Obstructive sleep apnea syndrome and perioperative complications: a systematic review of the literature.

Tajender S. Vasu, MD, MS
Stony Brook University Medical Center, Stony Brook, NY

Ritu G. Grewal, MD
Thomas Jefferson University, Ritu.Grewal@jefferson.edu

Karl Doghramji, MD
Thomas Jefferson University, karl.doghramji@jefferson.edu

Let us know how access to this document benefits you

Follow this and additional works at: https://jdc.jefferson.edu/sleepmedicinefp

Part of the Sleep Medicine Commons
Obstructive sleep apnea syndrome (OSAS) is a common sleep related breathing disorder. Its prevalence is estimated to be between 2% and 25% in the general population. However, the prevalence of sleep apnea is much higher in patients undergoing elective surgery. Sedation and anesthesia have been shown to increase the upper airway collapsibility and therefore increasing the risk of having postoperative complications in these patients. Furthermore, the majority of patients with sleep apnea are undiagnosed and therefore are at risk during the perioperative period. It is important to identify these patients so that appropriate actions can be taken in a timely fashion. In this review article, we will discuss the epidemiology of sleep apnea in the surgical population. We will also discuss why these patients are at a higher risk of having postoperative complications, with the special emphasis on the role of anesthesia, opioids, sedation, and the phenomenon of REM sleep rebound. We will also review how to identify these patients preoperatively and the steps that can be taken for their perioperative management.

Keywords: Obstructive sleep apnea syndrome, perioperative complications, postoperative complications, STOP Questionnaire, Berlin Questionnaire


Obstructive sleep apnea is characterized by intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep. These episodes disrupt sleep architecture, causing fragmented sleep and daytime sleepiness. OSAS has been shown to be associated with various health-related consequences, including increased rate of motor vehicle accidents, hypertension, diabetes mellitus, congestive heart failure, stroke, and all-cause mortality.1-9

 Recently, numerous studies have demonstrated that surgical patients with sleep apnea are at increased risk of having perioperative complications, including hypoxemia, pneumonia, difficult intubation, myocardial infarction, pulmonary embolism, atelectasis, cardiac arrhythmias, and unanticipated admission to the ICU. The majority of patients with OSA are undiagnosed upon admission and are at risk during the perioperative period, presumably due to their underlying sleep apnea. Therefore, it is very important to identify these patients preoperatively so that one can initiate appropriate perioperative measures.

Epidemiology

OSAS is an extremely common sleep related breathing disorder, and its prevalence has been increasing throughout the world because of obesity and increasing age of the general population. Its prevalence is between 2% and 25% in the general population, depending upon how sleep apnea is defined. In an epidemiological study, Young et al. noted that the prevalence of sleep apnea, defined as apnea-hypopnea index (AHI) ≥ 5/h was 9% for women and 24% for men.10 However, the prevalence of OSAS (defined as AHI ≥ 5/h and daytime sleepiness) was 2% in women and 4% in men.10 The National Sleep Foundation (NSF) 2005 Poll found that 1 in 4 Americans are at high risk of having sleep apnea based on the Berlin Questionnaire.11 The prevalence of sleep apnea is much higher in surgical patients and depends on the type of surgery. In the bariatric surgery population, the prevalence of sleep apnea has been found to be > 70%.12,13 It is the standard of care for these patients to get a formal sleep evaluation prior to undergoing the bariatric surgery. However, patients who are coming for general surgery also have a higher prevalence of sleep apnea.14 Chung et al. used the Berlin Questionnaire preoperatively and found that 24% of surgical patients were at high risk for sleep apnea.15 We used the STOP-BANG Questionnaire in our elective surgical population and found that 41% of patients were at high risk for sleep apnea based on the questionnaire.16 In a cross-sectional study, 39 patients underwent nocturnal polysomnography (NPSG) prior to undergoing epilepsy surgery. It was found that 1 in 3 patients undergoing epilepsy surgery had sleep apnea.17 In another study, the prevalence of sleep apnea was found to be 64% in a small population of patients undergoing surgery for intracranial tumor.18 The majority of these patients are unaware of their sleep apnea prior to undergoing elective surgery. In an observational study, Finkel et al. noted that > 80% of surgical patients were unaware that they had sleep apnea prior to undergoing surgery.14

