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Pharmacological treatment for central sleep apnoea in adults (Review)

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[Intervention Review]

Pharmacological treatment for central sleep apnoea in adults

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A B S T R A C T

Background

The term central sleep apnoea (CSA) encompasses diverse clinical situations where a dysfunctional drive to breathe leads to recurrent respiratory events, namely apnoea (complete absence of ventilation) and hypopnoea sleep (insufficient ventilation) during sleep. Studies have demonstrated that CSA responds to some extent to pharmacological agents with distinct mechanisms, such as sleep stabilisation and respiratory stimulation. Some therapies for CSA are associated with improved quality of life, although the evidence on this association is uncertain. Moreover, treatment of CSA with non-invasive positive pressure ventilation is not always effective or safe and may result in a residual apnoea-hypopnoea index.

Objectives

To evaluate the benefits and harms of pharmacological treatment compared with active or inactive controls for central sleep apnoea in adults.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 30 August 2022.

Selection criteria

We included parallel and cross-over randomised controlled trials (RCTs) that evaluated any type of pharmacological agent compared with active controls (e.g. other medications) or passive controls (e.g. placebo, no treatment or usual care) in adults with CSA as defined by the International Classification of Sleep Disorders 3rd Edition. We did not exclude studies based on the duration of intervention or follow-up. We excluded studies focusing on CSA due to periodic breathing at high altitudes.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were central apnoea-hypopnoea index (cAHI), cardiovascular mortality and serious adverse events. Our secondary outcomes were quality of sleep, quality of life, daytime sleepiness, AHI, all-cause mortality, time to life-saving cardiovascular intervention, and non-serious adverse events. We used GRADE to assess certainty of evidence for each outcome.

Main results

We included four cross-over RCTs and one parallel RCT, involving a total of 68 participants. Mean age ranged from 66 to 71.3 years and most participants were men. Four trials recruited people with CSA associated with heart failure, and one study included people with primary CSA. Types of pharmacological agents were acetazolamide (carbonic anhydrase inhibitor), buspirone (anxiolytic), theophylline (methylxanthine derivative) and triazolam (hypnotic), which were given for between three days and one week.

Only the study on buspirone reported a formal evaluation of adverse events. These events were rare and mild. No studies reported serious adverse events, quality of sleep, quality of life, all-cause mortality, or time to life-saving cardiovascular intervention.

Carbonic anhydrase inhibitors versus inactive control

Results were from two studies of acetazolamide versus placebo (n = 12) and acetazolamide versus no acetazolamide (n = 18) for CSA associated with heart failure. One study reported short-term outcomes and the other reported intermediate-term outcomes. We are uncertain whether carbonic anhydrase inhibitors compared to inactive control reduce cAHI in the short term (mean difference (MD) −26.00 events per hour, 95% CI −43.84 to −8.16; 1 study, 12 participants; very low certainty). Similarly, we are uncertain whether carbonic anhydrase inhibitors compared to inactive control reduce AHI in the short term (MD −23.00 events per hour, 95% CI −37.70 to 8.30; 1 study, 12 participants; very low certainty) or in the intermediate term (MD −6.98 events per hour, 95% CI −10.66 to −3.30; 1 study, 18 participants; very low certainty). The effect of carbonic anhydrase inhibitors on cardiovascular mortality in the intermediate term was also uncertain (odds ratio (OR) 0.21, 95% CI 0.02 to 2.48; 1 study, 18 participants; very low certainty).

Anxiolytics versus inactive control

Results were based on one study of buspirone versus placebo for CSA associated with heart failure (n = 16). The median difference between groups for cAHI was −5.00 events per hour (IQR −8.00 to −0.50), the median difference for AHI was −6.00 events per hour (IQR −8.80 to −1.80), and the median difference on the Epworth Sleepiness Scale for daytime sleepiness was 0 points (IQR −1.0 to 0.00).

Methylxanthine derivatives versus inactive control

Results were based on one study of theophylline versus placebo for CSA associated with heart failure (n = 15). We are uncertain whether methylxanthine derivatives compared to inactive control reduce cAHI (MD −20.00 events per hour, 95% CI −32.15 to −7.85; 15 participants; very low certainty) or AHI (MD −19.00 events per hour, 95% CI −30.27 to −7.73; 15 participants; very low certainty).

Hypnotics versus inactive control

Results were based on one trial of triazolam versus placebo for primary CSA (n = 5). Due to very serious methodological limitations and insufficient reporting of outcome measures, we were unable to draw any conclusions regarding the effects of this intervention.

Authors' conclusions

There is insufficient evidence to support the use of pharmacological therapy in the treatment of CSA. Although small studies have reported positive effects of certain agents for CSA associated with heart failure in reducing the number of respiratory events during sleep, we were unable to assess whether this reduction may impact the quality of life of people with CSA, owing to scarce reporting of important clinical outcomes such as sleep quality or subjective impression of daytime sleepiness. Furthermore, the trials mostly had short-term follow-up. There is a need for high-quality trials that evaluate longer-term effects of pharmacological interventions.

P L A I N   L A N G U A G E   S U M M A R Y

Medicines for central sleep apnoea in adults

Key messages

Studies in this area are small and we were unable to conclude whether any of the medicines studied helped people with central sleep apnoea (CSA) compared with dummy treatment.

What is central sleep apnoea and how is it treated?

CSA is a disorder in which breathing repeatedly stops and starts during sleep because the brain does not send proper signals to the muscles that control breathing. CSA mainly affects men and people with heart disease. The condition is different from and less common than obstructive sleep apnoea, where breathing is interrupted by blocked or narrowed airways. The treatment of CSA can involve using devices

to help breathing, but people with CSA do not always like using them. Treatment with medicines, such as hypnotics (used to reduce tension and induce calm) and respiratory modulators (used to stimulate breathing), may be an alternative for adults with CSA.

What did we want to find out?

The aim of this review was to find out whether medicines can improve the following outcomes in people with CSA.

• Central apnoea-hypopnoea index (a key indicator of CSA that measures the number of times someone's breathing pauses per hour of sleep)
• Death related to heart disease
• Quality of sleep
• Quality of life
• Daytime sleepiness
• Apnoea-hypopnoea index (another score of apnoea events)
• Death from any cause
• Time to a life-saving heart-related intervention (such as a transplant)

We also wanted to know whether these medicines had any unwanted effects.

What did we do?

We searched for studies that investigated the use of medicines for CSA compared with a different treatment (such as the breathing devices commonly used to treat CSA), dummy treatment (placebo), no treatment or usual care. Participants had to be at least 18 years of age. We only included randomised controlled trials (RCTs), which allocate people to treatment groups at random.

What did we find?

We found five studies involving a total of 66 adults with CSA and an average age of 66 to 71 years. The included studies used four different medicines and mostly looked at men who had CSA together with heart disease. In one study, five men received either triazolam (a medicine to help sleep) or placebo. In another study, 16 men received either buspirone (a medicine to help reduce anxiety) or placebo. In a third study, 15 men received either theophylline (a medicine to help wheezing, shortness of breath and chest tightness) or placebo. Thirty adults in the two remaining studies received either acetazolamide (a medicine to help stimulate breathing) or placebo/no acetazolamide.

The studies that provided information on the length of treatment tested the medicines for between three days and one week.

We are uncertain about the effects of the medicines on the central apnoea-hypopnoea index, death related to heart disease, the apnoea-hypopnoea index and daytime sleepiness. The studies also could not tell us whether unwanted events were more common with medicines than with placebo. No studies reported our other outcomes of interest.

What are the limitations of the evidence?

Our confidence in the evidence is very low, mainly because it comes from small studies with very few participants.

How up to date is the evidence?

The evidence is up to date to 30 August 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Carbonic anhydrase inhibitors versus inactive control for central sleep apnoea associated with heart failure in adults

Acetazolamide 250 mg or 3.5 mg/kg (once daily) compared to placebo/no acetazolamide for central sleep apnoea in adults

Patient or population: adults with central sleep apnoea associated with heart failure
Setting: outpatients
Intervention: acetazolamide 250 mg or 3.5 mg/kg (once daily)
Comparison: placebo/no acetazolamide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo/no acetazolamide	**Risk with acetazolamide**			
cAHI Follow-up: mean 4 weeks (short-term)	Mean cAHI was 49 events/hour	MD 26.00 events/hour lower (43.84 lower to 8.16 lower)	—	12 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]
Cardiovascular mortality Follow-up: mean 12 months	**Study population**		**OR 0.21** (0.02 to 2.48)	18 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,c]
	40 per 100	12 per 100 (1 to 62)			
Serious adverse events	Not reported				
Quality of sleep	Not reported				
Quality of life	Not reported				
AHI Follow-up: mean 4 weeks (short-term)	Mean AHI was 57 events/hour	MD 23.00 events/hour lower (37.70 lower to 8.30 lower)	—	12 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]
AHI Follow-up: mean 12 months (intermediate-term)	Mean AHI was 21.68 events/hour	MD 6.98 events/hour lower (10.66 lower to 3.30 lower)	—	18 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,c]
All-cause mortality	Not reported				

*****The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AHI: apnoea-hypopnoea index; **cAHI:** central apnoea-hypopnoea index; **CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to serious study limitations (risk of selection bias, performance bias, detection bias and reporting bias.
[b] Downgraded two levels due to very serious imprecision (very small sample size).
[c] Downgraded two levels due to very serious imprecision (few events and wide CI, including both null effect and appreciable benefit).

