects of SSRIs. The incidence of hospital admission was less in the treatment group compared to placebo, though the follow-up period was short. Hence, we remain cautious about drawing firm conclusions on this. One explanation for the reduced admission rate could be associated with a reduction in anxiety levels resulting in a lesser number of self-presentations due to stress and panic.

We observed a significant reduction in anxiety levels and some reduction in depression and hospitalization rates over a short follow-up period. It is possible that the large change in BAI may be related to the difference in the underlying nature of the anxiety disorder; for example, the intervention arm may have had a larger proportion of participants with panic disorder. However, we did not perform any stratification during the randomization of participants based on their levels of anxiety or the nature of their underlying anxiety disorder. We believe one of the most important messages of this study comes from issues with patient recruitment and retention, being that this particular group of people with COPD are difficult to engage due to their underlying panic and stress. This is also likely to be the underlying reason for these individuals demonstrating a low threshold for discontinuing their medication and becoming lost from close clinical follow-up. We recommend that further research into the problem of anxiety in people with COPD be focused on psychological interventions, for example, cognitive behavioral therapy, as this type of intervention could modify patients' behavior and thought process, without the introduction of side effects and hence may be a better long-term management option for this population.

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Disclosure

The authors report no conflicts of interest in this work.

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Chapter 6. Meta-analysis of pharmacological and psychological interventions for the management of anxiety in COPD

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Contribution to the paper	Developed protocol, researched the content, extracted the data, prepared the manuscript, wrote the first draft, contributed to writing the manuscript, agree with manuscripts results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version. Contribution towards the project, manuscript and publication 80%.		
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Signature		**Date**	27 August 2018

In the previous chapters, the findings of the systematic meta-analysis for the efficacy of psychological interventions for this population (as per the data available up to August 2015) and the RCT examining the efficacy and safety of paroxetine for management of anxiety in COPD patients were reported. Since publication of the meta-analysis presented in Chapter 4, more recent evidence has been published that will strengthen the evidence base to examine the efficacy of psychological interventions for anxiety in this COPD population. In addition, the RCT presented in Chapter 5 has contributed with methodologically rigorous data examining efficacy and safety of pharmacotherapy for this population. Hence, this chapter reports a meta-analysis and systematic review of all available RCT data addressing the effect of pharmacotherapy and/or psychotherapy, including a comparison of effectiveness against each other.

The aim of this review was to assess the efficacy and safety of pharmacological and psychological interventions for the management of anxiety in patients with COPD. This was conducted in light of the available RCTs pertaining to either of these interventions and addressing patients with co-existing anxiety and COPD. It then compared if one of these was superior.

A total of 1,792 citations resulted in nine included studies (five pharmacological and four psychological). Meta-analysis of these studies revealed significant reductions in anxiety symptoms, with and without adjusting for heterogeneity, in the treatment arm (MD –2.84; 95% CI –4.42 to –1.26; p = 0.0004, standardised mean difference [SMD] –0.44; 95% CI –0.74 to –0.14; p = 0.004) with psychological studies producing greater treatment efficacy (p = 0.005 for MD and p = 0.02 for SMD) over pharmacological (p = 0.10 for MD and p = 1.20 for SMD) within sub-group analysis. Significant improvement was noted in depression scores (p = 0.03), which were mainly driven by psychological interventions. A trend in favour of intervention was discovered for the physical composite of quality of life measured by St George's Respiratory Questionnaire (SMD –0.36; 95% CI –0.74 to 0.02; p = 0.06; three studies) but not for other measures of quality of life. No evidence of any effect was found for exercise capacity or FEV1. Psychological therapies appear to be more effective than pharmacological interventions, which have little or no effect on reducing anxiety in COPD patients.

Overall, psychotherapy (psycho-educative therapy and cognitive behavioural therapy) has proven to be more effective for control of anxiety and panic in COPD patients and advocacy is required for the incorporation of this intervention in COPD management guidelines along with the tools for early detection of anxiety in COPD.

REVIEW ARTICLE

Systematic meta-analysis of pharmacological and psychological interventions for the treatment of anxiety in patients with chronic obstructive pulmonary disease

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Abstract

Rates of anxiety symptoms in patients with COPD range from 13% to 51%, which is higher than rates for patients with other chronic diseases, yet evidence underpinning the effectiveness of the various treatment options is lacking. The aim of this review was to assess the efficacy and safety of both pharmacological and psychological interventions for the management of anxiety in COPD.

We searched two Cochrane Specialised Registers of Cochrane Airways group and Cochrane Collaboration of Depression, Anxiety and Neurosis with complementary screening of Medline, PsycINFO and CENTRAL. Reference lists of included studies and online clinical trial registries were also explored. Randomised controlled trials (RCTs) and cross-over studies of pharmacological or psychological interventions for patients (age ≥40 years) with diagnosed COPD and co-existing anxiety (confirmed by recognised diagnostic criteria or validated measurement scale) were identified for inclusion. Data was extracted by two independent review authors with meta-analyses of outcomes performed using the random-effect model using Review Manager Version 5.3.

A total of 1,792 citations resulted in nine included studies (five pharmacological and four psychological). Meta-analysis of these studies revealed significant reductions in anxiety symptoms, both with and without adjusting for heterogeneity, in the treatment arm (mean difference -2.84; 95%CI -

4.42 to -1.26; p=0.0004, standardised mean difference -0.44; 95% CI -0.74 to -0.14; p=0.004) with the psychological studies producing greater treatment efficacy (p=0.005 for MD and p=0.02 for SMD) over pharmacological (p=0.10 for MD and p=0.20 for SMD) within sub-group analysis. Sig- nificant improvement in depression scores was noted (p=0.03), mainly driven by psychological interventions. A trend in favour of the intervention was found for the physical composite of quality of life measured by St George's Respiratory Questionnaire (standardised mean difference -0.36; 95%CI -0.74 to 0.02; p=0.06; 3 studies), but not for other measures of quality of life. No evidence of any effect was found for exercise capacity or FEV1. Psychological therapies appear to be more effective than pharmacological interventions, which have little or no effect to reduce anxiety in COPD patients. However, poor methodological quality and small sample size of studies investigating pharmacotherapy may be contributing to this discrepancy.

Key words/phrases (MeSH terms): COPD, chronic obstructive pulmonary disease, anxiety, meta-analysis, review, pharmacotherapy, psychological

Trial registration number: PROSPERO:

Word count: 3105 (including Abstract, excluding references and appendices)

Conflict of interest: There are no conflicts of interest to declare for any author

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic lung condition characterised by the inflammation of airways and irreversible destruction of pulmonary tissue leading to progressively worsening dyspnoea and is a leading international cause of disability and death in adults [1]. Chronic Obstructive Pulmonary Disease (COPD) is a growing health problem, affecting an estimated 15 million Americans. COPD exacerbations are responsible for more than 800,000 hospital admissions in the United States each year. COPD is responsible for early mortality, high death rates and significant cost to health systems. The projection for 2020 indicates that COPD will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost through early mortality or handicap (disability-adjusted life years) [2].

COPD is a disease with some significant extra pulmonary effects that may contribute to the severity in individual patients (GOLD 2008). The two most common co morbidities of COPD are anxiety and depression. Various models could be considered to explain increased levels of anxiety and panic in patients with COPD [3, 4]. One model explains this relationship as misinterpretations of ambiguous bodily sensations (such as shortness of breath, rapid heart rate) which increase arousal, creating a positive feedback loop that results in a panic attack [5]. A crucial difference between physically healthy people and those with COPD is that in the latter, breathing, the most basic of all physical functions necessary for life, is objectively threatened (as measured by tests of lung function) and subjectively difficult. Dyspnoea can be an unpleasant and potentially frightening experience at any time, and, as the key symptom of an eventually fatal illness like COPD, it is an ambiguous sensation open to interpretation, leading to increased levels of anxiety and panic in people with COPD [6]. Also, patients with underlying stress and anxiety are more prone to smoking, which in itself is a major risk factor for development of COPD.

Anxiety can occur at any stage of COPD [7, 8].Lifetime prevalence of Generalised Anxiety Disorder (GAD) in particular amongst patients with COPD is estimated at between 10% and 15.8% [9].The prevalence of panic disorder in COPD population is estimated to be ten times higher than the general population [10, 11].

Co morbid COPD and anxiety is related to poor health outcomes in terms of exercise tolerance, quality of life, COPD exacerbations [12], inappropriate use of medications and persistence of smoking as a coping strategy for anxiety management [13]. By compromising health status, mood disorders lead to increased risk of hospitalisation and re-hospitalisation [14] and hence also increase direct and indirect costs to the health system. Psychological disorders like depression, anxiety, psychosis, alcohol abuse and drug abuse are independently associated with higher all-cause 30-day readmission rates for Medicare beneficiaries with COPD [15].

Management strategies for the treatment of anxiety disorders in people with COPD include both pharmacological and non-pharmacological interventions. Current evidence that pharmacological therapies (anti-anxiety and/or antidepressant medications) provide statistically or clinically significant benefits for this group of patients is limited [16, 17]. Psychological therapies include cognitive and/or behavioural therapies, psycho-dynamic psychotherapy, inter-personal psychotherapy, non-directive therapy, support therapy and counselling [18, 19]. A recently published Cochrane review has indicated some evidence of improvement in anxiety was with psychological therapy, however, lack of statistical power limits the reliability of those findings [20].

Despite of anxiety in COPD being such an important issue, there is an apparent lack of good quality and well powered RCTs addressing the treatment for patients with anxiety and COPD, hence we have conducted a systematic meta analysis including the RCTs of pharmacological and psychological interventions for patients with clinical anxiety and diagnosed COPD.

METHODS

A pre-specified protocol was established prior to commencement of the review (published on PROSPERO ID: 2017:CRD42017056172).

Search strategy

Two Cochrane Specialised Registers were searched with complementary screening of Medline, PsycINFO and CENTRAL (see search strategy in Appendix). Reference lists of included studies and online clinical trial registries (http://apps.who.int/trialsearch/) were also screened using key words of anxiety AND COPD.

Study selection

Randomised controlled trials (RCTs) and cross-over studies of pharmacological or psychological interventions for patients (age >40 years) with diagnosed COPD and co-existing anxiety (confirmed by recog- nised diagnostic criteria or validated measurement scale) were identified for inclusion. Studies where patients did not have confirmed COPD diagnosis or confirmed anxiety levels (using a formal questionnaire/test) were excluded.

Data extraction

Data was screened and extracted by two independent review authors (ZU and KC) with meta-analyses of outcomes performed using Review Manager Software Version 5.3. Pilot tested standardised data extraction templates were used with double data entry for characteristics of studies, results and

risk of bias assessments. Any discrepancies were resolved through consensus.

Intervention and comparator description:

Pharmacological and psychological interventions for the treatment of anxiety in COPD were included. Pharmacological interventions considered for inclusion were antidepressants or anxiolytics that are compared to placebo, usual care or no treatment. Psychological interventions that were considered included all types of formal psychotherapy as mentioned above. Comparisons included usual care, education only (e.g., written or oral education including provision of information about physical or mental health issues during a consultation or during a visit with another health professional where no formal counselling or psychological therapy was provided) or co-intervention (only if the co-intervention was also used in the control arm of the study).

Outcomes:

The primary outcome was change in anxiety from baseline to follow-up between groups.

Secondary outcomes were change in depression, quality of life, hospital utilisation (readmission rates and length of stay), exercise capacity (e.g., six minute walking distance) and adverse events.

Quality assessment and risk of bias

A quality assessment was conducted using standard Cochrane methodology via the risk of bias tool. This data was assessed and entered into Review Manager Software version 5.3, by two independent review authors (ZU and KC). Outcomes of interest include: Random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective reporting and other forms of bias.

Data analysis

Final follow-up outcomes were used as the primary end-point for all studies. Available data for meta-analysis was summarised using random effect model and reported as standardised mean difference (SMD) or/ and mean difference (MD). Meta-analysis was conducted comparing intervention and control arms of each study identified for inclusion. In the presence of considerable heterogeneity (visual inspection of the data combined with I-squared statistic of >75% to 100%) narrative synthesis was used in place of meta-analysis.

Sub-group analysis, heterogeneity and sensitivity analysis

Subgroup analyses occurred for pharmacological versus psychological interventions for the primary outcome of anxiety.

RESULTS

A total of 1,790 citations resulted in nine included studies (five pharmacological and four psychological) as presented in Figure 1.

The primary reasons for study exclusion were: minimum anxiety score not met or unable to get the baseline anxiety scores despite attempts to contact the authors, no appropriate comparator arm and anxiety outcomes not reported. Seven of the nine studies were RCT's, four psychological and three pharmacological, with the two remaining pharmacological studies being cross-over trials using a two-week washout period (see Table 1). Sample size ranged from 4 to 238 participants. Psychological interventions included: Psychoeducation therapy, CBT or a combination of these combined with co-interventions such as exercise and physiotherapy. Pharmacologi-

cal investigations included: paroxetine (two studies), citalopram hydrobromide, buspirone and doxepin hydrochloride.

