Title: Efficient treatment of Obstructive Sleep Apnea Syndrome.

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Summary

This OMF Knowledge Update is based on work previously published by the authors[a] in 2009, with new references and conclusions based on literature and events as of 2011. To give a brief outline, the following topics are discussed in detail:

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Obstructive Sleep Apnea is a serious chronic health issue for adults and children, primarily as a factor in Excessive Daytime Sleepiness. OSA has single-handedly raised the visibility and credibility of sleep medicine as an important sector of the health care industry. However, claims of the benefits of treatment, especially using Continuous

Positive Air Pressure, have exceeded scientific evidence. Most studies report an association but not a causality between OSA and other health conditions. Treatment to reduce EDS and perhaps hypertension is supported in the literature. Because most treatment modalities for OSA have a favorable risk-benefit ratio, a long list of medical conditions that may improve will likely be treated at the physician's discretion, much like using a drug off label. The next decade is expected to continue the trend for reducing the stringency of making the diagnosis of OSA while treating more weakly associated disorders. Consequently, the risk-benefit ratio will become less favorable, and the prudent health care provider will be best served by critically reviewing the literature.

Preface and Warning

One preface to this Knowledge Update is to distinguish between best practice based on the critically reviewed scientific literature, and practice based on the business of Medicine. The two can co-exist, and this OMSKU will not elaborate on the business aspects (but would be remiss it they were not acknowledged). For example, say a patient has obstructive sleep apnea syndrome, which is OSA by polysomnographic testing plus clinical excessive daytime sleepiness. You perform a nasal septal repair (with or without soft palate surgery). It may be routine to order another PSG six weeks later to see if the surgery was successful. Certainly the PSG will yield a number (the frequency of apneas or hypopneas per hour). But this is just a number. Patients with Apnea-Hypopnea Indexes of 60 may not be sleepy, those with 10 might be nearly comatose. The clinical care of the patient is to evaluate the purpose of the surgery - is the patient no longer sleepy in the daytime. The PSG can not assess this, only the patient and physician can. If EDS is resolved, the patient is now safe to drive and live with improved quality of life. Thus the PSG is completely irrelevant for making a clinical assessment (although financially it may be acceptable). There may be claims that treating the AHI is still important to prevent future events such as stroke, hypertension, myocardial infarction and a long list of associated illness. As of this writing, there is absolutely no evidence to support these claims. If it were sufficient to just make unsubstantiated claims, we as a profession would be either paralyzed to provide healthcare, or be required to order enough test and prescribe enough treatments to double the trillion dollars a year already spent on American healthcare.

Only a few decades ago, the entity known as obstructive sleep apnea was unknown and untreated. Now, there is a rush to put literally millions of Americans on continuous positive airway pressure devices. Community practice standards are changing yearly under pressure from strong forces based on economic incentives from industry, government, and physicians, independent of the actual medical evidence supporting treatment and efficacy. Medicare has lowered the diagnostic threshold for diagnosis and reimbursement; the International Classification of Sleep Disorders, Revision 2 (2005) has allowed OSA to be diagnosed exclusively by a laboratory test without the patient having clinical symptoms of excessive daytime sleepiness; and industry is poised to have the public buy computer-assisted continuous positive airway pressure machines without need of a physician prescription. Because of this paradigm shift away from

physician-directed diagnosis and treatment, this article will critically evaluate the present state of medical evidence regarding the clinical foundation for treatment of OSA.

We have included an Appendix in this educational paper which will help you understand a statistical parameter used commonly in epidemiologic studies, the odds ratio, and by analogy, similar variants such as risk ratio and hazard ratio. A second Appendix is included outlining the levels of scientific integrity and bias which are associated with a clinical study and its report. These levels are to provide the reader a gauge for the validity of the conclusions. Caveats are included in the Appendix.

Background

Patients seek medical attention for obstructive sleep apnea (OSA) by several routes:

1) chronic poor and nonrestorative sleep

2) snoring that disturbs the bed partner

3) fear of suffocation and death from apnea

4) media attention and publicity

5) routine screening by other health care providers who make a referral

Patients are generally referred to a sleep laboratory and/or a sleep physician before treatment. If the surgeon does not wish to be used exclusively for the technical implementation of management but rather wishes to be fully involved in the diagnostic as well as therapeutic management of sleep patients, then it is incumbent to understand the agendas and clinical foundation for treatment.

The cardinal symptom caused by sleep apnea is excessive daytime sleepiness (EDS). However, EDS is not specific to sleep apnea, and one third of persons with polysomnographic evidence of OSA do not have sleepiness. When EDS is caused by OSA (not merely associated with it), then it is called obstructive sleep apnea syndrome (OSAS). The gold standard is an overnight, technician-supervised polysomnogram (PSG) to quantify apneas and hypopneas (both obstructive and central) and compute the apnea-hypopnea index (AHI). Because the AHI is used to determine the presence of OSA, it has mistakenly been used as a surrogate for EDS and a measure of disease severity. Additionally, the AHI has unfortunately assumed the role of arbitrator for determining the specific treatment modality, for example, continuous positive airway pressure (CPAP) device versus oral appliance versus upper airway surgery.

To achieve the primary treatment goal, eliminating EDS, it must be confidently assessed before and after treatment. If the patient reports no further EDS after treatment, a follow-up PSG to document the AHI is medically unnecessary. Treatment goals should not be set to prevent or treat any cardiovascular disorders based solely on the presence of

OSA. Patients with OSAS should be treated primarily to reduce their EDS, with cardiovascular endpoints as secondary goals. Patients with "refractory" hypertension and OSA should have their sleep apnea treated while simultaneously monitoring the impact of treatment in reducing their blood pressure. This is certainly beyond the purview of an OMFS.

The field of sleep medicine has come a long way in a few short decades but suffers from a lack of critical science to back up ever-increasing claims of value to patient care. Consequently, the National Institutes of Health (NIH) nearly a decade ago funded the Apnea Positive Pressure Long-Term Efficacy Study (APPLES)[1] to scientifically evaluate the claims of CPAP's effectiveness in terms of neurocognitive function, mood, sleepiness, and quality of life (QoL).[2] Patient recruitment only recently started, and final published results are still years away. Preliminary data has just come out[2b] and was immediately critiqued[2c] as unlikely to show any benefits of CPAP on its intended endpoints of memory and cognitive functioning.

Meanwhile, physicians are hoping to use this treatment to cure almost anything: we received a sleep consult from the emergency department regarding a patient with bleeding hemorrhoids; one can only wonder where the CPAP mask was to be placed. Or consider the (negative) impact of a highly visited Web site, WebMD: "Surgery for obstructive sleep apnea (OSA) is usually not done unless other treatments have failed or you are unable or choose not to use other treatments."[3]

Definitions of OSA and OSAS

OSA is a diagnosis made by a test, usually a PSG, but also from simpler procedures, such as nocturnal oximetry. OSA subsumes both obstructive apneas (total absence of airflow independent of how low the oxygen saturation drops) and hypopneas (30% reduced airflow with at least an associated 4% oxygen desaturation, or 50% reduction of airflow with 3% desat) because both presumably have the same consequences on sleep and the associated medical pathophysiologies. In scoring these on the PSG, the respiratory event must last at least 10 seconds. The AHI is the averaged number of apneas and hypopneas per hour over the entire time asleep. A similar metric is the respiratory distress index (RDI), which measures AHI plus other (presumed) respiratory arousals.

OSA is extremely prevalent in the general population[4] (possibly as high as 30% using an AHI >5), but so is sleepiness, at 40%.[5] In the Sleep Heart Health Study (N = 6,440), one third of subjects with an AHI lower than 5 (no OSA) had EDS.[6] Yet only half of the subjects with an AHI greater than 30 (defined as severe OSA) had EDS.

Parenthetically, we should mention that the "severity" rating of OSA was arbitrarily defined by the Centers for Medicare and Medicaid Services (CMS) based on the AHI (5-14 with symptoms; >15 without need to document symptoms)[6b] without regard for the degree or time spent with oxygen desaturation, and without any scientific studies. It was for billing purposes only, and since CMS spends $800 Billion per year on healthcare,

their opinion is law. Subsequently other agencies and Sleep organizations adopted and expanded the definition to its present form (although again, no science for this): mild 5-14, moderate 15-30, severe > 30.

Note that for billing purposes, if the AHI is severe enough, no clinical symptoms are required. The original 2001 International Classification of Sleep Disorders made the first requirement of OSAS (OSA Syndrome) to be clinical[6d]

> *A. The patient has a complaint of excessive sleepiness or insomnia. Occasionally, the patient may be unaware of clinical features that are observed by others.*
> *B. Frequent episodes of obstructed breathing occur during sleep.*

However, the 2005 second edition[6e] dropped clinical symptoms to define OSAS, and only required a positive PSG or other laboratory test.

And while on the topic of how reimbursement drives policy and ignores science, of note is the second most important player in the healthcare field, UnitedHealthCare. They are the largest private company in healthcare in the U.S., with $95 Billion in revenue for 2010. Similar to CMS, their guidelines set medical standards, and their Dec 23, 2010 policy[6c] states the following surgical procedures are proven for treating polysomnography (PSG)-confirmed obstructive sleep apnea:
≅ Uvulopalatopharyngoplasty (UPPP)
≅ Maxillomandibular advancement surgery (MMA)
≅ Mandibular osteotomy and genioglossal advancement with hyoid myotomy and suspension (GAHM)
≅ Radiofrequency tissue volume reduction of the soft palate and/or tongue base is proven for treating mild to moderate polysomnography (PSG)-confirmed obstructive sleep apnea.
The following surgical procedures are unproven for treating obstructive sleep apnea:
≅ Laser midline glossectomy
≅ Uvulopalatoplasty (UPP)

Back to medical literature.

Pavlova et al[7] measured the RDI in 163 healthy adults (aged 18-81 years) who were without symptoms or signs of OSAS. The RDI in these nonsleepy subjects increased with age, reaching as high as 70 per hour. Long-term studies are required to document whether pathophysiologic consequences will develop over time in these individuals or whether this increase with age reflects a normal aging process.

Thus, as it pertains to sleep apnea, EDS has highly unsatisfactory false-positive and false-negative rates. Treatment is directed to patients with OSAS because these are the persons who usually present for medical care. However, increasing numbers of patients are now being referred who do not have OSAS, or even OSA, with the hope of treating an associated medical condition with CPAP.

<u>Pediatrics</u>

Pediatricians often take a different view on a disorder which is otherwise shared in the adult population. Sometimes raising the bar very high, as when they define OSA as requiring greater than only one apnea per hour (since children do not "naturally" hold their breath during sleep like adults who do it up to 5/hr). Their perspective on PSG[7a] should be extended to adults as well:

> *Pediatric polysomnography shows validity, reliability, and clinical utility that is commensurate with most other routinely employed diagnostic clinical tools or procedures. Findings indicate that the "gold standard" for diagnosis of sleep related breathing disorders in children is not polysomnography alone, but rather the skillful integration of clinical and polygraphic findings by a knowledgeable sleep specialist. Future developments will provide more sophisticated methods for data collection and analysis, but integration of polysomnographic findings with the clinical evaluation will represent the fundamental diagnostic challenge for the sleep specialist.*

Treatment of OSA

What Does the Patient Want?

Often the patient wants a solution to poor and nonrestorative sleep resulting in EDS. Conversely, it may be a desire to appease a spouse so that the bed partner can obtain a good night's sleep without the patient's snoring, kicking, and frequent awakenings. Snoring without EDS is a common issue. Children are usually seen because the parents or the school is concerned about QoL or scholastic issues. Increasingly, patients are self-referring themselves for fear that they will die in their sleep from apnea. Assuming sedative/narcotic issues are addressed, the hypercarbia induced during apnea will ultimately force a breath. These patients have been holding their breath in sleep for years without dying; however, the patient could die (or kill someone else) if he or she falls asleep driving. State laws address this issue.

What Does the Provider Who Requests the Consultation Want?

The provider implicitly wants to diagnose and improve the health of the patient. However, specialty-specific concerns are often superimposed. Examples include a cardiologist hoping to reduce recurrent bouts of congestive heart failure or an ophthalmologist hoping to prevent worsening ischemic optic neuritis. Unfortunately, these specialty-specific concerns are not yet scientifically supported by a critical review of the literature.

What Does the Patient Need?

