JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

The Apnea Positive Pressure Long-term Efficacy Study (APPLES): Rationale, Design, Methods, and Procedures

Clete A. Kushida, M.D., Ph.D.[1]; Deborah A. Nichols, M.S.[1]; Stuart F. Quan, M.D.[2]; James L. Goodwin, Ph.D.[2]; David P. White, M.D.[3]; Daniel J. Gottlieb, M.D., M.P.H.[3]; James K. Walsh, Ph.D.[4]; Paula K. Schweitzer, Ph.D.[4]; Christian Guilleminault, M.D.[1]; Richard D. Simon, M.D.[5]; Eileen B. Leary, R.P.S.G.T.[1]; Pamela R. Hyde, M.A.[1]; Tyson H. Holmes, Ph.D.[1]; Daniel A. Bloch, Ph.D.[1]; Sylvan Green, M.D.[2]; Linda K. McEvoy, Ph.D.[6]; Alan Gevins, D.Sc.[6]; William C. Dement, M.D., Ph.D.[1]

[1]Stanford University, Stanford, CA; [2]University of Arizona, Tucson, AZ; [3]Brigham and Women's Hospital, Boston, MA; [4]St. John's/St. Luke's Hospitals, Chesterfield, MO; [5]St. Mary Medical Center, Walla Walla, WA; [6]SAM Technology Inc. & The San Francisco Brain Research Institute, San Francisco, CA

Study Objective: To assess the size, time course, and durability of the effects of long-term continuous positive airway pressure (CPAP) therapy on neurocognitive function, mood, sleepiness, and quality of life in patients with obstructive sleep apnea.

Design: Randomized, double-blinded, 2-arm, sham-controlled, multicenter, long-term, intention-to-treat trial of CPAP therapy.

Setting: Sleep clinics and laboratories at 5 university medical centers and community-based hospitals.

Patients or Participants: Target enrollment is 1100 randomly assigned subjects across 5 clinical centers.

Interventions: Active versus sham (subtherapeutic) CPAP.

Measurements and Results: A battery of conventional and novel tests designed to evaluate neurocognitive function, mood, sleepiness, and quality of life.

Conclusions: The Apnea Positive Pressure Long-term Efficacy Study (APPLES) is designed to study obstructive sleep apnea and test the effects of CPAP through a comprehensive, controlled, and long-term trial in a large sample of subjects with obstructive sleep apnea.

Keywords: Obstructive sleep apnea, continuous positive airway pressure, APPLES, neurocognitive function

Citation: Kushida CA; Nichols DA; Quan SF et al. The apnea positive pressure long-term efficacy study (APPLES): rationale, design, methods, and procedures. *J Clin Sleep Med* 2006;2(3):288-300.

Continuous positive airway pressure (CPAP) (see Table 1 for list of abbreviations) therapy is in widespread use as the primary treatment for obstructive sleep apnea (OSA), a sleep-related breathing disorder estimated to affect more than 18 million Americans.[1] However, the therapeutic effectiveness of CPAP in providing significant, stable, and long-term neurocognitive and other functional benefits to patients with OSA has not been systematically investigated. The Apnea Positive Pressure Long-term Efficacy Study (APPLES) is a randomized, double-blinded, 2-arm, sham-controlled, multicenter, long-term (6-month), intention-to-treat trial of CPAP therapy. The primary outcomes of APPLES are measures of neurocognitive function.