Figure 1. PRISMA flow chart

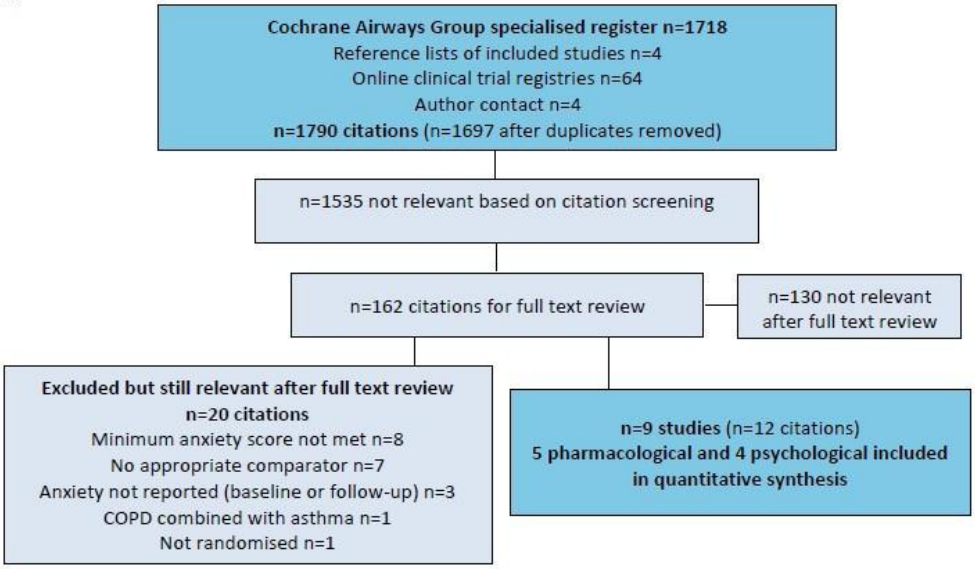


Table 1. Characteristics of included studies

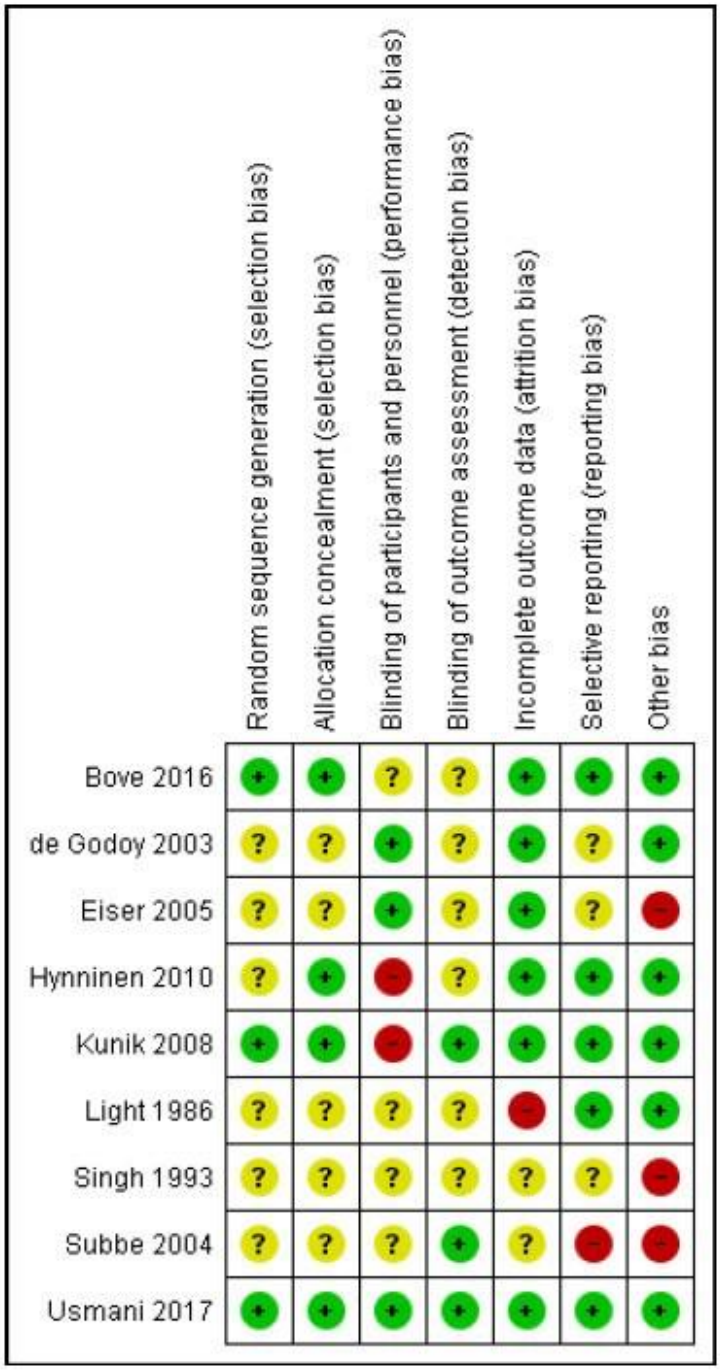
Included study	Design	Country	Int. sample	Cont. sample	Intervention	Comparator
Usmani 2018	RCT	Australia	10	12	4 months of paroxetine 20mg daily	Placebo
Bove 2016	RCT	Denmark	30	27	3 months of psychoeducative interventions using 1 hour face to face sessions laminated cards	Usual care
Hynninen 2010	RCT	Norway	25	26	7 weekly 2 hour sessions of psychoeducation awareness, relaxation, cognitive therapy, behavioural therapy, fear base exposure in group sessions	Enhanced standard care of COPD plus telephone contact every 2 weeks over 7 weeks
Kunik 2008	RCT	USA	118	120	8 one hour sessions of cognitive and behavioural training	COPD education
Eiser 2005	RCT	UK	9	8	6 weeks paroxetine 20mg daily	Placebo
Subbe 2004	RCT	UK	2	2	3 months and 1 week citalopram hydrobromide 10mg to 20mg	Placebo
De Godoy 2003	RCT	Brazil	14	16	12 weeks Psychotherapy + exercise and physiotherapy	Exercise and physiotherapy
Singh 1993	Cross-over (2 week washout)	USA	10	10	6 weeks buspirone 10mg tds to 20mg tds	Usual care (cross-over)
Light 1986	Cross-over (2 week washout)	USA	9	9	6 weeks of doxepin hydrochloride 25mg to 105mg	Usual care (cross-over)

Key: Darker rows are pharmacological studies whilst lighter rows include studies using psychological interventions.

Quality assessment and risk of bias

Random sequence generation and allocation concealment (selection bias) were assessed as unclear risk of bias for most studies due to inadequate reporting of methodology (see Table 2).

Table 2. Risk of bias assessment for included studies



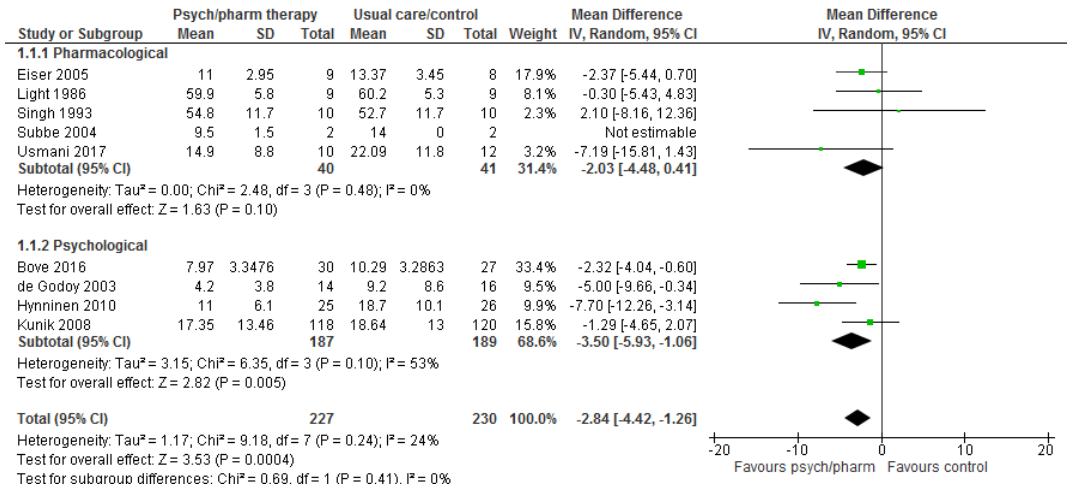
Three studies reported blinding of participants (performance bias) whilst three studies also reported blinding of outcome assessors (detection bias). Of note, it is diffi-

cult to blind psychological interventions as participants are aware of which treatment type they are receiving due to ethical considerations and full disclosure requirements. Attrition bias (reporting of incomplete outcome data) and reporting bias (selective reporting of outcome variables) were adequately addressed in six and five the nine studies respectively, whilst being unclear or inadequate in the remaining trials. Other types of bias were identified in three other trials One study (Eiser 2005) reported significant side effects from paroxetine in four of the 14 intervention subjects, resulting in a change to lofepramine 140mg, which subsequently may have affected the integrity of results. Another study (Singh 1993) including only n=10 subjects in each arm, included a population of only male subjects with authors reporting that dose and duration of treatment were a concern for lack of effect reported. Moreover, there was a population concern as baseline anxiety levels differed from initial screening levels. As such, patients had at most, mild anxiety. For the final study (Subbe 2004) raw data was obtained from study authors for COPD patients with baseline anxiety, resulted in inclusion of only n=4 participants in total. Two males were in the intervention arm and two females in the control arm, adding to the imbalance in participant data.

Effects of interventions

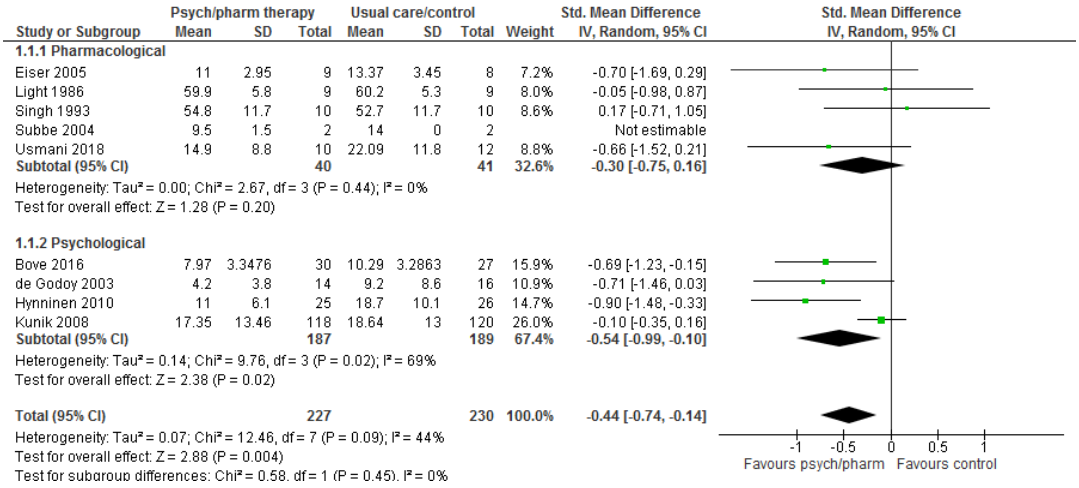
Anxiety: Meta-analysis of all nine completed trials revealed significant reductions to anxiety in the treatment arm (MD -2.67; 95%CI -3.88 to -1.47; p< 0.0001) with psychological studies producing greater treatment efficacy (p< 0.0001; 376 subjects) over pharmacological (p= 0.10; 81 subjects) within sub-group analysis. As significant heterogeneity was observed among the psychological sub-group (I^2= 53%) the data was re-analysed using the random effect model. Statistical significance was maintained (MD -2.84; 95%CI -4.42 to -1.26; p= 0.0004) with psychological studies still (MD -3.50; 95% CI -5.93 to -1.06; p= 0.005) outperforming pharmacological (MD – 2.30; 95% CI -4.48 to 0.41; p= 0.10; Figure 2). Minimal Important Difference (MID) for HADS-A in COPD patients has been reported as 1.5. We were unable to find a reference range for MID for BAI and STAI in COPD patients.

Figure 2. Meta-analysis of pharmacological and psychological interventions compared to usual care/control population for the outcome of anxiety using the random effect model



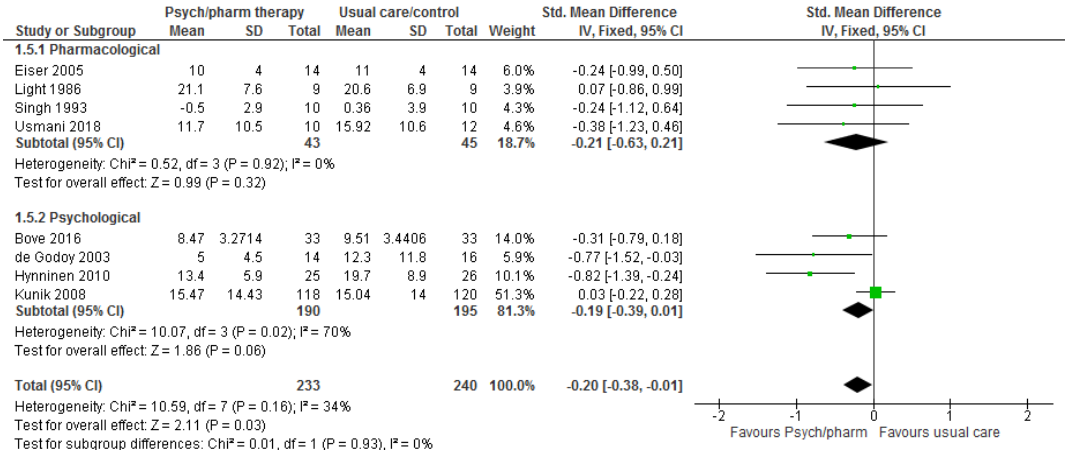
Studies included in the review, used different scales to assess levels of anxiety. One pharmacological and three psychological studies used BAI, whereas two pharmacological and one psychological studies reported anxiety as HADS-A and remaining two pharmacological studies used STAI to report anxiety scores/symptom. Hence, we also conducted a meta-analysis using standardised mean difference to account for different tools to be pooled together. The effect of intervention was still significant (SMD -0.44; 95% CI -0.74 to -0.14; p=0.004, Figure 3) with psychological interventions producing more significant effect (p= 0.02 for SMD) as compared to the pharmacotherapy (p= 0.20 for SMD).

Figure 3. Meta-analysis for anxiety using Standardised Mean Difference



Depression: Meta –analysis for depression scores showed overall significant improvement in depression symptoms with intervention (SMD -0.20; 95% CI -3.38 to -0.01; p=0.03, Figure 4) mainly driven by psychological interventions (p=0.06) as compared to the pharmacotherapy (p=0.32).Only one (Usmani 2018) of the five pharmacological studies reported depression as a secondary outcome, an improvement in depression scores (BDI) of more than clinically important difference was noted though the change did not reach statistical significance at four months of trial duration. All four of the psychological studies reported depression as an outcome with statistically significant reduction noted in two studies (de Gody 2003 and Hynninen 2010) and no significant change in depression scores were noted as result of intervention in the other two studies (Kunik 2008 and Bove 2016) . However it is important to note that Kunik et al compared education vs. CBT and significant reduction was noted post intervention for both the arms though not between the two groups likely as both were a type of intervention

Figure 4. Meta-analysis showing impact of interventions on depression symptoms.



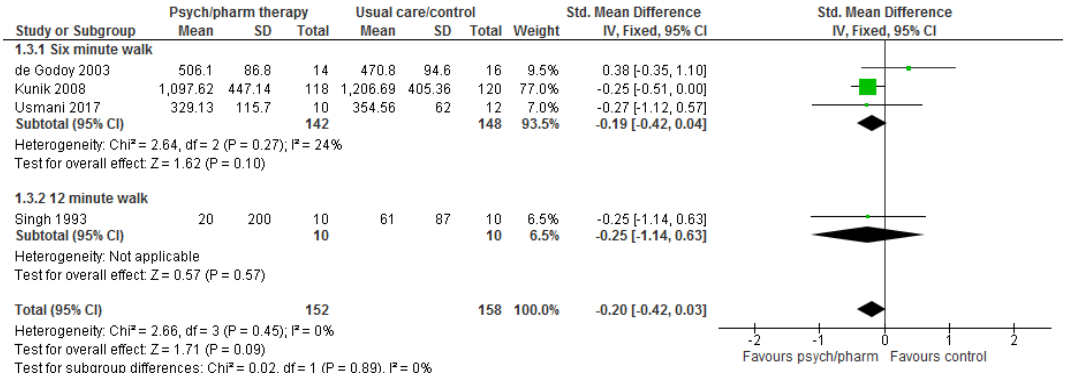
Quality of life: Quality of life was reported in all the three SSRI trials (Usmani 2018, Eiser 2005; Subbe 2004). Usmani et al used CRQ to measure quality of life and neither clinical nor statistical significant difference was noted for any of the domains of CRQ. Eiser et al reported QoL using SGRQ, the results comparing baseline with three months of open-labelled antidepressant treatment showed a clinically relevant difference for the intervention (total scores 65 to 58 for intervention and control groups respectively, p=0.033). Subbe et al used SGRQ to assess Qol, which demonstrated a clinically relevant but inconclusive effect favouring the control. Three of the four psychological studies reported QoL using different tools. Statistically significant improvement was noted in CRQ M and CRQ E component in the Bove 2016. . For Huynninen 2010 and Kunik 2008, psychological interventions were observed to be more effective compared to the control population for the combination of SGRQ and the physical composite of SF36 (standardised mean difference (SMD) -0.40, 95%CI -0.88 to -0.08; participants = 289; studies = 2; I2 = 61%; P = 0.10). No evidence of any effect was observed for SGRQ and the emotional composite of SF36 (SMD -0.30, 95%CI -1.03 to 0.44; participants = 289; studies = 2; I2= 82%). Alongside SF36, CRQ was also reported in the Kunik 2008 study with only one of the eight categories producing results in favour of the CBT group for general health (end of treatment eight-week score: intervention arm mean 34.14 + 28.53 and control arm mean 37.76 + 27.74; P = 0.05)

Exercise Capacity: No significant difference in exercise capacity was noted in any of the pharmacological or psychological trials assessing exercise capacity as an outcome (Figure 5).