The patient needs an accurate diagnosis and treatment directed to improve health and QoL. This may be in concert with what the patient and/or requesting provider wants.

The treating health care provider's first charge is toward the patient's interest, based on best medicine.

Do No Harm

Treatment decisions always require a balance of risks and benefits. This analysis should be based on actual data that cover both sides of the equation. However, pertinent information may be lacking, obscure, or controversial, leaving the practitioner unable to move beyond past dogma. For example, CPAP treatment originally used only unheated, unhumidified air. Some patients with special upper airway conditions or living in extremely temperate zones and dry climates seemed to benefit from heat and/or humidity. As companies started marketing heated humidity as a standard option, prescribers offered it to patients without considering the extra equipment maintenance involved. However, heated humidity does not improve the intrinsic effectiveness of CPAP[8] and may[9] or may not[8] improve patient compliance, but it has been reported to increase the incidence of respiratory infections by 3- to 10-fold.[10] In response, Ortolano et al[11] confirm that humidifiers aerosolize bacteria, and that the use of a hydrophobic filter (which is not standard equipment) may attenuate the passage of microbes from contaminated humidifier water.

It should be evident to the provider that all medical and surgical treatments pose some risk, and the acute and chronic morbidity and mortality risks need expert review. For example, CPAP can worsen some patients' conditions by converting OSA to central sleep apnea,[12] which generally does not respond to CPAP. Weight gain, congestive heart failure, and narcotics can adversely affect CPAP, and even tracheostomy can induce central sleep apnea.[13] There is extensive literature on the complications of each treatment modality. What has become even more important is whether there are complications from not treating.[14-17] We will address this later.

Treatment-Specific Modalities

Improvement or complete resolution of OSA can be accomplished through various medical and surgical modalities (e.g., weight reduction, oral appliance, upper airway surgery [phase I], maxillomandibular advancement [phase II], PAP devices, tracheostomy). Restoring QoL and reversing or preventing associated adverse health consequences should theoretically be modality independent. However, the present literature is heavily biased toward studies using CPAP, and positive results are attributed to CPAP alone. It may be that in addition to the elimination of obstructive apneas, the effects of positive airway pressure on lung physiology, intrathoracic pressure, and sympathetic tone provide an additional and key component to the efficacy of treating OSA, but this is speculative. Of all of the treatment modalities, only weight reduction would seem to provide a wider range of health benefits (i.e., treating OSA and obesity-related morbidities), and the other modalities should be viewed as providing treatment for OSA only.

Best Medicine

Community standard practice is often defined as what a prudent health care provider would do. Expert care is based on a critical review of published evidence. The difficulty is in the definition of "critical." Although reviews and recommendations from evidence-based medicine have become commonplace, the general medical community has been slow to accept the results.[18] A similar disconnection affects its counterpart, cost-effective medicine. When the literature reports a comparison between two treatments, one treatment is generally more effective, better tolerated, or better preferred by the patient. This is usually supported by a statistically significant probability (P) value. Often the treatments are separated by only a few percentage points.

Consider a study of QoL and blood pressure control in which it was found that captopril was better than propranolol.[19] It would be incorrect for clinicians to assume that the "winner" is the only treatment that should be offered to their patients.

Best care dictates that the physician has knowledge of all treatment modalities and will tailor the best treatment for the individual patient. Although there are multiple, effective modalities for treating sleep apnea, the "clear" winner according to the literature and in practice is nasally administered CPAP (despite its high 20%-30% failure rate).[20-22] Some studies report that oral appliances are preferred over CPAP,[23] whereas other studies reverse the percentages.[24] Battle lines are often drawn between medical and surgical specialties. If treatment modalities are chosen as winners, then patients will be the losers.

Health care providers know the difference between statistical significance and clinical significance. We are aware that we must go beyond both measures in making a good case for our analysis and conclusions in this article. Our caveat to the reader is the magnitude of the evidence (or lack thereof) in support of a particular recommendation. In 1941 (before the advent of randomized clinical trials), it took only 6 patients to prove the worth of penicillin.[25] In addition, it was not difficult to conclude the usefulness of insulin for diabetic patients. However, in our present era of randomized clinical trials, tens and hundreds of millions of dollars can be spent on a treatment without clear evidence of which treatment, if any, is effective. We bias our review by only using evidence of sufficient magnitude that should convince most providers.

General Treatment Goals

The goals of treating OSA(S) must be realistic in terms of patient compliance and medical outcome. Both are under appreciated. For example, is it better to treat a patient with an AHI of 50 per hour with nasal CPAP that reduced the AHI to 0 but who, after 3 months, uses it 4 hours per night, 3 nights per week, or to prescribe an oral appliance that reduced the AHI to 10 per hour that is used 7 hours per night, 6 nights per week? Clinical outcome data do not exist to help with this type of choice.

Treatment of OSAS is rarely successful with a 1-time intervention because, unfortunately, there is a high failure rate for all modalities when assessed both acutely

and long term. The health care provider should therefore be prepared to offer the patient alternate modalities. Equally important is to plan a staged approach to maximize success.

It should seem obvious (at least to this readership) that positive pressure devices like CPAP, BiPAP and VPAP require significant nasal patency. With a real-life failure rate of 50%, PAP can be a very uncomfortable experience for patients, and trying to get around the problem by using a chin strap or full face mask almost always fail: the jaw muscles are very strong and overcome the strap; the large interface of the full face mask which covers nose and mouth tends to leak air into the patients eyes, ears (and bed partner).

It has been our practice that patients are counseled against using PAP if they can not breath "well" through their nose as evidenced by history of mouth breathing or allergies, and by exam (Cottle maneuver, visualization of septal and other defects). Additionally, there are other patients who had gotten CPAP titrations elsewhere (or refused any other treatment modality and insisted to try CPAP) with resulting pressures greater than 18 cwp. We consider them at high risk to fail PAP therapy as well. A diagnostic PSG to confirm OSA is a prerequisite, and then patients are sent to OMFS or ENT for some version of NSR and any other surgery required to make PAP successful,[43a] including the external nose, internal nasal passages, or oropharyngeal areas. Sometimes this surgery by itself resolves the EDS (and OSAS).[44] However, if not, we proceed to a CPAP titration.

Nakata et al.[25a] have reported similar findings, and have nicely quantitated the result of surgery for 12 patients pre and post operatively. Rhinomanometry showed a reduction of nasal resistance from 0.57 ∀ 0.31 to 0.16 ∀ 0.03 Pa/cm3/sec, making all of them tolerant of CPAP. Rhinomanometry in 41 control (non-operated) OSA subjects was 0.24 ∀ 0.11 Pa/cm3/sec. The Epworth Sleepiness Scale in the OSA patients decreased from 12 to 3, whereas their baseline AHI did not change (again showing the disconnect between the clinical symptoms and the laboratory value). In five patients who had CPAP titration pre and post operative, pressure required to resolve the apneas decreased from 17 to 12 cwp, and their average AHI decreased from 56/h to 6/h.

OSAS is a chronic condition that in most patients does not spontaneously remit and will require years, if not a lifetime, of treatment. It may take considerable time to reach the most efficacious and enduring treatment modality. Although patients and referring providers typically press for treatment as soon as possible, treatment is not a medical emergency.

Driving

EDS can be a QoL issue, an economic issue, and a legal issue. If patients are too sleepy to drive, the law prohibits them from driving. Documenting this in the medical record is advisable. The most obvious and most serious issue for sleepy persons is traffic accidents. It is necessarily intuitive that anyone with OSAS is at increased risk of traffic accidents. This association has been reported in the literature and further

suggests that treatment with nasal CPAP reduces this risk.[26] It is likely that even in the absence of convincing evidence, health care providers would feel compelled to treat these persons, especially in this era of defensive medicine. However evidence to link OSAS and road traffic accidents is generally inconclusive,[27] and the best study to date is only marginally better.[28] Although many studies summarily report the association as if it were a fact, it has been exceedingly difficult to factor out confounding variables such as age, alcohol use, obesity, annual mileage, shift work, sleep debt, and social activities in these epidemiologic studies, and no randomized clinical trials are likely to be performed.

There is considerable pressure on the commercial driver and his or her healthcare provider to document efficacy for the treatment of EDS from OSAS. A person's commercial drivers license (CDL) depends on records showing time of use of their CPAP (which thus precludes other treatment modalities - no clock built into an oral appliance or surgical procedure). There is also great weight given to objective testing of wakefulness, and the Maintenance of Wakefulness Test (MWT) has become the industry standard. This test is uniformly acknowledged by sleep experts as inadequate for the task (USDOT[28c], FAA[28d] and the military also agree it is inadequate but use it anyway; see especially our annotated reference 28d).

During the MWT, the subject is instructed to stay awake in soporific circumstances during four 20- or 40-minute trials, each two hours apart. An Israeli group concluded that the 20 minute trials were inadequate and consequently studied whether 40 minute trials were better.[28a] Their patients (n=164) were all referred by the Medical Institute for Driving Safety. Eighty percent had OSA, with 20% being "severe" (RDI>40). Only 25% fell asleep at least once during the test. They concluded that,

> *for the evaluation of drivers with suspected EDS, the MWT40 is a more appropriate test than the MWT20. The test, however, is still affected by motivation and, as such, is not completely reliable. Thus, we believe that high motivation of the subjects may still contribute significantly to their ability to maintain wakefulness. Our subjects' results indicate that they are even more alert than healthy subjects without sleep disorders but also without high motivation to stay awake.*

Within the Department of Veterans Affairs, limited resources are balanced between patient care and other needs of the patients. Because of our patient population, possibly 30% of our enrolled veterans have a sleep disorder, many with OSAS. They routinely request help after having their commercial driver medical examine. One VA published on their obligations and effectiveness for this issue.[28b]

> *We searched the literature for an evidence-based justification for handling this referral, and we concluded that there is neither federal policy nor current evidence to suggest that any current diagnostic test, including PSG/MSLT and/or MWT, is capable of predicting which individual drivers*

are at risk for fall-asleep crashes. The best indicator of risk is self-reported sleepiness, regardless of cause. Thus, we concluded that an administrative request for a PSG/MSLT is not a rational use of VA resources.

Does OSA Cause EDS?

The answer is not an unequivocal yes. As mentioned earlier, patients diagnosed with OSA can be very sleepy with a low AHI or have no EDS by any measure with a high AHI. Patients with OSA frequently have comorbid sleep disorders such that even when the AHI is reduced to 0, their periodic limb movement disorder, restless leg syndrome, shift work, post-traumatic stress disorder, or obesity-hypoventilation syndrome will still leave them sleepy. This can call into question whether the comorbid condition alone produced the EDS. For example, because obese persons are frequently diagnosed with OSA, all obese persons are mistakenly thought to have OSA. In fact, only 55% to 75% of obese patients were found to have OSA.[29,30] Conversely, 35% of morbidly obese patients who had no polysomnographic evidence of OSA had significant EDS.[31]

There is an obvious selection bias in the literature and in our clinical practice for identifying and treating patients with subjective sleepiness. This does not have to imply that OSA never causes EDS, only that EDS is not an invariable consequence of OSA. In a very comprehensive and critical review of the literature, Wright et al[27] concluded that "evidence from epidemiological studies suggests that possibly the only significant adverse effect of obstructive sleep apnoea is daytime tiredness and a reduction in attention." Epidemiologic studies can point out only an association, not a causality. The apparent reversal of EDS with treatment in many patients, though of clinical utility, also is not hard scientific evidence that OSA is necessary and sufficient to cause EDS. Even sham nasal CPAP (placebo) has been shown to reduce EDS,[32] adding support to the contention that a response to CPAP should not be used to confirm a diagnosis of OSAS.

How to measure EDS

To the nonsleep expert, sleepiness is sleepiness, something we all know from personal experience and can see in others. However, for objective science, this quality must be measurable and quantified. Alas, there is no agreement on how to do this. A measure that seems to work well with one disorder (e.g., the Multiple Sleep Latency Test [MSLT] for narcolepsy) fails when applied to other disorders such as OSA. What is worse is that different measures neither correlate with one another nor correlate with other clinical measures.[33-37] Interviewing the patient and spouse, parent, or significant other provides as good a measure as a written evaluation with the Epworth Sleepiness Scale (ESS), polysomnographic measures such as the MSLT or Multiple Wakefulness Test (MWT), a simple index such as the AHI, or a complex test such as the Psychomotor Vigilance Test.