Pathophysiology

Surgical patients receive sedation, anesthesia, and opioids during the perioperative period. These medicines have been shown to increase pharyngeal collapse, decrease ventilatory response, and impair the arousal response, leading to worsening of sleep apnea in the perioperative period.
Impact of Sedation, Anesthesia, and Opioids

Patients with sleep apnea have recurrent episodes of partial or complete obstruction of the upper airway during sleep. These episodes usually occur when the negative pressure of inspiratory muscles exceeds the upper airway dilator muscle activity (critical airway pressure). General anesthetics have been shown to decrease the upper airway dilator muscle activity in a dose-dependent manner and thereby increase upper airway collapsibility. In 12 healthy subjects undergoing minor surgery, increasing depth of propofol anesthesia was associated with a progressive increase in critical airway pressure and upper airway collapsibility. This increased upper airway collapsibility was found to be secondary to progressive decrease in the genioglossus muscle activity. Upper airway collapsibility may cause worsening of the sleep apnea and increase the risk of hypoxemia, cardiac arrhythmias, and postoperative complications.

Anesthetic medicines also impair the arousal response, a protective defense mechanism against sleep apnea that helps in overcoming the airway obstruction. Anesthetics, opioids, hypnotics, and benzodiazepines may also cause respiratory depression and thereby decrease the minute ventilation. Studies have shown that halothane reduces the ventilatory response to hypoxemia and hypercapnia in humans. This depression is most likely secondary to a selective effect of halothane on the peripheral chemoreflex loop. Similarly, a subanesthetic dose of isoflurane has been shown to reduce the hypoxic ventilatory response via peripheral chemoreceptors.

Patients undergoing surgery frequently receive opioids for the pain control. Opioids have been shown to impair ventilatory function by affecting both peripheral and central carbon dioxide chemoreflex loops. Studies have shown that small doses of narcotics administered epidurally may also depress the respiratory function, even in healthy adults. The ventilatory depression of opiates appears to be affected by sex and ethnicity, as well. Morphine has been shown to reduce hypoxic and hypercapnic ventilatory response in women, but not in men. On the other hand, it raises the apneic threshold in men with no effect in women. The combination of opiates and benzodiazepines has been shown to cause more significant episodes of hypoxemia and apnea. This is most likely secondary to significant reduction of hypoxic ventilatory response to both opiates and benzodiazepines.

REM Sleep Rebound

Surgical patients have been shown to have highly fragmented sleep on postoperative nights 1 or 2, with a significant reduction in REM sleep, slow wave sleep, and increased stage 2 NREM sleep. These sleep disturbances usually occur secondary to surgical stress, pain, and the use of anesthetic and pain medications. The stress of surgical trauma leads to increased level of cortisol, and cortisol has been shown to cause significant reduction in REM sleep. Surgical trauma has also been shown to induce significant inflammatory response, characterized by the increased level of pro-inflammatory markers like tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and IL-6. These inflammatory markers, especially IL-1 and TNF-α, have been shown to suppress REM sleep.

There are studies that have shown that REM sleep is usually absent on postoperative nights 1 and 2. This is usually followed by a profound increase in the amount and density of REM sleep (REM sleep rebound) during recovery nights 3 to 5. The episodes of sleep disordered breathing and hypoxemia are usually worse during REM sleep due to hypotonia and unstable breathing. REM sleep is also associated with increased sympathetic discharge leading to tachycardia, hemodynamic instability, and myocardial ischemia.

It is well known that most complications after the surgery occur in the first postoperative week, especially between postoperative days 2 and 5, corresponding to periods of REM rebound. Episodes of hypoxemia after surgery have been reported to occur mostly between postoperative nights 2 to 5. These episodes may increase the risk of wound infection, cerebral dysfunction, and cardiac arrhythmias. In an observational study at Mayo Clinic, it was found that the incidence of acute myocardial infarction peaked on day 3 after surgery. Similarly, episodes of delirium, nightmares, and psychomotor dysfunction have been reported to occur between postoperative nights 3 to 5.