Hospital Admissions. Only one of the nine trials formally assessed and reported the hospital readmission rate (Usmani 2018). There were fewer COPD-related hospital admissions in the intervention group compared to the placebo group during the four-month treatment phase (1/10 and 6/12 respectively; p=0.050).

Side effects: Medication related side effects were reported in pharmacological studies more in the treatment arm however no adverse event was reported related to the medication No significant side effects were reported in any of the psychological studies.

Figure 5. Meta-analysis showing impact of interventions on exercise capacity for six and 12 minute walking distance



DISCUSSION AND SUMMARY

Anxiety associated with COPD increases the burden of overall morbidity not only on the psychological parameters but also on the physical symptoms and overall quality of life. This meta analyses is the first in our knowledge to have systematically analysed the effects of various treatment modalities and the quality of evidence which exists for management of anxiety in COPD.

There are some limitations of the review. It should be acknowledged that pharmacological and psychological studies are heterogeneous in terms of measures of outcomes and treatment types and though we have analysed them together in our main analysis, each type of intervention may be more bene- ficial for a particular subset of patients. Overall, there was a lack of randomised con- trolled trails and only nine studies were eli- gible to be included according to our prede- fined inclusion criteria. Majority of the stu- dies particularly, the pharmacological stu- dies had small sample sizes. The majority of the studies did not report sequence genera- tion and allocation concealment. Psycholog- ical studies had the limitation of lack of blinding at participant level. However most of the studies were relatively free of report- ing bias. For most of the psychological in- terventions adverse events, length of stay, readmission rates and objective markers of lung disease such as FEV_1 were not included as an outcome in any of the three included studies. Psychological studies included participants with both anxiety and depression, which may limit generalisability of results.

Overall, significant improvement in anxiety symptoms was noted with treatment, with psychological interventions having most of the effect. In other words, psychological interventions appear to have the greatest efficacy for anxiety management over pharmacological treatments; however, the strength of the evidence is limited by the paucity of data due to the small number of included studies. Associated reduction was also noted in co-existing depression symp- toms in most of the studies. Quality of life and exercise capacity were either not re- ported or if reported no significant change was noted. One study reported reduction in hospital readmission rate but this was based on small sample size and should be inter- preted with caution. Overall more side ef- fects were noted with pharmacological inter- ventions as expected.

CONCLUSIONS

Based upon the available evidence, psychological therapies appear to be more effective than pharmacological interventions to reduce

anxiety in COPD patients. However, poor methodological quality and/or small sample size of studies investigating pharmacotherapy may be contributing to this discrepancy. Except for depression, significant change was not noted in other parameters of quality of life. However, because of the short follow up period of the studies it is possible that the benefit might be seen in the longer term. Methodologically rigorous trials with much longer follow up period and inclusion of health economics outcomes are required for patients suffering from co existing anxiety and COPD.

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Cochrane Collaboration of Depression, Anxiety and Neurosis.

Author role:

All authors named on this manuscript contributed to meta-analysis design, evaluation, preparation and review of the final manuscript.

Competing interests:

None

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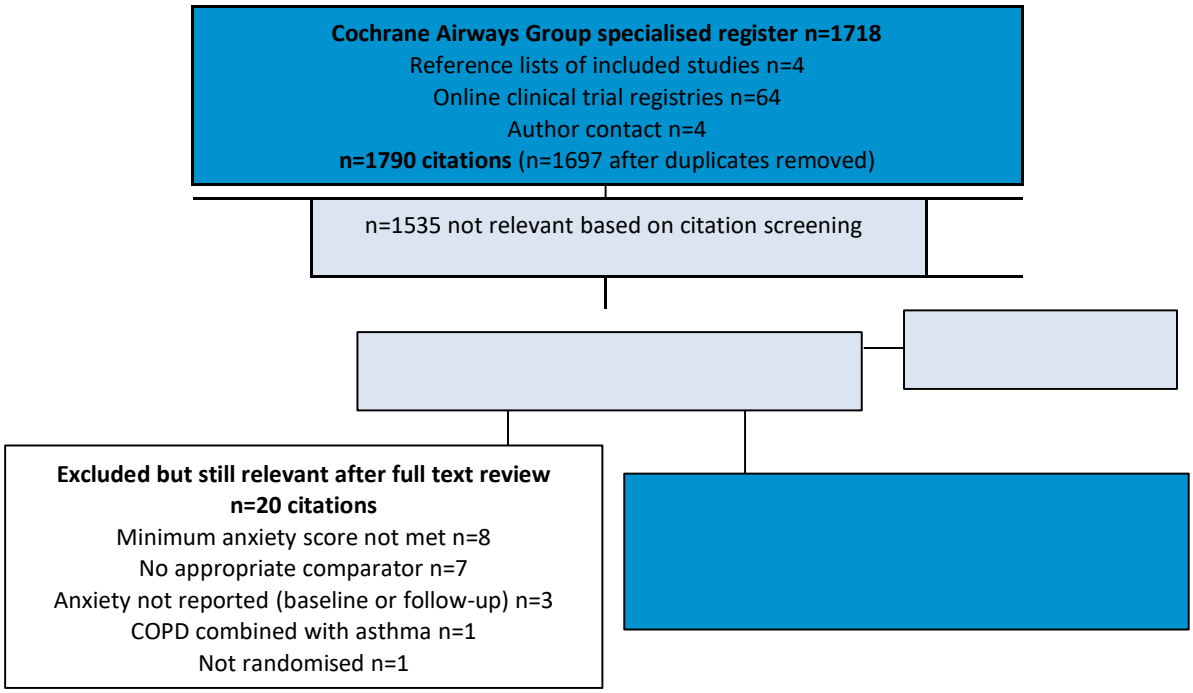
Appendices:

Figure 1. PRISMA flow chart



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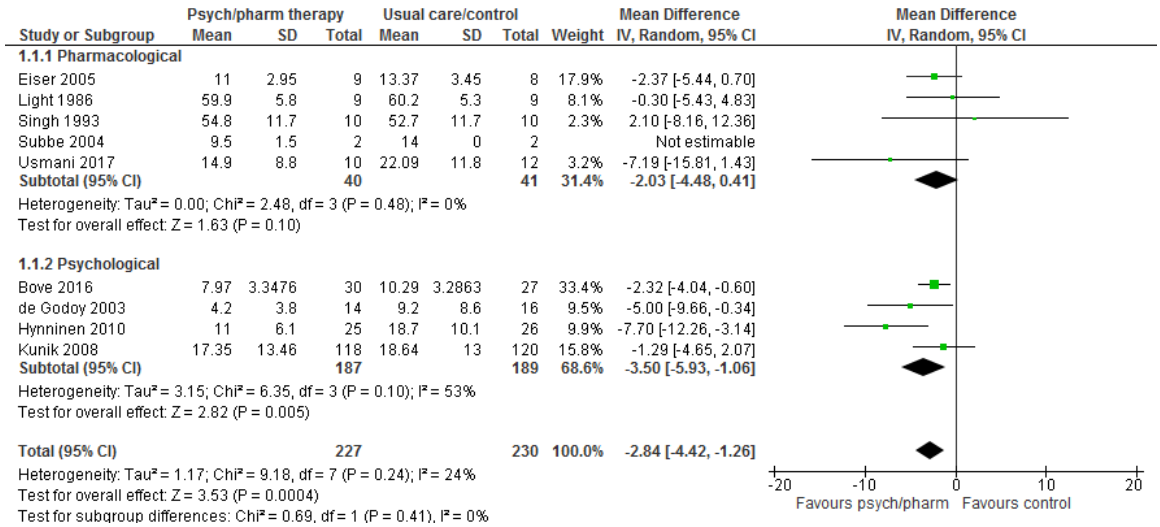

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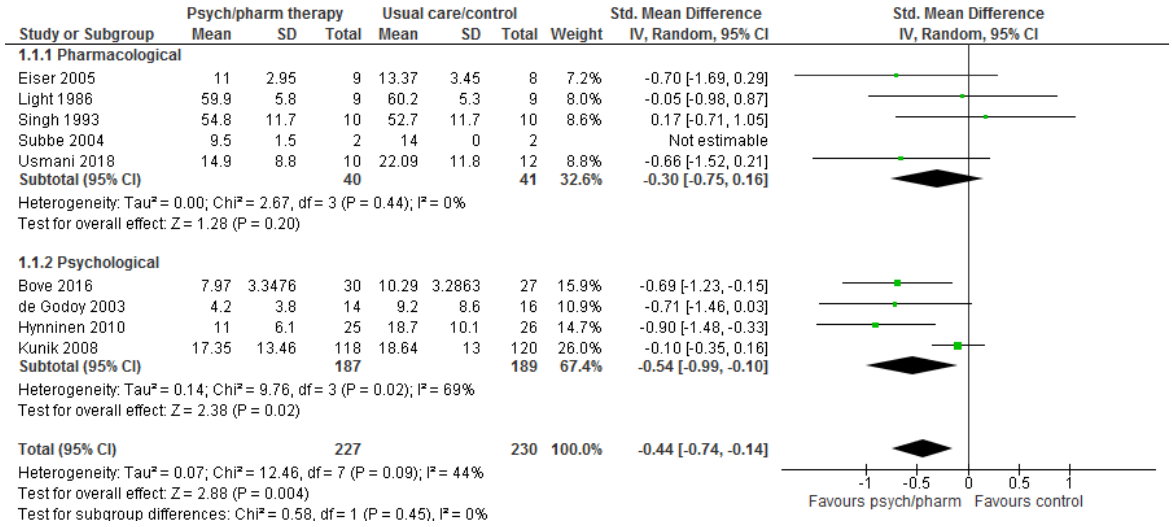

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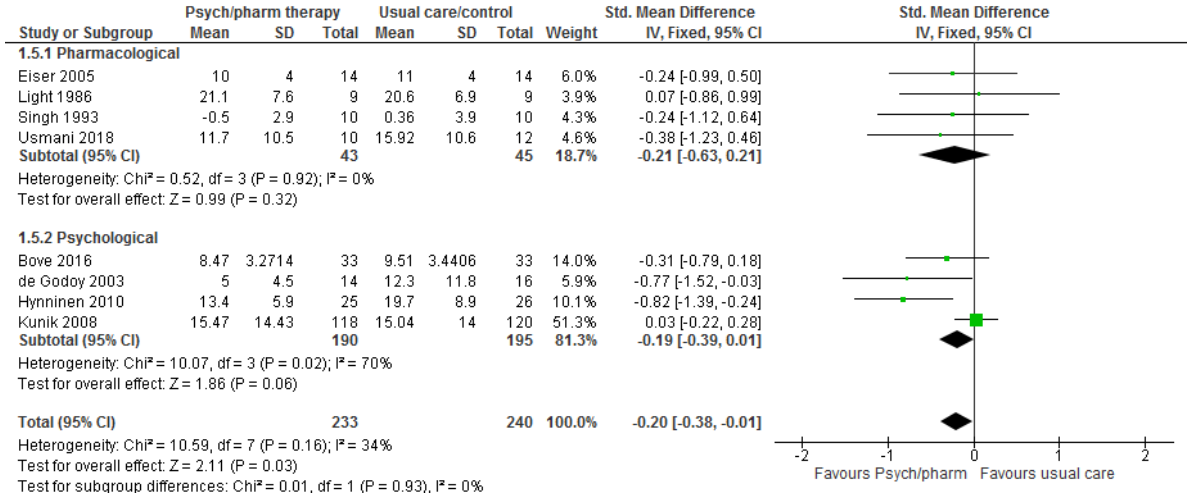

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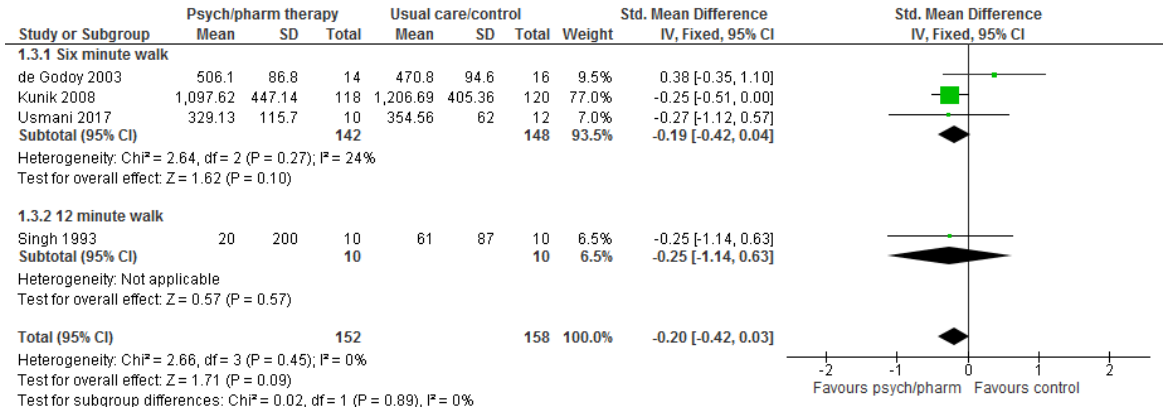

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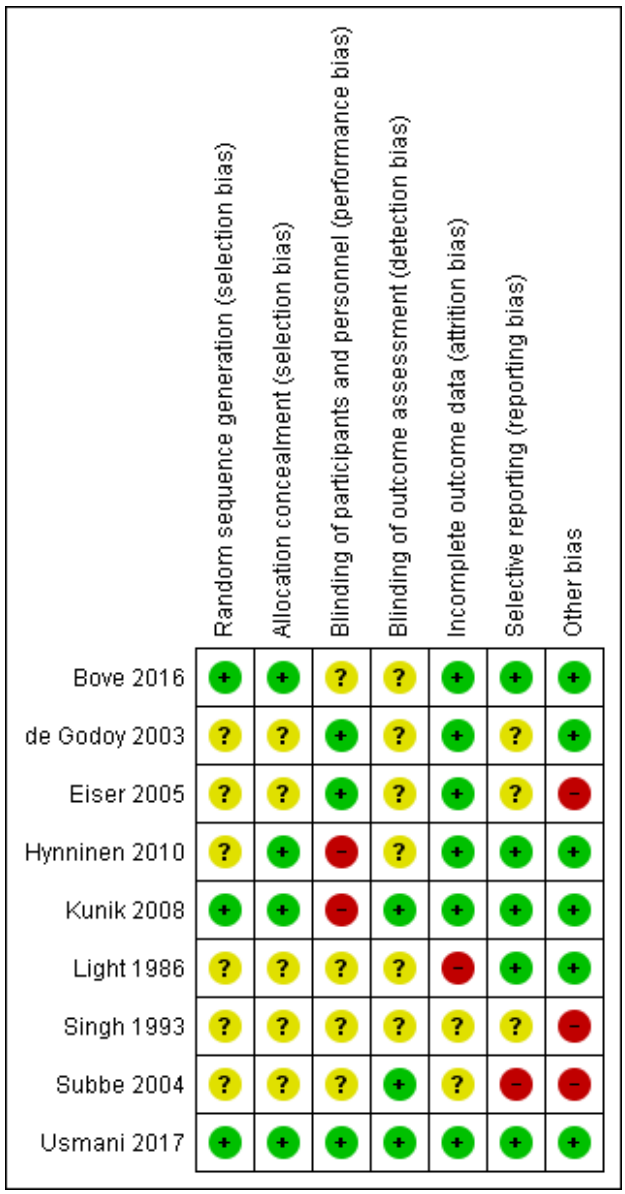
Singh 1993	Cross-over (2 week washout)	USA	10	10	6 weeks buspirone 10mg tds to 20mg tds	Usual care (cross-over)
Light 1986	Cross-over (2 week washout)	USA	9	9	6 weeks of doxepin hydrochloride 25mg to 105mg	Usual care (cross-over)

Key: Darker rows are pharmacological studies whilst lighter rows include studies using psychological interventions.