Disclosure Statement

This was not an industry supported study. Dr. Quan is on the Medical Advisory Board of ImmuneRegan Biosciences and speakers' bureau for Takeda; and has received research equipment from Respironics. Dr. White is the chief medical officer for Respironics; is a consultant for AspireMedical, PAVAD, Itamar Medical, and WideMed; and has received research support from Respironics, Itamar Medical, WideMed, and Cephalon. Dr. Walsh has received research support from Pfizer, Merck, Neurocrine Biosciences, Somaxon, Evotec Neurosciences, and Cephalon; and is a consultant for Pfizer, Sanofi-Aventis, Cephalon, Organon, Neurocrine Biosciences, Takeda America, Actelion, Sepracor, Elan, Guilford, Respironics, Merck KgaA- Darmstadt, King, TransOral, Neurogen, GlaxoSmithKline, SleepTech, Somaxon, Eli Lilly, Evotec Neurosciences, and Merck. Dr. Schweitzer has received research support from Cephalon and Merck. Dr. Simon is on the Advisory Board for Merck; and has received research equipment from Fisher Paykel. Dr. McEvoy is a full-time employee of SAM Technology. Dr. Gevins is the president and full-time employee of SAM Technology. Drs. Kushida, Nichols, Goodwin, Gottlieb, Guilleminault, Leary, Hyde, Holmes, and Bloch, Green, and Dement have indicated no financial conflicts of interest.

Submitted for publication May 12, 2006
Accepted for publication June 4, 2006

Address correspondence to: Clete A. Kushida, M.D., Ph.D., Stanford Sleep Disorders Clinic, 401 Quarry Road, Suite 3301, Stanford, CA 94305-5730; Tel: (650) 725-1915; Fax: (650) 725-8910; E-mail: clete@stanford.edu

BACKGROUND AND RATIONALE

OSA has been associated with hypertension, myocardial infarction, cardiac failure, stroke, cardiac dysrhythmias, increased risk for industrial and motor vehicle accidents, and sudden death[2-4] (reviewed by Weiss et al, 2000[5]). There is also an emerging body of evidence[6] (reviewed by Décary et al, 2000[7]) that neurocognitive abilities, especially in the domains of attention and psychomotor function, learning and memory, and executive and frontal-lobe function, may be impaired with OSA. Review of these studies has indicated that community-acquired subjects with sleep-disordered breathing of mild severity show small effect sizes for attentional and executive-function impairment. Studies evaluating subjects with moderate to severe indexes of sleep-disordered breathing have generally shown moderate to large impairment effect sizes in all 3 domains of neurocognitive function. However, these studies were limited by relatively small sample sizes, noncomprehensive test batteries, and inadequate control groups. Further, newer technologies, such as the Sustained Working Memory Test[8-17]

Table 1—List of Abbreviations[a]

2-M CPAP	Two-month post-CPAP follow-up visit
4-M CPAP	Four-month post-CPAP follow-up visit
6-M CPAP	Six-month post-CPAP follow-up visit
A/P	Attention and psychomotor function
APPLES	Apnea Positive Pressure Long-term Efficacy Study
BSRT	Buschke Selective Reminding Test
CC	Clinical Center
CCC	Clinical Coordinating Center
CE	Clinical evaluation
CPAP	Continuous Positive Airway Pressure
C-PSG	CPAP titration visit
DCC	Data Coordinating Center
D-PSG	Diagnostic Polysomnography Visit
DSMB	Data and Safety Monitoring Board
E/F	Executive and frontal-lobe function
EX	Exit interview
IRB	Institutional Review Board
L/M	Learning and memory
MOP	Manual of operations
MWT	Maintenance of Wakefulness Test
NHLBI	National Heart, Lung, and Blood Institute of the National Institutes of Health
OSA	Obstructive sleep apnea
PN	Pathfinder Number Test
PO	Physician Observer
PSG	Polysomnography
QA/QC	Quality assurance/quality control
SDB	Sleep-disordered breathing
SWMT	Sustained Working Memory Test
T1	Training session 1
T2	Training session 2

[a]See Tables 2 and 3 for additional abbreviations.

and functional magnetic resonance imaging studies, have not been systematically utilized to assess whether OSA-related neurocognitive deficits are associated with changes in cortical activation and whether CPAP therapy can reverse these changes.

