Online Supplement

The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea

An Official American Thoracic Society Clinical Practice Guideline

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Methodologists: Amy M. Ahasic, Kevin C. Wilson and Michelle Fiander.

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TABLE OF CONTENTS

Methods
  Panel Composition
  Questions
  Literature search
  Evidence synthesis
  Recommendations
  Manuscript preparation

Evidence profiles
  Table E1 – Exercise program vs. no exercise program
  Table E2 – Comprehensive weight loss program vs. no program
  Table E3 – Bariatric surgery vs. no bariatric surgery

High priority research questions

References
METHODS

Panel Composition

The project was proposed by the chair and co-chairs through the American Thoracic Society (ATS) Sleep and Respiratory Neurobiology Assembly and was approved by the ATS Board of Directors. Potential panelists were identified by the chair and co-chairs based on their expertise in sleep disordered breathing, weight management, and/or behavioral science. All potential panelists disclosed their conflicts of interest to the ATS. Panelists determined to have no substantial conflicts of interest were “approved without limitation”, while those with potential conflicts of interest that were considered manageable were “approved with management”, allowing participation in discussions about the evidence but not in the formulation of recommendations related to their conflicts of interest. Potential panelists whose conflicts of interest were deemed not manageable were disqualified. The final guideline panel consisted of 20 members: a chair, a chairs, 10 additional experts in sleep-disordered breathing, 1 expert in weight management, 1 behavioral scientist, 3 patients, 1 lead methodologist, and 2 medical librarians. One sleep-disordered breathing expert and one librarian served as additional methodologists.

Questions

The chair and co-chair and lead methodologist drafted key clinical questions in a PICO (Population, Intervention, Comparator, and Outcome) format. The questions were then
discussed, modified, and approved by the full guideline panel. Outcomes that might be affected by each of the interventions were numerically rated (from 1 to 9) according to their importance. The evidence was assessed only for outcomes whose average rating fell into the “important” or “critical” categories. The primary outcomes evaluated were: Quality of life, mortality, weight loss, change in obstructive sleep apnea (OSA) severity, resolution of OSA, cardiovascular events or stroke, major and minor adverse events, daytime sleepiness, other OSA-related symptoms, sexual function, and glycemic control.

**Literature search**

The published literature was searched in the following databases: Medline, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Cochrane Central Database of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), NHS Economic Evaluations Database, Database of Abstracts of Reviews of Effectiveness (DARE), and the Health Technology Assessment (HTA) Database.

Search strategies consisted of controlled vocabulary terms (such as Medical Subject Headings), keyword terms, and phrases. Conceptual sets included 1) OSA and obesity and 2) OSA and weight loss interventions (e.g., drug therapy or surgery or exercise therapy or nutritional therapy or diet), which were combined using Boolean “OR.” Filters were used as-needed to narrow the search results according to study design. Searches were not limited by publication date or language, and databases were searched from date of inception to search date. Searching was conducted in July and August 2015, and then updated in February 2017 and February 2018.
Grey literature searches consisted of searching Grey Matters (1), ClinicalTrials.gov (2), the World Health Organization’s International Clinical Trials Registry Platform (3), and the bibliographic databases on the websites of select organizations. The Grey Matters search encompassed the following: Australian Department of Health and Aging, Australia and New Zealand horizon scanning network (ANZHSN),
http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/technologies-assessed-lp-2; Blue Cross Blue Shield Technology Evaluation Centre,
http://www.bcbs.com/cce/; Canadian Agency for Drugs and Technologies in Health (CADTH) cadth.ca; Healthcare Improvement Scotland healthcareimprovementscotland.org; Institute for Clinical and Economic Review (ICER) http://icer-review.org; Institute of Health Economics http://www.ihe.ca; Monash Health Centre for Clinical Effectiveness (CCE), Current Evidence Reviews,
National Institute for Health Care and Clinical Excellence, http://www.nice.org.uk; Scottish
Evidence synthesis

The lead methodologist reviewed all publications retrieved from the literature searches for relevance, initially screening based on title and/or abstract and then reviewing the full text of potentially relevant publications. Included and excluded studies lists of related systematic reviews were also reviewed. Published abstracts were utilized if they contained data on at least one of our outcomes of interest. Findings from relevant publications were extracted into structured data tables. Duplicate data abstraction was not performed. When data from individual studies were amenable to pooling, the random effects model of DerSimonian and Laird as implemented in the Cochrane Collaboration Review Manager, version 5.3 was used to pool results across studies (4, 5). Relative risk (RR) was used to report the results for dichotomous outcomes and the mean difference (MD) was used to report the results for continuous outcomes, each with an accompanying 95% confidence interval (CI). Statistical heterogeneity of the pooled results was measured using the $I^2$ and Chi$^2$ tests, considering an $I^2$ value of $\geq 50\%$ or a Chi$^2$ $p \leq 0.05$ to indicate significant heterogeneity. Results from the meta-analyses are provided in the evidence tables.

