Sleep Medicine Reviews 28 (2016) 55–68

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The effect of treating obstructive sleep apnea with positive airway pressure on depression and other subjective symptoms: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form
26 June 2015
Accepted 13 July 2015
Available online 3 August 2015

Keywords:
Obstructive sleep apnea
Depression
Anxiety
Psychiatry
CPAP
Positive airway pressure
Excessive daytime sleepiness

SUMMARY

Patients with obstructive sleep apnea (OSA) frequently present with symptoms of depression and anxiety. The objective of this study is to determine if treatment with positive airway pressure (PAP) improves symptoms of depression and anxiety. A systematic review was conducted to identify clinical trials of PAP that contained a validated measure of depression severity. Meta-analysis was conducted for depression, anxiety, excessive daytime sleepiness (EDS), quality of life (QoL) and respiratory variables. The systematic review included 33 reports. Pre-post-test analysis of PAP showed a moderate effect size (Hedge's g, 95% CI) for depression 0.524 [0.401–0.647], but a low effect size compared to oral placebo (0.355 [0.187–0.524]) and no effect when compared to dental appliances (0.107 [−0.72–0.287]) and sham PAP (−0.049 [−0.292–0.194]). Anxiety, EDS, and QoL showed similar improvement in pre-post-test analysis, but a lack of superiority to dental appliances and sham PAP. PAP was superior to all comparators for respiratory variables. PAP has a moderate clinical effect on symptoms of depression and anxiety in OSA, but it is not superior to dental appliances or sham PAP. The improvement in subjective symptoms, such as depression and anxiety, may be mediated by patient expectations and contact with healthcare providers.

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive sleep-related episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway or respiratory effort related arousals (RERAs) [1,2]. Globally, OSA associated with daytime sleepiness is reported to occur in 2%–5% of adult women and 3%–7% of adult men [1,2]. OSA is associated with multiple other medical comorbidities including; hypertension, insulin-resistance, type II diabetes, and obesity [2]. Positive airway pressure (PAP) delivered in continuous (CPAP), bilevel (BiPAP) or autotitrating (APAP) modes is a standard therapy for moderate (respiratory disturbance index (RDI) ≥15 and ≤30) to severe (RDI>30/hour) OSA and an optional therapy for mild (RDI≥5 and <15) OSA [3,4]. PAP is believed to be effective in reducing the apnea-hypopnea index (AHI) or RDI by providing pneumatic splinting of the upper airway during sleep [3,5]. There is a large body of evidence showing that PAP improves objective symptoms of OSA including the AHI and blood pressure [6].

The presence of psychological symptoms in patients with OSA has been recognized since the 1970s [7] and significant evidence that there are elevated levels of OSA in patients with clinical depression has emerged since the early 2000s [8]. The recognition of the importance of depression in OSA is exemplified by the fact that in the most recent edition of the International classification of sleep disorders [ICSD3], diagnosis of a mood disorder (Criterion A.4) is among one of the four major groups of symptoms (eg., excessive daytime sleepiness, habitual snoring) or disorders (eg., hypertension, atrial fibrillation) that must be present along with ≥5 obstructive respiratory events per hour, before an OSA diagnosis can be made.

The relationship between objectively-rated features of OSA and symptoms like depression, anxiety, and excessive daytime sleepiness (EDS) is poorly understood [8–10]. This constellation of symptoms is often referred to as subjective symptoms of OSA, as there is typically no consistent correlation between the severity of these symptoms and the severity of OSA measured by objectively-rated sleep variables [11–17]. Current models for the relationship between OSA and psychiatric conditions suggest that underlying biological, metabolic and neurological dysregulation contributes to a feed-forward mechanism that manifests as psychiatric disorders, sleep fragmentation,

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http://dx.doi.org/10.1016/j.smrv.2015.07.002

