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Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial.

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Take Home Message

Chronic breathlessness generates suffering late in life. In this setting, titrated sertraline had similar benefits and harms to placebo in an adequately powered, multi-site, double blind, randomised controlled trial at four weeks.

Abstract

Does sertraline provide symptomatic relief for chronic breathlessness in people with advanced disease whose underlying cause(s) are optimally treated?

Two hundred and twenty three participants with chronic breathlessness (modified Medical Research Council (mMRC) breathlessness scale ≥2) who had optimal treatment of underlying cause(s) were randomised 1:1 to sertraline 25 mg-100 mg (titrated upwards over nine days) or placebo for four weeks. The primary outcome was the proportion who had an improvement in intensity of current breathlessness >15% from baseline on a 100 mm visual analogue scale (VAS).

The proportion of people responding to sertraline was similar to placebo for current breathlessness on days 26-28 (odds ratio [OR] 1·00, 95% CI 0.71 to 1·40) and for other measures of breathlessness. Quality of life in the sertraline arm had a higher likelihood of improving than placebo over the four weeks (OR 0·21, 95% CI 0·01 to 0·41, p=0·044). No differences in performance status, anxiety and depression, nor survival were observed. Adverse event rates were similar between arms.

Sertraline does not appear to provide any benefit over placebo in the symptomatic relief of chronic breathlessness in this patient population.

Introduction

Breathlessness is an uncomfortable sensation of breathing which is experienced by nearly fifty percent of people in their last year of life, regardless of diagnosis [1-3]. It is a source of physical and psychological distress for the patient and their caregivers [4].

The main therapy for chronic breathlessness is treating the underlying cause(s). Despite this, many people remain highly symptomatic [5]. Systemic opioids (oral and parenteral) can reduce breathlessness [6,7]. To date, no other pharmacological intervention has been shown to be of benefit. A meta-analysis of benzodiazepines found no net benefit despite widespread use [8]. Nebulised furosemide and systemic antidepressants are being explored [9,10].

Selective serotonin reuptake inhibitors (SSRI) are well tolerated anti-depressants. Early phase studies suggest that they may reduce chronic breathlessness, even in people who are not depressed. A potential mechanism is their anxiolytic effect. Sertraline, an SSRI, shows potential benefit for chronic breathlessness, is well tolerated [11] and used first-line as an anti-depressant. Two non-randomised pilot studies and a case series have reported benefits of sertraline 12·5mg-100 mg in people with chronic breathlessness due to optimally treated chronic obstructive pulmonary disease (COPD) [12-14]. Another study enrolled people with COPD and depression for up to 19 weeks of treatment with paroxetine (another SSRI) in a small double blind study. People experienced a clinically meaningful improvement in the St George Respiratory Questionnaire (SGRQ). [15] In another small randomised trial of 12 weeks of paroxetine in people with COPD, there were significant improvements in the emotional function and mastery domains of the Chronic Respiratory Questionnaire (CRQ). [16] These data support the need for an adequately powered study.

The aim of this study was to assess the effects of sertraline on intensity of chronic breathlessness despite optimal treatment of underlying cause(s). Secondary aims were to determine: sertraline's effects on quality of life and activities of daily living; and benefits and harms. The null hypothesis was that there is no difference between sertraline and placebo for chronic breathlessness.

Materials and Methods

Study design
This double blind, dose increment, parallel arm, multi-site, randomised, placebo-controlled, adaptive study was conducted in accordance with International Committee on Harmonization – Good Clinical Practice (ICH GCP) [17,18] and registered (ACTRN12610000464066).
The adaptive design was a blinded phase II / III study where the phase II study was not unblinded (having demonstrated acceptability and feasibility), moving directly to the phase III study. Phase II data were therefore included in the main analysis.

Participants were recruited from ten inpatient and outpatient services in palliative care, oncology, respiratory medicine and cardiology units across Australia. Their primary family caregiver was also invited to participate.

