High Priority Future Research Needs for Obstructive Sleep Apnea Diagnosis and Treatment

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Study Objectives: To identify and prioritize future research needs (FRN) topics for diagnosis and treatment of obstructive sleep apnea (OSA).

Methods: Twenty-one panel members represented six stakeholder categories: patients and the public, providers; purchasers of health care, payers, policymakers, and principal investigators. Building on a recently completed comparative effectiveness review, stakeholders nominated and discussed potential FRN topics. Stakeholders then nominated their top priority FRN topics based on the Agency for Healthcare Research and Quality Effective Health Care Program Selection Criteria. From these nominations, the highest priority FRN topics were determined and were elaborated upon to include possible study designs to address the topics.

Results: Thirty-seven topics were discussed and prioritized. The nine highest priority FRN topics included: cost-effectiveness of management strategies, defining age- and sex-specific criteria for OSA, evaluating routine preoperative screening for

OSA, evaluating involvement of a sleep medicine specialist in diagnosis of OSA, evaluating clinical prediction rules, assessing the effect of treating sleep disordered breathing and long-term clinical outcomes, comparing treatments for patients who do not tolerate positive airway pressure, evaluating strategies to improve treatment compliance, and evaluating the association between sleep apnea severity and long-term clinical outcomes.

Conclusions: While there are numerous specific research questions with low or insufficient strength of evidence for OSA management, OSA patients, their healthcare providers, and society at large would benefit from refocusing research efforts into the prioritized research questions and away from simple comparisons of short-term outcomes between specific interventions.

Keywords: Obstructive sleep apnea, diagnosis, treatment, future research needs, study design

Citation: Patel K; Moorthy D; Chan JA; Concannon TW. High priority future research needs for obstructive sleep apnea diagnosis and treatment. *J Clin Sleep Med* 2013;9(4):395-402.

A 2011 comparative effectiveness review of obstructive sleep apnea (OSA) diagnosis and treatment, conducted for the Agency for Healthcare Quality and Research (AHRQ) found many gaps in the evidence resulting in frequent low strengths or insufficient evidence to answer key research questions.¹ To identify and prioritize future research needs (FRN) topics for OSA management, we convened diverse panels of stakeholders with the goal of assisting researchers and funders of research to improve the body of comparative effectiveness evidence useful for decision-makers. The goal was to encourage researchers and their funders to address research topics that are of highest priority to a full range of health care stakeholders.

The comparative effectiveness review on OSA included seven key questions covering diagnosis, preoperative screening, and treatment. In brief, the review found a moderate strength of evidence that portable monitors are accurate in diagnosing OSA (as defined by polysomnography [PSG]) but are variably biased in estimating apnea-hypopnea index (AHI), a measure of the severity of disease; low strength of evidence that the Berlin Questionnaire is able to prescreen patients with OSA with moderate accuracy; and insufficient evidence to evaluate other questionnaires or clinical prediction rules. No study adequately addressed phased testing for OSA. There was insufficient evidence on routine preoperative testing for OSA. A high strength

of evidence indicates that AHI > 30 events/h is an independent predictor of death, while there was lesser evidence for predictors of other outcomes. Regarding treatment, there was a moderate strength of evidence that continuous positive airway pressure (PAP) is an effective treatment for OSA, moderate evidence that autotitrating and fixed PAP have similar effects, insufficient evidence regarding comparisons of other PAP devices, moderate evidence that oral devices are an effective treatment for OSA, moderate evidence that continuous PAP is superior to oral devices, and insufficient trial evidence regarding the relative value of most other OSA interventions including surgery. We found high and moderate strength of evidence, respectively, that AHI and Epworth Sleepiness Scale are independent predictors of PAP compliance, and low strength of evidence that some treatments improve PAP compliance.

In this paper, we summarize the stakeholder-prioritized FRN topics for both diagnosis and treatment of sleep apnea.

METHODS

Upon completion of the comparative effectiveness review, we recruited stakeholders from a variety of areas relevant to OSA, and included both clinicians and non-clinicians to participate in one or both of two stakeholder panels for diagnosis and, separately, treatment of OSA. Using a new taxonomy for

Table 1—Stakeholders

Category	Description	Included Entities	No. Included: Diagnosis	No. Included: Treatment
Patients and the Public	Current and potential consumers of patient-centered healthcare and population-focused public health, including caregivers, family members and patient advocacy organizations	Current patient Patient advocate Transportation sector employer	4	4
Providers	Individuals (e.g., nurses, physicians, counselors and other providers of care and support services) and organizations (e.g., hospitals, clinics, community health centers, community based organizations, pharmacies) that provide care to patients and populations	Dentist Hospital administrator Obesity/metabolism physician Oropharyngeal surgeon Primary care physician Psychiatrist Pulmonologist Sleep disorders nurse Sleep medicine physician	6	9
Purchasers	Employers, the self-insured, government, and other entities responsible for underwriting the costs of healthcare	Private employer Public purchaser	2	1
Payers	Insurers, Medicare and Medicaid, individuals with deductibles, and others responsible for reimbursement for interventions and episodes of care	Medicaid Private insurer	3	3
Policy makers	Organizations such as the Department of Health and Human Services, Congress, states, professional associations, and intermediary groups that collate and distribute information to policy makers	Agency for Healthcare Research and Quality (AHRQ) Centers for Disease Control (CDC) Professional organization	4	3
Principal investigators	Researchers and funders of research	Clinical research Health services/policy research	2	2
Product makers	Drug and device manufacturers		0*	0*
Total			21†	22†

*Product makers were invited to submit potential future research needs topics for consideration but were not included in the stakeholder panel. †Many stakeholders served on both panels. In total, there were 26 stakeholders on the two panels.

stakeholder engagement in patient-centered research developed in part at our institution,² we invited input from representatives from seven stakeholder categories, including patients and the public, providers, purchasers, payers, policy makers, principal investigators, and product makers. The product makers, though, were invited only to submit potential FRN topics, but not to participate in ranking or selecting the final list of FRN topics. Invited clinicians specialized in sleep medicine, primary care, and psychiatry. **Table 1** summarizes the categories and stakeholders on the two panels.

The panels identified potential FRN topics in a stepwise, iterative process. The comparative effectiveness review authors had identified several FRN topics during the original systematic review. These were provided to the stakeholders as a starting list of topics. After review of the findings of the comparative effectiveness review, stakeholders nominated additional topics by email or via a dedicated Microsoft Sharepoint discussion board. We supplemented the email and on-line process with one conference call with non-clinician stakeholders to obtain feedback of a less technical nature and to optimize their participation. Topics raised during the call, with their rationale, were added to the Sharepoint discussion board. All stakeholders were encouraged to review and discuss all proposed FRN topics.