Table 2. Risk of bias assessment for included studies



Chapter 7. Discussion and conclusion

7.1 Significance and contribution to knowledge

COPD is one of the most common medical conditions in the world, with anxiety being one of its most commonly associated comorbidities. Co-existing anxiety, not only affects patients' psychological status, but also impairs quality of life, length of stay and re-admission rates, increasing the healthcare costs of COPD patients. Despite the frequent use of pharmacotherapy in clinical practice, our initial work (prior to this thesis) demonstrated limited and poor-quality data for use of pharmacotherapy in this population.

The literature was appraised and gaps were identified in which there lacked clear evidence for pharmacotherapy to manage anxiety in COPD patients (Appendix 1). Hence, a systematic review and meta-analysis was conducted for evidence of psychological interventions for management of anxiety in COPD patients (data available until August 2015). The systematic search in the literature for evidence of psychological interventions for management of anxiety in COPD discovered three RCTs, with a relatively larger number of participants than the pharmacotherapy studies. However, the overall sample was smaller than what would be regarded as well-powered. The quality of evidence was low. The systematic meta-analysis and review for psychological interventions demonstrated a significant reduction in anxiety with the use of psychological interventions as assessed in the included studies using Cognitive Behaviour Therapy (CBT) from three to six months. However, the studies included interventions that were heterogeneous. Two of the three studies reported quality of life through the use of three different tools. No significant difference was noted in the composite scores over a short follow-up period. Significant change was not noted in exercise capacity. CBT was generally well-tolerated. Hospital re-admission rates were not reported in any of the psychological studies. At the time of this review, three studies were identified as ongoing.

Because there was a lack of well-powered RCTs in the literature that assess the efficacy of pharmacological interventions for management of anxiety in COPD patients, a double-blind RCT of paroxetine 20 mg for patients with co-existing anxiety and COPD was conducted. After four months of treatment, significant reduction in anxiety was noted. Clinically important improvement was noted for depression. However, this did not reach statistical significance at four months. Significant difference was not observed for exercise capacity or quality of life. It was noted that patients on paroxetine experienced more side

effects (heartburn, insomnia, nausea, stomach upset and shakes) than the placebo and had less frequency of hospital admissions over the short follow-up period.

Since publication of the meta-analysis in Chapter 4, more recent evidence has been published that strengthens the evidence base to examine efficacy of psychological interventions for anxiety in this COPD population. In addition, the RCT presented in Chapter 5 has contributed with methodologically rigorous data examining efficacy and safety of pharmacotherapy for this population. Hence, a systematic meta-analysis was conducted of all the available evidence for the effect of pharmacological and psychological interventions for management of anxiety in COPD patients up to May 2018. Results of this review demonstrated that anxiety was significantly reduced post-intervention with both modes of therapy (MD –2.84; 95% CI –4.42 to –1.26; p = 0.0004, SMD –0.44; 95% CI –0.74 to –0.14; p = 0.004), with the psychological interventions producing greater treatment efficacy (MD –3.5; 95% CI –5.93 to –1.06; p = 0.005, SMD –0.54; 95% CI –0.99 to –0.1; p = 0.02) over pharmacological interventions (MD –2.03; 95% CI –4.48 to 0.41; p = 0.1, SMD –0.3, 95% CI –0.75 to 0.16; p = 0.2) within sub-group analysis, which supports the theory that patients correlate and associate their dyspnoea with abnormal thoughts, apprehension and fear of worse outcomes, leading to symptoms of anxiety and panic disorder in this population. As such, correcting or modifying these beliefs and behaviours would have a greater effect on patients' symptoms. Psychological interventions were better tolerated. However, none of the psychological studies examined the effect on hospital admission rates. It shall be noted that the strength of the evidence is limited by the paucity of data due to the small number of included studies.

7.2 Limitations and problems encountered

7.2.1 Systematic reviews, Cochrane meta-analyses and policy publications

For the Cochrane review and systematic literature review, there is a possibility that potentially relevant information will not have been included. Although all attempts are made to ensure that the search strategies are as comprehensive as possible, with the inclusion of grey literature via screening of bibliographies for included studies, review of online clinical trial registries and author contact, there remains a possibility that relevant citations might have been be missed.

For the Cochrane reviews in particular, only studies of sound methodological quality that meet the pre-specified and pre-published eligibility criteria are included in the meta-analyses. This means that the number of included studies will be sacrificed at the expense

of review quality. However, studies that were excluded from the Cochrane reviews were later captured in the generic meta-analysis and identified in the discussion, as the evidence has useful implications that can be used to underpin clinical practice in the absence of other high-quality evidence. Pharmacological intervention studies were relatively smaller, compared to the psychological intervention studies (likely because they were under-powered or stopped early). This must be considered while interpreting the results.

7.2.2 Randomised controlled trial of paroxetine

Few previous studies were available to guide the original power calculation, although one study showed an effect size of 1.0. An estimated sample size of 50 patients is required in each study arm. However, after three years of an intense recruitment campaign, only 38 participants could be recruited and were randomised to either placebo or intervention group. An ITT analysis was conducted, regardless of whether they had taken all or some of the tablets, as long as subjects did not refuse to continue with the trial. To account for the missing data of withdrawals, the options of 'random data imputation' or 'last observation carried forward' were considered. However, random imputation is not ideal for such a small sample size and if we were to impute the last observation (which, in this case, would be baseline) this is not ideal, in view of significant acute effect observed at short interval. Hence, the data were analysed using a linear mixed effects model, which would have automatically imputed any missing data. Despite the limitations, namely small sample size and relatively large dropout rate, this trial is the largest known RCT investigating the effect of a pharmacological agent for management of anxiety in people with COPD. A statistically significant result was demonstrated as a result of intervention.

7.3 Future directions

7.3.1 Opportunities for future research

Multi-centre RCTs are recommended for assessment of psychological interventions with a longer follow-up and economic evaluation.

7.3.2 Opportunities for clinical practice

Management guidelines for COPD should incorporate strategies for the early detection of anxiety in COPD and psychological therapies that mainly use CBT as initial intervention for control of these symptoms.

7.4 Conclusion

The publications and manuscripts included in this thesis discussed several studies examining treatment options for anxiety in a cohort with COPD, an area that has never been addressed in detail despite its prevalence. Results from this research can be used to underpin current practice, policy and direct future investigations and research to improve the clinical management of anxiety among COPD patients. Overall, psychotherapy has proven to be more effective for managing anxiety and panic disorder in COPD patients. Advocacy is required for incorporation of this intervention in COPD management guidelines along with the tools for early detection of anxiety in COPD.

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Appendices

Appendix 1 Publication: Pharmacological interventions for the treatment of anxiety disorders in COPD (Cochrane review)

Appendix 2 PAC study Case Report Form

Appendix 3 PAC study Patient Information Sheet

Appendix 4 PAC study Human Research Ethics Committee approval

Appendix 5 PAC study Ethics Committee approval for additional sites

Appendix 6 PAC study protocol

Appendix 1 Cochrane: Pharmacological interventions for the treatment of anxiety disorders in COPD (Review)

Pharmacological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease (Review)

Usmani ZA, Carson KV, Cheng JN, Esterman AJ, Smith BJ

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 11

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Pharmacological interventions for the treatment of anxiety and panic in chronic obstructive pulmonary disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to assess the effects of pharmacological interventions for the treatment of anxiety in patients with COPD.

BACKGROUND

Description of the condition

Evidence suggests that there is an increased incidence of anxiety disorders in patients with chronic obstructive pulmonary disease (COPD) (Maurer 2008).

Chronic obstructive pulmonary disease

COPD consists primarily of chronic bronchitis and emphysema which are characterised by the inflammation of airways and the destruction of pulmonary tissues. The diagnosis of COPD is based on the documentation of a post bronchodilator FEV1/FVC < 70% (Rabe 2007).

Anxiety and panic

Generalised anxiety disorder (GAD) is defined as excessive anxiety which lasts for at least six months. Individuals must also experience three or more of the following symptoms: difficulty in concentrating; fatigue after little exertion; sleep disturbance; a sensation of being 'keyed up'; irritability and/or muscle tension (DSM IV criteria) (APA 1994). Panic disorder is the presence of recurrent, unexpected panic attacks followed by at least one month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks, or a significant behavioral change related to the attacks (APA 1994). Panic attacks are discrete periods (usually ten minutes or less) of intense fear, with 8 out of 13 of the following symptoms: sweating, tremors, unsteadiness, derealisation or depersonalisation, tachycardia, nausea, tingling, light headedness or dizziness and shortness of breath accompanied by the fear of losing control, 'going crazy' or dying (APA 1994).

Anxiety in people with COPD

The lifetime prevalence of GAD amongst patients with COPD is estimated between 10% to15.8% (Brenes 2003). The most likely lifetime prevalence for GAD in the general population is approximately 5% using DSM criteria (Wittchen 2001). This suggests that GAD is two to three times more common in people with COPD. Rates of anxiety symptoms in patients with COPD range from 13% to 51% and are higher than the rates in patients with heart failure, cancer, and other medical conditions (Brenes 2003). A study conducted by Brenes et al indicated the prevalence rate of 8% for panic disorder in people with COPD, which is approximately five times greater than the general population (Brenes 2003).

Description of the intervention

The management strategies for the treatment of anxiety in COPD patients include both pharmacological and non-pharmacological interventions. This review will examine the effects of pharmacological interventions for anxiety in people with COPD.

Anti-anxiety medications include antidepressants, benzodiazepines, azapirones, antipsychotic agents, anticonvulsants and β-adrenergic receptor antagonists and antihistamines.

There are many different types of antidepressant medications. Antidepressants are put into groups based on which chemicals in the brain they affect. Main classes of antidepressants include: non-selective antidepressants and selective reuptake inhibitors.

Non-selective antidepressants include:

1) Tricyclic antidepressants (TCAs) act by serotonin and noradrenaline reuptake inhibition with effects on multiple receptor system and sodium conductance e.g. amitriptyline, nortriptyline (Borson 1992) and doxepin.

2) Monamine oxidase inhibitors (MAOIs) act by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability e.g. phenelzine and selegiline.

Selective reuptake inhibitors include:

1) Selective serotonin reuptake inhibitors (SSRIs) act only on the neurotransmitter serotonin e.g. citalopram (Silvertooth 2004), fluoxetine, paroxetine and sertraline.

2) Serotonin and norepinephrine reuptake inhibitors (SNRIs) act by by slowing down the reuptake of both serotonin and noradrenaline, but more selectively than other drugs e.g., venlafaxine and duloxetine.

3) Norepinephrine and dopamine reuptake inhibitors (NDRIs) increase the levels of norepinephrine and dopamine e.g. bupropion.

Benzodiazepines e.g.,diazepam, alprazolam, and lorazepam show a therapeutic effect by acting on norepinephrine, serotonergic and dopaminergic system (Kaplan 2009).

Azapirones such as buspirone exert a therapeutic effect by acting as a 5-HT_{1A} partial agonist (Argyropoulou 1993).

Antipsychotics such as olanzapine, risperidone, quetiapine, ziprasidone, or aripiprazole can be used in the treatment of anxiety disorders. Antipsychotics have a complex mechanism of action and exert an effect to block alpha-adrenergic ($alpha_1$ and $alpha_2$), dopamine (primarily D_2, but also D_1 and D_4), histamine (H_1), muscarinic (primarily M_1), and serotoninergic (primarily 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{1C}) receptors (Kaplan 2009).

Anticonvulsants such as gabapentin, topiramate, and lamotrigine have varied mechanism of action, for example increasing alpha-aminobutyric acid (GABA) function thereby enhancing neuronal inhibition or reducing neuronal excitation by decreasing glutamatergic function (Kaplan 2009).

Alterations in beta adrenergic receptor activity has been theorised to affect anxiety disorders. Beta adrenergic receptor antagonists such as propanolol have therefore been suggested to be efficacious

in some populations of patient with anxiety and agitation (Kaplan 2009).

Although antihistamines such as hydroxyzine and diphenhydramine have been used in anxiety and agitation, there has not been any strong evidence supporting its direct benefits in anxiety disorders. Rather its effect is more to reduce psychomotor retardation and sleep latency (Kaplan 2009).

How the intervention might work

A previous review found the components of COPD associated with anxiety to be the dyspnoea score (Funk 2009). On a neurochemical level, this association was further explained by demonstrating that prolonged hypoxia in rat models affected the areas of the brain involved in mood control (Borson 1998).

The understanding of mechanisms of mood control by antidepressants has evolved over time. The strong antidepressant activity of TCAs has supported the role of both norepinephrine and serotonin (5-HT) in mood disorders. The next generation of antidepressants included the selective serotonin reuptake inhibitors (SSRIs), further supporting the role of serotonin, while the selective norepinephrine reuptake inhibitors (SNRIs) such as maprotiline and reboxetine underlined the relevance of norepinephrine. These developments suggest that either facilitation of serotonin or norepinephrine or both may lead to an antidepressant response. The antidepressant activity of SNRIs is based on inhibition of norepinephrine and serotonin reuptake, but unlike TCAs they do not have anticholinergic, antihistaminergic, and cardiotoxic effects. The latest development has been the introduction of the noradrenergic and specific serotonergic antidepressant mirtazapine. Its antidepressant effect appears to be related to dual enhancement of central noradrenergic and serotonergic neurotransmission by blockade of α2- adrenoceptors. In addition, mirtazapine directly blocks 5-HT2 and 5-HT3 receptors, which may account for its anxiolytic and sleep-improving properties as well as its lack of adverse events that are typical of SSRIs (Westenberg 1999). Furthermore, antidepressants have been hypothesised to work in COPD patients by decreasing autonomic over-activity, or detaching excessive distress associated with COPD, thus enabling patients to better endure increased physical activity and physiological changes (Borson 1992). Other types of antianxiety medications work either by causing calming or sedative effects or by symptomatic control of anxiety symptoms.

Why it is important to do this review

Anxiety in people with COPD has been shown to increase disability and impair functional status, resulting in an overall reduction in their quality of life (Weaver 1997, Beck 1988). Importantly, the impact of anxiety on these outcomes was shown after adjusting for other potential confounders such as general health status, other medical conditions and COPD severity (Brenes 2003). A study by Kim et al reported that anxiety and depression were more strongly related to functional status than the severity of COPD (Kim 2000). Co-morbid anxiety in an elderly population with COPD has been suggested to be a significant predictor of the frequency of hospital admissions (Yohannes 2000). However, the evidence for treatment of anxiety in COPD is limited. It is important therefore, to evaluate interventions which will be effective in the alleviation of these symptoms in patients with COPD.

OBJECTIVES

This review aims to assess the effects of pharmacological interventions for the treatment of anxiety in patients with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), including cross over trials and cluster randomised trials, which assess pharmacological interventions for the treatment of anxiety and panic in patients with COPD will be considered.