Study population
Potential participants were eligible when: ≥18 years; diagnosed with chronic breathlessness where the underlying cause(s) had been maximally treated as attested by their specialist treating physician; had breathlessness ≥2 mMRC breathlessness scale [19]; on stable medications for breathlessness for the previous week (with exception of 'as needed' medications); a life expectancy of ≥2 months; and able to read English.

Potential participants were ineligible if they had: a previous adverse reaction to sertraline; severe hepatic impairment, gastrointestinal bleeding, or respiratory failure; serum sodium <128mmol/L; uncontrolled seizures; respiratory depression; a respiratory or cardiac event in the past week; severe depression (HADS depression sub-score >16); treatment with any medicine that increased the risk of serotonin syndrome; or pregnant or breastfeeding.

Intervention
The active study arm was one capsule daily of oral sertraline (day 1-3 25mg daily; days 4-6 50mg daily; and then 100mg daily). Back titration was allowed to the next lowest dose if the current dose was not tolerated. Participants could continue on their blinded arm for up to 6 months after completing the first 28 days (primary end point). At study end, dose was titrated down, halving the dose every three days.

Control
Identical appearing capsules were administered as a placebo.

Both arms were permitted to take up to eight doses of 2·5 mg of immediate release oral morphine solution 'as needed' in any 24-hour period.

Randomisation (1:1) was stratified by baseline Hospital Anxiety and Depression Scale (HADS) anxiety sub-scale (0-10 mild to moderate; or 11-21 moderate to severe) and depression (0-10; 11-16) giving four strata [20], each within blocks of four per site. Pharmacists allocated participants to the next available code according to a supplied table to dispense identical-appearing sertraline or placebo. Ward pharmacists, investigators, treating clinicians, participants and carers remained blinded to treatment allocation at all times.

At study visits (days 0, 9 and 29), laboratory measures and Australian-modified Karnofsky Performance Status (AKPS) [21] were collected. Participants completed the CRQ – Dyspnea Subscale (CRQ) [22], participant and carer quality of life questionnaires (EORTC-QLQ-C15-Pal [23] and CQOLC [24]), HADS [20] and descriptors of breathlessness [25]. Participants completed a diary twice daily (days 0, 7, 14, 21, 26, 27, 28) to record current breathlessness intensity, unpleasantness, and worst breathlessness on a 0-100 mm VAS and a 4-point Likert scale, and the modified Medical Research Council (mMRC) (Appendix 1) breathlessness scale [17]. Optionally, participants could remain on blinded treatment for an additional five months (six months treatment in total).

Measurements
The primary outcome measure was the average of the morning and evening *current intensity of breathlessness* VAS scores over days 26, 27 and 28. Secondary end-points included exposure to treatment; breathlessness (average, worst and relief *over the previous 24 hours*, unpleasantness *now* on 0-100mm VAS); response by anxiety and, separately, depression; response in people with and without COPD, response by level of mMRC; use of as needed immediate release oral morphine solution; quality of life; CRQ (breathlessness, fatigue, mastery); functional status; anxiety and depression; survival; harms; global impression of change (GIC); and choice to enter the extension phase.

Statistical analysis
Response rates in previous studies of pharmacological interventions for the symptomatic relief of chronic breathlessness have been high. [26] For a new therapy to be considered clinically significant, there must be a substantial net benefit over placebo. By consensus, the expected response rate was set at 41% for sertraline, while anticipating that 20% of participants in the placebo arm would also improve. A sample size of 75 completed participants per group provided >80% power for a two-tailed type 1 error rate of 0·05 between arms. Allowing for expected attrition, recruitment of 240 participants was planned.

Analyses were conducted on an intention-to-treat basis. An interim blinded analysis assessing safety and reviewing the power calculation was conducted by an independent Data Safety Monitoring Committee (DSMC) after 50% of participants completed the study [17]

For the primary analysis, missing values were assumed missing at random (MAR), and imputed using multiple imputation (MI) with 100 samples drawn. Intermittent missing data were imputed using the Markov Chain Monte Carlo (MCMC) procedure. Remaining monotone missing data were imputed using stepwise sequential Bayesian regression.