Abbreviations

AHI	apnea hypopnea index
AI	arousal index
APAP	autotitrating positive airway pressure
BAI	Beck anxiety inventory
BDI or BDI-II	Beck depression inventory
BiPAP	bilevel positive airway pressure
BSI-A	brief symptom inventory – anxiety subscale
BSI-D	brief symptom inventory – depression subscale
CES-D	center for epidemiological studies depression scale
CONSORT	consolidated standards of reporting trials
CPAP	continuous positive airway pressure
DA	dental appliance
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
FOSQ	functional outcomes of sleep questionnaire
GHQ-28	general health questionnaire
GRADE	grades of recommendation, assessment, development and evaluation
HADS	hospital anxiety and depression scale
HAM-D	Hamilton rating scale for depression
ICSD3	International classification of sleep disorders 3
ITT	intention-to-treat
MADRS	Montgomery–Åsberg depression rating scale
Mean SaO_2	mean oxygen saturation
Min SaO_2	minimum oxygen saturation
MMPI	Minnesota multiphasic personality inventory
MSLT	multiple sleep latency test
N/A	not applicable
NHP-2	Nottingham health profile-2
OP	oral placebo
OSA	obstructive sleep apnea
PAP	positive airway pressure
POMS	profile of mood states
PRISMA	preferred reporting items for systematic reviews and meta-analyses
QoL	quality of life
RCT-P	parallel-group randomized controlled trial
RCT-X	crossover randomized controlled trial
RDI	respiratory disturbance index
REM%	rapid eye movement sleep percentage
RoB	risk of bias
SAQLI	sleep apnea quality of life index
SAT	single assignment trial
SDS	Zung self rated depression scale
SF-36	short form health survey
SSS	Stanford sleepiness scale
STAI	state trait anxiety inventory
TAS	tension anxiety scale
TEAE	treatment emergent adverse event
WHO-5	World Health Organization-five well-being index
WHOQoL-B	World Health Organization quality of life-brief questionnaire (all subscales)

cardiovascular and metabolic disease [8–10]. Given that the subjective symptoms of OSA are the result of complex biological dysregulation, it remains unclear whether these symptoms have a direct response to PAP therapy. Saunamaki et al. found that symptoms of depression and anxiety were commonly reported in treatment naïve OSA patients with multiple studies reporting improvements in these symptoms after ≥3 mo of PAP [11]. Sanchez et al. also reported on improvements in symptoms of EDS and mood in response to CPAP therapy [18]. Both of these reviews reached their conclusions by focusing on the number of studies reporting the positive effects of PAP; this type of analysis is less accurate as it presents the overall research in the field by study outcome, whereas meta-analysis pools participant data across studies to create a more accurate analysis of the effects of PAP based on the total population studied [11,18]. A recent meta-analysis concluded that treatment of OSA with PAP or mandibular advancement devices is superior to placebo for the treatment of depressive symptoms, but did not evaluate PAP vs. active therapies [19]. The goal of this systematic review and meta-analysis is to determine if PAP therapy improves depression and other subjective symptoms in OSA in comparison to both placebo and active treatments, as measured by validated rating scales.

Objective

The primary objective is to determine if treatment with PAP improves the psychological symptoms of depression in patients with OSA. The secondary objective was to evaluate if PAP improved additional subjective sleep outcomes including: anxiety and EDS.

Methods

The methodology for this paper follows PROSPERO protocol CRD42014007419 registered February 3, 2014 in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [20,21].

Eligibility criteria

Types of studies

This review considered single arm trials (SAT), case-control trials, and randomized controlled trials (RCTs) of both parallel-group and crossover design of PAP interventions for OSA.

Types of participants

Adult men and women with OSA diagnosed by polysomnography (PSG) were included. OSA was defined as an AHI ≥5 (or RDI equivalent). Studies were only included when participants were treatment naïve at study initiation. Studies where the primary study sample involved individuals with severe or acute co-morbid medical illness such as acute myocardial infarction, stroke, dementia or heart failure were also excluded.

Types of interventions

Studies included PAP devices titrated to an effective pressure to overcome the respiratory disturbance. The analyses include studies with comparators consisting of healthy controls, sham or placebo PAP groups or active comparator controlled studies. This analysis also considered participant controlled pre- and post-intervention data.

Types of outcome measures

The primary outcome measure for the meta-analysis was depression. On this basis, all studies were required to include at least one validated measure of depression such as the Beck depression inventory (BDI), Montgomery-Asberg depression rating scale (MADRS), hospital anxiety and depression scale (HADS), or Hamilton depression scale (HAM-D).