Types of participants

Participants will be adults (over 18 years of age) of either sex and of all ethnicities, diagnosed with COPD (FEV1/FVC < 70) along with concurrent diagnosis of a recognised anxiety disorder (e.g. GAD or panic disorder) using established diagnostic criteria e.g. DSM criteria (APA 1994) or anxiety symptoms (as the primary problem) as assessed using a formal psychological instrument e.g. Beck Anxiety Inventory (BAI) (Beck 1961; BAI 1993).

Types of interventions

Intervention

We will include studies that used any pharmacological intervention for the treatment of anxiety in people with COPD and compared this to either placebo or to no treatment. We will include studies where the pharmacological intervention is delivered in combination with another intervention (co-intervention) only if there is a comparison group that received the co-intervention alone.

1. Pharmacological - antidepressants and anxiolytics e.g. TCAs, MAOIs, SSRIs, SNRI, NDRIs, benzodiazepines and mirtazapine.
2. Pharmacological and co-intervention (only if co-intervention used in the control arm of the study. Co-interventions may include pulmonary rehabilitation, self management, written action plans or psychotherapy such as cognitive behavioral therapy).

Control

1. No treatment
2. Placebo
3. Co-intervention (only if same co-intervention used in the intervention arm of the study)

Multi-arm trials will be included provided there is an intervention arm with any of the interventions mentioned above and a control arm with any of controls mentioned above.

Types of outcome measures

Primary outcomes

The primary outcome measure will be the reduction of anxiety symptoms as measured by a standardised or validated anxiety measure e.g. State-Trait Anxiety Inventory (STAI) (STAI 1970), Beck Anxiety Inventory (BAI) (BAI 1993) or Hamilton Depression Rating Scale (HDRS) (HDRS 1980).

Secondary outcomes

Each of the secondary outcomes will be assessed based on a validated assessment scale. The secondary outcomes to be measured will be:

- improvement of forced expiratory volume in one second (FEV1)
- increased exercise tolerance e.g. the six minute walk test (ATS 2002)
- reduction of dyspnoea e.g. the chronic respiratory questionnaire (Wijkstra 1994)
- improvement in quality of life e.g. the chronic respiratory questionnaire (Wijkstra 1994)
- reduction in length of stay or readmission rate
- adverse drug reactions

Search methods for identification of studies

See: Depression, Anxiety and Neurosis Group search strategy.

Electronic searches

CCDAN Registers

The Cochrane Collaboration Depression Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK. A references register and a studies based register. The CCDANCTR-References Register contains over 24,000 reports of trials in depression, anxiety and neuro- sis. Approximately 70% of these references have been coded and tagged to individual trials. These coded records are held in the CCDANCTR-Studies Register.

References to trials for inclusion in the CCDAN registers are collated from routine (weekly), generic searches of MEDLINE, EMBASE and PsycINFO; quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); annual searches of PSYNDEX, LILACS, AMED and CINAHL and review specific searches of additional databases. Details of trials are also sourced from international trials registers, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

A list of CCDAN's generic search strategies can be found in the 'Specialized Register' section of the Group's module text.

The Registers will be searched using the following search terms:

CCDANCTR-Studies Register

Diagnosis= anxiety or panic

And

Co-morbid diagnosis = COPD or "chronic obstructive pulmonary disease"

CCDANCTR-References Register

Free-text= ((anxiety or anxious or panic or distress*) and ((obstruct* and (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or COPD or emphysema or (chronic* and bronchiti*))

The following electronic databases will also be searched to identify further relevant studies. Appropriate RCT filters will be applied where necessary.

Cochrane Airways Group Register
Cochrane Central Register of Controlled Trials (CENTRAL)
MEDLINE (1950 to present)
CINAHL (1982 to present)
EMBASE (1980 to present)
PsycINFO (1806 to present)
Database of Abstracts of Reviews of Effectiveness (DARE)

No language restrictions will be applied.

Searching other resources

Reference lists of retrieved articles will be perused to identify any other potentially relevant articles.

Data collection and analysis

Selection of studies

The studies identified by the search strategies will be independently assessed by two of the three reviewers (ZU, JNC, KC) to determine whether they satisfy the initially outlined inclusion criteria. Disagreements will be resolved through discussion and by a third party if necessary (BS).

Data extraction and management

The following data will be extracted from each trial by two separate reviewers independently and any discrepancies will be resolved by discussion between the reviewers and a third party.

Study eligibility

Study design, population group and description of pharmacological intervention.

Participants

Number of participants, age, gender distribution, ethnicity and co-morbidities.

Interventions

Medication name, trade name, dose, duration of treatment, placebo or co-intervention description.

Assessment of risk of bias in included studies

The risk of bias for all the included studies will be assessed by two independent reviewers as per the Ccochrane Handbook guidelines, using a domain-based evaluation. The risk of bias will be assessed for each domain as Yes (low risk of bias), No (high risk of bias) and Unclear (using the guidance from table 8.5.c of the Cochrane Handbook) (Higgins 2009). Conflicts in the assessment will be resolved either by consensus or by referring to a third party. The domains that will be evaluated are:

Sequence generation

Methods considered as adequate include random number table, computer random number generator, coin toss, shuffling cards or envelopes, throwing dice and drawing lots (Higgins 2009).

Allocation concealment

Methods considered as adequate include: central allocation (phone, web, pharmacy), sequentially numbered identical drug containers and serially numbered sealed and opaque envelopes (Higgins 2009).

Blinding

Blinding will be considered adequate if: participants and key study personnel blinded, blinding probably not broken, use of identical placebo for pharmacological interventions (Higgins 2009).

Incomplete outcome data

The risk of bias due to incomplete outcome data will be assessed on the grounds whether the incomplete outcome data was adequately addressed or not as per the Cochrane Handbook section 8.12 (Higgins 2009).

Selective outcome reporting

The studies will be considered as of minimal bias if a protocol is available and all pre-specified outcomes are reported in the pre-specified way or if a protocol is not available but all expected outcomes were reported.

Other bias

Study conducted in such a way to ensure there were no other influencing factors that could potentially affect the outcome, for example, carry over in a cross over trial or extreme baseline imbalance. The results of risk of bias assessment will be presented in a risk of bias table and described narratively in the text with the results of the review. The studies with inadequate or unclear randomisation and/or allocation concealment will be considered as high risk of bias and we will be perform sensitivity analysis for these studies to assess their impact on the overall results.

Measures of treatment effect

Continuous data

For continuous outcomes, data will be entered as validated anxiety rating scales, for example using the Beck Anxiety Inventory Scale (BAI 1993), or the State-Trait Anxiety Index (STAI 1970). Most of these scales generate a total score which will be recorded for all pair-wise comparisons as either short term and/or long-term follow up data. The secondary outcome of quality of life may be measured as SF-36 scores or other questionnaires, and exercise tolerance will be measured using the six or twelve minute walk test. The data will be summarised by either mean differences (MDs) or standardised mean differences (SMDs), using mean values and standard deviations. In the case of an asymmetrical distribution of outcomes, we will analyse the skewed data with the help of rough check using the highest possible score for the anxiety scale used and subtracting the observed mean from it (Higgins 2009). If needed we will seek a statistician's help.

Dichotomous data

For binary data we will calculate odds ratios with 95% confidence intervals.

Unit of analysis issues

In the case of crossover trials, the data from the second period (after the crossover) will not be used as input if there is any doubt about the validity of data due to a significant carry over effect.
In studies of long duration, results may be presented for several periods of follow up (e.g. at six months, one year and two years). In such cases we would define different outcomes, based on different periods of follow up e.g. time frames will be defined to reflect short-term (up to six months), medium-term (6-12 months) and long-term follow up (more than 12 months).
In the case of cluster randomised trials, the analysis will be performed at the level of individuals while accounting for the clustering in the data. This will be performed using statistical methods recommended in the Cochrane Handbook (chapter 16.3.3) (Higgins 2009) and checked by a statistician.
In the case of multi-arm trials we will include each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons. We will also seek statistician's help in this method.

Dealing with missing data

Missing information regarding participants will be evaluated on an available case analysis basis as described in chapter 16.2.2 of the Cochrane Handbook (Higgins 2009). Missing standard deviations will be addressed by imputing data from studies within the same meta-analysis or from a different meta-analysis as long as these studies use the same measurement scale, have the same degree of measurement error and the same time periods (between baseline and final value measurement) (as per the Chapter 16.1.3.2 of the Cochrane handbook) (Higgins 2009). Where statistics essential for analysis are missing (e.g. group means and standard deviations for both groups are not reported) and can not be calculated from other data, we will attempt to contact the authors to obtain data. Loss of participants that occur before the baseline measurements are performed will be assumed not to affect the eventual outcome data of the study. Any losses after the baseline measurements are taken will be assessed and discussed. Studies that have more than 30% dropout rate will be reported in the text.

Assessment of heterogeneity

The review is expected to have some heterogeneity, as contributed by factors such as baseline severity of anxiety, severity of underlying COPD, time of measurement of results and varying measuring tools used to assess outcomes. The chi square and I-squared statistic (Higgins 2003) will be used to quantify inconsistency across studies and exploring heterogeneity by looking at differences between studies (i.e. types of interventions, participants etc). Heterogeneity will be further explored with a subgroup analysis (as per Chapter 9.5.3 of the Cochrane Handbook) (Higgins 2009). Details of the subgroup analyses are further explained in the later sections of this protocol.

Assessment of reporting biases

If there are more than ten included studies we will assess potential reporting bias using a funnel plot. Asymmetry in the plot could be due to publication bias, but may well be due to true heterogeneity, poor methodological design or artefact. In case of asymmetry, we may include contour lines corresponding to perceived milestones of statistical significance (p = 0.01, 0.05, 0.1 etc) to funnel plots, which may help to differentiate between asymmetry due to publication bias from that due to other factors (Higgins 2009). In the case of less than ten studies, the reporting biases will be reported as "other bias" in the risk of bias table.

Data synthesis

The extracted data will be pooled in meta-analysis using the random-effects model to allow for the expected heterogeneity (due to expected differences in the interventions and population). All these data will be analysed in Review Manager 5.0. We will include all the included studies in the primary analysis and will perform sensitivity analysis for studies with an unclear or high risk of bias for randomisation and allocation concealment and also for studies with participants with significant comorbidities e.g. dementia and severe heart failure. We will perform separate meta-analyses for each class of antianxiety medications (separate analysis for TCAs, SSRIs, SNRIs, benzodiazepines, anticonvulsants).

Subgroup analysis and investigation of heterogeneity

We will provide a description of all included studies in table and narrative form reporting on study design, population, intervention characteristics and outcome measures. Meta-regression and visual presentation using bubble plots will be used to investigate the sources of heterogeneity.
Subgroup analysis will be performed for each class of antianxiety medications as pair-wise comparisons of various types of drugs vs placebo, vs no treatment and vs co-intervention:

- Antidepressansts (presented by types) vs placebo.
- Antidepressants (presented by types) vs no treatment
- Antidepressants (presented by types) vs co-intervention

Sensitivity analysis

Sensitivity analysis will be conducted on studies with an unclear or high risk of bias for sequence generation and/or allocation concealment and studies with participants with significant comorbidities.

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The Cochrane Depression, Anxiety and Neurosis Group

The Cochrane Airways Group

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* *Indicates the major publication for the study*

HISTORY

Protocol first published: Issue 4, 2010

CONTRIBUTIONS OF AUTHORS

All the authors contributed towards writing of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Sanjiv Ranjan-Department of Psychiatry TQEH, Australia.

External sources

- Veronica Pitt-ACC, Australia.

training and teaching

Appendix 2 PAC study Case Report Form

CASE REPORT FORM FOR THE STUDY TITLED

'Paroxetine for anxiety in patients with chronic obstructive pulmonary disease' (PAC Study)

STUDY ID ☐☐☐☐

INITIALS ☐☐☐

Due dates for contact:

PHONE CALL

1wk _____
2wk _____
3wk _____
1mth _____

VISIT

4mth _____
12mth _____

This study file has been successfully completed and monitored. All information contained herein is accurate and confidential and will be used for no other purpose than that outlined to patients as submitted through the Ethics Committee.

Enrolment Date: ……

Study monitor's name: ……
Study monitor's signature: ……
Study investigator's name: ……

Monitor's Signature …… Date:…… Study Investigator:…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

INCLUSION/EXCLUSION CRITERIA

The following inclusion/exclusion criteria must be met to proceed:

INCLUSION CRITERIA	YES	NO
Adult patient age >40 years of age		
Diagnosis of COPD as per the GOLD criteria (post bronchodilator FEV_1/FVC <0.70)		
Clinically significant anxiety assessed by using the Beck's Anxiety Inventory (BAI ≥ 15 needed for eligibility; See page 3)		

All answers to the questions above must be ticked **YES** in order to proceed.

EXCLUSION CRITERIA	YES	NO
Currently undergoing an acute exacerbation of COPD		
Severe dementia or significant cognitive impairment		
Terminally ill		
Other significant concurrent psychological illnesses i.e., schizophrenia or active suicidal ideation		
Current use or use within the past two weeks of Monoamine Oxidase Inhibitors (MAOI's)s		
Pregnancy and lactation		
Severe kidney and/or liver failure		
Significant cardiovascular or locomotor disease		
Not willing to participate		
Previous history of intolerance to SSRI's		
Uncontrolled epilepsy		
Previous use of Antianxiety and Antidepressant medication		
ECG showing prolonged QT Interval (QTc > 450 msec)		

All answers to the questions above must be ticked **NO** in order to proceed.

Monitor's Signature ……..……...… Date:……..….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK ANXIETY INVENTORY (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at all	**Mildly but it didn't bother me much**	**Moderately – it wasn't pleasant at times**	**Severely – it bothered me a lot**
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or light-headed	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky/unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/light-headed	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring – Sum each column, then sum the column totals to achieve a grand score. **Grand score:** ..…….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK DEPRESSION INVENTORY (BDI)

1.
- 0 I do not feel sad.
- 1 I feel sad.
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty.
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
- 0 I am no more irritated by things than I ever was.
- 1 I am slightly more irritated now than usual.
- 2 I am quite annoyed or irritated a good deal of the time.
- 3 I feel irritated all the time.

12.
- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13.
- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.
- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
- 3 I believe that I look ugly.

15.
- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
- 2 I have to push myself very hard to do anything.
- 3 I can't do any work at all.

16.
- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
- 2 I get tired from doing almost anything.
- 3 I am too tired to do anything.

18.
- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

Monitor's Signature ……..……..… Date:……..….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

Total Score_____Levels of Depression

Monitor's Signature ……..……...… Date:……..….. Study Investigator:……..…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

BODE Index for COPD

The Bode Index is a composite marker of disease taking into consideration the systemic nature of COPD (Celli et al., 2004).