Summary of findings 2.   Anxiolytics compared to inactive control for central sleep apnoea associated with heart failure in adults

Buspirone 15 mg (3 times daily) compared to inactive control for central sleep apnoea in adults

Patient or population: adults with central sleep apnoea associated with heart failure
Setting: outpatients
Intervention: buspirone 15 mg (3 times daily)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with buspirone			
cAHI Follow-up: mean 1 week (short-term)	Median difference between groups was −5.00 events/hour (IQR −8.00 to −0.50). The study reported median and IQRs due to skewed data distribution, so did not compare differences between groups.			16 (1 RCT)	—
Cardiovascular mortality	Not reported				
Serious adverse events	Not reported				
Quality of sleep	Not reported				
Quality of life	Not reported				
AHI Follow-up: 1 week (short-term)	Median difference between groups was −6.00 (IQR −8.80 to −1.80). The study reported median and IQRs due to skewed data distribution, so did not compare differences between groups.			16 (1 RCT)	—

All-cause mortality	Not reported

*The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AHI: apnoea-hypopnoea index; **cAHI:** central apnoea-hypopnoea index; **CI:** confidence interval; **IQR:** interquartile range.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 3.   Methylxanthine derivatives versus inactive control for central sleep apnoea associated with heart failure in adults

Theophylline 3.3 mg/kg (twice daily)compared to placebo for central sleep apnoea in adults

Patient or population: adults with central sleep apnoea associated with heart failure in adults
Setting: outpatients
Intervention: theophylline 3.3 mg/kg (twice daily)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	**Risk with theophylline**			
cAHI **Follow-up: mean 3 weeks (short-term)**	Mean cAHI was 26 events/hour	MD 20.00 events/hour lower (32.15 lower to 7.85 lower)	—	15 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]
Cardiovascular mortality	Not reported				
Serious adverse events	Not reported				
Quality of sleep	Not reported				
Quality of life	Not reported				
AHI **Follow-up: mean 3 weeks (short-term)**	Mean AHI was 37 events/hour	MD 19.00 events/hour lower (30.27 lower to 7.73 lower)	—	15 (1 RCT)	⊕⊖⊖⊖ **Very low**[a]
All-cause mortality	Not reported				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AHI: apnoea-hypopnoea index; **cAHI:** central apnoea-hypopnoea index; **CI:** confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a] Downgraded three levels due to serious study limitations (unclear risk of selection bias and reporting bias) and very serious imprecision (very small sample size and wide CI).

Summary of findings 4.   Hypnotics compared to inactive control for primary central sleep apnoea in adults

Triazolam 0.125 mg or 0.250 mg (once daily)compared to placebo for primary central sleep apnoea in adults

Patient or population: adults with primary central sleep apnoea
Setting: outpatients
Intervention: triazolam 0.125 mg or 0.250 mg (once daily)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	**Risk with triazolam**			
cAHI **Follow-up: 3 days (short-term)**	Mean cAHI was 9.40 events/hour in participants who received triazolam 0.125 mg versus 8.00 events/hour in those who received triazolam 0.250 mg versus 16.30 events/hour in those who received placebo. We could not compare the groups because the study did not report SDs for the treatment effects.			5 (1 RCT)	—
Cardiovascular mortality	Not reported				
Serious adverse events	Not reported				
Quality of sleep	Not reported				
Quality of life	Not reported				

AHI **Follow-up: 3 days** **(short-term)**	Mean AHI was 13.50 events/hour in the participants who received triazolam 0.125 mg versus 11.00 events/hour in those who received triazolam 0.25 mg versus 20.90 events/hour in those who received placebo. We could not compare the groups because the study did not report SDs for the treatment effects.	5 (1 RCT)	—
All-cause mortality	Not reported		

***The risk in the intervention group** (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).

AHI: apnoea-hypopnoea index; **cAHI:** central apnoea-hypopnoea index; **CI:** confidence interval; **RCT:** randomised controlled trial; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

BACKGROUND

Description of the condition

The term central sleep apnoea (CSA) encompasses a diversity of clinical situations where a dysfunctional drive to breathe leads to recurrent respiratory events, namely apnoea (complete absence of ventilation) and hypopnoea (insufficient ventilation) during sleep (Eckert 2007). Central respiratory events may emerge from distinct conditions such as chronic heart failure (CHF), chronic abuse of opioids, idiopathic disease, and high altitude. However, CSA due to periodic breathing at high altitudes is usually triggered by environmental exposure and is not a chronic health condition comparable to the other types of CSA. The International Classification of Sleep Disorders – Third Edition (ICSD-3) identifies the following six types of CSA in adults (American Academy of Sleep Medicine 2014).

- 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

CSA is far less common than obstructive sleep apnoea (OSA), which affects an estimated 936 million adults worldwide (Benjafield 2019). Less than 5% of people referred to a sleep clinic present with CSA (Malhotra 2004). Although there are no precise estimates of CSA prevalence in the general population, reported prevalences in special populations, such as people with CHF, range from 38% to 70% (Naughton 2016; Peer 2010; Vazir 2007)

The pathophysiology of CSA may involve abnormally increased chemosensitivity of respiratory centres located in the brainstem, with small changes in partial pressure of carbon dioxide in arterial blood (PCO_2) generating a hyperreactive response and ultimately culminating in unstable ventilatory patterns (Eckert 2007). Peripheral chemoreceptor sensitisation is also involved, and the risk of CSA seems particularly high when both receptors (peripheral and central) are oversensitive (Giannoni 2009; Nakayama 2003). Alternatively, structural lesions or genetic or substance-induced dysfunction of respiratory nuclei may lead to blunted ventilatory responses and central apnoeas.

Description of the intervention

The treatment of CSA 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 (Bradley 2005; Cowie 2015), and may be associated with residual apnoea-hypopnoea index (AHI; Aurora 2012). Unlike OSA, CSA appears to respond 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. Of note, in people with CSA associated with heart failure, optimised treatment may include the association of drugs for treating CSA with other options for treating heart failure,

such as sacubitril-valsartan and cardiac resynchronisation therapy (Simantirakis 2008; Fala 2015).

How the intervention might work

Pharmacological agents with very distinct mechanisms of action may act on ventilatory control, chemoreflex modulation, 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, as frequent arousals are associated with increased chemoresponsiveness, which leads to the pattern of hyperventilation and subsequent hypoventilation (Bonnet 1990). In fact, periodic breathing predominates during light non-rapid eye movement (NREM) sleep and disappears during rapid eye movement (REM) sleep (Berssenbrugge 1983).

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

Serotonin (5-hydroxytryptamine or 5-HT) neurons play an important role in central chemoreception. Buspirone is a 5-HT receptor agonist that decreases central chemosensitivity to carbon dioxide (CO_2) in a dose-dependent manner, leading to ventilatory stability and central apnoea disappearance (Giannoni 2020a).

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 (Emdin 2017; Hanly 1996; Wilcox 1998). It is not entirely clear whether treating CSA-CSB in this population improves survival, which would be of utmost importance. Additionally, sleep fragmentation due to CSA may lead to difficulty maintaining sleep and daytime sleepiness, impacting negatively on quality of life. Central apnoeas are also observed in the daytime and in the upright position. Of note, upright central apnoea in people with heart failure is associated with worse clinical conditions and a greater risk of cardiac death (Giannoni 2020b). Although some therapies for CSA are associated with improved quality of life, it remains unclear whether and to what extent pharmacological therapies might improve quality of life in this population (Sasayama 2009). Some experts have hypothesised that implantable phrenic nerve stimulation devices may provide a novel treatment approach; however, to date, no studies have drawn solid conclusions on this intervention (Schwartz 2021). In contrast to CPAP/BiPAP/ASV used only at night, pharmacological treatment could also be useful for daytime central apnoea.

Much of the evidence on the effectiveness of pharmacological agents for CSA is derived from non-randomised studies or from randomised studies with methodological limitations. A comprehensive search of 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.

Pharmacological treatment for central sleep apnoea in adults (Review)

OBJECTIVES

To evaluate the benefits and harms of pharmacological treatment compared with active or inactive controls for central sleep apnoea in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We had originally planned to include only randomised controlled trials (RCTs) with a parallel design and exclude cross-over trials. However, the initial search results indicated that most relevant trials for this review used cross-over methodology. Hence, with the approval of the editorial board, we made a post-hoc protocol change to include randomised cross-over trials.

We included studies published as full-text articles, studies published as abstract only, and studies with unpublished data.

Types of participants

We included studies that enrolled participants aged 18 years or older diagnosed with one of the following CSA syndromes, as defined by the ICSD-3 (American Academy of Sleep Medicine 2014).

- CSA with CSB
- CSA due to a medical disorder without CSB
- CSA due to a medication or substance
- Primary CSA
- Treatment-emergent CSA

We had originally planned to include studies of CSA due to periodic breathing at high altitudes but later decided not to include this group because the condition is usually triggered by environmental exposure and is not considered a chronic health condition.

Types of interventions

We included studies that evaluated any type of pharmacological agent aimed primarily at the mitigation of CSA, regardless of drug class, compared with active controls (e.g. non-invasive positive pressure ventilation) or inactive controls (e.g. placebo, no treatment or usual care, defined as the treatment of underlying diseases applied to intervention and control groups).

Eligible pharmacological agents anticipated in the protocol for this review included sleep stabilising agents (e.g. zolpidem, temazepam) and respiratory stimulants that increase the apnoeic threshold (e.g. acetazolamide, theophylline). Based on the types of pharmacological agents included in the identified evidence, we used the following intervention classifications as the basis for our analysis.

- Carbonic anhydrase inhibitors (acetazolamide)
- Anxiolytics (buspirone)
- Methylxanthine derivatives (theophylline)
- Hypnotics (triazolam)

We did not include pharmacological treatment of underlying diseases associated with CSA, such as beta-blockers for people with CHF.

Eligible comparisons included any drug versus any comparator. We expected to include the following comparisons.

- Agents stabilising sleep versus inactive control
- Respiratory stimulants versus inactive control
- Another class of pharmacological agent versus inactive control
- Any drug class versus any type of non-invasive positive pressure ventilation (e.g. CPAP, automatic positive airway pressure (APAP), BiPAP or ASV)

Based on the studies and intervention classes identified in the search, we were able to conduct the following comparisons.

- Hypnotics (e.g. triazolam) versus any type of active control or inactive control
- Carbonic anhydrase inhibitors (e.g. acetazolamide) versus any type of active control or inactive control
- Methylxanthine derivatives (e.g. theophylline) versus any type of active control or inactive control
- Anxiolytics (e.g. buspirone) versus any type of active control or inactive control

Three comparisons were in people with CSA-CSB due to heart failure and one comparison was in people with primary CSA.

Types of outcome measures

We assessed outcomes at all time points reported in primary studies and classified follow-up duration as follows.