Of particular relevance is whether the AHI provides a measure of sleepiness in patients with OSAS and whether retesting (via a PSG) after treatment of OSAS provides any

useful information. OSA (but not OSAS) is given a grade of mild, moderate, or severe based solely on the AHI. Polysomnographic factors such as the duration of the apneas or extent of the hypoxemia provide additional objective measures of OSA but have not been incorporated into a valid scale. This is quite surprising given how much emphasis is given to hypoxia as a contributor to cardiovascular disease and other organ damage (e.g. optic neuritis).

The AHI is a poor measure of EDS[38] and should not be used in isolation for making a treatment decision. In fact, we have seen doctors and companies prescribe CPAP even when the PSG failed to document OSA; on the basis that CPAP may still be beneficial.

In addition, clinical electrophysiologic variables such as the AHI are not good predictors of improvement with therapy.[39] The literature is unduly biased toward using any modality other than CPAP for high AHIs because it makes the implicit (but unjustified) assumption that AHI is the only factor to treat in OSA, and CPAP can reduce the AHI to 0 (also unjustified). However, treatments for OSA can reduce the AHI but not EDS, and vice versa. The present emphasis on AHI has negatively influenced recommendations from randomized clinical trials. An example is a study that showed equal efficacy between CPAP and an oral appliance for resolving EDS but recommended CPAP.[40]

Does treating OSAS reduce EDS?

Most review articles conclude that treatment of OSAS reduces EDS. However, qualifications on who the patients are, how EDS is defined, which treatment modality is used, and how long after treatment patients are assessed are all important for a proper interpretation. By the original definition (and the one the authors of this chapter endorse), patients with OSA are not sleepy; only those with OSAS are sleepy. Subjects enrolled in studies tend to have severe OSA and marked EDS. Generalization to patients with mild OSA or mild EDS may not be applicable. Methodological problems and statistical effects such as regression to the mean are frequent confounders.

Leaving aside all of the other variables, let us review which treatment modalities have an effect on EDS associated with OSAS. Babar and Quan[41] concluded that all treatment modalities "have disadvantages, and none, except for tracheotomy, are uniformly effective." The evidence for tracheostomy is akin to that for the initial use of penicillin: it has an immediate and dramatic effect.[42] We use tracheotomy as one of the many treatment options for our Veteran patients. Best practice is to have all medical/surgical options available for patient care.

The evidence of all randomized controlled studies shows that CPAP reduces EDS in patients with moderate to severe OSA up to 6 weeks (the usual time limit for the study), and patients with mild OSA do not receive this benefit.[33,40] It should be noted that population medicine does not mean all mild OSA patients do not receive benefit. Wright et al[27] concluded from a review of the literature that CPAP was more effective than placebo for improving EDS when either the ESS or the MWT was used as the measure of sleepiness but not the MSLT (which measures the tendency to fall asleep rather than

the ability to remain awake).[27] Although the statistical significance was good, the magnitude of the effect was modest. Jenkinson et al[32] performed a study with a true sham CPAP treatment and used the ESS, the MWT, and a QoL questionnaire to measure sleepiness. They found that CPAP reduced EDS compared with sham nasal CPAP, but there was a significant placebo effect.

There are many types of oral appliances, with mandibular advancement being the most common, followed by tongue repositioning. A review by Lim et al[24] concluded that an oral appliance improves subjective sleepiness compared with controls. These effects tended to last at least a year. A review by Ferguson[23] showed sufficient success to recommend oral devices as first-line treatment for mild and moderate OSA.

Combining all surgical treatments (excluding tracheostomy) as one type of treatment is unwarranted but frequently done, with an emphasis on the AHI rather than EDS. When viewed individually, every treatment has a positive effect on EDS, although small numbers, uncontrolled series, and biased patient selection will dilute the credibility of the results. Powell[43] recently re-reviewed the surgical literature and continues to find support for phase I and II surgeries in reducing or eliminating EDS. Cillo et al[44] found that a combined open rhinoplasty with spreader grafts and uvuloplasty significantly and for the long term reduced EDS in military veterans with all severity levels of OSAS.

Quality of Life

Like so many outcome measures, QoL seems straightforward until you try to measure it. Despite any P values for a particular treatment effect, if the patient (or significant other) does not perceive any physical or mental benefit, the treatment is not useful and does not provide any improvement in QoL. A reduction in EDS, more daytime energy, a feeling of well-being, fewer visits to the doctor for health issues, enhanced sexual performance, and many other variables can contribute to QoL. For example, in a study using a mandibular advancement splint for OSA, the AHI was reduced from 32 to 18, which was statistically significant at $P < 0.01$.[45] Although the patients still had OSA, the only noteworthy outcome was the number of separately sleeping couples who were re-united after therapy - a QoL issue. Some studies and reviews have concluded improved QoL after the treatment of OSAS,[46,47] whereas other have not.[33] The field of QoL research is particularly contentious because despite any negative published finding, most physicians will not accept the premise that treating disease and alleviating discomfort fail to improve the patient's QoL. [There are so many examples which could be given where successfully treating the disease does NOT improve QoL that we choose not to list them all, but you can contact the authors if desired].

Cognitive Function

Sleepy persons move and think more slowly. It therefore seems evident from our own personal experience with sleep deprivation that reinstituting a good night's sleep would immediately reverse this psychomotor retardation. However, in a study looking at cognitive impairment in patients with OSAS, 2 weeks of treatment with CPAP or

oxygen-supplementation was insufficient to show overall beneficial cognitive effects as compared with placebo-CPAP.[48]

In another report using either the Thornton Adjustable Positioner (Airway Management, Inc, Dallas, TX) or the Herbst mandibular advancement device in patients with OSA who had baseline impaired alertness and memory, significant improvements in objective measures were observed after 1 month of treatment with either the mandibular advancement devices or CPAP therapy; however, OSA patients in both treatment groups remained impaired relative to healthy controls.[49]

And as mentioned earlier, the preliminary results of the APPLES study[2b,2c] did not show any benefits of CPAP on memory and cognitive functioning.

Cardiovascular Disease

This is an area which carries a big stick. We have heard many patients tell us that their other doctors lectured them to use CPAP or they would die, or have a heart attack or stroke. Whether this was just a motivational ploy, or they actually believed it (or both) is speculative, but believable from reading the medical literature. In truth, you can not die in your sleep "holding your breathe" as we discussed earlier, and there is no credible evidence untreated OSA(S) will cause heart attacks or stroke, and zero evidence use of CPAP (or other modalities) reduces or abrogates this potential risk.

An association between two prevalent disorders, OSA and cardiovascular disease (CVD), is not unexpected, especially when obesity is presently thought to be linked to both. Nevertheless, sleep apnea is assumed to produce adverse cardiovascular consequences resulting from the increased negative intrathoracic pressure, hypoxemia, and increased sympathetic nerve activity produced by the apneas and hypopneas.[50-54] Studies to untangle the many overlapping comorbidities found in the typical overweight male study populations are at a disadvantage unless there is a particularly large effect. There are few studies in children, women, and thin men.

Critical reviews between 1997 and 2001 found evidence for only weak associations and no causality between OSA and hypertension, CVD, stroke, pulmonary hypertension, and right-sided heart failure.[27,55] Newer reviews have incorporated a few randomized trials,[56] which improved on making a case between OSA and CVD.

<u>Hypertension</u>

In 1997 the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure by the National Heart, Lung, and Blood Institute, NIH, listed the top 3 causes of refractory hypertension as smoking, obesity, and sleep apnea.[57] In the Seventh Report (2003), sleep apnea had moved up to the number one cause of identifiable (not just refractory) hypertension.[58] The Eighth Report is due out in 2012.[58a] Although the primary treatment modality is medication, weight loss for obese patients was also recommended. Nothing was specifically

proposed as a treatment for the patient with sleep apnea.

These strong conclusions by the NIH about hypertension and OSA were based on a few reports. The Wisconsin Sleep Cohort (N = 704) was a prospective, population-based study that found an association between increasing severity of OSA (as measured only by the AHI) and hypertension.[54]

In the Sleep Heart Health Study (a cohort of 6,424 subjects assembled from 23,000 participants in several population-based studies of CVD in diverse US populations), isolated systolic hypertension was not associated with OSA, but systolic/diastolic hypertension was associated with OSA for subjects aged under 60 years.[59] A reanalysis of 6,046 subjects in this study who identified the presence or absence of subjective sleepiness found that sleepy subjects with severe OSA (i.e., OSAS) had an odds ratio for hypertension of 2.8 compared with sleepy subjects without OSA.[60] It should be noted that only 787 of 6,046 reported that they were sleepy, and both sleepy and nonsleepy groups had equal numbers of subjects with PSG-confirmed OSA.

Evidence to move from association to causality can be supported but not proven by prevention or reversal of hypertension with an effective treatment for OSA. CPAP has been the treatment of choice to investigate this possibility. Many studies have reported positive benefits from chronic CPAP use associated with improvement in hypertension, echocardiographic parameters, and congestive heart failure.[61-66]

Conversely, others believe that CPAP is an unqualified success in treating EDS yet are unconvinced of its efficacy in correcting cardiovascular consequences.[47]

A typical study shows a large effect (decrease in systolic blood pressure by 20 mm Hg) sustained for 6 months in 12 patients.[67] All studies suffer from various methodological problems, which reduce the scientific validity that OSA is the sole cause and CPAP the sole reason for the hypertension and its resolution. Although CPAP takes center stage, weight reduction as a method to treat OSAS is also reasonably effective in reducing hypertension.[58,68]

A very good (by literature standards) retrospective study[68a] was done at a Veterans Administration hospital using 42 subjects with OSAS and medically resistant hypertension, compared to 56 subjects with hypertension controlled on medication. The resistant group was taking an average of 3.4 medications, the controlled was on 1.5. Of note, they started with 764 patients, and most were excluded for either a change in hypertension medication, the presence of renal disease, non-compliance with CPAP, non-compliance with medication, or alcoholism. Almost all were obese males with severe OSA and comorbid diabetes, dyslipidemia, COPD, coronary artery disease. They were followed for a year on CPAP which was used an amazing six hours a day. The results showed a reduced systolic blood pressure of a mere 5 mm HG for the

medically resistant group versus no effect on the medically controlled group. Aside from any statistical significance, would a physician be able to stop medications and substitute CPAP based on this?

The article was accompanied by an editorial[68b] which identified many flaws (except an important one - I'll get to that below), yet concludes:

> *However, despite the limitations of this study, it demonstrates that sleep apnea confers additive cardiovascular burden and CPAP can ameliorate this burden.*

This statement is unfounded and unsupported by the facts in the article:

> *The box and whisker plots in Figure 2 illustrate that, in subjects with resistant hypertension, median mean arterial pressure and systolic BP moved toward lower values at 180 days, with a significant trend continuing at 12 months, whereas patients with controlled hypertension (n = 56) demonstrated no significant change over the same time period (Figure 3). No significant difference in diastolic measurements was seen in either group of patients.... the use of CPAP therapy was accompanied by a reduction in daytime BP in patients with resistant hypertension; this reduction was first apparent at 6 months after treatment initiation and was sustained after 12 months of therapy.*

The change from baseline at 90 days and 180 days was NOT statistically significant, so there could be no trend apparent at 180 days.

Its puzzling that CPAP reduced BP in medically intractable patients but not well treated HBP patients. Did CPAP do this? The authors of the study actually treat patients (although in this study they did not, the patient's regular doctors treated them as they saw fit; it was retrospective). So if your patient had controlled BP on 1 or 2 medicines, you would unlikely be trying to adjust or reduce their medication (and they would not be trying to reduce or stop their antihypertensive medications just because they were on CPAP, no one does that). But for refractory patients, the doctors should be changing their treatment (BP meds, non-BP meds, compliance, weight, etc.) and independent of CPAP, might make improvements. The article acknowledges this, showing stable patients stayed on their same medications and the refractory patients had many medication changes. We can assume that the doctors would have been trying to get the BPs down even before CPAP, but we have no data in this paper on the duration of preexisting hypertension. Patients were excluded if their doctor was changing their HBP medications within 3 months of starting CPAP, an important bias. In general, the data shows a regression to the mean (a statistical phenomenon that can make natural variation in repeated data look like real change).[68c]

Conclusions concerning OSA and HTN

Is the National Heart, Lung, and Blood Institute, NIH correct in their assessment that OSA causes hypertension, or is this an example of hope beyond reason? Of all the claims for OSA causing a medical effect, excessive daytime sleepiness is the strongest, and hypertension may be the weak sister. Scientific evidence that CPAP can reverse this effect is weaker still, and presently of insufficient magnitude to be of clinical value.