For the primary end-point, the proportion achieving >15% reduction in breathlessness from baseline was compared between groups using the Wald Type 3 Chi-square from a logistic regression model of response with stratum and treatment group as predictor variables. An absolute reduction of >8.9mm VAS over baseline was analysed [27,28]. Time and group interactions were assessed using longitudinal mixed models with repeated measures (MMRM), with the endpoint from days 1 to 28 as the dependent variable, the baseline value as a covariate, stratum, day, treatment group, and treatment group by day interaction as fixed effects, and participant as a random effect. A compound symmetry variance-covariance matrix was used. Clinically relevant response predictors were modelled using multivariable regression.

Differences in secondary endpoints were compared using logistic regression for the response rate endpoints (using MI data), MMRM for the continuous endpoints measured over time (using the original data), and analysis of covariance (ANCOVA) for the continuous endpoints. Stratum was included as a factor in all statistical models, where strata were a combination of centre, HADS sub-scale scores, and participation in the blinded pilot study. Low frequency strata were combined using statistical judgement.

All analyses were performed using SAS version 9.4.

The study was approved by relevant Human Research Ethics Committees (HREC; Cancer Institute NSW 2010C/02/120 and Prince of Wales Hospital 13/327HREC/13/POWH/785). All participants provided written, informed consent. Study reporting complies with CONSORT guidelines. [34,35]

Results

Study population
Two hundred and forty nine people were screened, of whom 223 were randomised (Figure 1). Treatment groups were balanced in demographics and baseline clinical characteristics including breathlessness scores (Table 1). At baseline 23/223 (10.3%) had data missing for which their screening data were used. Data missing for days 26-28 (93/223 (41.7%)) were imputed.

Mean exposure to treatment was 38·5 (SD 66·9) days for sertraline and 55·0 (96·8) for placebo. At day 9 (end of titration), 65 participants taking sertraline were on 100mg, 10 on 50mg and 2 on 25mg. For placebo, corresponding 'doses' were taken by 91, 5 and 2 participants respectively.

Primary outcome
Breathlessness intensity lessened in both arms with no difference between groups in the primary outcome (p=0·636; Figure 2). There was no difference in the proportions with a 15% reduction in *current intensity of breathlessness* from baseline (odds ratio [OR] 1·00 (95% CI 0·71, 1·40, p=0·992; Figure 2). For the same sensation, there was no difference in the proportion achieving >8·9 mm reduction (OR 1·02, 95% CI 0·72, 1·44, p=0·921). In a model comparing baseline breathlessness to changes over the entire 28 days of the study in people with moderate / severe anxiety accounting rescue medication use, AKPS, Charlson Co-morbidity Index (CCI), and pulse oximetry, there was also no difference in any breathlessness measure. Sensitivity analyses assessing imputation methods were consistent with these results.

Secondary outcomes
There was no difference observed between groups in the proportion of participants who had a more than 15% change from baseline in any measure of breathlessness (Figure 2). No sub-group showed any response: those with and without COPD; mMRC scores of 2 versus 3 or 4; nor by HADS sub-scales.

Over the 28-day study period, participants took a similar number of doses of immediate release oral morphine solution. The mean daily doses taken on days 26-28 was 0·37 lower in the sertraline arm (95% CI -0·78 to 0·04, p=0·080).