Evidence on Sleep Apnea as a Risk Factor for Perioperative Complications

We systematically searched the literature on PubMed, Embase, and Scopus databases to identify relevant studies on association between obstructive sleep apnea and perioperative outcome. We included studies conducted in adults who underwent elective surgery. We excluded bariatric surgery and sleep apnea surgery population. Two authors (TSV and RG) independently searched for the relevant articles published in the English literature from 1966 to December 2011. We used the combination of terms including surgery, perioperative outcome, perioperative complications, perioperative pulmonary outcome, perioperative risk, postoperative complications, and obstructive sleep apnea. Bibliographies of all selected articles and review articles were also reviewed to find any other relevant article. These 2 authors (TSV and RG) also independently assigned the Oxford level of evidence and the grade of recommendation to each article. There was 100% agreement between the 2 authors. We identified 11 articles on obstructive sleep apnea and perioperative outcome. These articles along with their Oxford level of evidence are reported in the Table 1 and Table 2.

Surgical patients are at higher risk of having complications for a variety of reasons, including ASA (American Society of Anesthesiologists) class, age, type of paralytics, current smoking, low albumin, duration of surgery, type of anesthesia, and other comorbidities—especially chronic obstructive pulmonary disease, coronary artery disease, and renal failure. The risk of postoperative complications also depends on the type of surgery. The rate of complications is higher in patients undergoing abdominal surgery and is also increased with aortic aneurysm repair, thoracic, thoracic, and neck surgery.

Gupta et al. have shown an increased risk of postoperative complications (39% vs 18%), higher rate of transfer to ICU (24% vs 9%), and increased length of hospital stay in patients with obstructive sleep apnea compared with control subjects matched for age, sex, and body mass index (BMI). In this study, these investigators also reported that OSA patients who

Table 1

Table 2

Journal of Clinical Sleep Medicine, Vol. 8, No. 2, 2012
Table 1—Studies reporting association between obstructive sleep apnea and perioperative complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Diagnosis of OSAS</th>
<th>Type of Surgeries</th>
<th>Complications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al.98</td>
<td>Case control study</td>
<td>101 patients with OSA and 101 matched controls</td>
<td>Polysomnography (PSG)</td>
<td>Orthopedic (hip or knee replacement)</td>
<td>Reintubation, hypoxemia, acute hypercapnia, myocardial infarction, arrhythmia, delirium, and ICU transfer</td>
<td>Patients with OSA had a higher rate of postoperative complications (39% vs 18%). These patients also had increased hospital length of stay.</td>
</tr>
<tr>
<td>Auckley et al.</td>
<td>Historical cohort study</td>
<td>81 patients with completed Berlin Questionnaire</td>
<td>Berlin Questionnaire</td>
<td>Elective surgery (type of surgeries is not included in the abstract)</td>
<td>Hypoxemia, hypercapnia, reintubation, atelectasis, pneumonia, arrhythmia, thromboembolism</td>
<td>Patients with high-risk of sleep apnea based on the Berlin Questionnaire had a higher rate of postoperative complications (20% vs 4.5%).</td>
</tr>
<tr>
<td>Sabers et al.</td>
<td>Case control study</td>
<td>234 patients with OSA and 234 matched controls</td>
<td>Polysomnography</td>
<td>Non-otorhinolaryngologic outpatient surgical procedures</td>
<td>Unplanned hospital admission, bronchospasm, upper airway obstruction, hypotension, atrial fibrillation, pulmonary edema</td>
<td>No significant difference in the rate of unplanned hospital admissions (23.9% vs 18.8%) or other adverse events (2.1% vs 1.3%)</td>
</tr>
<tr>
<td>Kaw et al.100</td>
<td>Case control study</td>
<td>37 patients with OSA and 185 matched controls</td>
<td>Polysomnography</td>
<td>Cardiac</td>
<td>Encephalopathy, postoperative infections, and ICU length of stay</td>
<td>Patients with sleep apnea had higher rate of encephalopathy, postoperative infections (mediastinitis), and increased ICU length of stay.</td>
</tr>
<tr>
<td>Hwang et al.102</td>
<td>Historical cohort study</td>
<td>172 patients underwent home nocturnal oximetry</td>
<td>Home nocturnal oximetry</td>
<td>Abdominal, ENT, Thoracic, Vascular, Gyn, Neurosurgical, Urologic, Cardiothoracic, and Orthopedic</td>
<td>Arrhythmia, hypoxemia, atelectasis, GI bleed, pneumonia, pulmonary embolism,</td>
<td>Patients with ODI4% ≥ 5/h had a higher rate of postoperative complications than those with ODI4% &lt; 5/h (15.3% vs 2.7%).</td>
</tr>
<tr>
<td>Gali et al.104</td>
<td>Prospective cohort study</td>
<td>693 patients with completed Flemons Criteria and SACS score</td>
<td>Flemons Criteria and SACS score</td>
<td>Orthopedic, Gyn, ENT, Urologic, Thoracic, Plastics, Neurosurgery, General abdominal</td>
<td>Arrhythmia, MI, ICU admission, pneumonia, need for the ventilator support</td>
<td>Postoperative respiratory events were associated with high SACS and PACU events</td>
</tr>
<tr>
<td>Liao et al.99</td>
<td>Retrospective matched cohort study</td>
<td>240 patients with OSA and 240 matched controls</td>
<td>International Classification of Disease (ICD-9) codes</td>
<td>Cardiac, ENT, Orthopedic, Spine, Urologic, General, Gyn, and Plastic</td>
<td>Hypoxemia, pulmonary edema, bronchospasm, arrhythmia, confusion</td>
<td>Patients with OSA had a higher incidence of postoperative complications (48% vs 36%)</td>
</tr>
<tr>
<td>Vasu et al.16</td>
<td>Historical cohort study</td>
<td>135 patients with completed STOP BANG Questionnaire</td>
<td>STOP BANG Questionnaire</td>
<td>Orthopedic, Abdominal, Head and Neck, ENT, Gyn, Vascular, Cardi thoracic</td>
<td>Hypoxemia, pneumonia, pulmonary embolism, atelectasis, hypotension, atrial fibrillation</td>
<td>Patients with high-risk of sleep apnea based on STOP BANG Questionnaire had a higher rate of postoperative complications (19.6% vs 1.3%) and the hospital length of stay.</td>
</tr>
</tbody>
</table>