Heart Disease

A Swedish group followed 407 patients under age 70 y.o. with established coronary artery disease and compared the long-term outcome over 5 years between the group who had OSA and the group without OSA.[71] Sleep apnea was determined using overnight oximetry and respiratory effort (no EEG or sleep staging). The disordered breathing group as defined by having nocturnal oxygen desaturations of 4% or greater at least 5/hr (as a surrogate for OSA) had an increase in the primary endpoints of death, cerebrovascular events, and myocardial infarction. The risk ratio was 1.7 (i.e. a 70% relative increase, a 10.7% absolute increase, p=0.008). A hazard ratio of 2.62 was found for stroke. However, in all analyses, diabetes and left ventricular dysfunction accounted for the majority of the effect.

A Canadian group addressed the key issue of whether treating OSA with CPAP reversed the associated increased morbidity or mortality rates of cardiovascular disease (defined as ischemic heart disease; hypertension; congestive heart failure; arrhythmia), cerebrovascular disease, or diabetes mellitus, and found that the answer was no.[72] The encouraging results were that patients on CPAP with OSA but without cardiovascular disease reduced their consumption of health care resources. However, patients with OSA plus cardiovascular disease continued to need increasing amounts of health care. Treating OSA with CPAP did not help their ischemic heart disease.

Another important cohort observational study[73] enrolled
- 264 healthy men
- 377 simple snorers
- 403 patients with untreated mild to moderate OSA
- 235 patients with untreated severe OSA
- 372 patients with OSA who were treated with CPAP.

Patients with untreated severe disease had a higher incidence of
- fatal (death from myocardial infarction or stroke), and
- nonfatal (nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) cardiovascular events

than did all other groups. Multivariate analysis, adjusted for potential confounders, showed that untreated severe OSA significantly increased the risk of fatal (odds ratio, 2.9) and nonfatal (odds ratio, 3.2) cardiovascular events compared with healthy participants. Patients with simple snoring, those with untreated mild to moderate OSA, and those using CPAP had adjusted odds ratios for fatal cardiovascular events and for nonfatal cardiovascular events that did not differ significantly from 1.0, suggesting that these groups have cardiovascular mortality and morbidity rates closely similar to those in healthy individuals.

Although it would be tempting to assume that CPAP treatment reversed the risk in the patients presumably using CPAP, the uncontrolled, unmonitored and nonrandomized nature of the study precludes this conclusion. Conversely, it cannot be assumed that patients with mild OSA will not have cardiovascular events.

Further studies are warranted if the study design would be rigorous enough to allow useful and scientifically valid conclusions for healthcare.

Stroke

Stroke and CVD are frequently combined in studies looking at the effects of disease on death and morbidity. A Japanese study retrospectively analyzed 192 patients for asymptomatic cerebrovascular disease as defined by silent lacunar stroke or periventricular white matter disease as identified by magnetic resonance imaging, who also had a PSG to determine the presence of OSA.[74]

Asymptomatic cerebrovascular disease was found in
21% without OSA
12% with mild OSA
49% with moderate OSA
54% with severe OSA.

Uncontrolled variables included age, gender, BMI, smoking, alcohol consumption, hypertension, hyperglycemia, hyperlipidemia, AHI, and oxygen desaturation index. Patients with severe OSA had statistically significantly higher BMI and hyperglycemia than the other groups. Patients with moderate and severe AHI had a higher prevalence of asymptomatic cerebrovascular disease by use of the nonparametric Jonckheere-Terpstra test. This places the data on a firm statistical foundation, but the study methods preclude inferring cause and effect, or even generalizing to patients outside this specific demographic.

Pulmonary Arterial Hypertension

Primary or idiopathic pulmonary arterial hypertension (PAH) is a diagnosis of exclusion

with a poor prognosis. Considerable effort is therefore made to identify a potential etiology that may be amenable to treatment. Anecdotal reports have claimed tracheostomy or CPAP as absolutely necessary for successful treatment of secondary PAH in patients who have OSA. Frequently cited articles mention finding OSA in patients with PAH but that obesity is more likely to be a contributing factor than sleep-disordered breathing.[75,76]

The review by Wright et al[27] found no convincing association between PAH and OSA. Evidence-based clinical practice guidelines proposed in 2004 by the American College of Chest Physicians conclude that the prevalence of OSA is low in PAH and that other risk factors, such as left-sided heart disease, parenchymal lung disease, nocturnal desaturation, and obesity, contribute more than OSA.[77] Furthermore, treatment of pre-existing OSA with CPAP may only lower pulmonary artery pressures when the degree of PAH is mild.

PAH and sleep-disordered breathing Guidelines[77]

> *1) In the evaluation of patients with PAH, an assessment of sleep-disordered breathing is recommended.*
> *Quality of evidence: low; net benefit: small/weak; strength of recommendation: C*
>
> *2) In the evaluation of a patient with PAH for sleep-disordered breathing, polysomnography is recommended if OSA is suspected as the etiology, if a screening test for OSA is positive, or if a high clinical suspicion for OSA is present.*
> *Quality of evidence: expert opinion; net benefit: intermediate; strength of recommendation: E/B*
>
> *3) In the management of patients with OSA, routine evaluation for the presence of PAH is not recommended.*
> *Quality of evidence: low; net benefit: none; strength of recommendation: I*
>
> *4) In patients with OSA and PAH, treatment of OSA with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize, particularly when PAH is more severe.*
> *Quality of evidence: low; net benefit: small/weak; strength of recommendation: C*

In the first randomized crossover, placebo-controlled (sham CPAP) trial of OSA in PAH, Arias et al[78] reported the results of 23 patients observed over a period of 3 months. Ten patients with OSA and pulmonary hypertension (defined as pulmonary artery systolic pressure >30 mm Hg by Doppler echocardiography) were more obese, had more ventilatory limitation (reduced forced vital capacity), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 OSA patients without pulmonary hypertension. CPAP reduced pulmonary artery systolic pressure in all patients with OSA, though more so in those with PAH at baseline (mean reduction, 8.5 mm Hg vs 2.6 mm Hg). The baseline differences in obesity and lung function between groups preclude the attribution of PAH to OSA alone. Reviewers in this field conclude that more research is needed to assess the durability of CPAP therapy on pulmonary arterial pressure and right heart function and how CPAP therapy fits into the treatment paradigm amid an

ever increasing arsenal of pharmacologic treatments for PAH.[56]

In a study done in 2009, thirteen healthy patients with severe OSA (AHI 30-102/h) and without any history of tobacco use, diabetes, atherosclerotic heart disease, or heart failure used CPAP for an average of 5 hr/night for 3 months to assess its effects on cardiac function.[78a] Findings consisted of only a mild improvement in right ventricular volumes: RV end-diastolic volume index decreased from 58 ∀ 11.4 mL/m^2 to 48 ∀ 14 mL/m^2 ($p < 0.05$), and RV end-systolic volume index decreased from 30 ∀ 8 mL/m^2 to 22 ∀ 6 mL/m^2 ($p < 0.05$). There was no effect on RV ejection fraction, LV volumes, LV ejection fraction, myocardial perfusion reserve index, or thickness of the interventricular septum, RV free wall, or LV free wall in this study population. The authors acknowledge that "factors such as regression to the mean could potentially explain our findings." It will require another study to see if these small effects can be replicated in patients with heart disease and PAH.

The American College of Chest Physicians published an updated evidenced-based guideline on PAH and found no additional evidence to change their 2004 recommendations on OSA and PAH.[77a]

Conclusions concerning OSA and Cardiovascular Disease

In the last decade, an increasing number of studies have looked at the association between OSA and CVD. The evidence seems most compelling that OSA contributes to persistent systolic/diastolic hypertension in some patients independent of other risk factors and that successful treatment of OSA (CPAP, tracheostomy, weight loss, and probably other modalities) will improve control of the hypertension. We agree with Malhotra and White[70] that the association between OSA and other cardiovascular disorders is still incomplete. Treatment goals should not be set to prevent or treat any of these cardiovascular disorders based solely on the presence of OSA. Patients with OSAS should be treated primarily to reduce their EDS, with cardiovascular endpoints as secondary goals. Patients with refractory hypertension and OSA should have their sleep apnea treated while simultaneously monitoring the impact of treatment in reducing their blood pressure.

Death

Introduction

Sleep apnea was first reported independently in 1965 by groups in France and Germany.[68d,68e] At the time, no one in the United States believed that it was a real disorder. This was another example of the now classic NIH (not invented here) syndrome. Additionally, it would be another 16 years before CPAP was introduced as a treatment. In 1972, Christian Guilleminault, a French neurologist and psychiatrist, joined the new Stanford Sleep Program, and sleep apnea came to America. That same year, Dr. Guilleminault consulted on an obese, sleepy, and severely hypertensive 10-year-old

boy.[68f] He made the diagnosis of OSAS and recommended a tracheostomy. The attending physicians refused to consider any treatment other than medication. With delay and considerable controversy, he eventually received his tracheostomy, with accompanying resolution of the hypertension and EDS.

Now it seems common practice to prescribe CPAP for anyone and everyone, sometimes for trivial reasons (e.g. snoring with a normal PSG). Yet the doctor often admonishes the patient that non-compliance could lead to death. Patients often are concerned that they could die in their sleep from apnea (yet if this were true, would they not be dead already)? And then doctors add on to this the risks of stroke and heart attacks.

It is a sad state, but most physicians, surgeons and dentists take the medical literature at face value. Wrongly believing that peer review has done an adequate job of vetting the articles in press. However, even when reviewers point out errors of omission or commission, editors will still allow the paper to be published without correction. We will take exception to that in this important section on death and OSA as we are not constrained in this educational format. The next few examples will illustrate just how complicated and difficulty it is to interpret the literature.

Death - Epidemiology

The recommendations for treatment of OSA have reached very serious levels. An Australian group[17] has concluded:

> *Moderate-to-severe sleep apnea is independently associated with a large increased risk of all-cause mortality in this community-based sample.*

A Wisconsin group[16] concludes:

> *Our findings of a significant, high mortality risk with untreated SDB [sleep-disordered breathing], independent of age, sex, and BMI [body mass index] underscore the need for heightened clinical recognition and treatment of SDB, indicated by frequent episodes of apnea and hypopnea, irrespective of symptoms of sleepiness.*

The editorial preceding these articles identified important limitations of the studies, including low statistical power and complicated analysis precluding any simple conclusion.[69]

Opinions, often in a pro-and-con format, with no unequivocal evidence-based studies to support either side continue to be published. Two opposing camps often end up making

the same conservative recommendations, as in another pair of articles addressing whether all sleep apnea patients should be treated.[14,15] Both acknowledge the increasing evidence that cardiovascular risk has been associated (but not causally linked) with OSA and therefore suggest that it might be prudent to treat patients with OSA of any degree even if they have no EDS. This recommendation is opposite the results of the Sleep Heart Health Study, which showed that only sleepy patients were at increased risk of hypertension (the presumed standard marker for later CVD).[60,70]

The most recent study[70a] was to take the Sleep Heart Health Study a step further by following 289 elderly subjects (defined as >65 y.o. at entry to the study) for on average 13.8 years. They were studied with PSG to determine SDB, and MSLT to determine EDS, one time at the beginning of the study. Treatment was presumably based on decisions by their personal physicians as this was a longitudinal, uncontrolled study and the paper does not mention if or how treatment was administered.

Also unknown is whether the subjects who had OSA at onset of the study still had OSA 1-13 yrs later? OSA can remit (people lose weight, come off offending medications, etc). And the obverse, did those subjects without OSA(S) develop it later? The same questions for EDS.