Mean global QoL scores in the sertraline arm had a greater improvement (days 0-28; 0·21 95% CI 0·01 to 0·41, p=0·044)[23] and (days 26-28; 0·64, 95% CI 0·21, 1·07, p=0·003). There was a lower pain domain score for sertraline in the EORTC-QLQ-15 [23] (-8, 95% CI −14 to −2 p = 0·015; Figure 2). For CRQ, there was a consistent direction of benefit in the sertraline group for three domains favouring sertraline: breathlessness (0·36, 95% CI -0·07, 0·.80, p=0·098); fatigue (0·32, 95% CI -0·03 to 0·66, p=0·070); and mastery (0·38, 95% CI 0·00 to 0·77, p=0·.051).[22]

At the end of the study, 26/72 (36·1%) participants on sertraline felt appreciable improvement and 31/75 (41·3%) on placebo (p=0·6587). A minority felt sufficient benefit for long term use (sertraline 18·6%; placebo 26·3%), and fewer entered the blinded extension study (sertraline 17.3%; placebo 16.3%; NS). (Pilot study participants did not have the option of the extension study). [18]

There were no difference in functional status; nor anxiety or depression scores. Using baseline values for CO_2, mMRC, CCI, HADS anxiety, rescue medication use and AKPS as predictors of breathlessness response (≥8·9mm change), there was only one significant association: a higher Charlson Comorbidity Index was associated with a greater likelihood of response for VAS average breathlessness in the previous 24 hours alone (p=0·041) and with the other prognostic factors (0·028).

There were 30 deaths reported in the sertraline group, and 20 reported in the placebo group. Median survival was similar (184 days (95% CI 96, 216 days sertraline group; 167 days (95% CI 117, not reached; placebo).

Adverse events
The majority of participants in each treatment group experienced at least one treatment emergent adverse event (TEAE; sertraline 95·4%, placebo 90·7%; Table 2). Twenty four participants (22·2%) in the sertraline group and 34 (31·8%) in the placebo group experienced serious TEAEs. In the sertraline and placebo arms, the serious events experienced by the most participants were exacerbations of COPD (5·6% and 8·4%) and breathlessness (2·8% and 5·6%). No one experienced hyponatraemia.

Discussion
There was no net benefit observed for sertraline on chronic breathlessness in participants who had undergone optimal treatment of the underlying cause(s) in this multi-site RCT. This contrasts with very limited previous evidence that suggested potential benefit [12-14]. In this study, randomisation was stratified by underlying severity of depression and anxiety, and the majority of participants (nearly 80% in each group) had no or minimal features of anxiety or depression. (Table 1)

These results are consistent with one study that found no effect of SSRIs in the management of cancer-related breathlessness. [14] The outcomes of the phase 2 BETTER-B study which is evaluating mirtazapine for this indication are awaited with interest (EudraCT 2015-006064-11).

Potential benefits of sertraline were seen for Global QoL, pain, fewer doses of as needed immediate release morphine solution, and CRQ sub-scales. Any differences, if real, are small and not clinically significant. These signals should be interpreted with caution given multiple testing of a large number of secondary end-points. Measures of blinded preference or continuing onto the extension study reflected no perceived net benefit of sertraline by participants.

Mastery was a positive outcome in the landmark study by Higginson *et al* of an integrated palliative and respiratory care support service for chronic breathlessness [29]. This questions the ideal end-point in symptom studies when well-being and a sense of control are positive outcomes but symptom scores do not change. For example, people may exert themselves to the same level of breathlessness (and thus report no better symptom control) but be able to function more effectively.

Sertraline is registered for the treatment of social anxiety disorder [12]. The largest double-blind, pharmacological RCT for chronic breathlessness evaluated buspirone, an anxiolytic [30]. That study of people with chronic breathlessness receiving chemotherapy was strongly negative. The role of anxiety in chronic breathlessness is not well defined, noting that a consecutive case series of 100 people with cancer and breathlessness found that one person had anxiety as the only cause [31]. Future research needs to differentiate anxiety levels between acute and chronic breathlessness.

The majority of participants in the current study did not have high levels of anxiety or depression HADS scores. Given the relatively small proportion of people with higher levels of anxiety, there may be a case for further studies in this sub-group.

To date, the best quality evidence for relief of chronic breathlessness remains with morphine [6,7], and concerns around the potentially rare but catastrophic side effect of respiratory depression are slowly abating, primarily due to evidence that regular, low-dose, extended release morphine, which minimises peak drug concentrations, does not appear to be associated with this effect in steady state [6,7,32,33].

