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[Intervention Protocol]

Pharmacological treatment for central sleep apnoea in adults

Rachel Riera[1], Carolina OC Latorraca[1], Ana Luiza C Martimbianco[1], Rafael L Pacheco[1], Luciano F Drager[2], Geraldo Lorenzi-Filho[2], Daniela V Pachito[3]

[1]Cochrane Brazil, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil. [2]Department of Internal Medicine, University of Sao Paulo Medical School, Sao Paulo, Brazil. [3]Cochrane Brazil, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil

Contact address: Daniela V Pachito, Cochrane Brazil, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, Rua Borges Lagoa, 754, Vila Clementino, São Paulo, Sao Paulo, 04038001, Brazil. pachito@uol.com.br, danielapachito@hotmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of pharmacological treatment for central sleep apnoea syndromes (CSAS) in adults.

BACKGROUND

Description of the condition

Central sleep apnoea syndromes (CSAS) encompass a diversity of clinical situations where a dysfunctional drive to breathe leads to recurrent respiratory events, namely apnoeas (complete absence of ventilation) and hypopnoeas (insufficient ventilation) during sleep (Eckert 2007). Central respiratory events may emerge from distinct conditions such as chronic heart failure (CHF) or chronic abuse of opioids. The International Classification of Sleep Disorders 3^{rd} Edition identifies six CSAS in adults: central sleep apnoea (CSA) with Cheyne-Stokes Breathing (CSB); CSA due to a medical disorder without CSB; CSA due to high altitude periodic breathing; CSA due to a medication or substance; primary CSA; and treatment-emergent CSA American Academy of Sleep Medicine 2014.

CSAS are far less common than obstructive sleep apnoea syndrome, for which the prevalence is estimated in the range of 4% to 7% of the general population (Punjabi 2008). Less than 5% of patients referred to a sleep clinic present with CSA (Malhotra 2004). Although precise estimates of the CSAS prevalence among the general population remains to be determined, prevalence in special populations, such as patients with CHF, has been estimated to be as high as 40% to 50% (Peer 2010).

Pathophysiology may involve abnormally increased chemosensitivity of respiratory centres located in the brainstem, with small changes in $PaCO_2$ (partial pressure of carbon dioxide in arterial blood) generating an hyper reactive response and ultimately culminating in unstable ventilatory patterns (Eckert 2007). Alternatively, structural lesions, genetic or substance-induced dysfunction of respiratory nuclei may lead to blunted ventilatory responses and central apnoeas.

Description of the intervention

The treatment of CSAS with different types of non-invasive positive pressure ventilation, such as continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or adaptive servo-ventilation (ASV), is not always effective or safe (Cowie 2015), and may be associated with residual apnoea hypopnoea index (AHI) (Aurora 2012). Differently from obstructive sleep apnoea syndrome (OSAS), CSAS have been demonstrated to respond to some extent to pharmacological agents, such as zolpidem (Quadri 2009), triazolam (Bonnet 1990), acetazolamide (Javaheri 2006) and theophylline (Javaheri 1996). These drugs may reach the therapeutical goal of mitigating central apnoeas through very distinct mechanisms of action, such as sleep stabilisation and respiratory stimulation.

How the intervention might work

Pharmacological agents with very distinct mechanisms of action may act on ventilatory control and sleep stability. Hypnotics such as triazolam and zolpidem consolidate the sleep state, by reducing fluctuations between wakefulness and unstable sleep. This may exert a protective action, considering that frequent arousals are associated with increased chemoresponsiveness, leading to the pattern of hyperventilation and subsequent hypoventilation (Bonnet 1990). In fact, periodic breathing predominates during light non-rapid eye movement (NREM) sleep, disappearing during rapid eye movement (REM) sleep (Berssenbrugge 1983).

Respiratory stimulants may also exert a beneficial action in mitigating central apnoeas. Metabolic acidosis induced by acetazolamide increases the apnoeic threshold of PCO_2, leading to the reduction of central apnoeas (Nakayama 2002). The mechanism of action explaining the reason why theophylline improves central apnoeas is not completely understood. Theophylline competes with adenosine, which, in turn, depresses ventilatory function (Müller 2011). It is reasonable to attribute the ventilatory stimulation caused by theophylline to adenosine blockage at some extent (Javaheri 1996).

Why it is important to do this review

CSA associated with CSB (CSA-CSB) in the context of CHF is considered a severity marker and indicative of poor prognosis (Hanly 1996; Wilcox 1998). It is not entirely clear whether treating CSA-CSB in this population improves survival, which would therefore be of utmost importance. Additionally, sleep fragmentation due to CSA may lead to difficulty maintaining sleep and daytime sleepiness, impacting negatively in quality of life. Some therapies for CSAS are associated with improvement of quality of life (Sasayama 2009), however it is still not clear whether and to what extent pharmacological therapies might improve quality of life.