After a two-week discussion period, the stakeholders prioritized the FRN topics based on four general criteria: importance, desirability of research and duplication of research, feasibility, and potential impact. These criteria are derived from guidelines from AHRQ pertaining to selection of research topics.³ Stakeholders selected five to ten FRN topics each for diagnosis and treatment of OSA that they deemed to have the highest priority. Based on consensus of the stakeholders, we determined the five highest priority FRN topics for both diagnosis and treatment. We summarized the stakeholder panel discussions to produce topic backgrounds and evaluated the topics to select and describe practical and appropriate study designs for research to fill the FRN gap. A fuller description of the methods and FRN topics can be found at <http://www.effectivehealthcare.ahrq.gov>.^{4,5} For each FRN topic presented here, we have compiled a summary of the state of the relevant evidence from the 2011 comparative effectiveness review¹ together with lists of potentially relevant primary articles from the review (**Appendix**). For organizational reasons, the order of the prioritized FRN topics here differs from their order in the two AHRQ reports^{4,5}; the order is not indicative of their prioritization ranking. All FRN topics that were discussed by the stakeholders are listed in **Table 2**.

Table 2—Future research needs prioritization topics reviewed by stakeholders***Diagnostic Test Topics****High priority future research needs topics**

1. Age- and sex-specific criteria for defining the OSA syndrome (and abnormal breathing) [FRN Topic 2]
2. Effect of routine (or selected) preoperative screening for OSA [FRN Topic 3]
3. †Cost-effectiveness analysis of a management strategy (diagnosis of symptomatic or high-risk patients through treatments of patients diagnosed with OSA), specifically for patients with mild to moderate disease severity [FRN Topic 1]
4. ‡Value of having a sleep medicine specialist involved in the diagnosis of OSA (in addition to or instead of a non-specialist) [FRN Topic 4]
5. What is the prognostic accuracy of clinical prediction rules to predict clinical outcomes? [FRN Topic 5]

Other future research needs topics

6. Indications (patient signs, symptoms, or other features) for appropriate home testing
7. Diagnostic approaches to OSA in obese and non-obese patients
8. Can polysomnography be skipped in making the diagnosis of OSA?
9. What are the financial barriers to access to diagnosis?
10. Head-to-head comparisons of portable monitors, questionnaires, and prediction rules
11. Association between use of questionnaires and clinical outcomes
12. What are the available, objectively-measured predictors of OSA diagnosis?
13. What is consumer willingness-to-pay for screening, to identify consumer preferences for strategies to diagnose OSA?
14. Value of scoring nasal flow limitation in recognizing mild OSA
15. Value of brain MRI in evaluating OSA patients
16. Randomized trials of phased testing
17. Value of using 4-phase rhinomanometry in recognition of patients with high nasal resistance and OSA
18. Diagnostic approach to OSA in micrognathia and retrognathia

Treatment Topics**High priority future research needs topics**

1. What is the impact of treatment of sleep disordered breathing on major long-term clinical outcomes, including mortality, cardiovascular disease, and diabetes? [FRN Topic 6]
  - a. What are long-term outcomes of mandibular advancement devices treatment?
2. †Cost-effectiveness analysis of a management strategy (diagnosis of symptomatic or high-risk patients through treatments of patients diagnosed with OSA), specifically for patients with mild to moderate disease severity
  - a. Research on PAP devices that are both economical as well as clinically effective [FRN Topic 1]
3. Comparative studies of different OSA treatments based on patient characteristics [FRN Topic 7]
  - a. Analyses of PAP stratified by disease severity
  - b. Analyses of non-PAP treatments stratified by disease severity
  - c. Comparison of alternative treatments for patients who do not tolerate PAP
4. Trials to improve compliance with PAP, mandibular advancement devices, and other treatments, particularly evaluating cognitive therapy approaches [FRN Topic 8]
5. What is the association between OSA severity and long-term clinical outcomes? [FRN Topic 9]

Other future research needs topics

6. What are the barriers to, and predictors of, compliance with different treatments?
7. Direct comparison of compliance rates with different interventions and incorporation of compliance into an overall comparison of effective treatment
8. Trials to evaluate weight-loss programs as an adjunctive treatment for OSA
  - a. What is the value of bariatric surgery for treatment of OSA?
9. ‡What is the value of including a sleep medicine specialist in the management of the patient with OSA?
10. What is consumer willingness-to-pay for treatment, to identify consumer preferences for strategies to treat OSA?
11. What are the financial barriers to access to treatment?
12. Role of surgery for treatment of OSA
  - a. Comparison of surgery versus PAP
  - b. Role of orthognathic surgery (corrective jaw surgery)
  - c. Comparison of genio-tubercle advancement versus dental devices
13. Evaluation of postoperative PAP for all patients with OSA or at high risk of OSA undergoing any surgery with sedation
14. Trials comparing PAP versus pharmaceutical interventions
15. Trials comparing different PAP masks
16. Trials comparing PAP versus oropharyngeal exercises
17. Trials comparing different degrees of mandibular advancement
18. Studies of factors influencing therapist decisions concerning PAP mask choice
19. Research into how to maintain patients in OSA studies (where dropout rates are unacceptably high)

PAP, positive airway pressure (devices); FRN, future research needs; MRI, magnetic resonance imaging; OSA, obstructive sleep apnea. *The order of topics is as listed in the AHRQ reports,^{4,5} with the FRN Topic numbers, per this article, in brackets. The numbering of the topics in this list and the FRN Topic numbers are not strictly indicative of the stakeholders' prioritization order. Other than minor wording changes, the topics in this table are as worded by the stakeholder panel and thus differ somewhat from the FRN Topic wording in the text of this article. †Identical question prioritized by diagnostic test and treatment stakeholder panels. ‡Treatment topic 9 is essentially the same topic as diagnostic test topic 4 but it was not considered to be a high priority topic by the treatment stakeholder panel.

RESULTS

Stakeholders discussed and prioritized a total of 37 FRN topics, 18 for diagnosis and 19 for treatment (**Table 2**). The highest priority topics are listed below, along with background on the topics as well as a proposed study design to address each issue. The order of the topics does not represent a strict ranking of the FRNs by the stakeholders.

FRN Topic 1: Diagnosis and Treatment—What is the cost-effectiveness of different management strategies specifically for patients with mild to moderate disease severity?