Scoring the BODE Index

	0	**1**	**2**	**3**
FEV1 % pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI (kg/m2)	>21	≤21		

Total BODE Index Score _____

(FEV1 % pred = predicted amount as a percentage of the forced expiratory lung volumes in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnoea scale; BMI = Body mass index)

Modified MRC Dyspnoea Scale	
0	Breathlessness only with strenuous exercise
1	Short of breath when hurrying on the level or walking up a slight hill
2	Slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level
4	Too breathless to leave the house or I am breathless when dressing

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

CRQ-SAS- 1ST ADMINISTRATION – Patient to complete

Below is a list of activities which make some people with lung problems feel short of breath. For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

	ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1	**Feeling emotional such as angry or upset**	1	2	3	4	5	6	7	8
2	**Taking care of your basic needs (bathing, showering, eating or dressing)**	1	2	3	4	5	6	7	8
3	**Walking**	1	2	3	4	5	6	7	8
4	**Performing chores (such as housework, shopping groceries)**	1	2	3	4	5	6	7	8
5	**Participating in social activities**	1	2	3	4	5	6	7	8

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7 that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

(Place an "x" in one box only)

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

Monitor's Signature ……..… Date:…….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS?**

1. Extremely tired ☐
2. Very tired ☐
3. Quite a bit of tiredness ☐
4. Moderately tired ☐
5. Somewhat tired ☐
6. A little tired ☐
7. Not at all tired ☐

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

10. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..…..… Date:……..….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

11. How much energy have you had in the **LAST 2 WEEKS**?

1. No energy at all ☐
2. A little energy ☐
3. Some energy ☐
4. Moderately energetic ☐
5. Quite a bit of energy ☐
6. Very energetic ☐
7. Full of energy ☐

12. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

13. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..…..… Date:…….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1. Very dissatisfied, unhappy most of the time ☐
2. Generally dissatisfied, unhappy ☐
3. Somewhat dissatisfied, unhappy ☐
4. Generally satisfied, pleased ☐
5. Happy most of the time ☐
6. Very happy most of the time ☐
7. Extremely happy, could not be more satisfied or pleased ☐

Monitor's Signature ……..……..… Date:……..….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

THANK YOU

This Questionnaire is now complete, please return the folder to the investigator

Monitor's Signature ……..…..… Date:……..….. Study Investigator:…….…… Date:……

Study ID: ☐☐☐☐ Initials: ☐☐☐

SUBJECT DEMOGRAPHICS

Enrolment Date: ☐☐ ☐☐ ☐☐☐☐

DOB: ☐☐ ☐☐ ☐☐☐☐ AGE: years……. **M / F** *(circle)*

Ethnicity:

Caucasian: ☐ Asian: ☐ Aboriginal: ☐ Other: ☐ Specify…….....

Occupation:…….....

Highest level of education achieved: ……

Patient income: <20,000 ☐ 20,001-30,000 ☐ 30,001-40,000 ☐

40,001-50,000 ☐ 50,001-60,000 ☐ 60,001-70,000 ☐ >70,001 ☐

COPD Diagnosis Criteria: ....……

Weight……..…….. Height……....… BMI……..…Pulmonary rehab? .....

Hospital…….. Inpatient / Outpatient / Mail-out / Referral / Other *(circle)*

Additional Comments:

……

COMORBIDITIES/OTHER HEALTH ISSUES

Event start date	**Event description**	**Event end date**	**Rx**	**Patient reported**	**OACIS /case notes**
09/11/07	e.g., Asthma, wheeze, dry cough	Ongoing	✔	✔	✔

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

CONCOMITANT MEDICATIONS

Start date	Medication Name	Duration	Dosage	Indication
2011	e.g., Paracetamol	Ongoing	PRN 500mg	Headaches

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

SMOKING HISTORY

Age when smoking commenced: ……..… Year smoking commenced: …….

PACK YEARS

Age range (yrs) Eg. 15-18	Cigs/day

Calculation (Yrs Smoked x cigs per day) / 20 = pack years

Years Smoked (age 2 - age 1)	X	Cigs/day	÷	20	Pack years for age range
	x		÷	20	
	x		÷	20	
	x		÷	20	
	x		÷	20	
	x		÷	20	
	x		÷	20	
				Total Pack Years =	

SMOKING HABIT

How many cigarettes do you smoke in an average day, over the past 12 months? ..…….…….….

What types of cigarettes do you smoke (filtered/unfiltered and mg if known) ……...

QUIT ATTEMPTS

Number of attempts to quit smoking: …… Longest time you stopped smoking for? …..……...

Reason for recommencement: ……..……...

FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE **TOTAL:** ☐☐

1. How soon after you wake up do you smoke your first cigarette?
   - ! After 60 minutes (0)
   - ! 31-60 minutes (1)
   - ! 6-30 minutes (2)
   - ! Within 5 minutes (3)

2. Do you find it difficult to refrain from smoking in places where it is forbidden?
   - ▪ No (0)
   - ▪ Yes (1)

3. Which cigarette would you hate most to give up?
   - ▪ The first in the morning (1)
   - ! Any other (0)

4. How many cigarettes per day do you smoke?
   - ! 10 or less (0)
   - ! 11-20 (1)
   - ! 21-30 (2)
   - ! 31 or more (3)

5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?
   - ▪ No (0)
   - ▪ Yes (1)

6. Do you smoke even if you are so ill that you are in bed most of the day?
   - ! No (0)
   - ! Yes (1)

Monitor's Signature ……..… Date:…….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

6 MINUTE WALKING DISTANCE (6MWD) REPORT

Test done by…… Date……..

Pre Exercise					**Post Exercise**				
SpO_2	HR	Breathing	Legs	Fatigue	SpO_2	HR	Breathing	Legs	Fatigue

Distance walked: …….. Metres Number of stops: ……

SPIROMETRY

	Actual value	**% predicted**
FEV_1/FVC		
FEV_1		
FVC		

CARBON MONOXIDE TEST

CO Test: …….. ppm

BLOOD PRESSURE

SYS…… DIA …….. PULSE …….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

1 WEEK REVIEW

Retrospective? Y / N

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: ……

Comments:……

……..

……..

Current smoking status: Smoking ☐ Not Smoking ☐

On a scale of 1 to 10 what is: (1 being not ……..……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events……..……..……..

……

Protocol violations……..

Any new medications?……

2 WEEK REVIEW

Retrospective? Y / N

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: ……

Comments:……

……..

……..

Current smoking status: Smoking ☐ Not Smoking ☐

On a scale of 1 to 10 what is: (1 being not ……..……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events……..……..……..

……

Protocol violations……..

Any new medications?……

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

3 WEEK REVIEW

Retrospective? Y / N

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: ……

Comments:……

……..

……..

Current smoking status: Smoking ☐ Not Smoking ☐

On a scale of 1 to 10 what is: (1 being not ……..……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events……..……..……..

……

Protocol violations……..

Any new medications?……

1 MONTH REVIEW

Retrospective? Y / N

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: ……

Comments:……

……..

……..

Current smoking status: Smoking ☐ Not Smoking ☐

On a scale of 1 to 10 what is: (1 being not ……..……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events……..……..……..

……

Protocol violations……..

Any new medications?……

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

END OF TREATMENT: 4 MONTH REVIEW

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: …… Retrospective? Y / N

Comments:……

……..

……..

Current smoking status: Smoking ☐ Not Smoking ☐ CO level: ……

On a scale of 1 to 10 what is: (1 being not ……..……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events……..……..……..

……

Protocol violations……..

Any new medications?……

6 MINUTE WALKING DISTANCE (6MWD) REPORT

Test done by…… Date……..

Pre Exercise					**Post Exercise**				
SpO_2	HR	Breathing	Legs	Fatigue	SpO_2	HR	Breathing	Legs	Fatigue

Distance walked: …….. Metres Number of stops: ……

SPIROMETRY

	Actual value	**% predicted**
FEV_1/FVC		
FEV_1		
FVC		

CO AND BP

CO Test: …….. ppm SYS…… DIA …….. PULSE …….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK ANXIETY INVENTORY (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at all	**Mildly but it didn't bother me much**	**Moderately – it wasn't pleasant at times**	**Severely – it bothered me a lot**
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or light-headed	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky/unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/light-headed	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring – Sum each column, then sum the column totals to achieve a grand score. **Grand score**..…….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK DEPRESSION INVENTORY (BDI)

1.
- 0 I do not feel sad.
- 1 I feel sad.
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
- 0 I am no more irritated by things than I ever was.
- 1 I am slightly more irritated now than usual.
- 2 I am quite annoyed or irritated a good deal of the time.
- 3 I feel irritated all the time.

12.
- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13.
- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.
- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
- 3 I believe that I look ugly.

15.
- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
- 2 I have to push myself very hard to do anything.
- 3 I can't do any work at all.

16.
- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
- 2 I get tired from doing almost anything.
- 3 I am too tired to do anything.

18.
- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

Total Score_____Levels of Depression

Monitor's Signature ……...… Date:……..….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

BODE Index for COPD

The Bode Index is a composite marker of disease taking into consideration the systemic nature of COPD (Celli et al., 2004).

Scoring the BODE Index

	0	1	2	3
FEV1 % pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI (kg/m2)	>21	≤21		

Total BODE Index Score _____

(FEV1 % pred = predicted amount as a percentage of the forced expiratory lung volumes in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnoea scale; BMI = Body mass index)

Modified MRC Dyspnoea Scale	
0	Breathlessness only with strenuous exercise
1	Short of breath when hurrying on the level or walking up a slight hill
2	Slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level
4	Too breathless to leave the house or I am breathless when dressing

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

CRQ-SAS: Follow-up administration – Patient to complete

This questionnaire is designed to find out how you have been getting along since the last time you saw us. You previously completed this questionnaire telling us how short of breath you were while performing the following activities. For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

	ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1	**Feeling emotional such as angry or upset**	1	2	3	4	5	6	7	8
2	**Taking care of your basic needs (bathing, showering, eating or dressing)**	1	2	3	4	5	6	7	8
3	**Walking**	1	2	3	4	5	6	7	8
4	**Performing chores (such as housework, shopping groceries)**	1	2	3	4	5	6	7	8
5	**Participating in social activities**	1	2	3	4	5	6	7	8

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS?**

1. Extremely tired ☐
2. Very tired ☐
3. Quite a bit of tiredness ☐
4. Moderately tired ☐
5. Somewhat tired ☐
6. A little tired ☐
7. Not at all tired ☐

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

10. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

11. How much energy have you had in the **LAST 2 WEEKS**?

1. No energy at all ☐
2. A little energy ☐
3. Some energy ☐
4. Moderately energetic ☐
5. Quite a bit of energy ☐
6. Very energetic ☐
7. Full of energy ☐

12. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

13. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1. Very dissatisfied, unhappy most of the time ☐
2. Generally dissatisfied, unhappy ☐
3. Somewhat dissatisfied, unhappy ☐
4. Generally satisfied, pleased ☐
5. Happy most of the time ☐
6. Very happy most of the time ☐
7. Extremely happy, could not be more satisfied or pleased ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

THANK YOU

This Questionnaire is now complete, please return the folder to the investigator

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

12 MONTH REVIEW

Retrospective? Y / N

Date: ☐☐ ☐☐ ☐☐☐☐ Contact person: …… Retrospective? Y / N

Comments:……

……

……

Current smoking status: Smoking ☐ Not Smoking ☐ CO level: …….

On a scale of 1 to 10 what is: (1 being not …….……. and 10 being extremely ……..…)

Dyspnoea scale: ☐☐ Level of depression: ☐☐

COPD symptoms: ☐☐ Level of anxiety: ☐☐

Adverse events…….……..…….

……..

Protocol violations…….

Any new medications?……

6 MINUTE WALKING DISTANCE (6MWD) REPORT

Test done by…… Date……..

Pre Exercise					**Post Exercise**				
SpO_2	HR	Breathing	Legs	Fatigue	SpO_2	HR	Breathing	Legs	Fatigue

Distance walked: …….. Metres Number of stops: ……

SPIROMETRY

	Actual value	**% predicted**
FEV_1/FVC		
FEV_1		
FVC		

CO AND BP

CO Test: …….. ppm SYS…… DIA …….. PULSE …….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK ANXIETY INVENTORY (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at all	**Mildly but it didn't bother me much**	**Moderately – it wasn't pleasant at times**	**Severely – it bothered me a lot**
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or light-headed	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky/unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/light-headed	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring – Sum each column, then sum the column totals to achieve a grand score. **Grand score**..…….

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

BECK DEPRESSION INVENTORY (BDI)

1.
- 0 I do not feel sad.
- 1 I feel sad.
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

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- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
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8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….

Study ID: ☐☐☐☐ Initials: ☐☐☐

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
- 0 I am no more irritated by things than I ever was.
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12.
- 0 I have not lost interest in other people.
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- 2 I have lost most of my interest in other people.
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13.
- 0 I make decisions about as well as I ever could.
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- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.
- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
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- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
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- 3 I can't do any work at all.

16.
- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
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- 3 I am too tired to do anything.

18.
- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

Total Score_____Levels of Depression

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

BODE Index for COPD

The Bode Index is a composite marker of disease taking into consideration the systemic nature of COPD (Celli et al., 2004).

Scoring the BODE Index

	0	**1**	**2**	**3**
FEV1 % pred	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
MMRC	0-1	2	3	4
BMI (kg/m2)	>21	≤21		

Total BODE Index Score _____

(FEV1 % pred = predicted amount as a percentage of the forced expiratory lung volumes in one second; 6MWD = six minute walking distance; MMRC = modified medical research council dyspnoea scale; BMI = Body mass index)

Modified MRC Dyspnoea Scale	
0	Breathlessness only with strenuous exercise
1	Short of breath when hurrying on the level or walking up a slight hill
2	Slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level
4	Too breathless to leave the house or I am breathless when dressing

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

CRQ-SAS: Follow-up administration – Patient to complete

This questionnaire is designed to find out how you have been getting along since the last time you saw us. You previously completed this questionnaire telling us how short of breath you were while performing the following activities. For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

	ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1	**Feeling emotional such as angry or upset**	1	2	3	4	5	6	7	8
2	**Taking care of your basic needs (bathing, showering, eating or dressing)**	1	2	3	4	5	6	7	8
3	**Walking**	1	2	3	4	5	6	7	8
4	**Performing chores (such as housework, shopping groceries)**	1	2	3	4	5	6	7	8
5	**Participating in social activities**	1	2	3	4	5	6	7	8

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS?**

1. Extremely tired ☐
2. Very tired ☐
3. Quite a bit of tiredness ☐
4. Moderately tired ☐
5. Somewhat tired ☐
6. A little tired ☐
7. Not at all tired ☐

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

10. In the **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

11. How much energy have you had in the **LAST 2 WEEKS**?

1. No energy at all ☐
2. A little energy ☐
3. Some energy ☐
4. Moderately energetic ☐
5. Quite a bit of energy ☐
6. Very energetic ☐
7. Full of energy ☐

12. In general, how much of the time did you feel upset, worried, or depressed during the **LAST 2 WEEKS**?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

13. How often during the **LAST 2 WEEKS** did you feel you had complete control of your breathing problems?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1. None of the time ☐
2. A little of the time ☐
3. Some of the time ☐
4. A good bit of the time ☐
5. Most of the time ☐
6. Almost all of the time ☐
7. All of the time ☐

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1. Very dissatisfied, unhappy most of the time ☐
2. Generally dissatisfied, unhappy ☐
3. Somewhat dissatisfied, unhappy ☐
4. Generally satisfied, pleased ☐
5. Happy most of the time ☐
6. Very happy most of the time ☐
7. Extremely happy, could not be more satisfied or pleased ☐

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense, or uptight?