- Short-term: less than three months
- Intermediate-term: three months to one year
- Long-term: longer than one year

Primary outcomes

- Central apnoea-hypopnoea index (cAHI), defined as the number of central apnoea and hypopnoea events per hour of sleep, measured objectively by polysomnography
- 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)
- Serious adverse events, defined as those leading to death, life-threatening events, hospitalisation, disability or permanent damage, congenital anomaly, or intervention to prevent permanent impairment or damage

Secondary outcomes

- Quality of sleep, measured with validated scales or questionnaires, such as the Pittsburgh Sleep Quality Index (Buysse 1989)
- Quality of life, measured with validated scales or questionnaires, such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; Jenkinson 1996)
- Daytime sleepiness, measured with validated scales or questionnaires, such as the Epworth Sleepiness Scale (Johns 1991)
- Apnoea-hypopnoea index (AHI), defined as the number of obstructive, mixed, and central apnoea-hypopnoea events per hour of sleep, measured objectively by polysomnography

- All-cause mortality, defined as number of deaths from any cause
- Time to life-saving cardiovascular intervention (e.g. cardiac transplantation, implantation of cardioverter-defibrillator)
- Non-serious adverse events (e.g. nasal congestion, upper airway dryness, mask-induced pressure ulcer)

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases from their inception, applying no language restrictions.

- 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 OvidSP (1946 to 30 August 2022)
- Embase OvidSP (1974 to 30 August 2022)
- Scopus (from 2004 to 30 August 2022)

The Information Specialist searched CENTRAL, MEDLINE and Embase, and the review authors searched Scopus. Appendix 1 presents the MEDLINE strategy, which we adapted for use in the other databases. We handsearched conference abstracts and grey literature through the CENTRAL database.

We also searched the following trials registries.

- US National Institutes of Health (NIH) ongoing trials register ClinicalTrials.gov (clincialtrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch)

Searching other resources

We checked the reference lists of all included studies and relevant review articles for additional references. We also examined any errata or retraction notices for included studies and looked for additional information on ongoing trials on manufacturers' websites.

Data collection and analysis

Selection of studies

Two review authors (AR and ACP) independently screened titles and abstracts of all references returned by the searches using the predefined inclusion criteria, coding them as 'retrieve' (eligible/potentially eligible) or 'do not retrieve' (clearly ineligible). We retrieved the full-text reports of all eligible and potentially eligible studies, and two review authors (AR and ACP) independently screened them against our inclusion criteria, recording the reasons for exclusion of ineligible studies. We resolved any disagreements through discussion or by involving another review author (DP) when necessary. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Page 2020).

Data extraction and management

Two review authors (AR and ACP) independently extracted study characteristics and outcome data using the Cochrane data collection form as a template (EPOC 2017). We piloted the form on at least one included study. We assigned each study a unique study identifier and double-checked for eligibility before data extraction.

We extracted the following data.

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

We noted in the Characteristics of included studies table if a study had not reported outcome data in a usable way. We resolved disagreements by consensus or by involving a third review author (DP). One review author (AR) entered data into Review Manager Web (RevMan Web) software for analysis (RevMan Web 2022). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (DP) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (AR and ACP) independently assessed the risk of bias of all included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (DP). We assessed 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 judged each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. When considering the effects of treatment, we took into account the risk of bias for the studies that contributed to that outcome. We considered the domains 'blinding of participants and personnel' and 'blinding of outcome assessment' differently according to the type of outcome: for subjective outcomes, such as daytime sleepiness, quality of life and quality of sleep, we considered any deviation of blinding procedures indicative of high risk of bias; but for objective outcomes such as mortality, we did not consider the absence or inadequacy of blinding to impose a risk of bias. If any information on risk of bias had come from unpublished data or correspondence with a trialist, we would have noted this in the risk of bias table.

Measures of treatment effect

We analysed dichotomous data as odds ratios (ORs) and continuous data as mean differences (MDs). If we had been able to combine studies that had used different scales for the same outcome, we would have analysed them with standardised mean differences (SMDs). Had we combined data from rating scales in a meta-analysis, we would have ensured they were entered with a consistent direction of effect (e.g. lower scores always indicating improvement). We described skewed data narratively (e.g. as medians and interquartile ranges (IQRs) for each group).

Where a single study included multiple trial arms, we included only the relevant arms. Where there were two comparisons (e.g. drug A versus placebo and drug B versus placebo), we had planned to either combine the active arms or halve the control group to avoid double-counting. Where adjusted analyses were available (ANOVA or ANCOVA), we had planned to use them in our meta-analyses. Where studies included more than two arms with the same medication but different doses, we had planned to combine these arms.

If both change from baseline and endpoint scores had been available for continuous data, we would have used change from baseline unless there was low correlation between measurements in individuals. If a study had reported outcomes at multiple time points, we would have used data from all time points. We had planned to use intention-to-treat (ITT) or 'full analysis set' analyses where possible (i.e. where studies had imputed data for participants who were randomised but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of participants admitted to hospital, rather than number of admissions per participant). If a study had reported rate ratios, we would have analysed them on this basis.

Dealing with missing data

We contacted the authors of included studies to verify key study characteristics and obtain any missing numerical outcome data. If this had not been possible, and the missing data were thought to introduce serious bias, we would have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis. Where there were missing outcome data (e.g. standard deviations (SDs) or correlation coefficients) that could not be obtained from the study authors, we attempted to calculate them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2022a). Where this was not possible, and the missing data were thought to introduce serious bias, we took this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

Had we been able to combine data from different studies in a meta-analysis, we would have investigated statistical heterogeneity using the Chi² test (considering a P value below 0.1 to represent heterogeneity of intervention effects) and quantified statistical heterogeneity using the I² statistic (considering a value of 50% of greater to represent substantial heterogeneity (Higgins

2011), although we recognise that there is uncertainty in the I² measurement when a meta-analysis includes few studies). If we had identified substantial heterogeneity, we would have reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we had pooled more than 10 studies in the same meta-analysis, we would have created and examined a funnel plot to explore possible small-study effects and publication biases.

Data synthesis

We had planned to pool data from studies judged to be clinically homogeneous using Review Manager software. Had more than one study provided data for any comparison, we would have performed meta-analysis. We would have used a random-effects model and performed a sensitivity analysis with a fixed-effect model.

As we were unable to pool any data, we used RevMan Web to calculate the effect size from raw data reported in individual studies (RevMan Web 2022). We estimated the MDs between groups in cross-over RCTs, separately for each pharmacological comparison, using the data type generic inverse variance. For the parallel RCT, we estimated the MDs between groups using the inverse variance method. For dichotomous variables we estimated the ORs between groups using the Mantel-Haenszel method.

Subgroup analysis and investigation of heterogeneity

We had planned to carry out the following subgroup analyses on the outcomes AHI and cardiovascular mortality.

- Severity of CSA based on cAHI, with two prespecified subgroups, namely mild central apnoea, defined as less than 15 central apnoea events per hour of sleep, and moderate to severe central apnoea, defined as more than 15 central apnoea events per hour of sleep. The rationale for this subgroup analysis is based on the assumption that treatment of CSA may have different effects according to the severity of CSA.
- Severity of CHF based on the New York Heart Association (NYHA) functional classification (Class IV versus Class I to III; New York Heart Association 1994) or based on left ventricular ejection fraction (LVEF; below 30% versus above 30%). The rationale for scrutinising intervention effects regarding severity of CHF is based on the assumption that people with severe CHF may respond differently.
- Aetiology of CSA as defined by the ICSD-3 for comparisons involving heterogeneous populations
- Pharmacological agents for comparisons involving multiple agents within the same drug class

However, due to scarcity of studies, subgroup analysis was not possible. Had it been possible, we would have used the formal test for subgroup interactions in RevMan Web (RevMan Web 2022).

Sensitivity analysis

We had planned to carry out sensitivity analyses, removing the following studies from the primary outcome analyses.

- Studies that fulfilled criteria for high risk of bias or unclear risk of bias in at least two domains of the risk of bias table
- Studies in which the source of funding may have influenced the results (industry sponsorship)

We would have compared the results from a fixed-effect model with the random-effects model, if we had been able to conduct meta-analyses.

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro GDT to prepare summary of findings tables for the following outcomes (GRADEpro GDT).

- cAHI
- Cardiovascular mortality
- Serious adverse events
- Quality of sleep
- Quality of life
- AHI
- All-cause mortality
- Time to life-saving cardiovascular intervention

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess certainty of the body of evidence (Schumemann 2013). We provided justifications for downgrading certainty of the evidence in footnotes.

R E S U L T S

Description of studies

Results of the search

The electronic database search run on 30 August 2022 retrieved 5046 references; a handsearch of reference lists and manufacturers' websites identified no further studies. After excluding duplicate publications and irrelevant reports, we assessed 55 potentially eligible studies (63 reports). No studies were eligible for inclusion according to the original protocol of this review, as we had excluded cross-over RCTs. However, a post-hoc revision of the protocol, that considered cross-over RCTs eligible for the review, enabled us to include five studies (6 reports). Figure 1 shows the selection process.

Figure 1. Study flow diagram.


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┌──────────────────────┐   ┌──────────────────────┐
│ 5046 records         │   │ 0 additional         │
│ identified through   │   │ records identified   │
│ database searching   │   │ through other        │
│                      │   │ sources              │
└──────────────────────┘   └──────────────────────┘
            │                          │
            └──────────┬───────────────┘
                       ▼
            ┌──────────────────────┐
            │ 3970 records after   │
            │ duplicates removed   │
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            ┌──────────────────────┐        ┌──────────────────────┐
            │ 3970 records         │───────▶│ 3923 records         │
            │ screened             │        │ excluded             │
            └──────────────────────┘        └──────────────────────┘
                       │
                       │                     ┌──────────────────────┐
                       │                     │ 44 studies (50       │
                       │                     │ reports) excluded,   │
                       │                     │ with reasons         │
                       ▼                     │                      │
            ┌──────────────────────┐        │ 2 ongoing trials (2  │
            │ 55 studies (63       │───────▶│ reports)             │
            │ reports) fully       │        │                      │
            │ assessed for         │        │ 4 studies (5         │
            │ eligibility          │        │ reports) awaiting    │
            └──────────────────────┘        │ classification       │
                       │                     └──────────────────────┘
                       ▼
            ┌──────────────────────┐
            │ 5 studies (6         │
            │ reports) included    │
            │ in qualitative       │
            │ synthesis            │
            └──────────────────────┘
                       │
                       ▼
            ┌──────────────────────┐
            │ No studies           │
            │ included in          │
            │ quantitative         │
            │ synthesis            │
            │ (meta-analysis)      │
            └──────────────────────┘
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We found two ongoing studies (2015-003119-39; NCT04118387). The record for 2015-003119-39 was last updated in February 2016, but the lead investigator did not respond to our email requests for information.