Both the diagnosis and treatment stakeholder panels prioritized addressing cost-effectiveness, which allows the comparison of different interventions on similar benefit, cost, and utility scales. The objective of this FRN topic is to establish better evidence about the incremental costs and benefits of alternative diagnostic and treatment strategies for individual patients with mild-to-moderate disease severity. Benefits, utilities, and cost estimates may be derived from previous clinical studies data, where available, and otherwise from observational data. These estimates should include clinical outcomes, work-related outcomes, accidents, and quality of life. Out-of-pocket patient costs should also be included in cost estimates. A societal perspective should be assumed in the main analysis and the patient perspective in a sub-analysis.

For cost-effectiveness analysis on the diagnosis of OSA, a variety of diagnostic strategies should be considered, including but not limited to PSG in all evaluated patients, diagnostic algorithms and clinical prediction rules, portable monitoring, and phased testing. Cost-effectiveness analysis on OSA treatment should include fixed and alternative PAP, oral appliances, oropharyngeal and bariatric surgery (both as indicated), phased and combined interventions, and no treatment. Evidence for both the comparison of different diagnostic tests and for the relative effect of most treatments on patient-related outcomes is of low strength or insufficient; therefore, sensitivity analyses may be of great value, including *ad hoc* sensitivity estimates of how accurate a test and how effective an intervention must be for them to be cost-effective options. Because a cost-effectiveness analysis can draw from previously collected data, the cost, size, and duration of such studies can be limited; though challenges may exist due to inadequate relevant data.

FRN Topic 2: Diagnosis—Defining age- and sex-specific criteria for OSA

While most experts consider laboratory-based PSG as the reference method to identify people with AHI suggestive of OSA, facility-based PSG is not an error-free “gold standard.”^{1,6} Several stakeholders stated that there is a need for a new definition of the OSA syndrome that identifies individuals with breathing abnormalities during sleep who have or are at risk of developing clinical sequelae because of their exposure to sleep disordered breathing. Their discussion revolved around their opinion that development of separate age- and sex-specific criteria for defining individuals who are at increased health risk because of abnormal breathing during sleep (OSA syndrome)

would be of value. While it may prove to be unnecessary to have separate criteria based on age or sex, it was agreed that these demographic features provide a reasonable place to start to make the criteria for OSA more specific.

To address this research question, we suggest a prospective cohort study of people selected from the general population to test for associations between measurements of breathing and a battery of short-term pathophysiological measurements that distinguish people whose breathing patterns have immediate physiological impact from those whose breathing patterns do not have measurable functional sequelae. Multivariable analyses that control for potential confounders, such as comorbidity and body mass index, should be performed to evaluate the relationship between measurements of breathing (e.g., AHI scores) and functional outcomes by sex and age groups (or other readily distinguishable groups). It should be noted that the definitive definition of OSA will remain unclear because whether the functional outcomes are good proxy markers for clinical outcomes will likely remain unknown. With long-term follow-up, the proposed cohort study can also provide natural history data. Any subsequent treatments and additional diagnostic testing should also be recorded as these data could inform the clinical utility of the age- and sex-specific diagnostic criteria.

FRN Topic 3: Diagnosis—What is the value of routine (or selective) preoperative screening for sleep apnea?

The stakeholders concluded that the question of the value of preoperative screening for OSA was of high priority to minimize unnecessary perioperative complications among patients with undiagnosed OSA but that the evidence whether routine or selective preoperative screening is justified is insufficient. A randomized comparison of screening for OSA with extended anesthesia care when appropriate versus no screening with routine anesthesia care would provide the best information for effectiveness of the screening protocol. The design of choice would likely be a multicenter cluster-randomized trial, where whole centers would be randomized to screen patients or not. An observational design would not be as informative, as patients who undergo testing for OSA will always be different than unscreened patients. The advantage of using a cluster-randomized trial is that there is a minimal risk of protocol deviation or cross-contamination between group assignments, if active OSA screening is performed as part of a center's clinical protocols. It is also likely that recruitment and randomization will be logistically easier if it is done at the center level, rather than at the patient level within a center. Use of validated screening questionnaires and the shorter perioperative follow-up period make it easier to recruit. The goal of preoperative screening would be to minimize perioperative complications and not just reduce proxies of clinical outcomes or improve laboratory values. However, since the event rate for complications is low due to the advances in perioperative care, the required sample sizes number in the thousands, ranging from 2,000 to 100,000 depending on baseline assumptions (see **Table S1** for examples of required sample sizes). These could result in the use of large resources in terms of cost, time and effort, and the decision to use these resources for conducting trials has to be balanced against the benefit of screening on perioperative complications. If a convincing argument can be made that a continuous out-

come could be an adequate proxy outcome for perioperative complications, then it is likely that a smaller sample size would be needed for adequate power for this outcome. However, it is currently unclear that any continuous outcome would be a convincing proxy.

FRN Topic 4: Diagnosis—What is the value of having a sleep medicine specialist involved in the diagnosis of OSA?

Increasingly, patients with OSA are being diagnosed by primary care providers. Home studies have allowed the primary care physician to bypass the sleep center altogether, and national companies have started marketing the use of home studies to primary care providers. Clearly, clearly sleep medicine specialists play an important role in both diagnosis and treatment of OSA. However, the stakeholders agreed that it is a high priority to research whether they need to be involved in diagnosis (to avoid under- and over-diagnosis), but a lesser priority at this time whether they need to be involved with treatment of all patients with OSA.

A systematic review may be the first step to ascertain the level of existing evidence, as this topic has not been previously addressed by comparative effectiveness reviews. Analyzing claims data provided by an insurance provider or a health care system, such as from de-identified Medicare and/or Medicaid claims data, could help to ascertain cost differences with use of a specialist. While this approach would be able to provide a large sample of patients from diverse geographic locations, it would not be a controlled analysis.

Another study option would be to review existing studies and analyze any available information on diagnosis by a sleep specialist versus diagnosis by a non-specialist. This approach may require additional unpublished data from study authors.

A cross-sectional survey of providers would provide an in-depth view of issues associated with using a sleep specialist in the diagnosis of OSA. However, the size of the survey would be limited by participation rates, and the cross-sectional design would not be able to answer issues of causation.

FRN Topic 5: Diagnosis—What is the prognostic accuracy of clinical prediction rules to predict clinical outcomes?

The primary question is whether clinical prediction rules (CPRs) can predict who will experience a clinical outcome in the future. The stakeholders noted that the comparative effectiveness review found no studies on whether use of CPRs resulted in improved clinical outcomes. Prospective observational studies are best suited to assess the prognostic value of a CPR because they can study multiple risk factors of interest as well as clinical outcomes in a general patient population in whom the CPR will eventually be used, ensuring applicability and external validity of the results. The CPR would be applied to participants upon their entry to the cohort, and they would be followed to ascertain whether they experience an outcome or not. An alternative design is a nested case-control study, where all patients in a defined cohort who experience an event are designated as “cases” and are matched to a collection of “control” cohort participants who did not experience the outcome. While this study design may allow an adequately powered *post hoc* analysis of

prospectively collected data where the event rate is relatively rare, prospective data collection may be needed in cases where it is difficult to reconstruct the CPR or identify people who match the setting of interest from a retrospective database.