PSG, polysomnography; ICU, Intensive Care Unit; SACS, Sleep Apnea Clinical Score; PACU, Postanesthesia Care Unit.

Table 1 continues on the following page
OSA had higher incidence of encephalopathy, postoperative infections (mediastinitis), and increased ICU length of stay. Similarly, Memtsoudis et al. in their case-control study found that orthopedic and general surgical patients with sleep apnea were at a higher risk of having perioperative pulmonary complications. Hwang et al. demonstrated that the rate of postoperative complications was increased in proportion to episodes of over-received continuous positive airway pressure (CPAP) therapy prior to surgery had a reduced rate of serious complications and a one-day reduction in the length of hospital stay. In another case-control study, Liao et al. found that patients with OSA had higher rate of postoperative complications (44% vs 28%). Interestingly, they also noted that OSA patients who were not compliant with their CPAP had the highest rate of postoperative complications. Kaw et al. also demonstrated that patients with OSA had higher incidence of encephalopathy, postoperative infections (mediastinitis), and increased ICU length of stay. Similarly, Memtsoudis et al. in their case-control study found that orthopedic and general surgical patients with sleep apnea were at a higher risk of having perioperative pulmonary complications. Hwang et al. demonstrated that the rate of postoperative complications was increased in proportion to episodes of over-
night desaturation during home nocturnal oximetry. In this study, 172 patients underwent home nocturnal oximetry during preoperative evaluation for elective surgery. The number of episodes per hour of oxygen desaturation (or oxygen desaturation index) ≥ 4% (known as the ODI 4%) was calculated for every patient from the home nocturnal oximetry. Patients with an ODI 4% ≥ 5/h had a significantly higher rate of postoperative complications than those with ODI 4% < 5/h (15.4% vs 2.7%). Interestingly, the rate of postoperative complications increased with increasing ODI severity. Patients with an ODI 4% of 5-15 had a 13.8% incidence of complications, compared to 17.5% of those with an ODI 4% > 15.