NCT04118387 is entitled 'Central Sleep Apnea: Physiologic Mechanisms to Inform Treatment (CSA)', and it aims identify mechanistic pathways to guide future therapeutic interventions for central sleep apnoea based on the strong premise that multimodality therapy will normalise respiration and hence mitigate adverse long-term consequences of CSA. It compares positive airway pressure (PAP), pharmacological treatment (acetazolamide, zolpidem and buspirone) and supplemental oxygen to reduce cAHI and the CO_2 reserve during sleep in people with CEA. The trial is still recruiting and is scheduled to finish in December 2024.

Included studies

Methods

We included four cross-over RCTs (Bonnet 1990; Giannoni 2020a; Javaheri 1996; Javaheri 2006) and one parallel RCT (Sorokina 2019a). Three studies were conducted in the USA (Bonnet 1990; Javaheri 1996; Javaheri 2006), one in Russia (Sorokina 2019a) and one in Italy (Giannoni 2020a). All were single-centre studies and only one reported the period of recruitment (2016 to 2018; Giannoni 2020a). Table 1 provides an overview of the characteristics of the included studies.

Participants

The five studies randomised a total of 68 participants. Sixty-three participants, from four studies, had heart failure in addition to CSA (Giannoni 2020a; Javaheri 1996; Javaheri 2006; Sorokina 2019a). Bonnet 1990 included people with primary CSA. The studies included participants aged 18 years and older. All participants were men in four studies (Bonnet 1990; Giannoni 2020a; Javaheri 1996; Javaheri 2006), and most participants were men in Sorokina 2019a. The smallest study included five adults (Bonnet 1990), and the largest included 18 adults (Sorokina 2019a).

Interventions

In the studies that reported the duration of the intervention, it ranged from three days to one week, and the wash-out period ranged from one to two weeks. Sorokina 2019a did not report the duration of the intervention or wash-out period. Javaheri 2006 and Sorokina 2019a compared acetazolamide (a carbonic anhydrase inhibitor) with placebo or no acetazolamide (inactive control), Giannoni 2020a compared buspirone (an anxiolytic) with placebo (inactive control), Javaheri 1996 compared theophylline (a methylxanthine derivative) with placebo (inactive control), and Bonnet 1990 compared triazolam (a hypnotic) with placebo (inactive control).

Outcomes

All included RCTs evaluated AHI. Four studies evaluated cAHI (Bonnet 1990; Giannoni 2020a; Javaheri 1996; Javaheri 2006). Only Sorokina 2019a evaluated cardiovascular mortality. Two studies measured daytime sleepiness using the Epworth Sleepiness Scale (Bonnet 1990; Giannoni 2020a). Giannoni 2020a reported non-serious adverse events, but no other studies reported a formal evaluation of adverse events.

Conflicts of interest and study funding

Only Javaheri 2006 reported no conflicts of interest. Giannoni 2020a received funding from the US NIH and Javaheri 1996 was supported by Merit Review grants from the US Department of Veterans Affairs. Javaheri 2006 reported no financial support.

Excluded studies

Of the studies excluded during full-text assessment, we provided justification for the exclusion of 28 (34 references) in the Characteristics of excluded studies table. Fifteen studies had an ineligible population, 12 studies were not RCTs, and one study had an ineligible intervention.

Risk of bias in included studies

Full details of risk of bias judgements can be found in the Characteristics of included studies table. Figure 2 provide a graph and summary of the results.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Only Giannoni 2020a was at low risk of selection bias. The remaining RCTs were at unclear risk for this domain because they did not describe the method of generating or concealing the random sequence.

Blinding

For Javaheri 1996 and Sorokina 2019a), it was unclear whether the placebo was indistinguishable from the intervention, which may have compromised the blinding of participants and personnel. We considered Bonnet 1990 and Sorokina 2019a at unclear risk of detection bias, because they provided insufficient information about blinding of the outcome assessors. Bonnet 1990 and Giannoni 2020a reported subjective outcomes (daytime sleepiness): we considered Bonnet 1990 at unclear risk of detection bias for this outcome owing to lack of information, while Giannoni 2020a was at low risk of bias because the outcome assessors were blinded.

Incomplete outcome data

Bonnet 1990 had only five participants, one of whom dropped out. As the study provided no information about the imputation of data, we judged it at unclear risk of attrition bias. All other studies had no attrition, and we judged them at low risk of bias.

Selective reporting

All studies appeared to be free of selective outcome reporting; however, no trial registration information was available for four studies, and we judged them at unclear risk of reporting bias (Bonnet 1990; Javaheri 1996; Javaheri 2006; Sorokina 2019a).

Other potential sources of bias

All studies appeared to be free of other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Carbonic anhydrase inhibitors versus inactive control for central sleep apnoea associated with heart failure in adults ; **Summary of findings 2** Anxiolytics compared to inactive control for central sleep apnoea associated with heart failure in adults; **Summary of findings 3** Methylxanthine derivatives versus inactive control for central sleep apnoea associated with heart failure in adults; **Summary of findings 4** Hypnotics compared to inactive control for primary central sleep apnoea in adults

We had planned to perform sensitivity analyses considering risk of bias (excluding studies with high risk of bias) and industry sponsorship. We also planned to analyse subgroups to scrutinise differences of intervention effects according to aetiology. However, we were unable to perform any of the planned subgroup or sensitivity analyses for cAHI or cardiovascular mortality, owing to the small number of studies.

Carbonic anhydrase inhibitors versus inactive control

Javaheri 2006 and Sorokina 2019a compared acetazolamide with placebo/no acetazolamide in adults with CSA and heart failure.

Primary outcomes

Central apnoea-hypopnoea index

Only Javaheri 2006 reported cAHI. We are uncertain whether acetazolamide compared to placebo reduces cAHI after six nights (MD −26.00 events per hour, 95% CI −43.84 to −8.16; 12 participants; very low-certainty evidence due to risk of bias and imprecision; Analysis 1.1; Summary of findings 1).

Cardiovascular mortality

Only Sorokina 2019a reported cardiovascular mortality. We are uncertain about the effects of acetazolamide compared to no acetazolamide on cardiovascular mortality after 12 months (OR 0.21, 95% CI 0.02 to 2.48; 18 participants; very low-certainty evidence due to risk of bias and imprecision; Analysis 1.2; Summary of findings 1).

Serious adverse events

No studies reported a formal evaluation of serious adverse events.

Secondary outcomes

Quality of sleep

No studies reported quality of sleep.

Quality of life

No studies reported quality of life.

Daytime sleepiness

No studies reported daytime sleepiness.

Apnoea-hypopnoea index

Javaheri 2006 reported API at six nights (short-term) and Sorokina 2019a reported API at six months (intermediate term). We are uncertain whether acetazolamide compared to placebo/no acetazolamide can reduce API in the short term (MD −23.00 events per hour, 95% CI −37.70 to −8.30; 12 participants; very low−certainty evidence due to risk of bias and imprecision; Analysis 1.3; Summary of findings 1) or in the intermediate term (MD −6.98 events per hour, 95% CI −10.66 to −3.30; 18 participants; very low-certainty evidence due to risk of bias and imprecision; Analysis 1.4; Summary of findings 1).

All-cause mortality

No studies reported all-cause mortality.

Time to life-saving cardiovascular intervention

No studies reported time to life-saving cardiovascular intervention.

Non-serious adverse events

No studies reported a formal evaluation of non-serious adverse events.

Anxiolytics compared to inactive control

Giannoni 2020a compared buspirone with placebo in adults with CSA and heart failure.

Primary outcomes

Central apnoea-hypopnoea index

The median difference between groups for cAHI was −5.00 events per hour (IQR −8.00 to −0.50; 16 participants; Summary of findings 2). Giannoni 2020a presented the median and IQR due to data skew; therefore, we considered that estimating the mean and SD would not have given an accurate result, and we were unable to compare differences between groups.

Cardiovascular mortality

Giannoni 2020a did not report cardiovascular mortality.

Serious adverse events

Giannoni 2020a listed serious adverse events as an outcome measure, but reported none.

Secondary outcomes

Quality of sleep

Giannoni 2020a did not report quality of sleep.

Quality of life

Giannoni 2020a did not report quality of life

Daytime sleepiness

The median difference between groups for daytime sleepiness using the Epworth Sleepiness Scale was 0.00 (IQR −1.00 to 0.00; 16 participants).

Apnoea-hypopnoea index

The median difference between groups for AHI was −6.00 (IQR −8.80 to −1.80; 16 participants; Summary of findings 2).

All-cause mortality

Giannoni 2020a did not report all-cause mortality.

Time to life-saving cardiovascular intervention

Giannoni 2020a did not report time to life-saving cardiovascular intervention.

Non-serious adverse events

Three participants reported mild and transient buspirone-related side effects, including lower limb tingling (n = 1; 6%) and dizziness (n = 2; 12%).

Methylxanthine derivatives versus inactive control

Javaheri 1996 compared theophylline with placebo in adults with CSA and heart failure.

Primary outcomes

Central apnoea-hypopnoea index

We are uncertain whether theophylline compared with placebo reduces cAHI after five days (MD −20.00 events per hour, 95% CI −32.15 to −7.85; 15 participants, very low-certainty evidence due to risk of bias and imprecision; Analysis 2.1; Summary of findings 3).

Cardiovascular mortality

Javaheri 1996 did not report cardiovascular mortality.

Serious adverse events

Javaheri 1996 did not report a formal evaluation of serious adverse events.

Secondary outcome

Quality of sleep

Javaheri 1996 did not report quality of sleep.