Because of the substantial resources necessary for a prospective cohort study or a nested case-control study, it is probably not practical to design a study whose sole purpose is to assess the prognostic ability of CPRs. Instead, it would be preferable to incorporate the assessment of the prognostic performance of CPRs into a prospective cohort study in which assessment of prognostic performance will be one of several aims. For different scenarios of using CPRs with differential sensitivity and specificity pairs, the number of subjects that need to be studied ranges in the hundreds for nested case control studies to a few thousands for prospective cohorts. Patient recruitment should be straightforward and relatively simple, as patients are interested in knowing whether they have a condition that is known to cause complications and is associated with chronic disease outcomes.

FRN Topic 6: Treatment—What is the impact of treatment of sleep disordered breathing on major long-term clinical outcomes?

The stakeholders noted that there was insufficient evidence in the comparative effectiveness review on the effect of treatment of OSA on clinical outcomes, with only three of 190 comparative studies reporting clinical outcomes.⁷⁻⁹ The clinical outcomes of interest to the stakeholders are mortality, cardiovascular disease (including stroke, coronary artery disease, congestive heart failure, and atrial fibrillation), and diabetes, including surrogate or intermediate markers of the latter two conditions. In assessment of comparative effectiveness, the two overarching comparisons of interest would be autotitrating (and other non-fixed) PAP versus fixed continuous PAP and PAP versus mandibular advancement devices (MAD).

Any future trials of PAP or MAD should study clinical outcomes. However, these could result in the use of substantial study resources in terms of cost, time and effort, and the decision to use these resources for conducting trials has to be balanced against the value of information that can be gained from studying clinical outcomes. Based on the event rate in the control arm and the assumed value of relative risk, the number of trial subjects that would be required would vary from fewer than 100 to around 2000 (see **Table S1**). Regardless of the relative difference in effects between groups, trials using mortality as an outcome would need a sample size in the thousands and have a duration measured in years, while using surrogate outcomes would need smaller sample sizes and a relatively shorter duration. Loss-to-follow-up and compliance would be major concerns.

A second tier option for using existing data to evaluate the effects of different treatment on clinical outcomes would be to perform *post hoc* regressions or subgroup analyses within observational cohort studies like the Framingham Heart Study, Wisconsin Sleep Study, or Nurses Health Study. However, such *post hoc* analyses may be susceptible to type I error (falsely significant associations) due to multiple testing. These analyses of existing data can be done quickly with modest resources.

Though less informative than randomized trials for the evaluation of comparative effectiveness, observational studies would be less resource intensive in assessing impact of various treat-

ments. Case-control studies of patients treated for OSA, with or without a clinical outcome (e.g., a myocardial infarction), could also address this question, though they would be subject to all the biases and other problems of any case-control study. Statistical adjustments like propensity score matching could be used to mimic random assignment. Retrospective data could be gathered quickly though prospective cohorts would take relatively more time and effort.

FRN Topic 7: Treatment—Based on patient characteristics, how do different sleep apnea treatments, including alternative treatments, compare for patients who do not tolerate PAP?

The stakeholders again noted that for all comparisons between treatments, the comparative effectiveness review concluded that the strength of evidence is insufficient to determine which patients might benefit most from treatment or from which treatment. Trials of sleep apnea treatments do not compare their effectiveness in different patient subgroups, or groups stratified by obesity measures, sex, and other patient characteristics. Few studies have clearly been restricted to patients who do not tolerate PAP. There is a need for subgroup analyses to help clinicians base treatment decisions on baseline characteristics. These analyses can help to maximize early effective, tolerable treatment, to better match treatments to specific patient types, and to minimize costly trial-and-error.

For several treatments (particularly PAP and MAD), there are adequate trials to allow meta-analysis, but patient-level meta-analysis would be required to evaluate the differential effects of treatments in different populations. This approach allows unbiased regressions and subgroup analyses, as could be conducted in any individual trial, avoiding ecological fallacy and providing sufficient power to account for interactions. The analyses could be done quickly and with relatively few resources. However, acquiring the data is the typical main obstacle to conducting patient-level meta-analyses.

Reanalysis of existing trials could also provide unbiased regressions and subgroup analyses. These could also be conducted quickly and with limited resources. Acquiring the data from single studies can be relatively easy, but may be susceptible to both type I error (falsely significant associations) due to multiple testing or type II error (falsely nonsignificant associations) due to lack of statistical power.

In general, there is limited or no need for future randomized trials of PAP or MAD, particularly versus no or sham treatment.^{1,10} But future trials could investigate whether an interaction term (between the main effect and the predictor variable—the subgroup factor) is statistically significant. For example, the analysis of interest would be whether the relative effectiveness of PAP and MAD are different in different subpopulations. An *a priori* trial would be more definitive than a *post hoc* analysis, but such a trial would need to be substantially larger than an equivalent trial evaluating only the main effect.

Prospective or retrospective observational studies could evaluate the predictors of effective treatments using multivariable regression to determine which patient characteristics are associated with more successful treatment. Observational studies, particularly retrospective ones, could be conducted with fewer resources than randomized trials, but would still need to

be large to be powered for the multivariable analyses and would suffer from the inherent biases of observational data.

FRN Topic 8: Treatment—What interventions improve compliance with PAP, MAD, and other treatments?

The stakeholders discussed that the comparative effectiveness review failed to find adequate evidence whether any specific adjunct interventions may improve PAP compliance compared with usual care and that no general type of intervention was found to be more promising than others; these trials generally had small sample sizes with less than 1 year of follow-up. Particular interventions discussed by the stakeholders included intensive patient education, social support programs engaging spouse or other family support, cognitive behavioral therapy, feedback from daily adherence monitoring, and peer support in a Web-based fashion. The patient advocates on the stakeholder panel described a demand by patients for better training, education, and other means to improve compliance. A well-done trial will produce the most convincing results, and if patient eligibility criteria and study setting are realistic, should be fairly applicable to the majority of patients. Several study design considerations need to be addressed before a randomized trial can be properly designed and carried out, including using established metrics and objective (not self- or provider-reported) data to measure compliance, adopting behavioral change models and theories for designing interventions, and conducting program evaluation during trial period. It would be of greater interest to show long-term (several years) effects on compliance, since in most cases, treatment can be expected to be life-long.