Much of the evidence on the effectiveness of pharmacological agents for CSAS is derived from non-randomised studies or from randomised studies with methodological limitations. A comprehensive search in the literature and a critical appraisal of the quality of studies following the recommendations proposed by Cochrane will provide a reliable summary of the available evidence to guide decision making.

OBJECTIVES

To assess the effectiveness and safety of pharmacological treatment for central sleep apnoea syndromes (CSAS) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with a parallel design that have employed individual allocation. We will include studies reported in full text, those published as an abstract only and unpublished data.

Types of participants

We will include studies that have enrolled participants older than 18 years old diagnosed with one of the following CSAS, as defined by theInternational Classification of Sleep Disorders 3rd Edition (American Academy of Sleep Medicine 2014):

- central sleep apnoea (CSA) with Cheyne-Stokes Breathing (CSB);
- CSA due to a medical disorder without CSB;
- CSA due to high altitude periodic breathing;
- CSA due to a medication or substance;
- primary CSA;
- treatment-emergent CSA.

Types of interventions

We will include studies comparing any type of pharmacological agent aiming primarily at the mitigation of CSAs regardless of drug class, with active controls, such as non-invasive positive pressure ventilation, or inactive controls, such as placebo, no treatment, or usual care defined as the treatment of underlying diseases.

Pharmacological agents may include, but are not limited to:

- sleep-stabilising agents (e.g. zolpidem, temazepam);

- respiratory stimulants increasing the apnoeic threshold (e.g. acetazolamide, theophylline).

We will not include pharmacological treatment of underlying diseases associated with CSAS, such as β-blockers for patients with chronic heart failure (CHF).

Comparisons will include any given drug class (e.g. hypnotics) versus any type of comparator, and they will include:

- agents stabilising sleep versus inactive control (placebo, no treatment, or usual care defined as the treatment of underlying diseases and applied to intervention and control groups);
- respiratory stimulants versus inactive control (placebo, no treatment, or usual care defined as the treatment of underlying diseases and applied to intervention and control groups);
- another class of pharmacological agent versus inactive control (placebo, no treatment, or usual care defined as the treatment of underlying diseases and applied to intervention and control groups).

Comparators will also include any type of non-invasive positive pressure ventilation, such as continuous positive airway pressure (CPAP); auto-set positive airway pressure; bi-level positive airway pressure (BiPAP); and adaptive servo-ventilation (ASV).

For each comparison, we will discriminate two distinct groups of participants, namely CSA with CSB due to CHF and CSA due to other conditions. In this second group, we will scrutinise differences of intervention effects according to aetiology in subgroup analyses. We will also scrutinise differences in intervention effects, according to different agents within each drug class (e.g. zolpidem and temazepam within hypnotic category) in subgroup analyses.

Types of outcome measures

Primary outcomes

1. Central apnoea hypopnoea index (cAHI, defined as the number of central apnoeas and hypopnoeas per hour of sleep, measured objectively by polysomnography)
2. Cardiovascular mortality (defined as the number of deaths attributable to myocardial ischaemia and infarction, heart failure, cardiac arrest because of other or unknown cause, or cerebrovascular accident (Carrero 2011))
3. Serious adverse events (defined as those leading to death, life-threatening events, hospitalisation, disability or permanent damage, congenital anomaly, or to required intervention to prevent permanent impairment or damage)

Secondary outcomes

1. Quality of sleep (assessed by the use of validated scales or questionnaires, such as the Pittsburgh sleep quality index (Buysse 1989))
2. Quality of life (assessed by the use of validated scales or questionnaires, such as SF-36 (Jenkinson 1996))
3. Daytime sleepiness (assessed by the use of validated scales or questionnaires, such as the Epworth Sleepiness Scale (Johns 1991))
4. Apnoea hypopnoea index (AHI) (defined as the number of obstructive, mixed and central apnoea hypopnoea per hour of sleep, measured objectively by polysomnography)
5. All-cause mortality (defined as number of deaths regardless of causes)
6. Time to life-saving cardiovascular intervention (for example, cardiac transplantation, implantation of cardioverter-defibrillator)
7. Non-severe adverse events/side effects (for example, nasal congestion, upper airway dryness, mask-induced pressure ulcer)

We will assess outcomes at all time points reported in primary studies and we will pool data for the short, intermediate and long term, defined as follows:

- short term: up to three months;
- intermediate term: from three months to one year;
- long term: more than one year.

Search methods for identification of studies

Electronic searches

We will identify studies from the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org), which incorporates the Cochrane Airways Trials Register;
- MEDLINE Ovid SP 1946 to date;
- Embase Ovid SP 1974 to date;
- SCOPUS from inception to date.