Limitations in the study include that it was a requirement of the HREC for immediate release oral morphine solution to be made available to all participants, potentially masking benefits from, and attributing harms to the study medication. There was no endpoint assessing changes in function, such as accelerometry. The study duration was relatively long for frail people, and so completion rates are lower than in well participants.

The current findings do not support the use of sertraline for the symptomatic treatment of chronic breathlessness, nor does this study identify any sub-group for further study where there is signal of potential benefit using baseline clinico-demographic data.

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Declaration of Interests
DC has received an unrestricted research grant from Mundipharma, is an unpaid member of an advisory board for Helsinn Pharmaceuticals and has consulted to Mayne Pharma and received intellectual property payments from them. He is a paid consultant to Specialist Therapeutics. All other authors have nothing to declare.

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Table 1: Demographic and baseline characteristics by treatment group

	Sertraline 25 - 100 mg/day (N=112)	Placebo (N=111)
Age at Screening, years, mean (SD)	74·20 (8·96) n=110	74·23 (8·88) n=111
Gender, n (%)		
Male	70 (62·5%)	68 (61·3%)
Female	40 (35·7%)	42 (37·8%)
Smoking Status		
Never smoked	16 (14·3%)	13 (11·7%)
Ex-smoker	82 (73·2%)	86 (77·5%)
Current smoker	10 (8·9%)	8 (7·2%)
Missing	4 (3·6%)	4 (3·6%)
BMI, kg/m^2, mean (SD)	25·63 (6·66) n=110	26·50 (12·21) n=107
Pulse oximetry, %, mean (SD)	93·61 (3·74) n=109	93·84 (3·06) n=110
End tidal carbon dioxide, mmHg, means (SD)	25·83 (5·92) n=84	26·58 (6·39) n=84
Charlson Comorbidity Index Score, mean (SD)	3·92 (2·97) n=108	3·09 (2·28) n=109
Major cause(s) of breathlessness, n (%)		
Chronic obstructive airways disease	79 (70·5%)	80 (72·1%)
Primary lung cancer	22 (19·6%)	11 (9·9%)
Restrictive lung disease	21 (18·8%)	21 (18.9%)
Other	11 (9·8%)	16 (14·4%)
End stage heart failure	7 (6·3%)	5 (4·5%)
Pleural effusion (undrainable)	6 (5·4%)	5 (4·5%)
Known secondary lung cancer	4 (3.6%)	9 (8·1%)
Contributing infective problems	4 (3.6%)	1 (0·9%)
Malignancy (non-respiratory)	3 (2.7%)	1 (0·9%)
Lymphangitis carcinomatosis		
Bronchiectasis	2 (1.8%)	3 (2·7%)
Primary pulmonary hypertension	1 (0.9%)	1 (0·9%)
Thrombo-embolic cause	1 (0.9%)	2 (1·8%)
Neurological disease	1 (0.9%)	0 (0·0%)
Extrinsic compression of airways	1 (0.9%)	0 (0·0%)
Clinician reported mMRC breathlessness score at screening		
2	17 (15·2%)	17 (15·3%)
3	55 (49·1%)	56 (50·5%)
4	39 (34·8%)	38 (34·2%)
Missing	1 (0·9%)	0 (0·00%)
HADS strata at randomisation/baseline*		
Anxiety 0-10 (normal, mild) and Depression 0-10 (normal, mild)	86 (76·8%)	87 (78·4%)
Anxiety 11-21 (moderate, severe) and Depression 0-10 (normal, mild)	13 (11·6%)	13 (11·7%)
Anxiety 0-10 (normal, mild) and Depression 11-16 (moderate)	6 (5·4%)	3 (2·7%)
Anxiety 11-21 (moderate, severe) and Depression 11-16 (moderate)	6 (5·4%)	8 (7·2%)
Missing	1 (0·9%)	0 (0·00%)
AKPS Score, mean (SD)	62·02 (9·50) n=109	61·09 (10·70) n=110

	Sertraline 25 - 100 mg/day (N=112)	Placebo (N=111)

AKPS = Australia - Modified Karnofsky Performance Status.
HADS = Hospital Anxiety and Depression Scale
** For Sertraline study participants, HADS randomisation strata is presented. For the 20 phase II (pilot) study participants, baseline HADS category is presented.*
Participants may have more than one major cause of breathlessness.