We used the Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess certainty in the estimated effects (i.e., the quality of evidence) for each intervention on each outcome of interest (6). The lead methodologist created evidence profiles using the Guideline Development Tool (7), which categorized the overall certainty in the
evidence into one of four levels: high, moderate, low, or very low. Each level represents the certainty in the accuracy of the estimated effects for a specific intervention. The full guideline panel reviewed the evidence profiles and provided input and feedback.

**Recommendations**

The guideline panel met at the 2016 ATS International Conference in San Francisco and several subsequent conference calls to discuss the evidence profiles and develop recommendations to answer each PICO question using the Evidence-to-Decision (EtD) framework (8, 9). No relevant data could be identified for two of the initial PICO questions and so these were dropped from further consideration. These questions were: (1) Should both a reduced calorie diet and exercise/increased physical activity be recommended (rather than exercise alone) to patients with OSA who are overweight or obese?; and (2) Should weight loss medications be recommended to patients with OSA who are overweight or obese (rather than no weight loss intervention)?

The panelists made decisions about whether to recommend for or against an intervention based on: the balance of desirable consequences (benefits) and undesirable consequences (burdens, adverse effects, and costs), quality of evidence, cost and cost-effectiveness, feasibility, and acceptability to patients (i.e., patient values and preferences). Using the GRADE approach, the panelists rated each recommendation as either “strong” or “conditional”. All recommendations were formulated and graded by discussion and consensus; voting was never required.
**Manuscript preparation**

The initial draft of the manuscript was written by the chair and co-chair and lead methodologist. All members of the guideline panel reviewed the manuscript; comments were addressed by the chair and co-chair and the revised manuscript was redistributed to the full panel for further review. Once the manuscript was approved by the full panel, it was submitted for external peer review.

**Peer review**

External peer review was organized and overseen by the ATS Documents Editor. Comments from the reviewers were collated into a single decision letter and sent to the chair and co-chair. The manuscript was subsequently revised by the panel according to feedback received from the peer reviewers. Following several cycles of review and revisions, the manuscript was deemed satisfactory and sent to the ATS Board of Directors for further review and final approval.
## EVIDENCE PROFILES