FRN Topic 9: Treatment—What is the association between sleep apnea severity (as measured by AHI) and long-term clinical outcomes?

The comparative effectiveness review reported strong evidence demonstrating that baseline AHI > 30 events/h is an independent predictor of all-cause mortality over several years of follow-up. However, the stakeholders noted that evidence for the association of baseline AHI with other long-term clinical outcomes is lacking but needed, particularly to inform design of studies to assess long-term efficacy of treatment. The stakeholders worked under the assumption that AHI is the current best measure for the sleep apnea severity (but did not discuss or prioritize the question of what the best measure of sleep apnea severity may be).

Standard meta-analysis of existing studies is not feasible due to the large degree of clinical heterogeneity in existing studies. Patient-level meta-analysis could overcome these problems by incorporating the differences into a regression analysis and performing a unitary analysis. Existing studies such as the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study can be assessed to determine whether their data include a baseline measure of sleep apnea severity (e.g., AHI), and relevant demographic and clinical variables to allow for patient-level meta-analysis. This approach allows for unbiased regressions and subgroup analyses. Meta-regression could be used to evaluate associations between sleep apnea severity, and other patient characteristics, with long-term clinical outcomes. Similarly to Topic 6, an alternative to meta-regression could be performing *post hoc* regressions or subgroup analyses within already-published cohort studies.

If existing studies are inappropriate for *post hoc* or meta-analyses, prospective natural history studies can be conducted to investigate potential associations between sleep apnea severity and long-term clinical outcomes. Studies would require assessment of baseline sleep apnea severity in a specified patient population and documentation of all relevant demographic and clinical variables over time. Moderate resources may be necessary to recruit and follow a large cohort over a long timeframe.

DISCUSSION

Of 23 specific topics addressing the diagnosis and treatment of OSA considered by the stakeholder panels, only one had a high level of evidence found by our recent comparative effectiveness review,¹ with five having a moderate level of evidence, and the rest having a low or insufficient level of evidence. The large bulk of trial research efforts to date for diagnosis and treatment of OSA have focused on very narrow questions. For example, among 149 trials comparing treatments, 46 (31%) compared PAP to no or sham treatment, and 21 (14%) compared autotitrating and fixed PAP.¹ The stakeholder panels agreed that OSA patients, their healthcare providers, and society at large would benefit from refocusing research efforts into the prioritized research questions and away from simple comparisons of short-term outcomes between specific interventions.

Through a collaborative process involving an online discussion forum, stakeholders determined nine high-priority future research needs in OSA management, and we have proposed possible research designs for each. A limitation of our process was the limited amount of discussion on the online forum by a select number of stakeholders. The diagnosis and treatment of OSA involves a relatively large number of stakeholders with diverse backgrounds, and we attempted to choose a sample of stakeholders with diverse views and experiences. Panels comprising different stakeholders may have come to different conclusions. Despite these limitations, we were able to attain a multitude of different topics from which our final list was drawn.

The Board of Directors of the American Academy of Sleep Medicine (AASM) recently convened a task force to examine the future of sleep medicine in the care of adult patients.¹¹ Although their mandate was to consider current trends and needs of sleep medicine specialists for an array of sleep disorders and was not focused on new clinical research, there were some areas of overlap between their recommendations and the stakeholders' prioritized FRNs. In line with our stakeholders, the AASM task force called for more socioeconomic and quality of life data for the major sleep disorders to allow for better cost-effectiveness analyses. They also raised the issue of how sleep medicine specialists should partner with other physician specialties for patient management. In somewhat of a contrast with the stakeholders' priority to research sleep medicine specialist involvement in OSA diagnosis (FRN Topic 4), the AASM task force emphasized the need to move the field of sleep medicine from diagnosis-based to "being focused on long-term care management of chronic diseases."¹¹ The task force also recommended setting up patient registries, with a priority question of interest being interventions to facilitate PAP acceptance and adherence (similar to FRN Topic 8). However, it was our opinion that while retrospective analyses may provide a signal

as to which interventions may be effective, only randomized trials could provide sufficient evidence to make recommendations on how to improve adherence. Related to FRN Topic 9 (on the association between OSA severity and clinical outcomes), the AASM task force discussed the need to develop both better measures than AHI or PSG alone and phenotypes of patients to delineate their different cardiovascular risk profiles and to facilitate personalized care. Finally, the AASM task force called for future research to discover biomarkers that correlate with treatment efficacy, but our stakeholders did not consider novel or theoretical markers or interventions.

Assessing future research needs by way of discussion with stakeholders is a new process but one that should offer researchers, funders, and policymakers a basis for evaluating where to spend time and resources in future research. The next phase in this process may be developing a method to understand the salience of topics. Several considerations must be made when evaluating the feasibility of studies on FRN topics, such as sample size, funding, and existing research on the topic. Researchers and funders may garner insight from our experience in collecting a variety of FRN topics, selecting the most salient of these topics, and analyzing possible research designs to address the topics.

ABBREVIATIONS

AHI, apnea-hypopnea index
AHRQ, Agency for Healthcare Research and Quality
PAP, positive airway pressure
CPR, clinical prediction rule
FRN, future research needs
MAD, mandibular advancement device
OSA, obstructive sleep apnea

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ACKNOWLEDGMENTS

Work for this study was performed at Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA. This work was funded under contract (Contract No. 290-2007-10055 I) from the US Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, which did not participate in data analysis or preparation, review, or approval of the manuscript for publication. The authors of this manuscript are responsible for its content. Statements in the manuscript should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services. The authors thank and acknowledge the following stakeholders: Elise Berliner, Ph.D., Agency for Healthcare Research and Quality; Apostolos P. Dallas, M.D., Virginia Tech-Carilion School of Medicine and Research Institute; Carolyn M. D'Ambrosio, M.D., FCCP, DABSM, The Center for Sleep Medicine at Tufts Medical Center; Gary D. Foster, Ph.D., Temple University Center for Obesity Research and Education; Daniel J. Gottlieb, M.D., M.P.H., Veterans Administration Boston Healthcare System; Edward Grandi, American Sleep Apnea Association; Christian