In a recent cohort study, 471 patients who underwent non-cardiac surgery within 3 years of polysomnography were evaluated for postoperative complications and hospital length of stay. It was found that patients with sleep apnea had a higher rate of postoperative complications and hypoxemia. We used the STOP-BANG Questionnaire preoperatively to identify patients at high risk for OSAS. We found that patients at high risk of OSAS had a higher rate of postoperative pulmonary and cardiac complications than patients at low risk (19.6% vs 13.3%). We also noted that patients at high risk of OSAS had significantly higher length of stay in the hospital compared to patients at low risk. Gali et al. used Flenmons criteria and SACOS (sleep apnea clinical score) to identify patients at high or low risk for obstructive sleep apnea. They also noted that patients with high SACOS and PACU (postanesthesia care unit) events had a higher rate of postoperative respiratory events. Similarly, Auckley et al. used the Berlin Questionnaire to identify the high-risk patients. They demonstrated that patients at high risk of sleep apnea had more postoperative complications (20% vs 4.5%); however, this difference was not statistically significant.

There are two studies that have been conducted in patients undergoing ambulatory surgery to assess the impact of obstructive sleep apnea. These studies found that the presence of OSA did not increase the rate of unplanned hospital admissions in patients who underwent outpatient surgical procedures. Stierer et al. used a prediction model in a cohort of ambulatory surgical population to assess the probability of sleep apnea. They demonstrated that patients with ≥ 70% propensity for OSA had increased rate of difficult intubation, increased oxygen requirement, and intraoperative tachycardia.

**How to Identify Patients with Sleep Apnea**

Nocturnal polysomnography (NPSG) is considered to be the gold standard to identify patients with obstructive sleep apnea. However, in the perioperative setting, it is difficult to implement due to a variety of factors, including its prolongation of the process of surgery and contribution to the overall cost. In many hospital settings, it may also not be readily available. There are other methods that have been shown to identify patients who are at risk for obstructive sleep apnea including questionnaires, nocturnal pulse oximetry, and home sleep testing.

**Questionnaires**

There are many questionnaires that are available to identify surgical patients who are at high risk of having obstructive sleep apnea. Three of these questionnaires have been validated in the surgical population: the Berlin Questionnaire, ASA checklist, and the STOP-BANG questionnaire. The Berlin questionnaire is the most widely used questionnaire to identify patients at high risk for OSA. It contains 11 questions that are organized in 3 symptom categories and has been validated in the primary care patients. It has a sensitivity of 86% and positive predictive value of 89% for identifying patients with respiratory disturbance index (RDI) > 5/h in the primary care clinic. Recently, Chung et al. validated the Berlin questionnaire in surgical population and found that it had a sensitivity of 74.3% to 79.5% and a negative predictive value of 76% to 89.3% in identifying patients with moderate-to-severe OSA. However, this questionnaire has complex scoring system and is time consuming.

The American Society of Anesthesiologists (ASA) checklist also appears to be very useful and promising and has been proposed by ASA Task Force to identify patients with OSA. It contains 12 items for adults and 14 items for children. The ASA checklist has been shown to have a sensitivity of 78.6% to 87.2% and a negative predictive value of 72.7% to 90.9% in identifying surgical patients with moderate-to-severe OSA.

Recently, the STOP-BANG (Snoring, Tiredness during daytime, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, Gender) questionnaire was validated as a screening modality for OSA in the preoperative setting. It is a concise, self-administered, and easy-to-use questionnaire that consists of 8 yes/no questions. Patients are considered to be at high risk of OSA if they answer yes to ≥ 3 items. The sensitivity of the STOP-BANG questionnaire at an AHI > 5, > 15, and > 30 cutoff values was 83.6%, 92.9%, and 100%, respectively; corresponding negative predictive values (NPV) were 60.8%, 90.2%, and 100%. This questionnaire has a moderately high level of sensitivity, specificity, and NPV to detect patients with moderate (AHI > 15) to severe (AHI > 30) sleep apnea in the surgical population. Therefore, if the patient is ranked as a low risk for OSA by the STOP-BANG scoring model, practitioners can exclude the possibility that the patient would have moderate-to-severe sleep apnea with a good degree of accuracy.

Abrishami et al. conducted a systematic review to identify and evaluate the different screening questionnaires for sleep apnea. They noted that the Berlin and STOP-BANG questionnaires had high sensitivities and specificities in predicting moderate or severe sleep apnea. However, they found that the STOP and STOP-BANG questionnaires had the highest methodological validity, and these questionnaires are very easy to use.