Their conclusions:

> *The presence of SDB is an important risk factor for mortality from excessive daytime sleepiness in older adults. In the presence of SDB at an AHI = 20 events/h, EDS was associated with an increased all-cause mortality risk in older adults, even when adjusting for other significant risk factors, such as prolonged sleep duration [hazard ratio of 2.3, 95% CI: 1.5-3.6]. In older patients who had SDB without EDS, or EDS without SDB, there was no increased all-cause mortality rate.*

Thus, people (in this study elderly) who had OSA, but did not have EDS (ergo did not have OSAS), did not have increased mortality and by extension, there is no medical need to treat the OSA. Yet all our conclusions are hampered by not knowing the treatment history of these subjects: were they treated for OSA, which modality (CPAP, oral appliance, surgery, weight loss), were they compliant? Maybe sleepy patients were more compliant, and yet the study says they had a higher risk of death, implying that treatment is ineffective to modify this endpoint! But we do not know, since the study design precludes making any conclusions about cause and effect: it is retrospective, observational, associative. It may boil down to only QoL issues, or finances as relevant factors for treatment. Considering the magnitude of the problem and the high failure rate of treatment, the resources to treat every nonsleepy OSA patient would need to be immense.

Death - Anesthesia and Preoperative screening

There can be several ways to spur research and advance medical care, and the malpractice lawsuit is one such way. Successful lawsuits[70b] have been based on autopsy-negative hospital deaths where:

1) a patient with OSA on CPAP who did not bring the CPAP device to the hospital and died 24 hours postoperatively
2) a patient diagnosed with OSA who was never treated and died 24 hours postoperatively
3) a patient with OSA and uvulopalatopharyngoplasty who died 24 hours postoperatively.

The basis for these lawsuits has been the assertion that physicians were negligent in the care of patients who either had a pre-existing diagnosis of OSAS or a presumed diagnosis of OSA. Some hospitals have charged their risk-management divisions to seek a solution, and this has caused the profession to re-evaluate perioperative procedures and treatment goals.

A critical review in 1997 of the sleep apnea literature concluded that age, hypertension, and BMI had the largest and most significant effects on excess deaths.[27] The natural history of patients with OSAS and the positive effects of aggressive treatment (e.g. tracheostomy) have been reported for the last 2 decades.[42,109] The AHI was not predictive of excess deaths due to heart or lung causes. However, patients given sedatives or analgesics, which can depress neuromuscular control of the airway, are at increased risk of aspiration or respiratory arrest. Although patients with OSA might seem to be at even greater risk than non-OSA patients, there is little evidence-based literature to support this contention.[110]

A review of ambulatory surgery found that although patients with OSA were at increased risk of difficult tracheal intubation, the likelihood of airway obstruction and apnea after ambulatory surgery was unknown.[111] In a retrospective, case-control study, adverse postoperative outcomes occurred at a higher rate in patients with OSAS undergoing hip or knee replacement.[112] However, another case-control study found no difference in adverse events between controls and OSA patients receiving non-otorhinolaryngologic outpatient surgical procedures.[113]

The increasing concern about managing patients who have OSA induced, unmasked, or exacerbated by perioperative procedures and treatments is leading to published guidelines in the absence of evidence-based data.[114,115] Anesthesiologists and surgeons who manage patients for OSAS or bariatric surgery are already sensitized to the risks. But what about patients undergoing any other type of surgery? Professional societies are recommending screening of all elective surgical candidates for OSA.

Unfortunately, stating such goals in the absence of a simple and effective method puts the health care provider at risk.

The categories for screening include
1) patients with diagnosed OSA receiving treatment
2) patients with diagnosed OSA who are not receiving treatment (pending, refused, noncompliant, failed)
3) patients with OSA who have not been diagnosed
4) patients who do not have OSA at home but in whom it develops under conditions of illness, medication, or anesthetic agents.

Screening might include a history of snoring, frequent arousals, and daytime somnolence; a questionnaire on sleepiness; and a physical examination (obesity, a large neck). Not only do these and other traditional measures have unacceptable false-positive and false-negative rates for adult men, they also misidentify the risk in women, children, and thin men. Requiring a PSG or even overnight pulse oximetry for every elective surgery is impractical. Even when a patient is identified with OSA, it is unknown what additional measures would prove successful in preventing excess morbidity and death. Even careful monitoring in the recovery room and on the hospital floor has proved ineffective.[116-118] Treatment goals for OSA directed at reducing surgical or hospital-based morbidity and mortality rates are presently beyond the scope of community standard medicine.

Snoring

Snoring is a reason to obtain a medical consultation because of its newly proposed association with sleep apnea, and as a QoL issue for the patient and bed partner. Snoring as a surrogate for sleep apnea is unfortunately used by the healthcare profession, despite the fact that one has nothing to do with the other, the false-negative and false-positive rates are unacceptably high. Nevertheless, the following dictum seems to prevail "Don't confuse me with the facts, my mind is made up".

Now the need to perform a PSG on every person who snores, and treat for sleep apnea if the test is positive (sometimes even if it is negative), has reached a higher profile as the morbidity and death associated with OSA have entered into the public (and medical) consciousness. This is being leveraged in questionable ways. The authors of an article entitled "Heavy snoring as a cause of carotid atherosclerosis"[79] admitted in a letter to the editor[80]

> *We indeed hoped that the slightly provocative nature of this title might generate interest in a relatively novel hypothesis . . .*

The group[81] that contested the original article, and strenuously objecting to the word

"cause" in the title and paper, pointed out that a cross-sectional design

> *makes it impossible to establish a cause-effect relationship between heavy snoring and atherosclerosis.*

Whereas additional methodological problems in this and other papers further degrade the validity of the association between snoring and stroke, the issue has been put on the table. *Caveat emptor*.

Biochemical Abnormalities

The potential impact on health from OSA has produced studies spanning all fields of medicine. The list, and evidence, is too long, too detailed and too convoluted to cover in this Knowledge Update. The claim, simply put, are that "hard" biochemical findings associated with OSA translate into reversible causes of morbidity and death. For example, OSA has been implicated in detrimental metabolic consequences associated with decreased insulin sensitivity,[82,83] activation of inflammatory processes,[84,85] increased oxidative stress,[86] increased matrix metalloproteinase levels,[87] and intravascular thrombosis.[88]

Rahangdale et al[88a] found a 20% difference in platelet activation in OSA, as measured by a decrease in platelet surface GPIb receptor fluorescence intensity. This decrease in fluorescence intensity indicates a decrease in the surface receptor density for GPIb. GPIb, a platelet surface receptor for vWF, plays a role in primary hemostasis and arterial thrombosis and is downregulated upon activation of platelets. Consequently it is used as a marker for risk of stroke and cardiovascular disease (despite there being umpteen associations without any proof of cause and effect for each step, much less a clear relationship between the base assumption and the final clinical outcome).

Specifically, they screened 341 subjects and entered 30 as not having OSA, and 47 with OSA (AHI>10). No difference in GPIb receptor fluorescence intensity was found between these two groups. They therefore excluded a few patients and re-sorted them into three groups: no OSA (n=27); OSA in which patients (n=29) spent less than 1 min/hr at 90% desaturation; OSA in which patients (n=13) spent greater than 1 min/hr at 90% desaturation. It was only this last group who showed a statistically significant decrease in platelet surface GPIb receptor fluorescence intensity.

The authors suggest "that when assessing the severity of OSA and the potential for cardiovascular complications developing, desaturation time must be considered in addition to the AHI." However, a commentary[88b] immediately following this article raised issues to discount their finding based on methodical issues; re-affirmed it was associational, not causal; questioned its clinical significance; and challenged whether the platelet changes would be reversible with any treatment modality for OSA.

Chronic CPAP use has been associated with improvement in inflammatory processes,[85,89] insulin sensitivity,[90,91] and thrombotic tendency.[92] For example, does long term CPAP use in subjects with diagnosed OSAS affect their immune status.[92a] Healthy, non-smoking OSAS patients (male, n=52) were divided into two groups: CPAP usage >4 hrs/night, and <4hrs/night. Note, this cutoff is quite arbitrary but frequently used by industry to set the bar low effort to be able to claim acceptable usage. It may have decided posthoc during data analysis to maximize the findings. Laboratory data was compared pre-CPAP and after 6 months. Biases introduced already include excluding 81 females from the initial 279 patients, and excluding 146 males who were unhealthy.

The "compliant" CPAP users showed a 8% decrease in the absolute count of total lymphocytes 2528 vs 2319 (P = 0.003) and of CD4+ cells 1263 vs 1130 (P = 0.001), but no change in CD8+, B, and N/K cells. There was also a 33% decrease in TNF-a levels 8.4 vs 5.7 (P = 0.001) and a 30% decrease in uric acid levels 8.8 vs 6.2 (P < 0.001). No alterations occurred in any of the tested parameters in the other CPAP group.

> *Conclusions: The selective reduction of soluble and cellular immune response factors only in those OSAS patients who exhibited good compliance to CPAP therapy provides further evidence for an ongoing systemic immune process in OSAS, thus rendering CPAP an important tool not only for the therapeutic manipulation of respiratory events in OSAS, but also for its inflammatory sequelae.*

Before commenting further on the above article, let us establish a baseline reference to this field of chemistry versus healthcare. Consider one of the best chemical associations in medicine: glucose and diabetes. Dogma stated that "diabetes = glucose" and that hyperglycemia was the cause of diabetic morbidity and death. Yet hyperglycemia is an epiphenomenon, and a 1983 publication documented what was already evident to doctors and patients, that tight glucose control would not prevent neuropathy.[93] Three recent trials have further shown that tight glucose control will not prevent stroke or myocardial infarction,[94] and in fact tight exogenously induced glucose control may be harmful.

How reliable are the findings for OSA? The publications concerning OSA and laboratory abnormalities show associations. Just because this is bench science does not preclude the pitfalls of methodology, statistics and bias concerning the touted "associations". Further, there is a "house of cards" as the methods and biochemical values themselves build on other chemical and disease state associations. No causal relationships are documented. Although this research is warranted, and may yet show indisputable facts which can translate into healthcare, it is not there yet for sleep apnea.

Other Disorders

Disorders that are not traditionally associated with sleep, such as Cheyne-Stokes respirations, dyspnea on exertion, and obesity-hypoventilation syndrome (OHS), are nonetheless being treated by nocturnal CPAP in the hope of some benefit, despite the lack of any evidence-based literature.

Hypercarbia

For example, nocturnal CPAP and bilevel positive airway pressure have been used to treat daytime hypercarbia in obese patients who also have OSA. In a retrospective study the partial pressure of arterial carbon dioxide decreased from 54 ∀ 7 to 49 ∀ 7 mm Hg.[95] Numerous study design flaws require caution in assessing this small but statistically significant effect.

A leading Sleep Medicine journal has a Board Review section. In a very recent review[95a] discussing the obesity hypoventilation syndrome (originally coined Pickwickian syndrome by Burwell in 1956), they made the claim (which already had been accepted by many Internists and Pulmonary specialists)

> *Positive pressure therapy is the primary medical management for OHS patients. Continuous positive airway pressure therapy (CPAP) will correct SDB in a significant proportion of patients. Bilevel positive airway pressure (BPAP) therapy can be used if awake hypercapnia or overnight oxygen desaturation persist despite elimination of obstructive events, or if the patient is intolerant to CPAP owing to the high pressures that may be required to alleviate SDB.*[ref2]

Can this be true? Using BPAP at night will affect your daytime (awake) CO2 levels? Of course it can not (unless the PAP cured the OHS), and their reference 2[95b] clearly states BPAP does NOT help awake hypercarbia.

Brain Damage

Sometimes, there is confusion over the order of cause and effect such that the goals of treatment cannot be preventive or curative. For example, although sustained anoxia will cause brain injury and neuronal death, does this also occur from the repetitive hypoxia in OSA? Studies in mice suggest that this can occur.[96] Therefore it might seem reasonable to treat everyone with OSA to prevent brain damage. Yet the evidence is just as convincing that pre-existing neuronal abnormalities may form the basis for altered neuromuscular control of the airway, which predisposes the individual to OSA.[97] Until much better research is available, treatment goals of OSA cannot be justified in this area.

Ophthalmology

Various ophthalmologic findings are being associated with OSAS, including eyelid hyperlaxity[98] and floppy eyelid syndrome,[99] with a case report of its reversal.[100] Ischemic optic neuritis or retinopathy is a serious condition, and the recurring bouts of nocturnal hypoxia associated with OSA make treatment with CPAP or any other effective modality seem desirable. But note that the average patient have desaturations of only 3-4%, and patients who desaturate 30-50% have pre-existing lung disease (and thus are hypoxic even in the daytime). Further, in the Sleep Heart Health Study, after adjustment for age, BMI, hypertension, diabetes, and other factors, the presence of retinopathy was not associated with sleep apnea.[101] Nevertheless, this does not preclude the possibility that eliminating OSA in patients with retinopathy would not be beneficial, but this awaits a better study.