The proposed MEDLINE strategy is listed in Appendix 1. This will be adapted for use in the other databases. All databases will be searched from their inception to the present, and there will be no restriction on language of publication. We will handsearch conference abstracts and grey literature through the CENTRAL database.

In addition, we will search the following trials registries:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' web sites for study information.

We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (DVP, COCL, RLP or ALCM) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (DVP, COCL, RLP or ALCM) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (RR). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data adapted from EPOC 2013, which has been piloted on at least one study in the review. One review author (DVP) will extract the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
- Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (DVP, COCL) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (RR). One review author (DVP) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RR) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (DVP, COCL) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (RR). We will assess the risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other bias.

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed.

We will consider the domains of 'blinding of participants and personnel' and 'blinding of outcome assessment' differently according to the type of outcome. For subjective outcomes, such as quality of life and quality of sleep, any deviation of blinding procedures will be judged as high risk of bias. For objective outcomes, such as mortality, the absence or inadequacy of blinding will not be judged as imposing risk of bias.

Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA), we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline unless there is low correlation between measurements in individuals. If a study reports outcomes at multiple time points, we will use data from all time points.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of participants admitted to hospital, rather than number of admissions per participant). However, if rate ratios are reported in a study, we will analyse them on this basis.

Dealing with missing data

We will contact the authors of primary studies in order to verify key study characteristics and obtain missing numerical outcome data. If not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. If outcome data are not available, such as standard deviations or correlation coefficients and they cannot be obtained from the authors, we will calculate them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*. Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by pre specified subgroup analysis. We will consider substantial heterogeneity for values of I^2 equal or above 50% (Higgins 2011), although we recognise that there is uncertainty in the I^2 measurement when there are few studies in a meta-analysis. We will use a significance level of $P < 0.1$ to indicate whether there is a problem with heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 studies in the same meta-analysis, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will pool data from studies judged to be clinically homogeneous using Review Manager software. If more than one study provides data in any single comparison, we will perform meta-analysis. We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes.

- Apnoea hypopnoea Index (AHI).
- Cardiovascular mortality.
- Quality of sleep.
- Quality of life.
- All-cause mortality.
- Time to lifesaving cardiovascular intervention (cardiac transplantation, implantation of cardioverter-defibrillator).
- Serious adverse events.

We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Since many comparisons are expected, we will create 'Summary of findings' tables for up to eight comparisons considered more clinically relevant. Clinical relevance will be decided by authors' agreement.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

- Severity of CSA based on cAHI, with two prespecified subgroups, namely mild central apnoea, defined as less than 15 central apnoeas per hour of sleep and moderate to severe central apnoea, defined as more than 15 central apnoeas per hour of sleep. The rational for this subgroup analysis is based on the assumption that treatment of CSA may impact differently according to the severity of CSA.
- Severity of CHF based on the functional classification of New York Heart Association (New York Heart Association 1994)

or based on the ejection fraction (Class IV of NYHA or ejection fraction lesser than 30% versus Class I to III of NYHA or ejection fraction equal to or greater than 30%). The rational for scrutinising intervention effects regarding severity of CHF is based on the assumption that patients with severe CHF may respond differently.

- Aetiology of CSA as defined by the International Classification of Sleep Disorders 3rd Edition for comparisons involving heterogeneous populations.
- Pharmacological agents for comparisons involving multiple agents within the same drug class.

We will use the following outcomes in subgroup analyses.

- Apnoea hypopnoea Index (AHI).
- Cardiovascular mortality.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses.

- Risk of bias (analysis excluding studies with high risk of bias). We will consider high risk of bias, studies fulfilling criteria for high risk of bias or unclear risk of bias in at least two domains of the 'Risk of bias' table.
- Industry sponsorship.

We will compare the results from a fixed-effect model with the random-effects model.

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REFERENCES

Additional references

American Academy of Sleep Medicine 2014
American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. Darien, IL: American Academy of Sleep Medicine, 2014.

Aurora 2012
Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep* 2012;**35**(1): 17–40.

Berssenbrugge 1983
Berssenbrugge A, Dempsey J, Iber C, Skatrud J, Wilson P. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. *Journal of Physiology* 1983;**343**:507–24.

Bonnet 1990
Bonnet MH, Dexter JR, Arand DL. The effect of triazolam on arousal and respiration in central sleep apnea patients. *Sleep* 1990;**13**(1):31–41.

Buysse 1989
Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research* 1989;**28**(2):193–213.

Carrero 2011
Carrero JJ, de Jager DJ, Verduijn M, Ravani P, De Meester J, Heaf JG, et al. Cardiovascular and noncardiovascular mortality among men and women starting dialysis. *Clinical Journal of the American Society of Nephrology* 2011;**6**(7): 1722–30.