**Nocturnal Pulse Oximetry**

Nocturnal pulse oximetry has also been used for the screening of OSA. Malbois et al. compared the sensitivity of nocturnal oximetry to ambulatory monitoring in order to identify patients with sleep apnea prior to undergoing bariatric surgery. They demonstrated that nocturnal oximetry with a 3% desaturation index as a screening tool for OSA could rule out significant OSA (AHI > 10) and also detect patients with severe OSA. This cheap and widely available technique could accelerate preoperative work-up of these patients.
Patients at increased perioperative risk from OSA should be very closely monitored in the post anesthesia care unit (PACU) for hypoxemia or other complications. They should have continuous monitoring of oxygenation with the help of pulse oximetry. Whenever possible, these patients should be placed in the non-supine position after the surgery to decrease the severity of apnea. These patients are very susceptible to opioids and benzodiazepines and one should minimize the use of these medicines in the perioperative period. Consider using NSAIDs, acetaminophen, tramadol, and regional analgesia for pain control. Dexmedetomidine can be very useful for sedation because of its opioid sparing effect and the lack of respiratory depression. Patients with the known diagnosis of sleep apnea should use their CPAP after surgery. There is no randomized controlled trial that has demonstrated that CPAP is beneficial in the postoperative setting. However, one may consider using auto-CPAP in high-risk patients after surgery, although it might be difficult for the CPAP-naïve patient to get used to it in the perioperative period. Once again, the use of auto-CPAP has not been formally studied in this population, and there may be a need to conduct a randomized controlled trial to assess the efficacy of auto-CPAP. These patients should also get formal sleep evaluation after discharge from the hospital.

Evidence for Perioperative use of CPAP

CPAP acts as a pneumatic splint and helps in opening the collapsed upper airway at night. The application of CPAP also improves functional residual capacity (FRC) and oxygenation with reduction in work of breathing. CPAP has been shown to improve excessive daytime sleepiness in patients with OSAS. There is some evidence that the perioperative use of CPAP may help in reducing postoperative complications. In a case control study, Gupta et al. noted that OSA patients who were compliant with their CPAP had reduced rate of complications and also decreased hospital length of stay. Similarly, Liao et al. noted that OSA patients who were not compliant with their CPAP were at the greatest risk of having postoperative complications.
Squadron et al. demonstrated that the use of CPAP leads to reduction in the incidence of endotracheal intubation and other severe complications in patients who develop hypoxemia after elective major abdominal surgery. In a randomized controlled trial, Kinger-Milles et al. found that the prophylactic use of nasal CPAP was associated with a reduction in pulmonary complications and hospital length of stay in patients undergoing thoracoabdominal aortic aneurysm repair. In another study, Zarbock et al. also noted significant reduction in the rate of pulmonary complications with the prophylactic use of nasal CPAP in patients undergoing elective cardiac surgery. A recent meta-analysis of nine randomized controlled trials in the abdominal surgical population reported reduction in the rate of atelectasis, postoperative pulmonary complications, and pneumonia with the perioperative use of CPAP.

Conclusions

Obstructive sleep apnea syndrome (OSAS) is a common type of sleep disordered breathing, with a high prevalence in the surgical population. The majority of patients with sleep apnea are undiagnosed and are therefore unaware of their OSAS at the time of the surgery. These patients are at increased risk for perioperative complications. Sedation, anesthesia, opioids, and REM sleep rebound have been shown to cause worsening of sleep apnea in the perioperative period that may lead to an increase in the rate of perioperative complications. It is important to identify these patients preoperatively so that appropriate actions can be taken during their perioperative care. Screening questionnaires such as the Berlin, STOP-BANG, or ASA checklist are easy to administer preoperatively and have been shown to identify high-risk patients. There should be a standard protocol for the perioperative management of high-risk patients in order to reduce the rate of complications. These high-risk patients should also have a formal sleep evaluation for the long-term management of their sleep apnea after the discharge from the hospital.

REFERENCES


120. Ferreyra GP, Baussano I, Squadrone V, et al. Continuous positive airway pressure for treatment of respiratory complications after abdominal surgery: a systematic review and meta-analysis. JAMA 2009;301:1707; Fax: (631) 444-7502; E-mail: Tajender.Vasu@sbumed.org

DISCLOSURE STATEMENT
This was not an industry supported study. The authors have indicated no financial conflicts of interest.