Guilleminault, M.D., D.Biol., Stanford University; Joseph A. Hanak, M.D., Tufts Medical Center Division of Adult Physical Medicine and Rehabilitation; Vishesh Kapur, M.D., M.P.H., University of Washington Medicine Sleep Center; Sheri Katz, D.D.S., American Academy of Dental Sleep Medicine; Meir Kryger M.D., FRCP, Connecticut Veterans Administration Healthcare System; Atul Malhotra, M.D., Harvard Medical School Divisions of Sleep Medicine Pulmonary & Critical Care and Sleep Medicine; Tracy R. Nascia, Talk About Sleep, Inc.; Allan I. Pack, M.B.Ch.B., Ph.D., Perelman School of Medicine at the University of Pennsylvania Division of Sleep Medicine; Sanjay R. Patel, M.D., M.S., Brigham and Women's Hospital Division of Sleep Medicine; Jeffrey R. Prinsell, D.M.D., M.D., Marietta, GA; Andrew Scibelli, M.B.A., M.A., NextEra Energy, Inc.; Patrick J Strollo Jr., M.D., FCCP, F.A.A.S.M., University of Pittsburgh School of Medicine Sleep Medicine Center; Victor G. Villagra, M.D., FACP, National Rural Electric Cooperative Association; Thomas Weakley, Owner-Operator Independent Drivers Association Foundation, Inc.; Lichuan Ye, Ph.D., R.N., Boston College William F. Connell School of Nursing; Robert W. Zvoski, M.D., M.P.H., Medical Care Administration, Connecticut Department of Social Services; an anonymous Medical Director; and an anonymous Federal agency stakeholder.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication November, 2012

Submitted in final revised January, 2013

Accepted for publication February, 2013

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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Concannon is under contract as consultant for Impaq International which expires May 29, 2013. The other authors have indicated no financial conflicts of interest.

APPENDIX

Topic-Related Conclusions and References from the 2011 Comparative Effectiveness Review

FRN Topic 1: Diagnosis and Treatment—What is the cost-effectiveness of different management strategies specifically for patients with mild to moderate disease severity?

The comparative effectiveness review (CER, cited below) did not evaluate or search for cost-effectiveness studies. In concept, any or all of the 240 articles cited in the CER could be informative to provide data for the diagnostic accuracy of testing or the treatment effectiveness, depending on the structure of the cost-effectiveness model.

Balk EM, Moorthy D, Obadan NO, et al. Diagnosis and treatment of obstructive sleep apnea in adults. Comparative Effectiveness Review No. 32. (Prepared by Tufts Evidence-based Practice Center under Contract No. 290-2007-10055-I) AHRQ Publication No 11-EHC052-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2011. Available at: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=683>, last accessed Jan 17, 2013.

FRN Topic 2: Diagnosis—Defining age- and sex-specific criteria for OSA

Key Question 1 of the CER asked **How do different available tests compare in their ability to diagnose sleep apnea in adults with symptoms suggestive of disordered sleep? How do these tests compare in different subgroups of patients based on: race, sex, body mass index, existing noninsulin dependent diabetes mellitus, existing cardiovascular disease, existing hypertension, clinical symptoms, previous stroke, or airway characteristics?** Conceptually, these studies could have provided data to help define age- and sex-specific criteria for OSA. However, no eligible study in the CER for this Key Question compared available tests for clinical outcomes. For the most part, they used current diagnostic criteria based on in-lab polysomnography as their gold standard. They did not provide evidence that could be used to define or change the current criteria for OSA.

Key Question 4 of the CER addressed a related topic, AHI (or sleep apnea severity) as a predictor of clinical outcomes: **In adults being screened for obstructive sleep apnea, what are the relationships between apnea-hypopnea index or oxygen desaturation index, and other patient characteristics with long-term clinical and functional outcomes?** The CER did not evaluate analyses that may have defined age- or sex-specific criteria for OSA, per se.

In brief the CER found “A *high strength of evidence* from four studies (three quality A, one quality B) indicates that an AHI > 30 events/h is an independent predictor of all-cause mortality; although one study found that this was true only in men under age 70 years. All other outcomes were analyzed by only one or two studies. Thus, only a *low strength of evidence* exists that a high AHI (> 30 events/h) is associated with incident diabetes. This association, however, may be confounded by obe-

sity, which may result in both OSA and diabetes. The strength of evidence is insufficient regarding the association between AHI and other clinical outcomes. The two studies of cardiovascular mortality did not have consistent findings, and the two studies of hypertension had unclear conclusions. One study of nonfatal cardiovascular disease found a significant association with baseline AHI (as they did for cardiovascular mortality). One study each found no association between AHI and stroke or long-term quality of life.”

The articles evaluated for this Key Question were:

- Arzt M, Young T, Finn L, et al. Association of sleep-disordered breathing and the occurrence of stroke. *American Journal of Respiratory & Critical Care Medicine* 2005 Dec 1;172(11):1447-51. PMID 16141444
- Botros N, Concato J, Mohsenin V, et al. Obstructive sleep apnea as a risk factor for type 2 diabetes. *American Journal of Medicine* 2009 Dec;122(12):1122-27. PMID 19958890
- Lavie P, Here P, Peled R, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. *Sleep* 1995;18(3):149-57. PMID 7610310
- Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *European Respiratory Journal* 2005 Mar;25(3):514-20. PMID 15738297
- Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005 Mar 19;365(9464):1046-53. PMID 15781100
- O'Connor GT, Caffo B, Newman AB, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *American Journal of Respiratory & Critical Care Medicine* 2009 Jun 15;179(12):1159-64. PMID 19264976
- Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine* 2000 May 11;342(19):1378-84. PMID 10805822
- Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Medicine / Public Library of Science* 2009 Aug;6(8):e1000132. PMID 19688045
- Reichmuth KJ, Austin D, Skatrud JB, et al. Association of sleep apnea and type II diabetes: a population-based study. *American Journal of Respiratory & Critical Care Medicine* 2005 Dec 15;172(12):1590-95. PMID 16192452
- Silva GE, An MW, Goodwin JL, et al. Longitudinal evaluation of sleep-disordered breathing and sleep symptoms with change in quality of life: the Sleep Heart Health Study (SHHS). *Sleep* 2009 Aug 1;32(8):1049-57. PMID 19725256
- Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the

Wisconsin sleep cohort. *Sleep* 2008 Aug 1;31(8):1071-78. PMID 18714778

FRN Topic 3: Diagnosis—What is the value of routine (or selective) pre-operative screening for sleep apnea?

The CER asked this question (Key Question 3: **What is the effect of preoperative screening for sleep apnea on surgical outcomes?**) and concluded that “The *strength of evidence is insufficient* regarding postoperative outcomes with mandatory screening for sleep apnea. Two quality C prospective studies assessed the effect of preoperative screening for sleep apnea on surgical outcomes. One study found no significant differences in outcomes between patients undergoing bariatric surgery who had mandatory PSG or PSG based on clinical parameters. The second study found that general surgery patients willing to undergo preoperative PSG were more likely to have perioperative complications, particularly cardiopulmonary complications, possibly suggesting that patients willing to undergo PSG are more ill than other patients.”