Table 2: Grade 3, 4 or 5 treatment emergent adverse events of special interest by treatment group

System Organ Class / Preferred Term	Sertraline 25 - 100 mg/day (n=108) n (%)	Placebo (n=107) n (%)
Participants with at least one AE	12 (11·1%)	13 (12·1%)
Gastrointestinal disorders	2 (1.9%)	3 (2·8%)
Dry mouth	1 (0·9%)	0 (0·0%)
Nausea	1 (0·9%)	3 (2·8%)
Injury, poisoning and procedural complications	2 (1·9%)	3 (2·8%)
Fall	2 (1·9%)	3 (2·8%)
Nervous system disorders	3 (2·8%)	5 (4·7%)
Dizziness	0 (0·0%)	4 (3·7%)
Somnolence	2 (1·9%)	2 (1·9%)
Tremor	1 (0·9%)	2 (1·9%)
Psychiatric disorders	4 (3·7%)	4 (3·7%)
Agitation	1 (0·9%)	2 (1·9%)
Insomnia	3 (2·8%)	1 (0·9%)
Restlessness	2 (1·9%)	3 (2·8%)
Reproductive system and breast disorders	1 (0·9%)	0 (0·0%)
Ejaculation disorder	1 (0·9%)	0 (0·0%)
Vascular disorders	0 (·.0%)	1 (0·9%)
Hypertension	0 (0·0%)	1 (0·9%)

Investigator text for Adverse Events encoded using MedDRA (Version 19.1).
Treatment emergent AEs are AEs that started or worsened after baseline.