1. All of the time ☐
2. Most of the time ☐
3. A good bit of the time ☐
4. Some of the time ☐
5. A little of the time ☐
6. Hardly any of the time ☐
7. None of the time ☐

THANK YOU

This Questionnaire is now complete, please return the folder to the investigator

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:…….……

Study ID: ☐☐☐☐ Initials: ☐☐☐

ADVERSE EVENTS

START DATE	END DATE (tick if ongoing)	REPORTED EVENT	OUTCOME	STUDY DRUG RELATED? Unlikely/Possible/Probable

Monitor's Signature ……..… Date:……..….. Study Investigator:…… Date:……..……

Study ID: ☐☐☐☐ Initials: ☐☐☐

STUDY VIOLATIONS

VIOLATION 1 - MEDICATION	TIME POINTS
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
VIOLATION 2 – FOLLOW UP P/CALLS	**TIME POINTS**
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
VIOLATION 3 – DATA COLLECTION	**TIME POINTS**
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐

Monitor's Signature ………………..… Date:…………..….. Study Investigator:…………………… Date:……….………

Study ID: ☐☐☐☐ Initials: ☐☐☐

STUDY VIOLATIONS CONT.

VIOLATION 4 – INC/EXC CRITERIA	TIME POINTS
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
VIOLATION 5 – WITHDRAWAL	**TIME POINTS**
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
VIOLATION 6 – OTHER	**TIME POINTS**
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐
	B/L ☐ 1w ☐ 2w ☐ 3w ☐ 1m ☐ 2m ☐ 4m ☐ 12m ☐

Monitor's Signature ………………..… Date:…………..….. Study Investigator:…………………… Date:……….………

Study ID: ☐☐☐☐ Initials: ☐☐☐

PATIENT COMPLETION / WITHDRAWAL

Has this patient withdrawn from the study? Yes ☐ No ☐

What is the reason for withdrawal?

Adverse event ☐ Study violation ☐

Patient withdrawal ☐ Investigator withdrawal ☐

Details: ……...

……

……

……

Does a (Serious Adverse Event) SAE form need to be filled out? Yes ☐ No ☐

ADVERSE EVENT

If adverse event please provide a follow up call: Date: ☐☐ ☐☐ ☐☐☐☐

Number of days post event at time of call: ☐☐☐

Details: ……...

……

……

INVESTIGATORS STATEMENT

This study file has been successfully completed and monitored. All information contained herein is accurate and confidential and will be used for no other purpose than that outlined to patients as submitted through the Ethics Committee.

Study monitor's name:……...

Study monitor's signature:…….

Study investigator's name:……

Monitor's Signature ……..… Date:…….….. Study Investigator:…… Date:…….……

Appendix 3 PAC study Patient Information Sheet

Government of South Australia
SA Health

THE QUEEN ELIZABETH HOSPITAL

PATIENT INFORMATION SHEET

Paroxetine (an antidepressant medication) for treatment of anxiety and depression in patients with Chronic Obstructive Pulmonary Disease (COPD or emphysema)

Protocol Number: 2012012

INVITATION TO PARTICIPATE

We invite you to participate in a research project which we believe is of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand

why we are doing it, and
what it would involve if you agreed.

We are therefore providing you with the following information.
Please read it carefully and be sure to ask any questions you have.
The Doctor conducting the research will be happy to discuss it with you and answer any questions that you may have.
You are also free to discuss it with outsiders if you wish (i.e. family, friends and / or your local Doctor).
You do not have to make an immediate decision.
Your participation is purely voluntary. Should you agree to enter the trial, you may change your mind and withdraw at any stage.

PARTICIPATION IS VOLUNTARY

Participation in any research project is voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage without providing a reason.

Your decision to take part, not to take part or to withdraw will not affect your routine treatment, your relationship with those treating you, or your relationship with The Queen Elizabeth Hospital.

BACKGROUND TO THE STUDY

What is the research about?
To assess the effects of Paroxetine (an antidepressant, commonly used to treat anxiety and depression) in improving anxiety and depression symptoms, quality of life, exercise capacity and hospital admissions for patients with co-existing emphysema and anxiety and/or depression.

Paroxetine is a serotonin reuptake inhibitor medication, that is why it is called "SSRI" for short. This means that it helps to boost your serotonin levels, which in turn may help to relieve any depression and anxiety that you experience. At the present time, we do not know who will be helped by this medication, so in order to discover wether we can predict ahead-of- time who will respond to this medication, we need to ask you to give us a sample of 2 tablespoons of blood in the usual way. We would also like to measure how much oxygen is in your blood whilst you are

off oxygen for a few minutes and this will be done by clipping a small peg-like instrument to your index finger. These two procedures well be required at baseline, at 4 months and at 12 months.

Why is the research being done?
Patients with COPD (emphysema and chronic bronchitis) are more likely to have anxiety and depression compared with the general population and patients with other common diseases. These symptoms adversely affect various aspects of daily life, including activities of daily living, emotional status and recurrent hospitalisations. Medications are widely used to treat these symptoms; however, so far no major research project has looked into the effects of these medications in patients with emphysema. Hence, we have designed this research project to investigate the potential benefits of Paroxetine (an depressant commonly used to treat anxiety and depression) for patients with co-existing emphysema and anxiety and/or depression

How and why have I been chosen as a possible participant in the research?
You have been asked to participate in this study because:

You have emphysema, and initial screening with anxiety and depression scales has shown that you have at least mild anxiety and/or depression that may be impairing your functional and emotional status.

How many other people have been asked to consider participating?
We are aiming to recruit 186 people to this study.

PROCEDURES AND TREATMENT

Will I have to come back to the clinic more often or remain in hospital for longer than would normally be the case?
Participation in this study will not prolong your current hospital admission. However, you willl be required to attend three out patient sessions for assessment of questionnaires and a six minute walk test. You will also be required to give us another blood test sample and have an oxygen measure taken on these occasions. First visit will be at recruitment, second after four months and the third visit will be at 12 months of recruitment.

What will I be asked to do at each visit?
You will be asked to:
- Complete anxiety and depression questionnaires.
- Functional status questionnaires.
- Give a blood sample (2 tablespoons) and have an oxygen reading via a peg-like clip placed on your finger.
- Perform a 6 minute walk test.
- Report any adverse effects that you have noticed.
- Perform spirometry (breathing test only the short version)
- Exhalation test (blow into a small tube) to assess smoking dependence.

How long will my participation in the study last?
12 months (to take the pill for 4 months only)

What procedures will I be asked to submit to including exposure to radiation and what will be the likely effects?
The y tests that you will be asked to undertake will be a blood test, an oxygen measurement by placing a peg-like clip on your finger, shorter version of breathing test and monitoring level of your carbon mono oxide test (by blowing into a small tube), and a 6 minute walk test (6MWT). Lung function trsting and six minute walk test is usually a part of standard care of patients with emphysema to asses their exercise capacity. Some people can experience shortness of breath; however, you can choose to walk as slowly as you want. Incase of any episode of chest pain or significant leg pain the test will be terminated and you will be reviewed by a clinician.

What treatment will I get if I do take part? Will this be different from the treatment I would get otherwise? If so, how and in what ways?
You will either receive Paroxetine (an antidepressant medication) or an identical placebo tablet. Paroxetine is usually used and indicated for patients with anxiety and depression. This belongs to one of the newer classes of antidepressants and has fewer side effects as compared with the traditional antidepressants (eg, tricyclic antidepressants).

If I decide not to take part what other treatments are available to me?
Standard treatment for anxiety and depression include antidepressants (either paroxetine or other antidepressants from the same or other class) or cognitive behavioural therapy These would be available to you as part of usual care.

Will the decisions about my treatment be made by my usual doctor or by someone else?
If you decide not to participate in this study, this will not in any way affect your usual care and all the decisions about your care will be made by your usual clinician or your GP.

Are there any factors, which would exclude me from participating, like pre-existing illness, the possibility of becoming pregnant or other drugs being taken?
If you have or will develop any of the following, you will be excluded from the study:

- Currently undergoing through an acute exacerbation of COPD.
- Have severe dementia or significant cognitive impairment.
- Are terminally sick.
- Have concurrent other significant psychological disease eg, schizophrenia or have active suicidal thoughts.
- Current or use within last two weeks of Monoamine Oxidase Inhibitors (MAOIs).
- Pregnant or breastfeeding.
- Severe liver and or kidney failure.
- Significant heart or locomotor disease.
- Not willing to participate.
- Current regular use of antianxiety or antidepressant medications

MEDICINES AND DRUGS

What are the names and amounts of the drugs which I will be given and how will they be administered?
Paroxetine (Aropex) 20 mgs daily, which will be administered orally.

PATIENT MANAGEMENT

What should I do if I were to feel severe discomfort or pain?
It is very unlikely that the blood test or this medication will give you any significant pain or discomfort; however, if you do experience discomfort or pain then you should report it to Dr Zafar Usmani, You should also stop taking the medication and contact Dr Zafar Usmani (0882226670) or your GP during working hours. If you are unable to contact either of these people, or it is after-hours, you should visit the local hospital's emergency department.

DISCOMFORTS, RISKS AND SIDE EFFECTS

Will there be any discomforts, such as additional needles, biopsies, or pain?

You may have had a blood sample taken before, and if so you will remember that there is a slight discomfort associated with giving a blood sample. However your blood sample will be taken by experience staff or nurses who are regularly undertaking this procedure, and the risk associated with this procedure is very low.

There is no discomfort associated with having your oxygen levels recorded.

Are there likely to be side effects from the research procedures, and if so what are they?

Possible side effects of Paroxetine include,

- Sleepiness (15% to 24%)
- Insomnia (11% to 24%).
- Headache (17% to 18%).
- Dizziness (6% to 14%).
- Decreased libido (3% to 15%).
- Nausea (19% to 26%),
- Dry mouth (9% to 18%).
- Constipation (5% to 16%) and diarrhea (9% to 12%).
- Ejaculatory disturbances (13% to 28%).
- Tremor (4% to 11%).
- Chest pain (3%), palpitation (2% to 3%), hypertension (≥1%).
- Rash (2% to 3%).
- Blurred vision (4%), abnormal vision (2% to 4%).
- Sweating (5% to 14%).

Who should I contact if I am worried about any effects that I experience?
If you experience any significant side effects then you should stop taking the medication and contact Dr Zafar Usmani (0882226670) or your GP during working hours. Incase if you are unable to contact either of these two and after hours, you should visit the local hospital's emergency department.

Would I be withdrawn from the study if my condition became worse or if any extra risks came to light during the course of it?
Yes

Are there any activities I should refrain from during and in the period following the research, and for how long?
The effects of paroxetine on the foetus are not completely understood.
Therefore, if you are a female, you must not become pregnant during the study. You should either be using a highly effective method of contraception such as oral contraceptives or intra uterine device (IUD), be surgically sterile or post-menopausal in order to participate in this study.

Your study doctor must be told immediately if you become pregnant. He/she will withdraw you from the study and advise on further medical attention should this be necessary. You will not be able continue in the study if you become pregnant

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED?

How will my confidentiality be protected – will the information and results be de-identified?
By signing this form you consent to the project team collecting and using your personal data for the study ("Study Data"). This includes information such as your date of birth, sex, ethnicity, and clinical information on your health or condition. Your consent to the use of your Study Data does not have a specific expiration date, but you may withdraw your consent at any time by notifying the project team.

Please note, the results of the study may be published in medical literature, but you will not be identified.

You have the right to request information about your Study Data held by the project team. You also have the right to request that any inaccuracies in such data be corrected. If you wish to make a request, then please contact the project team.

If you withdraw your consent the project team will no longer use your Study Data or share it with others. The project team may still use Study Data that was shared with it before you withdrew your consent.

By signing this form I consent to the use of Study Data as described in this form.

Will I be informed about the results of the study?
All the participants will be notified of the results of their investigations and further management plan via phone call. If you wish to know the results of the whole study, please notify us of your wish.

Anyone who has an abnormal result on their blood test that is easily correctable will be notified or their designated GP or chest physician notified (as they direct).

How long will my information be stored for?
15 Years

WHAT ARE MY RIGHTS?

If you become injured during this study, and your injury is a direct result of the effects of study procedures, The Queen Elizabeth Hospital will provide reasonable medical treatment. Your participation in this study shall not affect any other right to compensation you may have under common law.

How can I obtain more information
For more information, please contact:
Dr Zafar A Usmani,
On 08 8222 6670

PAYMENT FOR PARTICIPATION

Will I be paid for my participation?
This is a voluntary study to improve clinical practice and no payments will be made for participation. However, cab vouchers for transport to and from the hospital may be provided if necessary as required.

BENEFITS OF THE RESEARCH

Is there any chance that the proposed research will be of benefit to me personally, or to future patients with the same condition?
Yes, this research will highlight the importance of recognising and treating mood disorders in patients with emphysema in order to improve their quality of life and reduce hospitalization
If any of your biomarkers are easily correctible, your GP pr chest physician will be notified at the end of the trial and you may be offered appropriate treatment.

Were the new treatment to be of benefit to me, could I continue with the treatment after the trial?
Yes, this could be requested to be prescribed by your usual clinician or GP.

WHAT IF I HAVE A QUESTION ABOUT THE STUDY?

For more information or for questions about this study, please contact:

In case of a study-related injury or whenever you have questions about the study or your study medication, please contact project team:

Zafar Usmani	**Phone: 8222 7966 or 82226000 or 0438360714**
Kristin Carson	**Phone: 8222 8685 or 0402 396 707 or Pager: 47742**
Malcolm Brinn	**Phone: 8222 7834**

Address: 4A,TQEH, 28 Woodville Rd, WOODVILLE SA 5011

The Human Research Ethics Committee (TQEH/LMH/MH) has approved this study.

Should you wish to speak to a person not directly involved in the study in relation to:

- *matters concerning policies,*
- *information about the conduct of the study*
- *your rights as a participant, or*
- *Should you wish to make a confidential complaint,*

then you may contact The Executive Officer of this Committee, on (08) 8222 6841.

THE QUEEN ELIZABETH HOSPITAL

CONSENT FORM

Title: Paroxetine (an antidepressant medication) for treatment of anxiety and depression in patients with Chronic Obstructive Pulmonary Disease (COPD or emphysema)

Protocol Number: 2012012

I, the undersigned .....

hereby consent to my involvement in the research project explained above.

- I have read the information sheet, and I understand the reasons for this study. The research worker has explained the ways in which it will affect me. My questions have been answered to my satisfaction. My consent is given voluntarily.
- I understand that the purpose of this research project is to improve the quality of medical care, but my involvement may not be of benefit to me.
- The details of the research project have been explained to me, including:
  - The expected time it will take
  - The nature of any procedures being performed, and the number of times they will be performed
  - The nature of any medications I may be given
  - Any discomfort which I may experience
- I understand that I (or my partner) should not be pregnant during the course of this trial. In the event of pregnancy occurring (in myself or my partner), I will notify the investigator as soon as practically possible.
- I have been given the opportunity to have a member of family or a friend present while the project was explained to me.
- My identity will be kept confidential, and nothing will be published which could possibly reveal my identity.
- My involvement in the study will not affect my relationship with my medical advisers. I understand that I am able to withdraw from the study at any stage without having to give a reason, and that by withdrawing it will not affect my treatment at this hospital in the future.

PATIENT NAME ……

PATIENT SIGNATURE ……..... **DATE** ……/……/…….

WITNESS NAME ……..……..

WITNESS SIGNATURE: ……..... **DATE** ……/……/…….

INVESTIGATOR NAME: ……..……

INVESTIGATOR SIGNATURE: ..... **DATE** ……/……/…….