### Evidence table E1: Exercise program vs. no exercise program

**Bibliography:**

<table>
<thead>
<tr>
<th>Assessment of certainty in estimated effects</th>
<th>No of patients</th>
<th>Exercise</th>
<th>No exercise program</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (follow up: range 4 weeks to 12 weeks)</strong></td>
<td>3 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>serious c,d</td>
<td>none</td>
<td>0/45 (0.0%)</td>
</tr>
<tr>
<td><strong>Serious adverse events (follow up: range 4 weeks to 12 weeks; assessed with: number of participants reporting an SAE)</strong></td>
<td>3 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>serious c,d</td>
<td>none</td>
<td>0/45 (0.0%)</td>
</tr>
<tr>
<td><strong>Weight loss (follow up: range 4 weeks to 6 months; assessed with: BMI at end of study)</strong></td>
<td>5 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>serious d,e</td>
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<td>50</td>
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<tr>
<td><strong>Weight loss (follow up: range 12 weeks to 13 weeks; assessed with: weight (kg) at end of study)</strong></td>
<td>2 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>serious d,e</td>
<td>none</td>
<td>36</td>
</tr>
<tr>
<td><strong>Weight loss (follow up: range 4 weeks to 12 weeks; assessed with: neck circumference (cm) at end of study)</strong></td>
<td>5 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>serious d,e</td>
<td>none</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>randomized trials</td>
<td>serious (^{a,e})</td>
<td>not serious (^{f})</td>
<td>serious (^{b})</td>
<td>serious (^{d,g})</td>
<td>none</td>
<td>52</td>
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<tr>
<td>4</td>
<td>Severity of OSA (follow up: range 4 weeks to 12 weeks; assessed with: AHI at end of study)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>randomized trials</td>
<td>very serious (^{a,e,h})</td>
<td>serious (^{i})</td>
<td>serious (^{b})</td>
<td>serious (^{d,g})</td>
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<td>65</td>
</tr>
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<td>5</td>
<td>Daytime sleepiness (follow up: range 4 weeks to 6 months; assessed with: Epworth Sleepiness Scale (ESS) at end of study; Scale from: 0 to 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>randomized trials</td>
<td>serious (^{a})</td>
<td>not serious</td>
<td>serious (^{b})</td>
<td>serious (^{d})</td>
<td>none</td>
<td>35</td>
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<td>3</td>
<td>Other OSA symptoms (sleep quality) (follow up: range 4 weeks to 12 weeks; assessed with: PSQI score at study end; Scale from: 0 to 21)</td>
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<tr>
<td>3</td>
<td>Adverse events (follow up: range 4 weeks to 12 weeks; assessed with: number of participants reporting an AE)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CI: Confidence interval; MD: Mean difference
a. None of the studies were blinded.
b. Short follow-up can be a source of indirectness.
c. Low number of events.
d. Sample size does not meet “optimum information size” criteria.
e. Some studies without descriptions of random sequence generation.
f. While heterogeneity statistics suggest inconsistency, this appears to be accounted for by the inclusion of one study with a 4-week inpatient rehabilitation program as the intervention, thus varying in intensity from other outpatient interventions.
g. Results do not exclude the possibility of significant benefit or significant harm.
h. Three studies with high dropout rates, two of which only reported data for study completers.
i. Significant heterogeneity detected across studies.
Evidence table E2: Comprehensive weight loss program (i.e., diet + behavioral intervention +/- exercise) vs. no program


<table>
<thead>
<tr>
<th>Nr of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Diet and/or exercise combined with behavioral intervention (&quot;comprehensive weight loss program&quot;)</th>
<th>No such program</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
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<td>Quality of Life (change in SF-12 physical component score) (follow up: 9 weeks; Scale from: 0 to 100)</td>
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</tr>
<tr>
<td>1 randomised trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>not serious c</td>
<td>none</td>
<td>30</td>
<td>33</td>
<td>-</td>
<td>MD 10.55 higher (7.7 higher to 13.4 higher)</td>
<td>⨁◯◯ LOW</td>
<td>CRITICAL</td>
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<tr>
<td>Quality of life (change in SF-12 mental component score) (follow up: 9 weeks; Scale from: 0 to 100)</td>
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<tr>
<td>1 randomised trials</td>
<td>serious *</td>
<td>not serious</td>
<td>serious b</td>
<td>not serious c</td>
<td>none</td>
<td>30</td>
<td>33</td>
<td>-</td>
<td>MD 1.25 higher (1.17 lower to 4.21 higher)</td>
<td>⨁◯◯ LOW</td>
<td>CRITICAL</td>
<td></td>
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<tr>
<td>Mortality (follow up: range 9 weeks to 12 months)</td>
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<td></td>
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<tr>
<td>4 randomised trials</td>
<td>serious *</td>
<td>not serious</td>
<td>not serious #</td>
<td>serious *</td>
<td>none</td>
<td>0/154 (0.0%)</td>
<td>0/155 (0.0%)</td>
<td>not estimable</td>
<td>0 fewer per 1,000 (from 20 more to 20 fewer)</td>
<td>⨁◯◯ LOW</td>
<td>CRITICAL</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (follow up: range 9 weeks to 12 months; assessed with: number of participants with at least one SAE)</td>
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<td>not serious</td>
<td>not serious #</td>
<td>serious *</td>
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<td>0/152 (0.0%)</td>
<td>0/156 (0.0%)</td>
<td>not estimable</td>
<td>0 fewer per 1,000 (from 20 more to 20 fewer)</td>
<td>⨁◯◯ LOW</td>
<td>CRITICAL</td>
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<tr>
<td>Weight loss with diets NOT including any meal replacement (follow up: range 12 weeks to 6 months; assessed with: change in weight (kg))</td>
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<tr>
<td>Procedure</td>
<td>Trials</td>
<td>Serious No.</td>
<td>Not Serious No.</td>
<td>Serious No.</td>
<td>None</td>
<td>MD (95% CI)</td>
<td>GRADE</td>
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<tr>
<td>Weight loss with diets including any meal replacement (follow up: range 9 weeks to 12 months; assessed with: change in weight (kg))</td>
<td>2</td>
<td>serious a</td>
<td>not serious b</td>
<td>serious c</td>
<td>none</td>
<td>MD 0.77 lower (3.02 lower to 1.49 higher)</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Weight loss (follow up: 12 months; assessed with: change in neck circumference (cm))</td>
<td>1</td>
<td>serious a</td>
<td>not serious b</td>
<td>not serious c</td>
<td>none</td>
<td>MD 11.58 lower (17.84 lower to 5.31 lower)</td>
<td>CRITICAL</td>
<td></td>
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<tr>
<td>Resolution of OSA (follow up: 12 months; assessed with: Achieving AHI&lt;5 as determined by blinded PSG)</td>
<td>1</td>
<td>serious a</td>
<td>not serious b</td>
<td>not serious c</td>
<td>none</td>
<td>MD 1.3 lower (1.85 lower to 0.75 lower)</td>
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<tr>
<td>OSA Severity (follow up: range 9 weeks to 12 months; assessed with: change in AHI)</td>
<td>4</td>
<td>not serious a</td>
<td>not serious b</td>
<td>not serious c</td>
<td>none</td>
<td>MD 8.54 lower (10.83 lower to 6.25 lower)</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Daytime sleepiness (follow up: range 9 weeks to 12 months; assessed with: change in Epworth Sleepiness Scale (ESS) score; MID has not been establish; Scale from: 0 to 24)</td>
<td>2</td>
<td>serious a</td>
<td>not serious b</td>
<td>serious c</td>
<td>none</td>
<td>MD 2.43 lower (5.37 lower to 0.51 higher)</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glycemic control (follow up: 24 weeks; assessed with: resolution in DM defined by cessation of glucose-lowering medications)</td>
<td>1</td>
<td>serious a</td>
<td>not serious b</td>
<td>serious c</td>
<td>none</td>
<td>0 fewer per 1,000 (from 40 more to 40 fewer)</td>
<td>CRITICAL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Any adverse event (follow up: range 9 weeks to 12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VERY LOW</td>
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</tr>
</tbody>
</table>