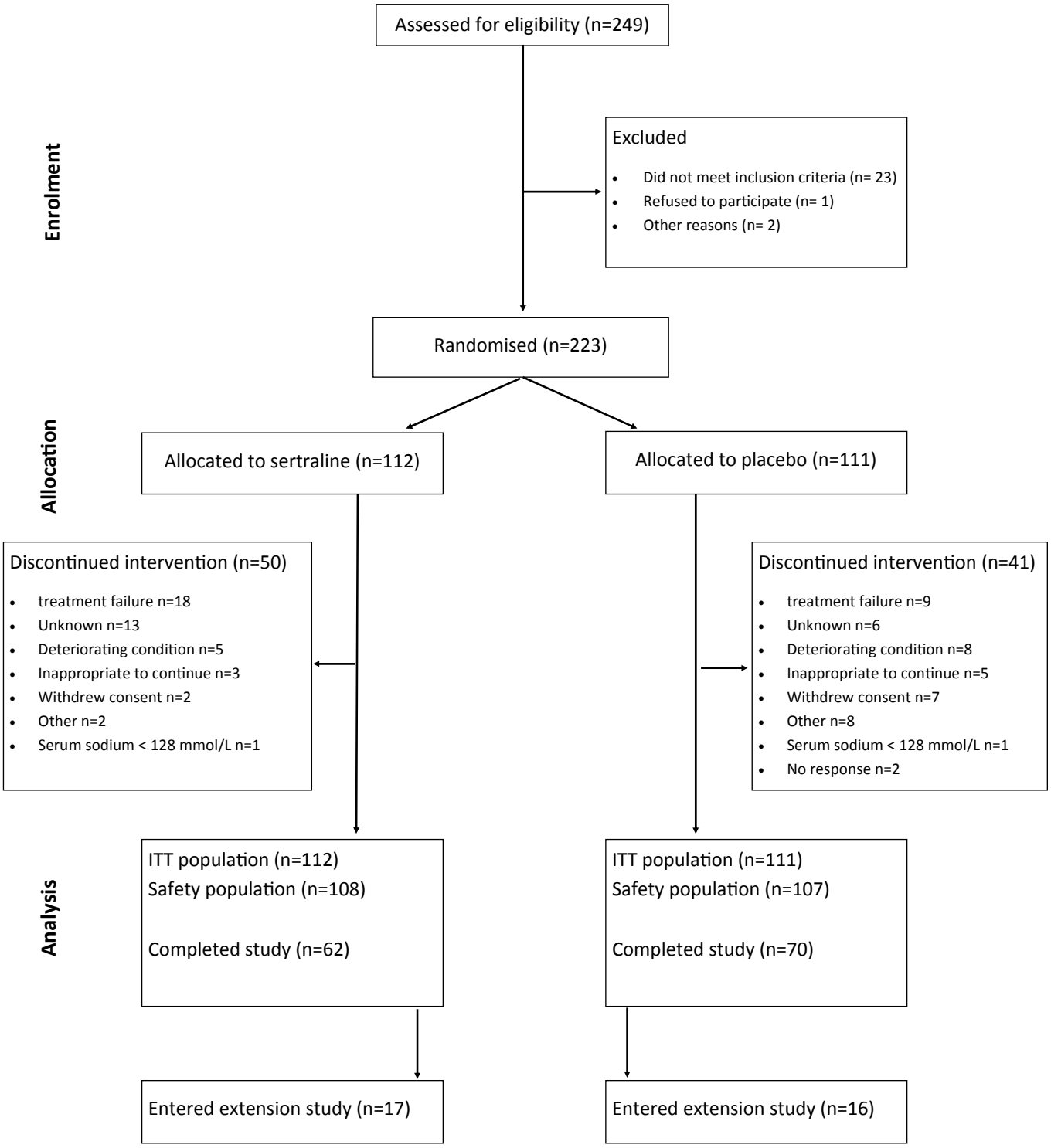
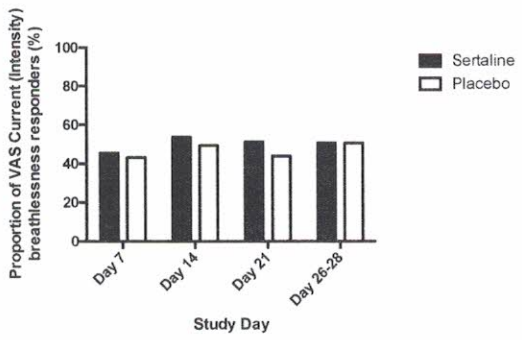
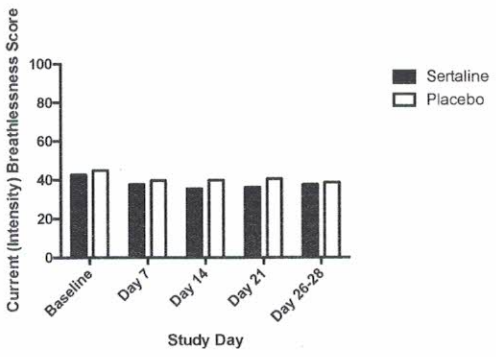
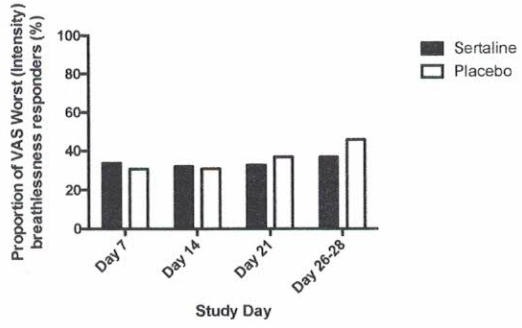
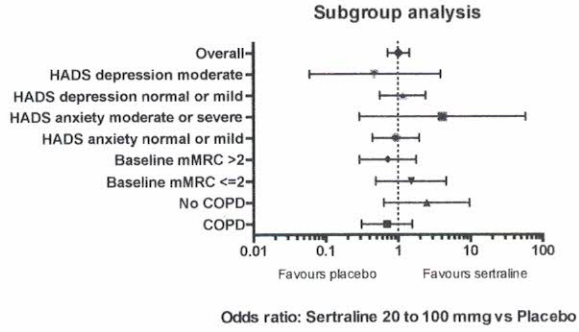