Only 2 relevant studies were found:

- Chung F, Yegneswaran B, Liao P, et al. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* 2008 May;108(5):822-30. PMID 18431117.
- Hallowell PT, Stellato TA, Petrozzi MC, et al. Eliminating respiratory intensive care unit stay after gastric bypass surgery.[erratum appears in *Surgery*. 2008 Feb;143(2):301]. *Surgery* 2007;142(4):608-12. PMID 17950355.

FRN Topic 4: Diagnosis—What is the value of having a sleep medicine specialist involved in the diagnosis of OSA?

The CER did not address this question. Conceptually, some of the studies that addressed Key Question 1 (**How do different available tests compare in their ability to diagnose sleep apnea in adults with symptoms suggestive of disordered sleep?**) or Key Question 2 (**How does phased testing (screening tests or battery followed by full test) compare to full testing alone?**) could have provided some evidence regarding this FRN topic, but none analyzed the value of a sleep medicine specialist.

FRN Topic 5: Diagnosis—What is the prognostic accuracy of clinical prediction rules to predict clinical outcomes?

A subsection of the CER's Key Question 1 (**How do different available tests compare in their ability to diagnose sleep apnea in adults with symptoms suggestive of disordered sleep?**) addressed this question. The CER concluded that “There is a *low strength of evidence* among seven studies (three quality A, three quality B, and one quality C) that some clinical prediction rules may be useful in the prediction of a diagnosis of OSA. Ten different clinical prediction rules have been described. Nine clinical prediction rules have been used for the prediction of a diagnosis of OSA (using different criteria). The oropharyngeal morphometric model gave near perfect discrimination (area under the curve [AUC] = 0.996) to predict the diagnosis of OSA, and the pulmonary function data model had 100 percent sensitivity with 84 percent specificity to predict

diagnosis of OSA. The remaining models reported diagnostic lower sensitivities and specificities. Each model was deemed useful to predict the diagnoses of OSA by the individual study authors. However, while all the models were internally validated, external validation of these predictive rules has not been conducted in the vast majority of the studies.”

The studies eligible to address this question were:

- Crocker BD, Olson LG, Saunders NA, et al. Estimation of the probability of disturbed breathing during sleep before a sleep study. *American Review of Respiratory Disease* 1990 Jul;142(1):14-18. PMID 2368960
- Gurubhagavatula I, Maislin G, Pack AI. An algorithm to stratify sleep apnea risk in a sleep disorders clinic population. *American Journal of Respiratory & Critical Care Medicine* 2001 Nov 15;164(10:Pt 1):1904-9. PMID 11734444
- Kushida CA, Efron B, Guilleminault C. A predictive morphometric model for the obstructive sleep apnea syndrome. *Annals of Internal Medicine* 1997 Oct 15;127(8:Pt 1):581-7. PMID 9341055
- Onen SH, Dubray C, Decullier E, et al. Observation-based nocturnal sleep inventory: screening tool for sleep apnea in elderly people. *Journal of the American Geriatrics Society* 2008 Oct;56(10):1920-25. PMID 18775037
- Rodsutti J, Hensley M, Thakkinian A, et al. A clinical decision rule to prioritize polysomnography in patients with suspected sleep apnea. *Sleep* 2004 Jun 15;27(4):694-99. PMID 15283004
- Rowley JA, Aboussouan LS, Badr MS. The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. *Sleep* 2000 Nov 1;23(7):929-38. PMID 11083602
- Zerah-Lancner F, Lofaso F, d'Ortho MP, et al. Predictive value of pulmonary function parameters for sleep apnea syndrome. *American Journal of Respiratory & Critical Care Medicine* 2000 Dec;162(6):2208-12. PMID 11112139

FRN Topic 6: Treatment—What is the impact of treatment of sleep disordered breathing on major long-term clinical outcomes?

This was a question of primary interest for the CER, specifically under Key Question 5, **What is the comparative effect of different treatments for obstructive sleep apnea in adults?** However, the studies that reported major long-term clinical outcomes were sparse. For all treatments, the CER concluded that there was insufficient or weak evidence for an effect on clinical outcomes.

The eligible studies that reported long-term clinical outcomes were:

- Mansfield DR, Gollogly NC, Kaye DM, et al. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *American Journal of Respiratory & Critical Care Medicine* 2004 Feb 1;169(3):361-66. PMID 14597482.

Evaluated the impact of CPAP treatment on heart failure symptomatology, as assessed by the New York Heart Association class.

- Keenan SP, Burt H, Ryan CF, et al. Long-term survival of patients with obstructive sleep apnea treated by uvulopalatopharyngoplasty or nasal CPAP. *Chest* 1994 Jan;105(1):155-59. PMID 8275724.

Evaluated the effects of uvulopalatopharyngoplasty (UPPP) compared with CPAP on long-term survival.

- Weaver EM, Maynard C, Yueh B. Survival of veterans with sleep apnea: continuous positive airway pressure versus surgery.[erratum appears in *Otolaryngol Head Neck Surg.* 2004 Jul;131(1):144]. *Otolaryngology - Head & Neck Surgery* 2004 Jun;130(6):659-65. PMID 15195049.

Evaluated the effects of UPPP compared with CPAP on long-term survival.

FRN Topic 7: Treatment—Based on patient characteristics, how do different sleep apnea treatments, including alternative treatments, compare for patients who do not tolerate PAP?

Only one study in the CER included only patients who did not tolerate PAP. No other studies reported on a subgroup of patients who had not tolerated PAP. This study was:

- Bloch KE, Iseli A, Zhang JN, et al. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. *American Journal of Respiratory & Critical Care Medicine* 2000 Jul;162(1):246-51. PMID. 10903249.

FRN Topic 8: Treatment—What interventions improve compliance with PAP, MAD, and other treatments

Key Question 7, specifically addressed this topic: **What is the effect of interventions to improve compliance with device (positive airway pressure, oral appliances, positional therapy) use on clinical and intermediate outcomes?** The CER concluded that “There is a *low strength of evidence* that some specific adjunct interventions may improve CPAP compliance, but studies are heterogeneous and no general type of intervention (e.g., education, telemonitoring) was more promising than others. The 18 trials (two quality A, eight quality B, and eight quality C) had inconsistent effects across a wide variety of interventions. Studies generally had small sample sizes with less than 1 year of follow-up. Compared with usual care, several interventions were shown to significantly increase hours of CPAP use per night in some studies. These included intensive support or literature (designed for patient education), cognitive behavioral therapy (given to patients and their partners), telemonitoring, and a habit-promoting audio-based intervention. However, the majority of studies did not find a significant difference in CPAP compliance between patients who received interventions to promote compliance with device use and those who received usual care. No study of nurse-led care (which was not focused primarily on compliance) had an effect on compliance rates.”