Headache

Headaches are nearly universal, so an association with OSA or OSAS would seem certain. Headache is a common finding in both OSAS and insomnia patients.[102] Present studies, such as a report of an increased incidence of morning headaches in patients who completed an overnight PSG compared with the general public[103] or a lower-than-expected incidence of OSA in patients with headache referred to a specialist,[104] do not constitute adequate epidemiologic studies to draw any conclusions. Case-control studies show a high incidence of OSA in patients with cluster headaches, although no trials have been published on the effects of treating the OSA in these patients.[105,106]

Surprisingly, there was no literature associating sleep apnea and migraine until this 2011 article.[106a] The underlying assumptions were:

1) In migraine pathophysiology, the release of inflammatory neuropeptides might play an important role, and hypoxia might be a trigger.

2) In OSAS, the activation of inflammatory pathways may be caused by intermittent hypoxia.

3) CPAP therapy improves morning headache in OSAS and seems to be effective in cluster headache. [we just discussed this was not true]

The study prospectively evaluated 107 consecutive inpatients with OSAS, and found 11 who had both OSAS and migraine according to the International Classification of Headache Disorders. The eleven patients were followed for one year, and all described improvement of their migraine with a mean attack frequency decreasing from 5.8 to 0.1; 10 patients achieved headache freedom for the last 3 months. This study provided Class III evidence that CPAP given for 1 year to patients with migraine and OSAS significantly decreases the frequency of their migraine headaches. By this point, the reader should be able to evaluate the strength and clinical significance of this claim.

GI

Sleep disturbance is common in patients with gastroesophageal reflux disease (GERD). The primary treatment modality is medication, which can be effective 50% of the time.[107] When reflux is controlled, the quality of sleep is improved. Any association between OSA and GERD is therefore important, especially in refractory patients. Morse et al[108] could find no objective correlation between OSA and GERD in their patient population.

CONCLUSIONS

The present state of evidence-based literature does not support interventional treatment of OSA or OSAS by any modality to prevent or ameliorate the myriad of medical conditions that have been presented in this section. Although health care providers have good intentions and individual patients may benefit, population medical guidelines for ordering studies and instituting treatment remain unsupported.

References

a. Dasheiff RM, Finn R: Clinical Foundation for Efficient Treatment of Obstructive Sleep Apnea. J Oral Maxillofac Surg 67:2171-2182, 2009

1. APPLES-Apnea Positive Pressure Long-Term Efficacy Study: Available at: https://apples.stanford.edu/overview.htm. Accessed May 20, 2011

2. APPLES Manual of Procedures: Available at: https://apples.stanford.edu/pdf/files/APPLES%20MOP%2005-25-04%20fin.pdf. Accessed May 20, 2011

2b. Quan SF, Chan CS, Dement WC, et al. The association between obstructive sleep apnea and neurocognitive performance-The Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep 34:303-14, 2011

2c. Bliwise DL, Greenaway MC. Will APPLES Hit a Ceiling? Commentary on Quan et al. The association between obstructive sleep apnea and neurocognitive performance - the Apnea Positive Pressure Long-term Efficacy Study (APPLES). SLEEP 34:303-314, 2011

3. WebMD Sleep Disorders Health Center: Available at: http://www.webmd.com/sleep-disorders/tc/sleep-apnea-surgery. Accessed May 20, 2011

4. Tishler PV, Larkin EK, Schluchter MD, et al: Incidence of sleep-disordered breathing in an urban adult population: The treatment of osa relative importance of risk factors in the development of sleep-disordered breathing. JAMA 289:2230, 2003

5. Olson LG, King MT, Hensley MJ, et al: A community study of snoring and sleep-disordered breathing: Prevalence. Am J Respir Crit Care Med 152:711, 1995

6. Kapur VK, Baldwin CM, Resnick HE, et al: Sleepiness in patients with moderate to severe sleep-disordered breathing. Sleep 28:472, 2005

6b. Medicare Coverage Issues Manual. Available at http://www.cms.gov/transmittals/downloads/R150CIM.pdf. Accessed May 19, 2011

6c. Surgical Treatment of Obstructive Sleep Apnea. Available at https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Surgical_Treatment_of_Obstructive_Sleep_Apnea.pdf. Accessed May 19, 2011

6d. American Academy of Sleep Medicine. International classification of sleep disorders, revised: Diagnostic and coding manual. American Academy of Sleep Medicine, Chicago, Illinois, 2001

6e. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd edition: Diagnostic and coding manual. American Academy of Sleep Medicine, Westchester, IL, 2005

7. Pavlova MK, Duffy JF, Shea SA: Polysomnographic respiratory abnormalities in asymptomatic individuals. Sleep 31:241, 2008

7a. Wise MS, Nichols CD, Grigg-Damberger MM, et al: Executive Summary of respiratory indications for polysomnography in children: an evidence-based review. Sleep 34:389, 2011

8. Mador MJ, Krauza M, Pervez A, et al: Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure. Chest 128:2151, 2005

9. Massie CA, Hart RW, Peralez K, et al: Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. Chest 116:403, 1999

10. Sanner BM, Fluerenbrock N, Kleiber-Imbeck A, et al: Effect of continuous positive airway pressure therapy on infectious complications in patients with obstructive sleep apnea syndrome. Respiration 68:483, 2001

11. Ortolano GA, Schaffer J, McAlister MB, et al: Filters reduce the risk of bacterial transmission from contaminated heated humidifiers used with CPAP for obstructive

sleep apnea. J Clin Sleep Med 3:700, 2007

12. Gay PC: Complex sleep apnea: It really is a disease. J Clin Sleep Med 4:403, 2008

13. Fletcher EC: Recurrence of sleep apnea syndrome following tracheostomy. A shift from obstructive to central apnea. Chest 96:205, 1989

14. Levy P, Pepin JL, McNicholas WT: Should all sleep apnoea patients be treated? Yes. Sleep Med Rev 6:17, 2002

15. Montserrat JM, Barbe F, Rodenstein DO: Should all sleep apnoea patients be treated? Sleep Med Rev 6:7, 2002

16. Young T, Finn L, Peppard P, et al: Sleep-disordered-breathing and mortality: Eighteen-year follow-up of the Wisconsin Sleep Cohort. Sleep 31:1071, 2008

17. Marshall NS, Wong KKH, Liu PY, et al: Sleep apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. Sleep 31:1079, 2008

18. Little M: "Better than numbers . . ." a gentle critique of evidence-based medicine. ANZ J Surg 73:117, 2003

19. Paran E, Anson O, Neumann L: The effects of replacing beta-blockers with an angiotensin converting enzyme inhibitor on the quality of life of hypertensive patients. Am J Hypertens 9:1206, 1996

20. McArdle N, Devereux G, Heidarnejad H, et al: Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 159:1108, 1999

21. Monasterio C, Vidal S, Duran J, et al: Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 164:939, 2001

22. Hollandt JH, Mahlerwein M: Nasal breathing and continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea (OSA). Sleep Breath 7:87, 2003

23. Ferguson KA: The role of oral appliance therapy in the treatment of obstructive sleep apnea. Clin Chest Med 24:355, 2003

24. Lim J, Lasserson TJ, Fleetham J, et al: Oral appliances for obstructive sleep apnoea. Cochrane Database Syst Rev 25: CD004435, 2006

25. Hayes GW, Keating CL, Newman JS: The golden anniversary of the silver bullet. JAMA 270:1610, 1993

25a. Nakata S, Noda A, Yagi H, et al: Nasal resistance for determinant factor of nasal surgery in CPAP failure patients with obstructive sleep apnea syndrome. Rhinology 44:296, 2005

26. Cassel W, Ploch T, Becker C, et al: Risk of traffic accidents in patients with sleep-disordered breathing: Reduction with nasal CPAP. Eur Respir J 9:2606, 1996

27. Wright J, Johns R, Watt I, et al: Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: A systematic review of the research evidence. BMJ 314:851, 1997

28. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J: The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 340:847, 1999

28a. Arzi L, Shreter R, El-Ad B, et al Forty- versus 20-minute trials of the Maintenance of Wakefulness Test regimen for licensing of drivers. J Clin Sleep Med 5:57-62, 2009

28b. Miller CM, Khanna A, Strohl KP. Assessment and policy for commercial driver license referrals. J Clin Sleep Med 3:417-423, 2007

28c. Federal Motor Carrier Safety Administration. January 14, 2008. Expert Panel Recommendations. Obstructive Sleep Apnea and Commercial Motor Vehicle Driver Safety. Panel: Ancoli-Israel S, Czeisler CA, George CFP, Guilleminault C, Pack AI Available at: http://www.fmcsa.dot.gov/rules-regulations/TOPICS/mep/report/Sleep-MEP-Panel-Recommendations-508.pdf Accessed May 20, 2011

28d. National Transportation Safety Board, Safety Recommendation, August 7, 200.: Available at: http://www.ntsb.gov/recs/letters/2009/A09_61_66.pdf Accessed May 20, 2011 [concerning February 13, 2008 Mesa Airlines flight 1002, in which they overflew the destination airport because both the captain and first officer fell asleep. NTSB determined that contributing to the incident were the captain's undiagnosed obstructive sleep apnea (OSA) and the flight crew's recent work schedules, which included several consecutive days of early-morning start times]

29. Kalra M, Inge T, Garcia V, et al: Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. Obes Res 13:1175, 2005

30. O'Keeffe T, Patterson EJ: Evidence supporting routine polysomnography before bariatric surgery. Obes Surg 14:23, 2004

31. Resta O, Barbaro MPF, Bonfitto P, et al: Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. J Intern Med 253:536, 2003

32. Jenkinson C, Davies RJ, Mullins R, et al: Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised prospective parallel trial. Lancet 353:2100, 1999

33. Patel SR, White DP, Malhotra A, et al: Continuous positive airway pressure therapy for treating a diverse population with obstructive sleep apnea: Results of a meta-analysis. Arch In-tern Med 163:565, 2003

34. Chasens ER, Weaver T, Maislin G, et al: The Multisite Study Group. Discordance in subjective and objective measures of daytime sleepiness. Sleep 25:A1, 2002 (suppl, abstract)

35. Kim H, Young T: Subjective daytime sleepiness: Dimensions and correlates in the general population. Sleep 28:625, 2005

36. Arand D, Bonnet M, Hurwitz T, et al: The clinical use of the MSLT and MWT. Sleep 28:123, 2005

37. Johns MW: Sensitivity and specificity of the Multiple Sleep Latency Test (MSLT), the Maintenance of Wakefulness Test and the Epworth Sleepiness Scale: Failure of the MSLT as a gold standard. J Sleep Res 9:5, 2000

38. Chervin RD, Aldrich MS: Characteristics of apneas and hypopneas during sleep and relation to excessive daytime sleepiness. Sleep 21:799, 1998

39. Bennett LS, Langford BA, Stradling JR, et al: Sleep fragmentation indices as predictors of daytime sleepiness and nCPAP responses in obstructive sleep apnea. Am J Respir Crit Care Med 158:778, 1998

40. Clark GT, Blumenfeld I, Yoffe N, et al: A crossover study comparing the efficacy of continuous positive airway pres-sure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest 109:1477, 1996

41. Babar S, Quan SF: Continuous positive airway pressure. Placebo power, or does it really work? Arch Intern Med 163:519, 2003

42. Thatcher GW, Maisel RH: The long-term evaluation of tracheostomy in the management of severe obstructive sleep apnea. Laryngoscope 113:201, 2003

43. Powell N: Upper airway surgery does have a major role in the treatment of obstructive sleep apnea. "The tail end of the dog." J Clin Sleep Med 1:236, 2005

43a. Bertrand B, Rombaux P, Rodenstein D: Nasal Obstruction and Its and Surgical Management in Sleep-Related Breathing Disorders. In Rhinologic and sleep apnea surgical techniques. S. E. Kountakis, M. Önerci (eds), Springer, New York 2007, Chp 30, pp 289-302

44. Cillo JE, Finn R, Dasheiff RM: Combined open rhinoplasty with spreader grafts and uvuloplasty for sleep-disordered breathing: Long-term subjective outcomes. J Oral Maxillofac Surg 64:1241, 2006