Enrolment
Assessed for eligibility (n=249)
Excluded
Did not meet inclusion criteria (n= 23)
Refused to participate (n= 1)
Other reasons (n= 2)
Randomised (n=223)
Allocation
Allocated to sertraline (n=112)
Allocated to placebo (n=111)
Discontinued intervention (n=50)
treatment failure n=18
Unknown n=13
Deteriorating condition n=5
Inappropriate to continue n=3
Withdrew consent n=2
Other n=2
Serum sodium < 128 mmol/L n=1
Discontinued intervention (n=41)
treatment failure n=9
Unknown n=6
Deteriorating condition n=8
Inappropriate to continue n=5
Withdrew consent n=7
Other n=8
Serum sodium < 128 mmol/L n=1
No response n=2
Analysis
ITT population (n=112)
Safety population (n=108)
Completed study (n=62)
ITT population (n=111)
Safety population (n=107)
Completed study (n=70)
Entered extension study (n=17)
Entered extension study (n=16)

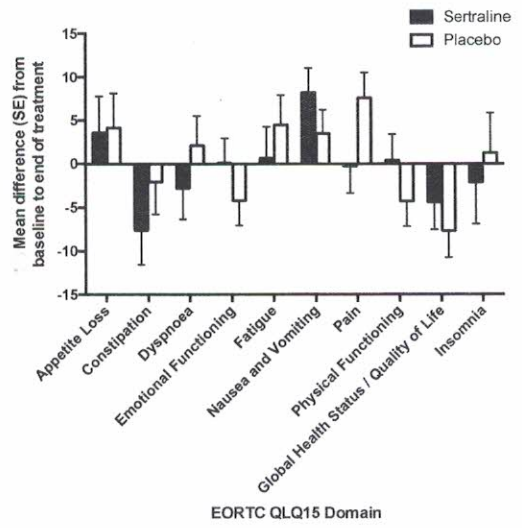
Figure 2: Effectiveness data in a double blind, placebo controlled trial of sertraline for chronic breathlessness (n=223) of: proportion of responders; 0-100mm breathlessness intensity scores now; 0-100mm worst breathlessness in the previous 24 hours; sub-group analyses; quality of life; and Chronic Respiratory Questionnaire.

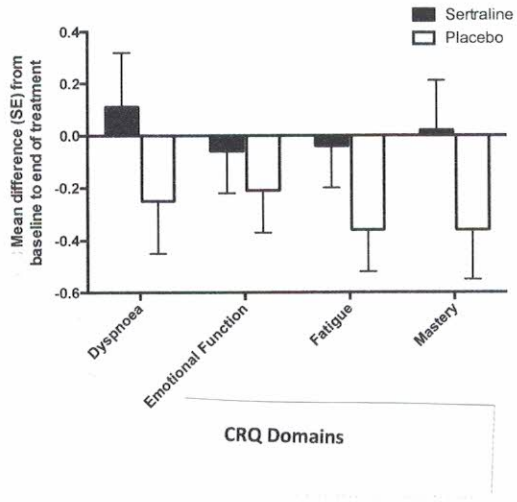












Modified Medical Research Council (MRC) Dyspnoea Scale

0. Not troubled with breathlessness except on strenuous exercise
1. Short of breath when hurrying on the level or walking up a slight hill
2. Walks slower than contemporaries on level ground because of shortness of breath or has to stop for breath when walking at own pace on the level
3. Stops for breath after walking about 100 m or after a few minutes on the level
4. Too breathless to leave the house or breathless when dressing or undressing