Quality of life

Javaheri 1996 did not report quality of life.

Daytime sleepiness

Javaheri 1996 did not report daytime sleepiness.

Apnoea-hypopnoea index

We are uncertain whether theophylline compared to placebo decreases AHI after five days (MD −19.00 events per hour, 95% CI −30.27 to −7.73; 15 participants; very low-certainty evidence due to risk of bias and imprecision; Analysis 2.2; Summary of findings 3).

All-cause mortality

Javaheri 1996 did not report all-cause mortality.

Time to life-saving cardiovascular intervention

Javaheri 1996 did not report time to life-saving cardiovascular intervention.

Non-serious adverse events

Javaheri 1996 did not report a formal evaluation of non-serious adverse events.

Hypnotics versus inactive control

Bonnet 1990 analysed triazolam 0.125 mg versus triazolam 0.250 mg versus placebo in adults with primary CSA. We were unable to perform comparisons between groups, as the study did not report SDs for the treatment effects. Had it provided SDs, we would have combined the groups that received triazolam versus placebo. Furthermore, several other features of Bonnet 1990 limit the external validity of the results; for example, the participants refrained from alcohol and caffeine consumption prior to the study and during the laboratory sessions. Most people with CSA are unlikely to follow these recommendations in the long term.

Primary outcomes

Central apnoea-hypopnoea index

The mean cAHI was 9.40 events per hour in participants who received triazolam 0.125 mg versus 8.00 events per hour in those who received triazolam 0.250 mg versus 16.30 events per hour in those who received placebo (Summary of findings 4).

Cardiovascular mortality

Bonnet 1990 did not report cardiovascular mortality.

Serious adverse events

Bonnet 1990 did not report a formal evaluation of serious adverse events.

Secondary outcome

Quality of sleep

Bonnet 1990 did not report quality of sleep.

Quality of life

Bonnet 1990 did not report quality of life.

Daytime sleepiness

Bonnet 1990 assessed daytime sleepiness using the Epworth Sleepiness Scale. Mean daytime sleepiness was 1.50 points in participants who received triazolam 0.125 mg versus 2.00 points in those who received triazolam 0.250 mg versus 2.20 points in those who received placebo.

Apnoea-hypopnoea index

The mean AHI was 13.50 events per hour in the participants who received triazolam 0.125 mg versus 11.00 events per hour in those who received triazolam 0.25 mg versus 20.90 events per hour in those who received placebo (Summary of findings 4).

All-cause mortality

Bonnet 1990 did not report all-cause mortality.

Time to life-saving cardiovascular intervention

Bonnet 1990 did not report time to life-saving cardiovascular intervention.

Non-serious adverse events

Bonnet 1990 did not report a formal evaluation of non-serious adverse events.

DISCUSSION

Summary of main results

In this review, we evaluated the available evidence on pharmacological treatment for CSA in adults. We included four cross-over RCTs and one parallel RCT. Sample sizes were very small; the largest study enrolled 18 adults with CSA associated with heart failure. We evaluated four different pharmacological agents (acetazolamide, theophylline, buspirone and triazolam). We were unable to perform a meta-analysis because of the clinical heterogeneity between the studies. In the four trials that reported treatment duration, it lasted one week or less.

It is unclear whether carbonic anhydrase inhibitors (acetazolamide) and methylxanthine derivatives (theophylline) compared with inactive control can reduce cAHI and AHI in adults with CSA associated with heart failure, as we found only very low-certainty evidence. We are uncertain about the effects of carbonic anhydrase inhibitors on cardiovascular mortality, as the estimated effect included the possibility of both increasing and reducing cardiovascular mortality, and the evidence was of very low certainty. Only one RCT assessed the effects of hypnotics in primary CSA. Due to several methodological limitations and the insufficient reporting of outcome results in this study, a number of questions still persist on the effects of this intervention. Only the study on the anxiolytic reported adverse events: these events were rare and mild (dizziness, sweating), but the safety of this drug should be evaluated in larger and longer multicentre trials before considering

it a reasonable treatment option in people with CSA associated with heart failure. No studies reported serious adverse events, quality of sleep, quality of life, all-cause mortality or time to life-saving cardiovascular intervention.

Overall completeness and applicability of evidence

As most participants in the included studies were men with CSA associated with heart failure, the generalisability of our results is limited. The studies did not report whether the abnormal respiratory pattern could be classified as CSB or if it was associated with non-periodic CSA. This may have important implications for practice because people with CSB have poor prognosis (Lanfranchi 1999; Lorenzi-Filho 2005). In addition, no RCTs assessed clinically relevant outcome measures related to treatment efficacy, such as quality of sleep, quality of life, all-cause mortality, or time to life-saving cardiovascular intervention. Only one RCT reported daytime sleepiness, a commonly disabling symptom related to sleep disorders. Daytime sleepiness is less easily identified in people with CSA and heart failure than in those with CSA without heart failure, as those with heart failure have several symptoms that may strongly overlap, limiting the validity of sleepiness metrics. All included RCTs reported AHI, cAHI or both. However, it is unclear whether the treatment effect in any individual study was clinically meaningful because, to the best of our knowledge, the minimally important difference of AHI or cAHI remains to be established by studies applying anchoring methods.

No studies included participants with treatment-emergent CSA or CSA due to a medication or substance. Our findings should not be extrapolated to these populations, given the varying pathophysiological aspects of CSA syndromes.

Quality of the evidence

We judged four of the five included RCTs at unclear risk of bias for random sequence generation, blinding of outcome assessment and participants, and selective reporting. Because these domains were poorly described, we downgraded the certainty of evidence by one level due to study limitations for all outcomes. We also downgraded the certainty of evidence for imprecision due to the small sample sizes and wide CIs in some cases. The certainty of the evidence was very low for all outcomes.

Potential biases in the review process

We conducted this review in accordance with the Methodological Expectations of Cochrane Intervention Reviews guidelines (Higgins 2022b). Except for some minor deviations (see Differences between protocol and review), we followed our protocol (Riera 2018). We conducted sensitive searches in the most important databases and clinical trial registers and manual searches to identify and collect all relevant RCTs. Although we identified several trials, some studies lacked sufficient data to permit inclusion or exclusion; we assessed these trials as awaiting classification. When studies reported skewed data (e.g. medians and IQRs for each group), we chose to describe them narratively instead of transforming them into means and SDs. We were also unable to design a funnel plot to assess publication bias due to an insufficient number of eligible RCTs to perform meta-analyses.

Agreements and disagreements with other studies or reviews

The effectiveness of pharmacological agents such as respiratory stimulants, anxiolytics and sedatives are uncertain because of the important methodological issues of the includes studies. To our knowledge, no other systematic reviews have specifically examined the effects of pharmacological medications for central apnoea in adults. One previous systematic review and meta-analysis evaluating acetazolamide versus no acetazolamide for CSA and OSA in adults showed improved OSA and CSA in the intervention group (Schmickl 2020a). However, it combined data from different study populations (CSA-CHF; CSA-high altitude; CSA-idiopathic) and different study designs (randomised and non-randomised). The RCT evaluating acetazolamide for CSA that was included in that review was also identified in the present review (Javaheri 2006).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend the use of pharmacological therapy in the treatment of central sleep apnoea (CSA). Although small studies found that certain agents reduced the number of respiratory events during sleep in people with CSA associated with heart failure, they could not evaluate whether this reduction affected participants' quality of life as they did not measure important clinical outcomes such as sleep quality or subjective impression of daytime sleepiness. Furthermore, the trials were mostly short term, so more trials evaluating longer-term effects are needed.

Implications for research

Most participants of the included randomised controlled trials (RCTs) in this review were older men with heart failure. Central apnoea can be observed in up to 60% of people with heart failure at night and 30% during the day (Brack 2007; Emdin 2017). Of note, central apnoeas are also observed at daytime and in the upright position, which is associated with worse clinical conditions and with a greater risk of cardiac death (Giannoni 2020b). Therefore, it is important to evaluate the effect of pharmacological treatment in people with apnoea in upright position and on central apnoeas over 24 hours, considering the prognostic significance of daytime apnoeas. In addition, future studies should report the time with oxygen saturation below 90% in each group at baseline, as hypoxaemic burden is a robust and independent predictor of all-cause mortality in people with heart failure (Oldenburg 2015).

The number of older adults with heart failure may increase in the future, and this condition can lead to difficulty maintaining sleep and daytime sleepiness, reducing quality of life. Moreover, the overall drugs safety profile in adults with CSA is not yet consolidated in the literature. One study evaluated the safety of acetazolamide under different conditions, showing that adverse events of acetazolamide are rare and that some common side effects, such as paraesthesia, are dose-dependent (Schmickl 2020b). However, studies evaluating other pharmacological agents, such as those included in our review, are still scarce, and questions about the safety of sleep apnoea treatment remain unanswered.

Most trials included in this review measured outcomes in the short term only, so the long-term sustainability of treatment effects remains unclear. There is a need for larger multicentre RCTs that explore relevant clinical outcomes, including quality of life metrics and survival, after a longer follow-up period, to clarify the effectiveness of pharmacological treatment for adults with CSA.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bonnet 1990

Study characteristics	
Methods	3-arm RCT with cross-over design
Participants	**Number randomised/analysed:** 5/4 or 5 (unclear)
	Sex (% male): 100%
	Age: average 70 years (range 65–74)
	Inclusion criteria
	• Age 55–75 years • General good health • CSA with some increase in daytime sleepiness
	Exclusion criteria
	• significant psychopathology • uncontrolled diabetes • thyroid dysfunction • evidence of narcolepsy • clear obstructive sleep apnoea
Interventions	**Intervention group 1:** triazolam (benzodiazepine) 0.125 mg once daily for 3 days
	Intervention group 2: triazolam (benzodiazepine) 0.250 mg once daily for 3 days
	Control group: placebo (inactive control) once daily for 3 days
	Wash-out period: at least 1 week
	Details of intervention: on 4 nights of 3 nonconsecutive laboratory weeks, participants took a pill 30 minutes before bedtime (between 10 PM and 12 AM). All participants received placebo on the first night, then their allocated treatment for the next 3 consecutive nights.