45. O'Sullivan RA, Hillman DR, Mateljan R, et al: Mandibular advancement splint: An appliance to treat snoring and ob-structive sleep apnea. Am J Respir Crit Care Med 151:194, 1995

46. Baldwin CM, Griffith KA, Nieto FJ, et al: The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep 24:96, 2001

47. Davies RJ, Stradling JR: The efficacy of nasal continuous positive airway pressure in the treatment of obstructive sleep apnea syndrome is proven. Am J Respir Crit Care Med 161: 1775, 2000

48. Lim W, Bardwell WA, Loredo JS, et al: Neuropsychological effects of 2-week continuous positive airway pressure treatment and supplemental oxygen in patients with obstructive sleep apnea: A randomized placebo-controlled study. J Clin Sleep Med 3:380, 2007

49. Berka C, Johnson R, Morgan T, et al: Influence of sleep-disordered breathing on neurocognitive functions pre- and posttreatment with oral appliance therapy. Sleep 31:A152, 2008

50. Leung RST, Bradley TD: Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 164:2147, 2001

51. Smith ML, Muenter NK: Effects of hypoxia on sympathetic neural control in humans. Respir Physiol 121:163, 2000

52. Bradley TD, Hall MJ, Ando S, et al: Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure. Chest 119:1827, 2001

53. Zou D, Grote L, Eder DN, et al: Obstructive apnea events induce alpha-receptor mediated digital vasoconstriction. Sleep 27:485, 2004

54. Peppard PE, Young T, Palta M, et al: Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342:1378, 2000

55. White J, Cates C, Wright J: Continuous positive airways pressure for obstructive sleep apnoea. Cochrane Database Syst Rev 19:CD001106, 2006

56. Golbin JM, Somers VK, Caples SM: Obstructive sleep apnea, cardiovascular disease, and pulmonary hypertension. Proc Am Thorac Soc 5:200, 2008

57. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 157:2413, 1997

58. Chobanian AV, Bakris GL, Black HR, et al: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 289:2560, 2003

58a. The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8): Available at: http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/index.htm. Accessed May 23, 2011

59. Haas DC, Foster GL, Nieto FJ, et al: Age-dependent associations between sleep-disordered breathing and hypertension: Importance of discriminating between systolic/diastolic hy-pertension and isolated systolic hypertension in the Sleep Heart Health Study. Circulation 111:614, 2005

60. Kapur VK, Resnick HE, Gottlieb DJ: Sleep disordered breathing and hypertension: Does self-reported sleepiness modify the association? Sleep 31:1127, 2008

61. Becker HF, Jerrentrup A, Ploch T, et al: Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 107:68, 2003

62. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. Lancet 359:204, 2002

63. Tkacova R, Liu PP, Naughton MT, et al: Effects of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. J Am Coll Cardiol 30:739, 1997

64. Cloward TV, Walker JM, Farney RJ, et al: Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. Chest 124:594, 2003

65. Sin DD, Logan AG, Fitzgerald FS, et al: Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 102:61, 2000

66. Berger HA, Somers VK, Phillips BG: Sleep disordered breathing and hypertension. Curr Opin Pulm Med 7:386, 2001

67. Mayer J, Becker H, Brandenburg U, et al: Blood pressure and sleep apnea: Results of long-term nasal continuous positive airway pressure therapy. Cardiology 79:84, 1991

68. Pi-Sunyer FX: A review of long-term studies evaluating the efficacy of weight loss in ameliorating disorders associated with obesity. Clin Ther 18:1006, 1996

68a. Dernaika T, Kinasewitz G, Tawk M. Effects of Nocturnal Continuous Positive Airway Pressure Therapy in Patients with Resistant Hypertension and Obstructive Sleep Apnea. J Clin Sleep Med 5:103, 2009

68b. Budhiraja R, Quan S. When Is CPAP an Antihypertensive in Sleep Apnea Patients? J Clin Sleep Med 5:108, 2009

68c. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol. 34:215, 2005

68d. Gastaut H, Tassinari C, Duron B. Stude polygraphique des manifestations 6 pisodiques (hypinques et respiratoires) du syndrome de Pickwick. Rev Neurol (Paris) 112:568, 1965

68e. Jung B, Kuhlo W. Neurophysiological studies of abnormal night sleep and the pickwickian syndrome. Prog Brain Res 18:140, 1965

68f. Dement WC. History of sleep physiology and medicine. In: Kyrger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia; W.B. Saunders: 2000. p.11

69. Pack AI, Platt AB, Pien GW: Does untreated obstructive sleep apnea lead to death? A commentary. Sleep 31:1067, 2008

70. Malhotra A, White DP: Obstructive sleep apnoea. Lancet 360: 237, 2002

70a. Gooneratne NS, Richards KC, Joffe M, et.al: Sleep Disordered Breathing with Excessive Daytime Sleepiness is a Risk Factor for Mortality in Older Adults. Sleep 34:435, 2011

70b. Personal communications.

71. Mooe T, Franklin KA, Holmstrom K, et al: Sleep-disordered breathing and coronary artery disease: Long-term prognosis. Am J Respir Crit Care Med 164:1910, 2001

72. Albarrak M, Banno K, Sabbagh AA, et al: Utilization of healthcare resources in obstructive sleep apnea syndrome: A 5-year follow-up study in men using CPAP. Sleep 28:1306, 2005

73. 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 365:1046, 2005

74. Nishibayashi M, Miyamoto M, Miyamoto T, et al: Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. J Clin Sleep Med 4:242, 2008

75. Partinen M, Guilleminault C: Daytime sleepiness and vascular morbidity at 7 year follow up in obstructive sleep apnea patients. Chest 97:27, 1990

76. Bady E, Achkar A, Pascal S, et al: Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax 55:934, 2000

77. Atwood CW, Jr, McCrory D, Garcia JGN, et al: Pulmonary artery hypertension and sleep-disordered breathing. ACCP evidence-based clinical practice guidelines. Chest 126:72S, 2004

77a. Badesch DB, Abman SH, Simonneau G, et al: Medical Therapy for Pulmonary Arterial Hypertension: Updated ACCP Evidence-Based Clinical Practice Guidelines. Chest 131:1917, 2007

78. Arias MA, Garcia-Rio F, Alonso-Fernandez A, et al: Pulmonary hypertension in obstructive sleep apnoea: Effects of continuous positive airway pressure: A randomized, controlled cross-over study. Eur Heart J 27:1106, 2006

78a. Magalang UJ, Richards K, McCarthy B, et al: Continuous positive airway pressure therapy reduces right ventricular volume in patients with obstructive sleep apnea: a cardiovascular magnetic resonance study. J Clin Sleep Med 5:110, 2009

79. Lee SA, Amis TC, Byth K, et al: Heavy snoring as a cause of carotid atherosclerosis. Sleep 31:1207, 2008

80. Lee SA, Amis TC, Byth K, et al: Heavy snoring: Time to take it more seriously? A response. Sleep 31:1337, 2008

81. Drager LF, Lorenzi-Filho G: Heavy snoring and carotid atherosclerosis: Is there more than an association? Commentary. Sleep 31:1335, 2008

82. Ip MSM, Lam B, et al: Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Med 165:670, 2002

83. Punjabi NM, Sorkin JD, Katzel LI, et al: Sleep-disordered breathing and insulin resistance in middle-aged and over-weight men. Am J Respir Crit Med 165:677, 2002

84. Shamsuzzaman ASM, Winnicki M, Lanfranchi P, et al: Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 105:2462, 2002

85. Minoguchi K, Tazaki T, Yokoe T, et al: Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome. Chest 126:1473, 2004

86. Lavie L, Vishnevsky A, Lavie P: Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 27:123, 2004

87. Tazaki T, Minoguchi K, Yokoe T, et al: Increased levels and activity of matrix metalloproteinase-9 in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 170:1354, 2004

88. Sanner BM, Konermann M, Tepel M, et al: Platelet function in patients with obstructive sleep apnea syndrome. Eur Respir J 16:648, 2000

88a. Rahangdale S, Yim SY, Novack V, et al: The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. J Clin Sleep Med 7:172, 2011

88b. Peker, Y: Platelet Activity and Cardiovascular Risk in Obesity and Obstructive Sleep Apnea: Compelling Need for Interdisciplinary Research? J Clin Sleep Med 7:179, 2011

89. Yokoe T, Minoguchi K, Matsuo H, et al: Elevated levels of C-reactive protein and interleukin-6 in patients with obstruc-tive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 107:1129, 2003

90. Harsch IA, Schahin SP, Radespiel-Troger M, et al: Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 169:156, 2004

91. Brooks B, Cistulli PA, Borkman M, et al: Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: Effect of continuous positive airway pressure treatment on insulin responsiveness. J Clin Endocrinol Metab 79:1681, 1994

92. Bokinsky G, Miller M, Ault K, et al: Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure. A preliminary investigation. Chest 108:624, 1995

92a. Steiropoulos P, Kotsianidis I, Nena E, et al: Long-Term Effect of Continuous Positive Airway Pressure Therapy on Inflammation Markers of Patients with Obstructive Sleep Apnea Syndrome. Sleep 32:537, 2009

93. Service FJ, Daube JR, O'Brien PC, et al: Effect of blood glucose control on peripheral nerve function in diabetic patients. Mayo Clin Proc 58:283, 1983

94. Taubes G: Diabetes. Paradoxical effects of tightly controlled blood sugar. Science 322:365, 2008

95. Mokhlesi B, Tulaimat A, Evans AT, et al: Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med 2:57, 2006

95a. Sam A, Budhiraja R: Sleeping on a Royal Flush. J Clin Sleep Med 7:109, 2011

95b. Piper AJ, Grunstein RR: Obesity Hypoventilation Syndrome: Mechanisms and Management. Am. J. Respir. Crit. Care Med. 183:292, 2011

96. Veasey SC, Davis CW, Fenik P, et al: Long-term intermittent hypoxia in mice: Protracted hypersomnolence with oxidative injury to sleep-wake brain regions. Sleep 27:194, 2004

97. Macey PM, Henderson LA, Macey KE, et al: Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 166:1382, 2002

98. Robert PY, Adenis JP, Tapie P, et al: Eyelid hyperlaxity and obstructive sleep apnea (O.S.A.) syndrome. Eur J Ophthalmol 7:211, 1997

99. Mojon DS, Goldblum D, Fleischhauer J, et al: Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. Ophthalmology 106:1182, 1999

100. McNab AA: Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnoea. Clin Exp Ophthalmol 28: 125, 2000

101. Boland LL, Shahar E, Wong TY, et al: Sleep-disordered breathing is not associated with the presence of retinal microvascular abnormalities: The Sleep Heart Health Study. Sleep 27:467, 2004

102. Alberti A, Mazzotta G, Gallinella E, et al: Headache characteristics in obstructive sleep apnea syndrome and insomnia. Acta Neurol Scand 111:309, 2005

103. Goder R, Friege L, Fritzer G, et al: Morning headaches in patients with sleep disorders: A systematic polysomnographic study. Sleep Med 4:385, 2003

104. Jensen R, Olsborg C, Salvesen R, et al: Is obstructive sleep apnea syndrome associated with headache? Acta Neurol Scand 109:180, 2004

105. Nobre ME, Leal AJ, Filho PM: Investigation into sleep disturbance of patients suffering from cluster headache. Cephalalgia 25:488, 2005

106. Graff-Radford SB, Newman A: Obstructive sleep apnea and cluster headache. Headache 44:607, 2004

106a. Ulf Kallweit, Hildegard Hidalgo, Verena Uhl, et al: Continuous positive airway pressure therapy is effective for migraines in sleep apnea syndrome. Neurology 2011;76;1189

107. Johnson DA, Orr WC, Crawley JA, et al: Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: A randomized, placebo-controlled trial. Am J Gastroenterol 100:1914, 2005

108. Morse CA, Quan SF, Mays MZ, et al: Is there a relationship between obstructive sleep apnea and gastroesophageal reflux disease? Clin Gastroenterol Hepatol 2:761, 2004

109. Partinen M, Jamieson A, Guilleminault C: Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. Chest 94:1200, 1988

110. Loadsman JA, Hillman DR: Anaesthesia and sleep apnoea. Br J Anaesth 86:254, 2001

111. Bryson GL, Chung F, Finegan BA, et al: Patient selection in ambulatory anesthesia. An evidence-based review: Part I. Can J Anaesth 51:768, 2004

112. Gupta RM, Parvizi J, Hanssen AD, et al: Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: A case-control study. Mayo Clin Proc 76:897, 2001

113. Sabers C, Plevak DJ, Schroeder DR, et al: The diagnosis of obstructive sleep apnea as a risk factor for unanticipated admissions in outpatient surgery. Anesth Analg 96:1328, 2003

114. Jain SS, Dhand R: Perioperative treatment of patients with obstructive sleep apnea. Curr Opin Pulm Med 10:482, 2004

115. Lickteig C, Grigg P: Risks of OSA and anesthesia. J Sleep Rev 1, 2003. Available at: http://www.sleepreviewmag.com/issues/articles/2003-01_02.asp. Accessed May 20, 2011

116. Lofsky A: Sleep apnea and narcotic postoperative pain medication: A morbidity and mortality risk. APSF Newsl 17:24, 2002

117. Benumof JL: Creation of observational unit may decrease sleep apnea risk. APSF Newsl 17:39, 2002

118. Fisher KS: Value of pulse oximetry monitoring on the ward is questioned. APSF Newsl 17:24, 2002

APPENDIX 1 - How to understand Odds Ratios

Statistics of Smoking and Cancer

This first example allows the reader to see best practice regarding statistical analysis, and most importantly, something of marked clinical significance so as to get a gauge of what is and is not a clinically significant odds ratio.