Cowie 2015
Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive Servo-Ventilation for central sleep apnea in systolic heart failure. *New England Journal of Medicine* 2015;**373**(12):1095–105.

Eckert 2007
Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. *Chest* 2007;**131**(2): 595–607.

EPOC 2013
EPOC. Data collection form. EPOC Resources for review authors. epoc.cochrane.org/epoc-specific-resources review-authors. Oslo: Norwegian Knowledge Centre for the Health Services, (accessed prior to 24 July 2017).

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed prior to 24 July 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Hanly 1996
Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with cheyne-stokes respiration in patients with congestive heart failure. *American Journal of Respiratory and Critical Care Medicine* 1996;**153**:272–6.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Javaheri 1996
Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. *New England Journal of Medicine* 1996;**335**:562–7.

Javaheri 2006
Javaheri S. Acetazolamide improves central sleep apnea in heart failure. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(2):234–7.

Jenkinson 1996
Jenkinson C, Layte R, Wright L, Coulter A. *Manual and Interpretation Guide for the UK SF-36*. Oxford: Health Services Research Unit, 1996.

Johns 1991
Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; Vol. 14, issue 6: 540–5.

Malhotra 2004
Malhotra A, Berry RB, White DP. Central sleep apnea. In: Carney PR, Berry RB, Geyer JD editor(s). *Clinical Sleep Disorders*. Philadelphia, PA: Lippincott Williams and Wilkins, 2004:331-46.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7): e1000097. [DOI: 10.1371/journal.pmed.1000097

Müller 2011
Müller CE, Jacobson KA. Xanthines as adenosine receptor antagonists. *Handbook of Experimental Pharmacology* 2011; **200**:151–99.

Nakayama 2002
Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(9):1251–9.

New York Heart Association 1994
New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. Boston, MA: Lippincott Williams and Wilkins, 1994.

Peer 2010
Peer A, Lorber A, Suraiya S, Malhotra A, Pillar G. The occurrence of Cheyne-Stokes respiration in congestive heart failure: The effect of age. *Frontiers in Psychiatry* 2010;**1**:1–6.

Punjabi 2008
Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society* 2008;**5** (2):136–43.

Quadri 2009
Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. *Journal of Clinical Sleep Medicine* 2009;**5**(2):122–9.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sasayama 2009
Sasayama S, Izumi T, Matsuzaki M, Matsumori A, Asanoi H, Momomura S, et al. Improvement of quality of life with nocturnal oxygen therapy in heart failure patients with central sleep apnea. *Circulation Journal* 2009;**73**(7): 1255–62.

Wilcox 1998
Wilcox I, McNamara SG, Wessendorf T, Willson GN, Piper AJ, Sullivan CE. Prognosis and sleep disordered breathing in heart failure. *Thorax* 1998;**53 Suppl 3**(Suppl 3):S33–6.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. Sleep Apnea, Central/
2. (central adj2 sleep adj2 (apnea$ or apnoea$)).tw.
3. (central adj2 alveolar adj2 hypoventilation$).tw.
4. (central adj2 sleep disordered breathing).tw.
5. (ondine$ adj2 (syndrome or curse)).tw.
6. Cheyne-Stokes Respiration/
7. Cheyne$ Stokes.tw.
8. (periodic adj2 (breathing or respiration)).tw.
9. or/1-8
10. (controlled clinical trial or randomized controlled trial).pt.
11. (randomized or randomised).ab,ti.
12. placebo.ab,ti.
13. dt.fs.
14. randomly.ab,ti.
15. trial.ab,ti.
16. groups.ab,ti.
17. or/10-16
18. Animals/
19. Humans/
20. 18 not (18 and 19)
21. 17 not 20
22. 9 and 21

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: DVP, ALCM, COCL, RLP, LD, GLF, RR

Designing the protocol: DVP, ALCM, COCL, RLP, LD, GLF, RR

Co-ordinating the protocol: DVP, RR

Designing search strategies: DVP and Elizabeth Stovold, Information Specialist of Airways Group

Writing the protocol: DVP, RR

Providing general advice on the protocol: DVP, ALCM, COCL, RLP, LD, GLF, RR

DECLARATIONS OF INTEREST

DVP: None known

ALCM: None known

COCL: None known

RLP: None known

LD: None known

GLF: Stocks of Biologix - Start up of a simple device for sleep apnoea diagnosis

RR: None known

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Internal sources

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- Universidade Federal de São Paulo (UNIFESP), Brazil.

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- Universidade de São Paulo - Instituto do Coração (USP - INCOR), Brazil.

Institutional support for LD, GLF

External sources

- No sources of support supplied