Bonnet 1990 *(Continued)*

Participants could not use tranquillisers or hypnotics during the study. They were asked not to consume alcohol for 2 days prior to study initiation and during the laboratory sessions, or to consume caffeine during the study.

Co-interventions: none reported

Outcomes	
	• cAHI measured objectively by polysomnography on final 2 laboratory nights
	• Daytime sleepiness measured by Stanford sleepiness scale on final 2 laboratory nights
	• AHI measured objectively by polysomnography on final 2 laboratory nights

Notes	**Study funding source:** not reported
	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge selection bias.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "On each night, a pill was taken 30 min prior to a standard 10 pm to 12 am bedtime. The pill was matched placebo, 0.125 mg, triazolam, or 0.25 mg triazolam."; "The assignment of medication and placebo conditions to subjects was random and double blind."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge the measures used to blind outcome assessors.
Blinding of outcome assessment (detection bias) (subjective outcomes)	Unclear risk	Insufficient information to judge the measures used to blind outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "One subject did not participate in the 0.25 mg condition." Comment: there is no information about data imputation.
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the study protocol to judge reporting bias.
Other bias	Low risk	The study appears to be free of other sources of bias.

Giannoni 2020a

Study characteristics

Methods	RCT with a cross-over design
Participants	**Number randomised/analysed:** 16/16
	Sex (% male): 100%
	Age: mean 71.3 (SD 5.8) years

Giannoni 2020a *(Continued)*

Inclusion criteria

- Age 18–80 years
- Systolic heart failure (LVEF < 50%)
- Moderate-severe central apnoea (nocturnal AHI ≥ 15 events/hour)

Exclusion criteria

- NYHA class IV, acute coronary syndrome or heart failure, coronary artery revascularisation, cardiac resynchronisation therapy within 3 months before examination
- Severe renal dysfunction (eGFR < 30mL/min/1.73 m2 by the Modification of Diet in Renal Disease equation)
- Liver failure
- Severe chronic obstructive pulmonary disease
- OSA
- Treatments acting on ventilation
- Pregnancy/no contraception in premenopausal women
- Alcohol/drug abuse
- Allergies to buspirone/drug components
- Myasthenia gravis
- Tight angle glaucoma
- Active neoplasia.

Interventions	**Intervention group:** buspirone (anxiolytic) 15 mg 3 times daily for 1 week **Control group:** placebo (inactive control) 3 times daily for 1 week **Wash-out period:** 1 week **Details of intervention:** to minimise adverse reactions, the cumulative dose was titrated every 2 days from 15 mg/day (5 mg 3 times daily), to 30 mg/day (10 mg 3 times daily), to 45 mg/day (15 mg 3 times daily) in participants with eGFR ≥ 70 mL/min/1.73 m2. For participants with eGFR of 50–69 mL/min/1.73 m2, the drug was titrated to a maximum dose of 30 mg/day; and for those with eGFR of 30–49 mL/min/1.73 m2, the drug was kept at 15 mg/day. **Co-interventions:** optimal medical therapy (not described)
Outcomes	- cAHI measured objectively by polysomnography 1 week after treatment administration - Serious adverse events (participant-reported) - Daytime sleepiness measured by Stanford Sleepiness Scale 1 week after treatment administration - AHI measured objectively by polysomnography 1 week after treatment administration - Non-serious adverse events (participant-reported
Notes	**Study funding source:** 1 study author (GBR) received funding from the US National Institutes of Health (U01NS090414). **Conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...who created a computerized randomisation list 0 = placebo, 1 = buspirone) and delivered to the study staff the masked complete treatments (I and II) in sealed opaque envelopes. The randomisation list remained hidden from patients and investigators (double blind) until the conclusion of the study."

Giannoni 2020a *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "a hospital pharmacist [...] delivered to the study staff the masked complete treatments (I and II) in sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomisation list remained hidden from patients and investigators (double blind) until the conclusion of the study."; "The galenic preparation (tablets with identical appearance) of the experimental drugs (buspirone or placebo)"; "To maintain masking, similar procedures related to drug titration were used for placebo."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The randomisation list remained hidden from patients and investigators (double blind) until the conclusion of the study."
Blinding of outcome assessment (detection bias) (subjective outcomes)	Low risk	Quote: "The randomisation list remained hidden from patients and investigators (double blind) until the conclusion of the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient withdrew from the study, two patients were intolerant to the chemoreflex test, while all other measurements were available in all patients."; "The primary effectiveness endpoint was evaluated in all patients who were randomised to either placebo or buspirone in the intention-to-treat (ITT) analysis. Patients randomised without chemoreflex data (intolerance to the test) or who withdrew from the study were imputed as treatment failures. A per-protocol (PP) analysis was also performed for the primary outcome. Finally, imputation analysis by median substitution was also performed. In order to test the primary endpoint, a two-sided McNemar's exact test was used with a type I error rate of 0.05."
Selective reporting (reporting bias)	Low risk	Study was registered (EudraCT 2015-005383-42). All the primary outcomes were reported.
Other bias	Low risk	Study funding source was reported and possible conflicts of interest were declared.

Javaheri 1996

Study characteristics

Methods	RCT with a cross-over design
Participants	**Number randomised/analysed:** 15
	Sex (% male): 100%
	Age: not reported (adults)
	Inclusion criteria
	• Compensated heart failure (LVEF ≤ 45 %)
	• > 10 apnoea-hypopnoea episodes/hour
	• No change in signs or symptoms of heart failure within previous 4 weeks
	• Optimal therapy, with no change in medications within previous 4 weeks
	Exclusion criteria
	• Unstable angina
	• Unstable congestive heart failure

Javaheri 1996 *(Continued)*

- Acute pulmonary oedema
- Congenital heart disease
- Intrinsic pulmonary diseases, including interstitial lung disease and obstructive lung defects (ratio of predicted forced expiratory volume to forced vital capacity: 80%)
- Intrinsic renal and liver disorders
- Untreated hypothyroidism or kyphoscoliosis
- Use of morphine derivatives, benzodiazepines or theophylline

Interventions	**Intervention group:** theophylline (methylxanthine derivative) 3.3 mg/kg orally twice daily for 5 days
	Control group: placebo (inactive control) for 5 days
	Wash-out period: 1 week
	Details of intervention: no further details
	Co-interventions: optimal therapy, which included angiotensin-converting-enzyme inhibitors (in 13 participants), hydralazine (in 2 participants), digoxin (in 11 participants), isosorbide dinitrate (in 7 participants) and furosemide (in all 15 participants)
Outcomes	- cAHI measured objectively by polysomnography at baseline, during administration of placebo, and during administration of theophylline (reported at baseline and on day 5) - AHI measured objectively by polysomnography at baseline, during administration of placebo, during administration of theophylline (reported at baseline and on day 5)
Notes	**Study funding source:** supported by Merit Review grants from the US Department of Veterans Affairs
	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients received placebo or theophylline orally twice daily for five days, in a randomised, double-blind fashion." Comment: no further details; insufficient information to judge selection bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients received placebo or theophylline orally twice daily for five days, in a randomised, double-blind fashion." Comment: no further details; insufficient information to judge selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "To maintain blinding, the patients were monitored during both the theophylline and the placebo phases of the study." Comment: no further details of how blinding was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The polysomnograms were scored blindly."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.

Javaheri 1996 (Continued)

Selective reporting (reporting bias)	Unclear risk	There is insufficient information about the study protocol to judge reporting bias.
Other bias	Low risk	The study appears to be free of other sources of bias.

Javaheri 2006

Study characteristics

Methods	RCT with a cross-over design
Participants	**Number randomised/analysed:** 14/12
	Sex (% male): 100%
	Age: mean 66 (SD 6) years
	Inclusion criteria
	• Systolic heart failure
	• CSA with CSB (AHI > 15 events/hour)
	Exclusion criteria
	• Unstable cardiovascular status
	• Significant intrinsic pulmonary, renal, or liver disorders
	• Use of morphine derivatives, benzodiazepines, or theophylline.
Interventions	**Intervention group:** acetazolamide (carbonic anhydrase inhibitor) 3.5 mg/kg orally (once daily) 1 hour before bedtime for 6 nights
	Control group: placebo (inactive control) for 6 nights
	Wash-out period: 2 weeks
	Details of intervention: participants received 3 identical capsules of either placebo or one acetazolamide and two potassium chloride (to compensate for acetazolamide-induced urinary potassium loss). To induce mild metabolic acidosis and decrease total CO_2 by about 5 mmol/L, a venous blood sample was obtained on the morning of the third day after randomisation, and the dose of acetazolamide was increased to 4 mg/kg to achieve the target concentration of total CO_2.
	Co-interventions: potassium chloride (total, 30 mEq).
Outcomes	• cAHI measured objectively by polysomnography at baseline and the end of each arm of the study (6 nights)
	• AHI measured objectively by polysomnography at baseline and at the end of each arm of the study (6 nights)
Notes	**Study funding source:** not reported
	Conflicts of interest: no relationship with any commercial entity that could be interested in the study

Risk of bias

Javaheri 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised to a double-blind cross-over protocol with acetazolamide or placebo." Comment: no further details; insufficient information to judge selection bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomised to a double-blind cross-over protocol with acetazolamide or placebo." Comment: no further details; insufficient information to judge selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only a researcher in pharmacology and a physician, both of whom were monitoring the patients, were not blind to randomization. The patients, the principal investigator, and the technicians who performed various tests were unaware of randomization. The procedures were identical for placebo and acetazolamide arms."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[...] the technicians who performed various tests were unaware of randomisation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient refused to take part in the study (because of long travel distance) and one patient did not complete the study." Comment: data loss was low; reasons provided.
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the study protocol to judge reporting bias.
Other bias	Low risk	The study appears to be free of other sources of bias.