A historically important case-control study of smoking and lung cancer (Doll & Hill. Smoking and Lung Cancer, 1950) found 647 of 649 lung cancer cases were smokers. In contrast, 622 of 649 non-cancer controls were smokers.

A contingency table is thereby created.

	Cases	Controls	
Smoke+	647	622	1269

Smoke-	2	27	29
	649	649	1298

The odds ratio is 14, and the 95% confidence interval for this OR: 3.5, 122 using the exact method computed by STATCALC (Mehta et al., 1985).

The data indicate a strong positive association between smoking and lung cancer. Smokers have 14 times the lung cancer rate of non-smokers. Compare this to the usual 1.2 or even 3.0 odds ratio typically quoted in most medical literature, and also consider there was tremendous debate whether smoking caused cancer despite these numbers.

Reference for the above and below is from the Centers for Disease Control and Prevention website. 2004 Surgeon General's Report-The Health Consequences of Smoking. Available at:
http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm Accessed on May 25, 2011

Chp 1 (at the end) gives an excellent discussion on association vs causality.
Available on this CD (click here)
or on the web: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/chapter1.pdf
Accessed on May 25, 2011

EDITOR AND PUBLISHER - these chapters are in the public domain. Can we hyperlink the Adobe PDF directly off this OMSKU DVD so the reader does not need to go online?

Chp 2. The powerful epidemiologic evidence on smoking and lung cancer reported during the 1950s was one of the first warnings of the strength of smoking as a cause of cancer and other diseases (Doll and Hill 1954,1956).
Available on this CD (click here)
or on the web: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/chapter2.pdf
Accessed on May 25, 2011

Below is the analysis of the two American Cancer Society prospective cohort studies (Cancer Prevention Study I [CPS-I] and II [CPS-II]) by Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW Jr. Excess mortality among cigarette smokers: changes in a 20-year interval. American Journal of Public Health 85(9):1223-30, 1995

The relative risks (RRs) of lung cancer changed (see graph)
from 11.9 in CPS-I to 23.2 in CPS-II for men, and
from 2.7 in CPS-I to 12.8in CPS-II for women.

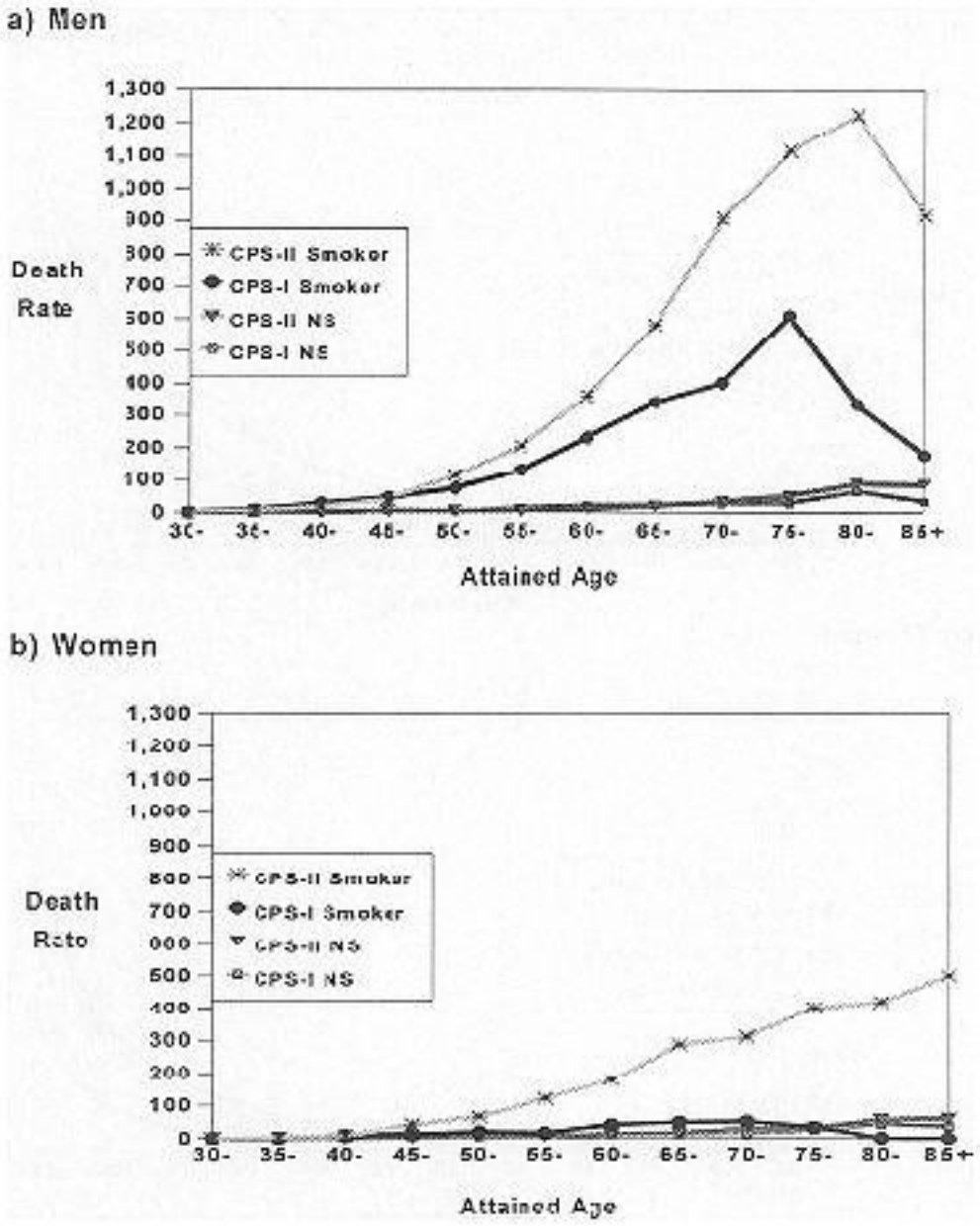

FIGURE 1—Age-specific death rates (per 100 000 person-years) from lung cancer among lifelong nonsmokers and current cigarette smokers, based on smoking status at enrollment in CPS-I (1959) or CPS-II (1982).

EDITOR AND PUBLISHER - this figure needs a release. Source: Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW Jr. Excess mortality among cigarette smokers: changes in a 20-year interval. American Journal of Public Health 85(9):1223-30, 1995. How to Obtain Permission http://ajph.aphapublications.org/misc/permissions.dtl

Odds Ratio versus Clinical Significance

The article by Kraemer H et al. Measures of Clinical Significance. J Amer Acad Child Adol Psych 42:1524 -1529, 2003 provides some explanation:

> *Statistical significance does not provide information about the strength of the relationship (effect size) or whether the relationship is meaningful (clinical significance). Odds ratios and risk ratios vary from 0 to infinity, with 1 indicating no effect. The clinical significance of a treatment is based on external standards provided by clinicians, patients, and/or researchers. Unfortunately, to date there is little consensus about the criteria for these efficacy standards.*
>
> *A major limitation of the odds ratio as an effect size index is that the magnitude of the odds ratio may approach infinity if the outcome is rare, or very common, even when the association is near random. The magnitude of the odds ratio varies strongly with the choice of cut-point. Thus, there are no agreed-upon standards for what represents a large odds ratio because some very large odds ratios are obtained for situations very close to random association. Consequently, odds ratios can be quite misleading as an effect size indicating clinical significance.*
>
> *For example, If you set a cut off so that the failure rate[of some treatment] includes both "not improved" and "somewhat improved" patients you might get an Odds Ratio of 3*
> *If you change the cut off so the failure rate included only "not improved" patients you would get an Odds Ratio of 19.*

Interpretation of the Strength of a Positive Relationship

	Odds Ratio	***Effect Size - d**	****Correlation - r**
Smoking & Lung cancer	14		
Much larger than typical	1.52	>1.0	>0.7
Large or larger than typical†	1.43	0.8	0.5
Medium or typical††	1.28	0.5	0.3
Small or smaller than typical	1.11	0.2	0.1

*Used when the independent variable is binary (dichotomous) and the dependent variable is ordered, ranges from minus to plus infinity, with zero indicating no effect;

however, it is unusual to find d values much greater than 1.

**Most researchers would not consider a correlation (r) of 0.5 (or lower) to be very strong because only 25% (or less) of the variance in the dependent variable is predicted.

†Grossly perceptible as the mean difference in height between 13- and 18-year-old girls.

††Visible to the naked eye, as in the course of normal experiences, one would become aware of an average difference in IQ between clerical and semi-skilled workers.

APPENDIX 2 - Levels of Scientific Evidence

The two tables below were taken from - Gross A and Johnston KC: Levels of evidence. Neurology 72:8, 2009.

An intelligent commentary on levels of evidence can be found in this article in which their title tells you what they will say - Gronseth G, French J: Practice parameters and technology assessments: what they are, what they are not, and why you should care. Neurology 71:1639, 2008.

Table 1

American Academy of Neurology classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:
a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required
1. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the

mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

2. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment.

3. The interpretation of the results of the study is based on an observed-cases analysis.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e Class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e Class I, above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion

Table 2

American Academy of Neurology classification of recommendations

A Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

The following commentary is by French JA and England JD: Invited Article:

Comparative effectiveness research, evidence-based medicine, and the AAN. Neurology75:562, 2010

Clinical Guidelines are never followed

ABSTRACT

Comparative effectiveness research (CER) is the study of the relative effects of treatments to determine which will be most likely to improve overall health for a specific condition. This area has received a great deal of political focus, and substantial funding for CER is included in the American Reinvestment and Recovery Act of 2009. The results of CER are intended to inform evidence-based guidelines and to improve the quality and effectiveness of medical care. In the absence of such research, guidelines often depend on consensus to rank available therapies. We believe that an increase in CER would clearly enhance evidence-based guidelines. However, the research must be performed and analyzed with great care to avoid reaching unhelpful, or even harmful, conclusions. Specifically, individual patient characteristics must be taken into account, study endpoints must approximate the most important patient outcomes, therapies must be used optimally within the studies, and the most relevant therapies for a given indication must be included for comparison. CER that is not performed or interpreted correctly could have the potential to affect negatively our choices of therapies. The neurology community must help inform the process of CER to ensure the highest-quality research, which in turn will result in the most valid outcomes.

"if the issues above are not appropriately considered, a far different and less favorable outcome may ensue. Third-party payers, regulatory bodies, and even physicians who uncritically accept the results of CER may inappropriately limit patients' choices based on the overall average effect on the measured outcomes."

"specialty societies create guidelines in the absence of comparative scientific research. Citing cardiology as an example, they claimed that "just 11% of more than 2,700 recommendations approved by cardiologists for treating heart patients are supported by high-quality scientific testing." Whereas AAN guidelines rely on high-quality evidence for high-level recommendations, the relative lack of CER does affect them. Many AAN guidelines list available treatments without providing clear guidance to the clinician of relative merit. Because the AAN process does not use consensus-based recommendations, in the absence of comparative trials, therapies are addressed only in terms of the strength of the clinical trial that led to the recommendation, not necessarily the likelihood that a particular therapy will be of greater benefit to patients."