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**Notes:**
- MD: Mean Difference
- CI: Confidence Interval
- RR: Risk Ratio
- MID: Minimal Important Difference
- GRADE: Quality of Evidence

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**Legend:**
- CRITICAL
- MODERATE
- LOW
- VERY LOW

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**Calculation Notes:**
- MD = (Mean of intervention - Mean of control) / Standard Deviation
- CI = MD ± (1.96 * Standard Error)
- RR = (Number of events in intervention group / Number of participants in intervention group) / (Number of events in control group / Number of participants in control group)
- MID = 0.5 * (Mean of intervention group - Mean of control group) / Standard Deviation

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**Assessment:**
- Serious: May influence patient's management
- Not Serious: No influence on patient's management

---

**Follow up Times:**
- 9 weeks to 12 months
- Range
- 24 weeks
- 2 months
<table>
<thead>
<tr>
<th>4</th>
<th>randomised trials</th>
<th>serious a,p</th>
<th>serious q</th>
<th>serious d,q</th>
<th>not serious</th>
<th>none</th>
</tr>
</thead>
</table>

Two studies reported number of participants experiencing any AE; there were 0 AEs across all participants for both studies. Four studies reported the number of events per group with 2 studies reporting no events (the same 2 studies also reporting no participants experiencing events), but 2 other studies reporting occurrences of AEs. In one of the latter two studies, there were 8 AEs in the intervention group and none in the control group. The the second of the latter two studies, many AEs were reported in both groups. When considering only those 2 studies reporting the occurrence of any AEs, the risk difference (pooled estimate) is 0.27 [0.15, 0.38] favoring control. When considering all 4 studies, together the risk difference (pooled estimate) is 0.12 [-0.07, 0.32].