Sorokina 2019a

Study characteristics	
Methods	RCT
Participants	**Number randomised/analysed:** 18/18 **Sex (% male):** not reported (mostly men) **Age:** not reported (adults) **Inclusion criteria** • CSA (AHI > 15 events/hour) • CHF (NYHA functional class II or III) **Exclusion criteria** • Chronic respiratory failure • Renal failure • Previous stroke • Anaemia • Obesity

Sorokina 2019a *(Continued)*

Interventions	**Intervention group**: acetazolamide (carbonic anhydrase inhibitor) 250 mg plus standard medical treatment (n = 8) **Control group:** standard medical treatment (inactive control; n = 10) **Wash-out period:** not applicable (not a cross-over trial) **Details of intervention:** no further details **Co-interventions:** no description of standard medical treatment
Outcomes	- Cardiovascular mortality at 12 months - AHI measured by cardiorespiratory monitoring during sleep at 6 months
Notes	**Study funding source:** not reported **Conflict of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "[...] patients with CSA were randomised into two groups." Comment: no further details; insufficient information to judge selection bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "[...] patients with CSA were randomised into two groups." Comment: no further details; insufficient information to judge selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about measures used to blind participants and professionals.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about measures used to blind the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Insufficient information about the study protocol to judge reporting bias.
Other bias	Low risk	The study appears to be free of other sources of bias.

AHI: apnoea-hypopnoea index; cAHI: central apnoea-hypopnoea index; CHF: chronic heart failure; CSA: central sleep apnoea; CSB: Cheyne-Stokes breathing; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OSA: obstructive sleep apnoea; RCT: randomised controlled trial; SD: standard deviation.

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

Study	Reason for exclusion
Belyavskiy 2010	Wrong population (obstructive sleep apnoea).
Caravita 2022	Wrong population (mixed population without individual data).
Connaughton 1984	Non-randomised study.
DeBacker 1995	Non-randomised study.
Dubowitz 1998	Wrong study design (case-control).
Ginter 2020	Wrong population.
Jaffuel 2021	Non-randomised study.
Javed 2020	Wrong intervention.
Murray 1977	Non-randomised study.
Naghan 2019	Wrong population.
Naghan 2020	Wrong population.
NCT00746954	Wrong population.
NCT01500473	Non-randomised study.
NCT02670096	Wrong population.
Obernadorfer 2000	Wrong population.
Passino 2021	Wrong population.
Prowting 2021	Wrong population.
Rastogi 2020	Wrong population.
Saletu 1999	Wrong population.
Schumacher 2014	Wrong population.
Schwarz 2020	Non-randomised study.
Shore 1983	Non-randomised study.
Sin 1999	Non-randomised study.
Sorokina 2019b	Non-randomised study.
Ulrich 2013	Wrong population.
Ulrich 2015	Wrong population.
Westwood 2012	Non-randomised study.
Yasuma 2006	Non-randomised study.

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

Ahmad 2022

Methods	RCT with cross-over design
Participants	People with CSA, defined as an AHI ≥ 15 and a cAHI ≥ 5 (n = 11)
Interventions	Zolpidem 5/10 mg versus placebo for 2 nights
Outcomes	• AHI measured objectively by polysomnography • cAHI measured objectively by polysomnography
Notes	Only abstract available. We contacted the study authors to ask for the full text.

Guo 2003

Methods	Prospective double-blind placebo-controlled clinical study
Participants	40 people with sleep apnoea-hypopnoea syndrome (20 obstructive and 20 central) and 40 healthy people
Interventions	Zolpidem 5mg versus zolpidem 10 mg versus placebo
Outcomes	• cAHI • Adverse effects
Notes	Only abstract available.

NCT02569970

Methods	Randomised parallel assignment
Participants	People with CSA and seizure
Interventions	Fluoxetine 20mg versus placebo 20 mg
Outcomes	• Change score on Sleep Apnea Sleep DisordersQuestionnaire • Change score on Epworth Sleepiness Scale • Change in quality of life score
Notes	Study with status 'completed' in ClinicalTrials.gov but without results. We contacted the study authors to check the availability of data.

Sorokina 2022

Methods	Randomised parallel assignment
Participants	People with Cheyne-Stokes respiration and CHF

Sorokina 2022 *(Continued)*

Interventions	Standard medical therapy in combination with acetazolamide 250 mg once daily (n =10) versus standard therapy (n = 11)
Outcomes	- AHI - Mortality
Notes	Only abstract available. We contacted the study authors to ask for the full text.

API: apnoea-hypopnoea index; cAHI: central apnoea-hypopnoea index; CHF: chronic heart failure; CSA: central sleep apnoea; RCT: randomised controlled trial.

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

2015-003119-39

Study name	Effects of a short therapy of zolpidem with support servo-ventilation versus placebo in patients with central sleep apnoea with chronic heart failure
Methods	Prospective double-blind placebo-controlled clinical study
Participants	People with CSA and CHF
Interventions	Zolpidem versus placebo
Outcomes	- Score on Epworth Sleepiness Scale - AHI
Starting date	25 February 2016
Contact information	MCoutard@chu-grenoble.fr
Notes	

NCT04118387

Study name	CSA: physiologic mechanisms to inform treatment
Methods	RCT with a cross-over design
Participants	People with CSA, defined as AHI >15 events/hour with cAHI > 5 events/hour
Interventions	Acetazolamide + supplemental oxygen + PAP therapy versus zolpidem + PAP therapy versus buspirone + PAP therapy
Outcomes	cAHI
Starting date	7 January 2021
Contact information	sbadr@med.wayne.edu

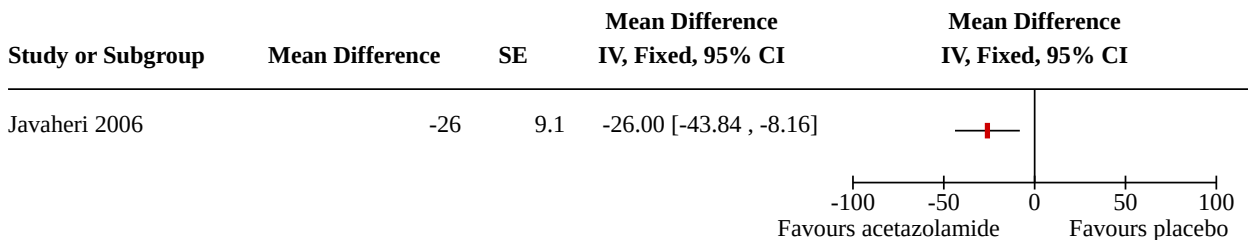| Notes	Recruitment status: recruiting

AHI: apnoea-hypopnoea index; cAHI: central apnoea-hypopnoea index; CHF: chronic heart failure; CSA: central sleep apnoea; PAP: positive airway pressure; RCT: randomised controlled trial.
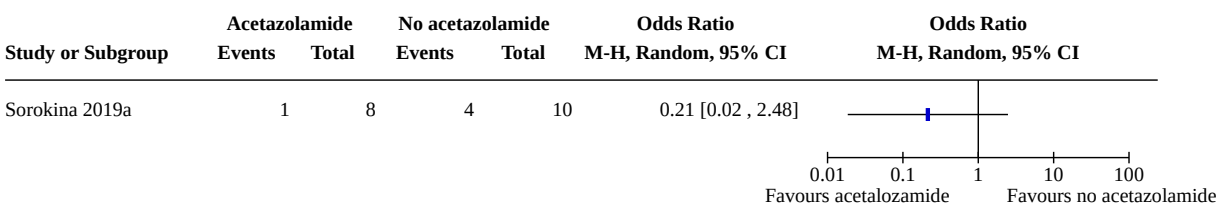
DATA AND ANALYSES

Comparison 1. Carbonic anhydrase inhibitors versus inactive control

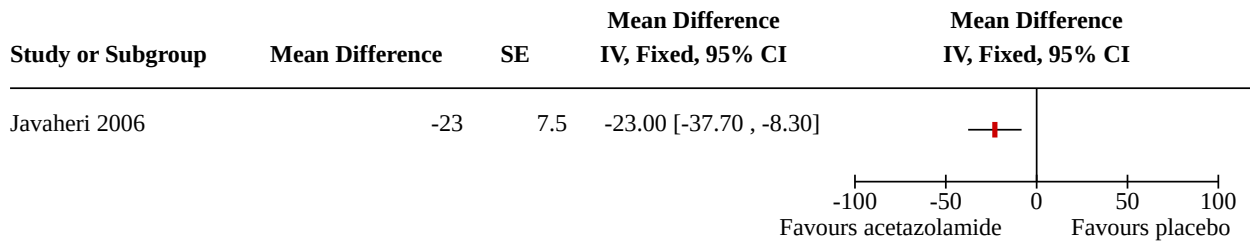| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Central apnoea-hypopnoea index (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Cardiovascular mortality (intermediate-term)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Apnoea-hypopnoea index (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Apnoea-hypopnoea index (intermediate-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Carbonic anhydrase inhibitors versus inactive control , Outcome 1: Central apnoea-hypopnoea index (short-term)
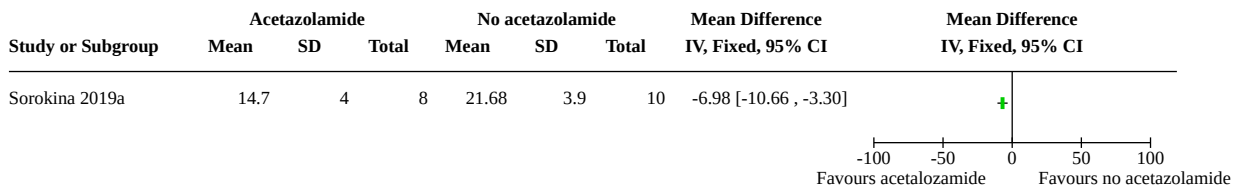
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Javaheri 2006	-26	9.1	-26.00 [-43.84 , -8.16]	

-100 -50 0 50 100
Favours acetazolamide   Favours placebo

Analysis 1.2. Comparison 1: Carbonic anhydrase inhibitors versus inactive control , Outcome 2: Cardiovascular mortality (intermediate-term)

Study or Subgroup	Acetazolamide Events	Total	No acetazolamide Events	Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Sorokina 2019a	1	8	4	10	0.21 [0.02 , 2.48]	

0.01 0.1 1 10 100
Favours acetalozamide   Favours no acetazolamide

Analysis 1.3. Comparison 1: Carbonic anhydrase inhibitors versus inactive control , Outcome 3: Apnoea-hypopnoea index (short-term)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Javaheri 2006	-23	7.5	-23.00 [-37.70 , -8.30]	