The eligible studies for this key question were:

- Antic NA, Buchan C, Esterman A, et al. A randomized controlled trial of nurse-led care for symptomatic moderate-severe obstructive sleep apnea. *American Journal of Respiratory & Critical Care Medicine* 2009 Mar 15;179(6):501-08. PMID 19136368
- Bradshaw DA, Ruff GA, Murphy DP. An oral hypnotic medication does not improve continuous positive airway

pressure compliance in men with obstructive sleep apnea. *Chest* 2006 Nov;130(5):1369-76. PMID 17099012

- Chervin RD, Theut S, Bassetti C, et al. Compliance with nasal CPAP can be improved by simple interventions. *Sleep* 1997 Apr;20(4):284-89. PMID 9231954
- Damjanovic D, Fluck A, Bremer H, et al. Compliance in sleep apnoea therapy: influence of home care support and pressure mode. *European Respiratory Journal* 2009 Apr;33(4):804-11. PMID 19129293
- DeMolles DA, Sparrow D, Gottlieb DJ, et al. A pilot trial of a telecommunications system in sleep apnea management. *Medical Care* 2004 Aug;42(8):764-69. PMID 15258478
- Fletcher EC, Luckett RA. The effect of positive reinforcement on hourly compliance in nasal continuous positive airway pressure users with obstructive sleep apnea. *American Review of Respiratory Disease* 1991 May;143(5:Pt 1):936-41. PMID 2024846
- Holmdahl C, Schollin IL, Alton M, et al. CPAP treatment in obstructive sleep apnoea: a randomised, controlled trial of follow-up with a focus on patient satisfaction. *Sleep Medicine* 2009 Sep;10(8):869-74. PMID 19179111
- Hoy CJ, Vennelle M, Kingshott RN, et al. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *American Journal of Respiratory & Critical Care Medicine* 1999 Apr;159(4:Pt 1):1096-100. PMID 10194151
- Hui DS, Chan JK, Choy DK, et al. Effects of augmented continuous positive airway pressure education and support on compliance and outcome in a Chinese population. *Chest* 2000 May;117(5):1410-16. PMID 10807830
- Lewis KE, Bartle IE, Watkins AJ, et al. Simple interventions improve re-attendance when treating the sleep apnoea syndrome. *Sleep Medicine* 2006 Apr;7(3):241-47. PMID 16564210
- Massie CA, Hart RW. Clinical outcomes related to interface type in patients with obstructive sleep apnea/hypopnea syndrome who are using continuous positive airway pressure. *Chest* 2003 Apr;123(4):1112-18. PMID 12684301
- Meurice JC, Ingrand P, Portier F, et al. A multicentre trial of education strategies at CPAP induction in the treatment of severe sleep apnoea-hypopnoea syndrome. *Sleep Medicine* 2007 Jan;8(1):37-42. PMID 17157557
- Palmer S, Selvaraj S, Dunn C, et al. Annual review of patients with sleep apnea/hypopnea syndrome--a pragmatic randomised trial of nurse home visit versus consultant clinic review. *Sleep Medicine* 2004 Jan;5(1):61-65. PMID 14725828
- Richards D, Bartlett DJ, Wong K, et al. Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. *Sleep* 2007 May 1;30(5):635-40. PMID 17552379
- Smith CE, Daut E, Clements F, et al. Patient education combined in a music and habit-forming intervention for adherence to continuous positive airway (CPAP) prescribed for sleep apnea. *Patient Education & Counseling* 2009 Feb;74(2):184-90. PMID 18829212

- Stepnowsky CJ, Palau JJ, Marler MR, et al. Pilot randomized trial of the effect of wireless telemonitoring on compliance and treatment efficacy in obstructive sleep apnea. *Journal of Medical Internet Research* 2007;9(2):e14. PMID 17513285
- Taylor Y, Eliasson A, Andrada T, et al. The role of telemedicine in CPAP compliance for patients with obstructive sleep apnea syndrome. *Sleep & Breathing* 2006 Sep;10(3):132-38. PMID 16565867
- Jean WH, Boethel C, Phillips B, et al. CPAP compliance: video education may help! *Sleep Medicine* 2005 Mar;6(2):171-74. PMID 15716221

FRN Topic 9: Treatment—What is the association between sleep apnea severity (as measured by AHI) and long-term clinical outcomes?

Key Question 4 of the CER addressed this topic: **In adults being screened for obstructive sleep apnea, what are the relationships between apnea-hypopnea index or oxygen desaturation index, and other patient characteristics with long-term clinical and functional outcomes?** The CER concluded that “A *high strength of evidence* from four studies (three quality A, one quality B) indicates that an AHI > 30 events/h is an independent predictor of all-cause mortality; although one study found that this was true only in men under age 70 years. All other outcomes were analyzed by only one or two studies. Thus, only a *low strength of evidence* exists that a high AHI (> 30 events/h) is associated with incident diabetes. This association, however, may be confounded by obesity, which may result in both OSA and diabetes. The strength of evidence is insufficient regarding the association between AHI and other clinical outcomes. The two studies of cardiovascular mortality did not have consistent findings, and the two studies of hypertension had unclear conclusions. One study of nonfatal cardiovascular disease found a significant association with baseline AHI (as they did for cardiovascular mortality). One study each found no association between AHI and stroke or long-term quality of life.”

The eligible studies analyzed for this question are listed under FRN Topic 2.

Table S1—Sample size calculations

Topic	Risk Ratio Estimate	Control Rate Estimate	Sample size
FRN Topic 3: Screening versus no screening for postoperative complications*	0.6	0.01	20,844
		0.05	4,032
		0.1	1,930
	0.7	0.01	39,354
		0.05	7,598
		0.1	3,628
	0.8	0.01	93,712
		0.05	18,060
		0.1	8,602
FRN Topic 6: MAD versus CPAP for combined cardiovascular outcomes†	0.6	0.7	128
		0.8	92
	0.7	0.7	226
		0.8	156
	0.8	0.7	496
		0.8	328
	0.9	0.7	1,908
		0.8	1,194

CPAP, continuous positive airway pressure; FRN, future research needs; MAD, maxillary advancement device. *Data on postoperative complication rate derived from Hallowell et al., 2008,⁶ which reported a relative risk of 0.6 and an event rate of 0.05. Calculations assume a power of 90 percent. †Data on cardiovascular outcomes derived from trials analyzed in Balk et al., 2011,¹ which reported a relative risk ranging from 0.6 to 0.9 and an event rate ranging from 0.7 to 0.8. Calculations assume a power of 90 percent.