Appendix 4 PAC study Human Research Ethics Committee approval

Government of South Australia
SA Health

HUMAN RESEARCH ETHICS COMMITTEE (TQEH/LMH/MH)

17 July 2012

The Queen Elizabeth Hospital
Lyell McEwin Hospital
Modbury Hospital

Dr Zafar Usmani
Respiratory Unit
The Queen Elizabeth Hospital

Ph: +61 08 8222 6841
Fax: +61 08 8222 6007
Email: geh.ethics@health.sa.gov.au

DX 465101
The Queen Elizabeth Hospital
28 Woodville Road
Woodville South SA 5011

Dear Dr Usmani

Application Number **2012012**

The Human Research Ethics Committee has considered additional information to your protocol entitled:
"Paroxetine for Anxiety and Depression in Patients with Chronic Obstructive Pulmonary Disease"

In accordance with the National Statement on Ethical Conduct in Human Research, the following documents have been reviewed and approved:

- Human Research Ethics Committee Proposal for Research, version 1.3, dated 08 July 2012
- GPs/Clinicians Contact Template, version unknown, undated
- Patient Telephone Conversation Template, version unknown, undated
- Patient Information Sheet and Consent Form, version 1.2, dated 25 January 2012
- Support letter from A/Prof Smith -Director of Respiratory Medicine TQEH, dated 24 January 2012
- Response to HREC, dated 08 July 2012
- Support email from Ms Challen -Pharmacy TQEH, dated 03 July 2012

Approval Status: **FINAL**

Period of Approval: **17 July 2012 – 17 July 2013**

***Please note the terms under which Ethical approval is granted:**

1. Researchers are required to immediately report to the Human Research Ethics Committee anything which might warrant review of ethical approval of the protocol, including:
   a) serious or unexpected adverse effects on participants;
   b) proposed changes in the protocol; and
   c) unforseen events that might affect continued ethical acceptability of the project
2. Protocols are approved for up to twelve months only and a report is required at the end of the study or 12 month period. Extensions will not be granted without a report to the Committee.
3. Confidentiality of the research subjects shall be maintained at all times as required by law
4. All research subjects shall be provided with a Patient Information Sheet and Consent Form, unless otherwise approved by the Committee
5. The Patient Information Sheet and Consent Form shall be printed on the relevant site letterhead stating the contact details for the researchers
6. The Patient Information Sheet must state that the Executive Officer can be contacted for information regarding conduct of the study, policies and procedures, or if the participant wishes to make a confidential complaint
7. A report and a copy of any published material should be forwarded to the Committee at the completion of the project.

Yours sincerely

A/Professor Timothy Mathew
Chairman, Human Research Ethics Committee (TQEH/LMH/MH) TM:mm

Appendix 5 PAC study Ethics Committee approval for additional sites

Government of South Australia
SA Health

Human Research Ethics Committee (TQEH/LMH/MH)
Basil Hetzel Institute DX465101
The Queen Elizabeth Hospital
28 Woodville Road
Woodville South SA 5011
Telephone: 08 8222 6841
Email: qeh.ethics@health.sa.gov.au

21 August 2015

Dr Zafar Usmani
Respiratory Unit
The Queen Elizabeth Hospital

Dear Dr Usmani

Application Number: 2012012
Project title: Paroxetine for Anxiety and Depression in Patients with Chronic Obstructive Pulmonary Disease.

RE: Approval of Additional sites

Thank you for your request for additional sites to be added to the approval for the above project.

I am pleased to advise that request is granted by the Chairman of the Queen Elizabeth Hospital Human Research Ethics committee. The approved sites now includes:

- **The Repatriation Hospital**
- **Flinders Medical Centre**
- **The Royal Adelaide Hospital**

Please note: The site additions may require approval from each sites Research Governance Office. Please contact all relevant site Research Governance Officer(s) and enquire whether any further review/approval is required by the Site.

This Committee is constituted in accordance with the NHMRC *National Statement on the Ethical Conduct of Human Research (2007) and incorporating all updates.*

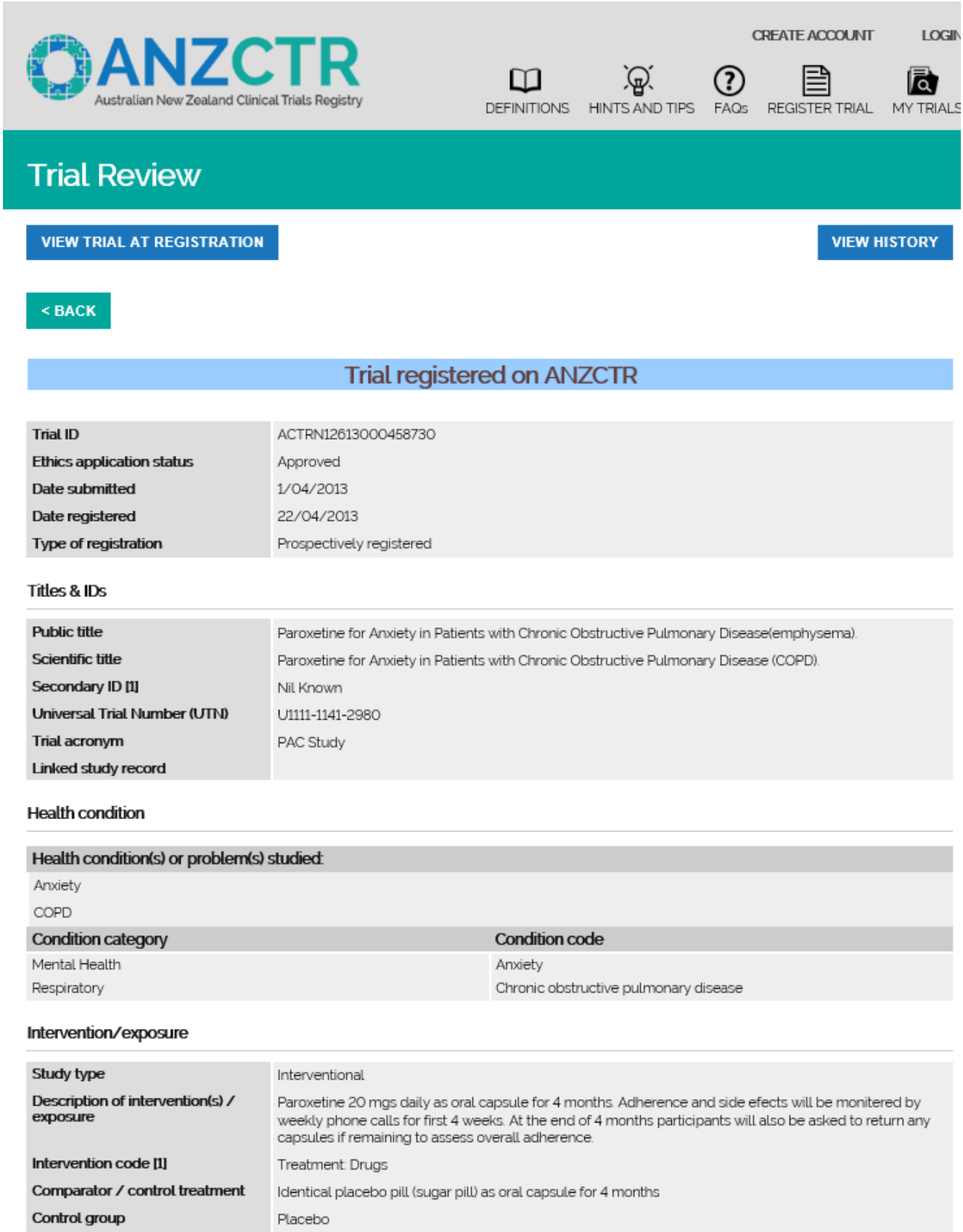
Should you have any queries about the HREC's consideration of your project please the HREC Executive Officer on 08 8222 6841 or qeh.ethics@health.sa.gov.au

Yours sincerely

Mrs Heather O'Dea
Team Leader, Executive Officer
Human Research Ethics Committee (TQEH/LMH/MH)

Page 1 of 1

Appendix 6 PAC study protocol



ANZCTR
Australian New Zealand Clinical Trials Registry

CREATE ACCOUNT LOGIN

DEFINITIONS HINTS AND TIPS FAQs REGISTER TRIAL MY TRIALS

Trial Review

VIEW TRIAL AT REGISTRATION VIEW HISTORY

< BACK

Trial registered on ANZCTR

Trial ID	ACTRN12613000458730
Ethics application status	Approved
Date submitted	1/04/2013
Date registered	22/04/2013
Type of registration	Prospectively registered

Titles & IDs

Public title	Paroxetine for Anxiety in Patients with Chronic Obstructive Pulmonary Disease(emphysema).
Scientific title	Paroxetine for Anxiety in Patients with Chronic Obstructive Pulmonary Disease (COPD).
Secondary ID [1]	Nil Known
Universal Trial Number (UTN)	U1111-1141-2980
Trial acronym	PAC Study
Linked study record	

Health condition

Health condition(s) or problem(s) studied:	
Anxiety	
COPD	
Condition category	**Condition code**
Mental Health	Anxiety
Respiratory	Chronic obstructive pulmonary disease

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	Paroxetine 20 mgs daily as oral capsule for 4 months. Adherence and side efects will be monitered by weekly phone calls for first 4 weeks. At the end of 4 months participants will also be asked to return any capsules if remaining to assess overall adherence.
Intervention code [1]	Treatment: Drugs
Comparator / control treatment	Identical placebo pill (sugar pill) as oral capsule for 4 months
Control group	Placebo

Outcomes

Primary outcome [1]	Anxiety as measured by Beck Anxiety Inventory (mean difference)
Timepoint [1]	4 months and 12 months.
Secondary outcome [1]	Depression as measured by beck Depression inventory (mean difference)
Timepoint [1]	4 months and 12 months.
Secondary outcome [2]	Quality of Life as assessed by Chronic Respiratory Questionnaire (CRQ) (mean difference)
Timepoint [2]	4 months and 12 months.
Secondary outcome [3]	Exercise capacity as measured by 6MWD in meters (mean difference).
Timepoint [3]	4 months and 12 months.
Secondary outcome [4]	Dyspnea as assessed by MMRC dyspnea scale (mean difference as compared with placebo)
Timepoint [4]	4 months and 12 months.
Secondary outcome [5]	Hospital bed utilization/health economics analysis
Timepoint [5]	4 months and 12 months.
Secondary outcome [6]	Lung Function as measured by FEV1
Timepoint [6]	4 months and 12 months.
Secondary outcome [7]	Adverse events will be monitered by weekly phone calls for first four weeks and will also be documented at 4 months visit. Patients will also be advised to report to the investigators of any side effects that they will experience other than these follow-up calls/visits. Coomon side effects can be Central nervous system: Somnolence , insomnia , headache, dizziness. Endocrine & metabolic: decreased Libido. Gastrointestinal: Nausea , xerostomia , constipation , diarrhea Genitourinary: Ejaculatory disturbances. Neuromuscular & skeletal: Weakness , tremor Cardiovascular: Chest pain , palpitations. Dermatologic: Rash. Ocular: Blurred vision Miscellaneous: Diaphoresis.
Timepoint [7]	week 1,2,3 &4. 4months and 12 months.
Secondary outcome [8]	Smoking dependence as measured by exhaled carbon monooxide.
Timepoint [8]	4 months and 12 months.
Secondary outcome [9]	Prediction of COPD related mortality as assessed by using BODE index. BODE: B- BMI in Kgms/m2; O- Obstruction as measured by spirometry in FEV1 ; D- dyspnea as measured by MMRC and E- exercise capacity as measured using 6MWT.
Timepoint [9]	4 months and 12 months.

Eligibility

Key inclusion criteria	Patients with: COPD, as confirmed by lung function testing ie FEV1/FVC <0.70, and Anxiety symptoms with Beck Anxiety Inventory (BAI) score of >15.
Minimum age	40 Years
Maximum age	No limit
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	Severe cognitive impairment Terminal cancer. Pregnancy and lactation.

	Unstable psychiatric condition like schizephrenia or active suicidal ideation. Current use of MAOinhibitors. Intolerance or allergy to SSRIs. Prolonged QT interval on ECG. Current acute exacerbation of COPD Current use of regular antianxiety and antidepressant medications.

Study design

Purpose of the study	Treatment
Allocation to intervention	Randomised controlled trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	central randomisation by computer
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	Computerised sequence generation
Masking / blinding	Blinded (masking used)
Who is / are masked / blinded?	The people receiving the treatment/s The people administering the treatment/s The people assessing the outcomes The people analysing the results/data
Intervention assignment	Parallel
Other design features	
Phase	Phase 4
Type of endpoint(s)	Efficacy

Recruitment

Recruitment status	Not yet recruiting
Anticipated date of first participant enrolment	27/05/2013
Actual date of first participant enrolment	
Anticipated date last participant enrolled	
Actual date last participant enrolled	
Anticipated date of last data collection	
Actual date of last data collection	
Target sample size	100
Actual sample size	

Recruitment in Australia	
Recruitment state(s)	SA
Recruitment hospital [1]	The Queen Elizabeth Hospital - Woodville
Recruitment hospital [2]	Lyell McEwin Hospital - Elizabeth Vale
Recruitment hospital [3]	Repatriation Hospital - Daw Park
Recruitment hospital [4]	The Royal Adelaide Hospital - Adelaide
Recruitment hospital [5]	Flinders Medical Centre - Bedford Park

Funding & Sponsors

Funding source category [1]	Hospital
Name [1]	Department of Respiratory Medicine, The Queen Elizabeth Hospital, (TQEH) South Australia, Australia
Address [1]	4A, TQEH 28 Woodville Road, Woodville South, SA 5011
Country [1]	Australia
Primary sponsor type	Hospital
Name	Department of Respiratory Medicine, TQEH
Address	4A, TQEH 28 Woodville Road, Woodville South, SA 5011
Country	Australia
Secondary sponsor category [1]	None
Name [1]	
Address [1]	
Country [1]	

Ethics approval

Ethics application status	Approved
Ethics committee name [1]	HUMAN RESEARCH ETHICS COMMITTEE (TQEH/LMH/MH)
Ethics committee address [1]	DX 465101 The Queen Elizabeth Hospital 28 Woodville Road Woodville South SA 5011
Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	18/01/2012
Approval date [1]	30/04/2012
Ethics approval number [1]	2012012

Summary

Brief summary	An association between increased dyspnoea scores, mood disorders and anxiety levels in patients with COPD has been well established. On a neurochemical level, this association has been further explained in rat models showing that prolonged hypoxia affects the areas of the brain involved in mood control. The understanding of mechanisms of mood control by antidepressants has evolved over time. The strong antidepressant activity of Tricyclic Antidepressants (TCAs) has supported the role of both norepinephrine and serotonin (5-HT) in mood disorders. The next generation of antidepressants included the Selective Serotonin Reuptake Inhibitos (SSRIs), further supporting the role of serotonin. Furthermore, antidepressants have been hypothesised to work in COPD patients by decreasing autonomic over-activity, or detaching excessive distress associated with COPD, thus enabling patients to better endure increased physical activity and physiological changes. Hence, our hypothesis is that subjects recruited from public hospitals with COPD and clinically significant depression and/or anxiety that are given paroxetine 20 mgs daily for 4 months will: (Hypothesis 1: principle hypothesis): have a significant reduction in their anxiety symptoms as compared with the placebo at 4 months follow-up, and;

	(Hypothesis 2): these improved levels of anxiety will be associated with: improved quality of life and exercise capacity, and (Hypothesis 3): these improved levels of anxiety will be associated with: a.) a reduction in hospital bed utilisation, and; b.) a reduction in health care costs in relation to existing practice in long term (12 months)
Trial website	
Trial related presentations / publications	
Public notes	Primary outcome assessments will occur at 4 months. However in order to assess the longterm effects all the outcomes will be reassessed at 12 months.

Contacts

Principal investigator	
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