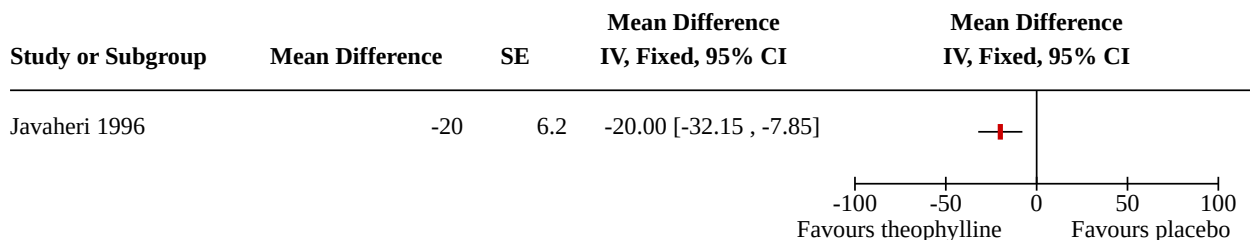-100 -50 0 50 100
Favours acetazolamide   Favours placebo

Analysis 1.4. Comparison 1: Carbonic anhydrase inhibitors versus inactive control , Outcome 4: Apnoea-hypopnoea index (intermediate-term)
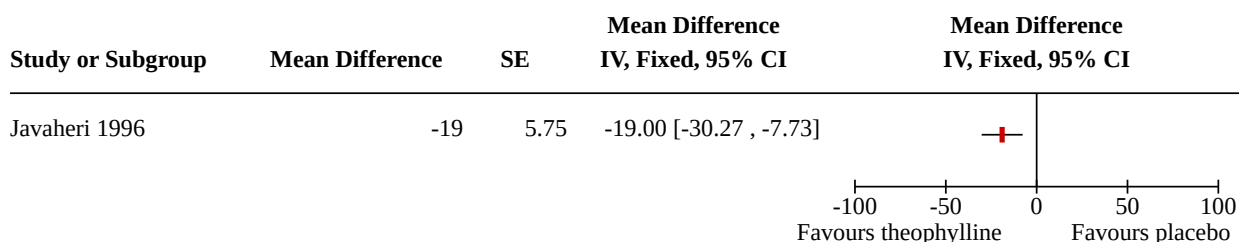
Study or Subgroup	Acetazolamide			No acetazolamide			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Sorokina 2019a	14.7	4	8	21.68	3.9	10	-6.98 [-10.66 , -3.30]	

-100 -50 0 50 100
Favours acetalozamide   Favours no acetazolamide

Comparison 2. Methylxanthine derivative agents versus inactive control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Central apnoea-hypopnoea index (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Apnoea-hypopnoea index (short-term)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Methylxanthine derivative agents versus inactive control , Outcome 1: Central apnoea-hypopnoea index (short-term)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Javaheri 1996	-20	6.2	-20.00 [-32.15 , -7.85]	

-100 -50 0 50 100
Favours theophylline   Favours placebo

Analysis 2.2. Comparison 2: Methylxanthine derivative agents versus inactive control , Outcome 2: Apnoea-hypopnoea index (short-term)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Javaheri 1996	-19	5.75	-19.00 [-30.27 , -7.73]	

-100   -50   0   50   100
Favours theophylline   Favours placebo

ADDITIONAL TABLES

Table 1. Study characteristics

Study design (publication type)	Participants	Age (years)	Definition of CSA	Comparators	Duration of intervention period (washout)
Bonnet 1990 Cross-over (full report)	5 men with primary CSA	Average 70 (range 65–74)	Central apnoeas were scored when there was an event of complete absence of chest movement from both chest leads and a complete absence of airflow throughout the event (lasting >10 seconds).	Triazolam 0.125 mg versus triazolam 0.250 mg (once daily) versus placebo	3 days (≥ 1 week)
Giannoni 2020a Cross-over (full report)	16 men with systolic heart failure (LVEF < 50%) and moderate-severe CSA	Mean 71.3 (SD 5.8)	Echocardiographic evidence of LVEF < 50% and nocturnal AHI ≥ 15 events/hour	Buspirone 15 mg (3 times daily) versus placebo	1 week (1 week)
Javaheri 1996 Cross-over (full report)	15 men with compensated heart failure (LVEF ≤ 45%) and AHI > 10 events/hour	Not reported (adults)	Polysomnograms showed periodic breathing, with > 10 episodes of apnoea and hypopnoea/hour.	Theophylline 3.3 mg/kg (twice daily) versus placebo	5 days (1 week)
Javaheri 2006 Cross-over (full report)	12 men with systolic heart failure whose initial polysomnograms showed CSB with AHI > 15 events/hour	Mean 66 (SD 6)	Systolic heart failure (initial polysomnograms showed CSB with an AHI > 15 events/hour)	Acetazolamide 3.5 mg/kg (once daily) versus placebo	6 days (2 weeks)
Sorokina 2019a RCT (abstract)	18 people (mostly men) with CSA associated with CHF	Not reported (adults)	AHI > 15 events/hour by echocardiographic evidence were considered as living with CSA. CHF ranged from II to III NYHA functional classes.	Standard medical treatment + acetazolamide 250 mg versus standard medical treatment without acetazolamide	Not reported; follow-up was 12 months

AHI: apnoea-hypopnoea index; CHF: chronic heart failure; CSA: central sleep apnoea; CSB: Cheyne-Stokes breathing; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SD: standard deviation.

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 randomised controlled trial).pt.

11. (randomised 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

Appendix 2. Scopus search strategy

#1 "central sleep apnoea*" OR "central sleep apnea*"

#2 "central alveolar hipoventilation*"

#3 "central sleep disordered breathing"

#4 "ondine* syndrome" OR "ondine curse"

#5 "cheyne-stokes respiration"

#6 "cheyne* stokes"

#7 "periodic breathing" OR "periodic respiration"

#8 OR/1-7

#9 TITLE-ABS (controlled)

#11 TITLE-ABS (randomised or randomised)

#12 TITLE-ABS (placebo)

#13 TITLE-ABS (randomly)

#14 TITLE-ABS (trial)

#15 TITLE-ABS (groups)

#16 OR/10-16

17 #8 AND #16

WHAT'S NEW

Date	Event	Description
28 March 2023	Amended	Affiliation amended for Luciano F Drager

HISTORY

Protocol first published: Issue 1, 2018
Review first published: Issue 2, 2023

CONTRIBUTIONS OF AUTHORS

AR: conception of the review; design of the review; co-ordination of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; assessment of the certainty in the body of evidence; interpretation of data; writing of the review.
ACP: conception of the review; design of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; assessment of the certainty in the body of evidence; interpretation of data; writing of the review.
DP: conception of the review; design of the review; search and selection of studies for inclusion in the review.
GLF: writing of the review.
AA: co-ordination of the review; writing of the review.
LD: writing of the review.

Contributions of editorial team

Sally Spencer (Co-ordinating Editor): edited the review; advised on methodology, interpretation, and content; approved the review prior to publication.
Teresa Anna Cantisani (Contact Editor): edited the review; advised on methodology, interpretation, and content.
Rebecca Fortescue (Co-ordinating Editor): checked the data entry prior to the full write-up of the review.
Emma Dennett (Deputy Co-ordinating Editor): advised on methodology, interpretation, and content; edited the review.
Emma Jackson (Managing Editor): co-ordinated the editorial process; conducted peer review; obtained translations; edited the plain language summary and reference sections of the review.
Kayleigh Kew (Freelance Editor): advised on methodology, interpretation, and content; edited the review.
Elizabeth Stovold (Information Specialist): designed the search strategy and ran the searches.
Vittoria Lutje (Freelance Information Specialist): ran the updated search and edited the search methods section.

DECLARATIONS OF INTEREST

AR: none known
ACP: none known
DP: none known
GLF: owns stocks in Biologix (a start-up company producing a simple device for sleep apnoea diagnosis)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to exclude cross-over trials but decided to include them in the full review as most of the studies we identified used this design, and potential carry-over effects were considered minimal (Riera 2018). To be included, the study should have a sufficient wash-out period, based on the drug half-life (from two or three hours to 11 hours) to avoid the risk of carry-over effect.

We did not include studies focusing on central sleep apnoea (CSA) due to periodic breathing at high altitudes because this is usually triggered by environmental exposure and is not a chronic health condition comparable to the other types of CSA included in the review.

We initially planned to include seven outcomes in the summary of findings table: apnoea-hypopnoea index (AHI), cardiovascular mortality, quality of sleep, quality of life, all-cause mortality, time to cardiovascular intervention, and serious adverse events. However, we were unable to find studies that evaluated some of these outcomes, such as time to lifesaving cardiovascular intervention. Nonetheless, we were able to assess the primary outcome of this review, which is central apnoea-hypopnoea (cAHI). Therefore, we revised our selection of outcomes to be included in the summary of findings table in line with Cochrane methodology, which recommends presenting a maximum of seven outcomes (Schumemann 2013): we added cAHI, defined as the number of central apnoeas and hypopnoeas per hour of sleep, objectively measured by polysomnography; and we removed time to lifesaving cardiovascular intervention. We made this minor change to improve the presentation of outcome results reported in the studies included in this review.

We made the following changes to the specified team members performing different roles within the review:

AR and ACP screened the titles and abstracts and full texts (instead of DP, COCL, RLP or ALCM).
DP acted as the third person to resolve disagreements (instead of RR).
AR and ACP conducted data extraction (instead of DP and COCL).
AR transferred data to Review Manager (instead of DP).
DP spot-checked study characteristics for accuracy against the study report (instead of RR)
AR and ACP assessed studies for risk of bias (instead of DP and COCL).

INDEX TERMS

Medical Subject Headings (MeSH)

Acetazolamide; Apnea; Buspirone; Carbonic Anhydrase Inhibitors; *Disorders of Excessive Somnolence; *Heart Failure; Hypnotics and Sedatives; *Sleep Apnea, Central [drug therapy]; Theophylline; *Triazolam

MeSH check words

Adult; Aged; Female; Humans; Male