**CI:** Confidence interval; **MD:** Mean difference

a. Participants and personnel not blinded.
b. Short follow-up period can be a source of indirectness.
c. It is difficult to assess precision when MID is not known.
d. Varying lengths of follow-up (including some shorter follow-up periods) may be a source of indirectness.
e. Low number of events with overall small pooled sample size.
f. Lack of clear definition of what constituted an SAE in each study could be a source of indirectness.
g. One study also reported change in BMI: MD -0.50% [-1.12, 0.12].
h. One additional study (Ng, et al.) reported only change in BMI rather than weight. Results were similar with mean difference of -3.60 (95% CI -5.86, -1.34) between intervention and control groups over a 12-month follow-up period.
i. High dropout rate.
j. Results (confidence interval) do no exclude appreciable benefit with comprehensive weight loss vs. no difference.
k. Sample size does not meet OIS criteria.
l. Three studies also reported change in BMI (follow-up ranging from 9 weeks to 12 months) with MD (pooled estimate) of -4.13% [-6.28, -1.98].
m. One study with short-term (9 weeks) follow-up introduces significant inconsistency. Unclear if difference in length of follow-up from other studies fully explains inconsistency. This study also included only men.

n. PSG scorers and sleep technicians blinded. However, patients and personnel not blinded to intervention, and thus this could still represent risk of bias.
o. Unclear how many patients were using glucose-lowering medications at the start of the study. Patients with Type 1 DM were excluded; patients with Type 2 DM were only eligible if they had an A1C<7% and had no medication changes in the last 3 months.
p. Variations in adverse events reporting could represent selective reporting, and thus a source of bias.
q. There is significant variability in adverse events reported. Adverse events are variably defined and reported across studies.
**Evidence table E3: Bariatric surgery vs. no surgery**


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Ne of patients</th>
<th>Effect</th>
<th>Ne of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Bariatric surgery</th>
<th>No surgery</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (follow up: range 2 to 3 years; assessed with: #events/group)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>not serious</td>
<td>serious #</td>
<td>none</td>
</tr>
<tr>
<td>Serious adverse events (follow up: range 2 to 3 years; assessed with: #events/group)</td>
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<td>2 randomized trials</td>
<td>serious *</td>
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<tr>
<td>Weight loss (follow up: range 2 to 3 years; assessed with: change in weight in kg)</td>
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<td>2 randomized trials</td>
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<td>not serious</td>
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<td>not serious c</td>
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<tr>
<td>Resolution of OSA (follow up: 3 years; assessed with: cessation of nocturnal NIV, not including nonadherence)</td>
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<td>1 randomized trials</td>
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<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
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<tr>
<td>Severity of OSA (follow up: range 2 to 3 years; assessed with: AHI at study end)</td>
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<td>2 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
<td>not serious</td>
<td>serious ∈</td>
<td>none</td>
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<tr>
<td>Daytime sleepiness (follow up: 2 years; assessed with: ESS at study end)</td>
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<td>1 randomized trials</td>
<td>serious *</td>
<td>not serious</td>
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</tbody>
</table>

CI: Confidence interval; MD: Mean difference; RR: Risk ratio
a. Low number of events.
b. Lack of blinding of patients/personnel creates a risk of co-intervention.
c. Sample size does not meet OIS criteria.
d. High rate of dropout.
HIGH PRIORITY RESEARCH QUESTIONS

Specific research questions that the panel believes should be a high priority for future research include the following:

- What is the impact of weight loss on:
  - OSA severity
  - Reduction in continuous positive airway pressure (CPAP) pressure or need
  - Cardio-metabolic comorbidities

- Can overweight or obese OSA patients without excessive daytime sleepiness (with or without cardio-metabolic comorbidities) be treated with weight loss alone?

- Should weight management precede upper airway management in overweight or obese OSA patients?

- Can asymptomatic overweight or obese OSA patients in high-risk employment situations be treated with weight loss alone?

- Are there comorbidities and, if so, how severe do they need to be, to prohibit an initial attempt at weight management alone?

- When do more additional aggressive management tools need to be initiated in overweight or obese OSA patients if weight loss does not occur, or if weight is regained after initial loss?

- What are the long-term mortality, cardio-metabolic, and quality of life outcomes in overweight or obese OSA patients who are treated with weight loss strategies
alone, with upper airway management alone, or with a combination of weight loss and upper airway management?
REFERENCES

1. Grey Matters: a practical tool for searching health-related grey literature. Canadian Agency for Drugs and Technologies in Health (CADTH); 2015.