The etiology of the neurocognitive impairment in patients with OSA is currently unknown. One theory to explain this phenomenon states that the hypoxemia of OSA is responsible for neurocognitive decline. This theory is controversial, as research on patients with OSA[18] and patients with hypoxemic chronic obstructive pulmonary disease[19,20] have failed to find a relationship between measures of hypoxemia and neurocognitive function, whereas other investigators[21] have reported that patients with OSA and hypoxemia have significantly more cognitive impairment than patients with OSA and no hypoxemia. Another theory is that the impairment in neurocognitive function in patients with OSA is related to sleepiness. Patients with OSA perform worse on neuropsychological tests than do both healthy volunteers and patients with other disorders of excessive sleepiness.[18] Perhaps the most parsimonious explanation is that these OSA-related neurocognitive deficits are the result of a combination of both hypoxemia and decreased vigilance.[22,23]

The first-line treatment modality for OSA is CPAP, which decreases the frequency of abnormal respiratory events and arousals; however, there is some controversy as to whether sleep architecture is significantly improved.[24,25] CPAP has been shown to improve neurocognitive function using tests of attention and psychomotor function,[6,26] learning and memory,[26] and executive and frontal-lobe function in a few studies with limited sample sizes,[27] whereas other investigators have detected persistent deficits in similar measures of neurocognitive function with CPAP use.[28-31] These conflicting results raise questions about the causal nature of the association and may indicate that some neurocognitive deficits are due to irreversible central nervous system damage.

The etiology of the daytime sleepiness associated with OSA is also unknown. It is widely accepted that OSA results in brief arousals from sleep and that this sleep fragmentation produces daytime sleepiness. However, this hypothesis has not been adequately tested and remains controversial.[32,33] Regardless of its etiology, sleepiness is a primary criterion for the diagnosis of OSA. CPAP has been demonstrated to improve the sleepiness associated with OSA in long-term studies[34] and in comparisons with sham CPAP,[35] yet, the improvement in levels of sleepiness in these studies does not approach the baseline levels of controls without OSA.

The effect of CPAP on mood in patients with OSA is largely unknown. Results have been mixed, with some studies reporting improvement,[36,37] 1 study revealing significant improvement in both active CPAP and placebo groups,[38] and other studies showing no significant effects.[26,39] However, these studies were limited by small sample sizes, standard and nonstandard indexes of mood state, and different types of controls across the studies.

Quality-of-life assessment has become an integral component of health-outcomes research. Several small studies have documented significant improvement in quality-of-life indexes following CPAP treatment in patients with OSA.[35,40-42]

A large, multicenter, randomized, double-blinded, sham-controlled, long-term study of CPAP therapy has not been previously conducted, despite the widespread use of CPAP as the primary treatment for OSA[43] and the perception by the majority of patients with OSA that it is an effective treatment for this disorder.[44] To date, the efficacy of CPAP has generally been evaluated against control groups that may not meet the requirements of true sham or placebo groups because these controls were not subjected to instrumental constraints[41,45-47] identical to those of the experimental group. Sham CPAP has been used successfully as a placebo in a few, albeit short-term, studies.[24,35,48,49] This lack of an adequate long-term placebo-controlled study combined with the high per-patient costs of CPAP has called into question the usefulness of CPAP as primary therapy for OSA.[50,51] Our study is designed to address the following specific aims:

1. To assess the long-term effectiveness of CPAP therapy on neurocognitive function, mood, sleepiness, and quality of life by administration of standard and novel tests of these indexes to subjects with OSA.
2. To identify specific deficits in neurocognitive function associated with OSA in a large heterogeneous population of subjects with OSA.
3. To evaluate which deficits in neurocognitive function in subjects with OSA are reversible and most sensitive to the effects of CPAP
4. To explore the development of multivariate composite indexes for assessment of clinical effectiveness of CPAP in improving neurocognitive function, mood, sleepiness, and quality of life in patients with OSA.
5. To use functional magnetic resonance imaging in a subset of

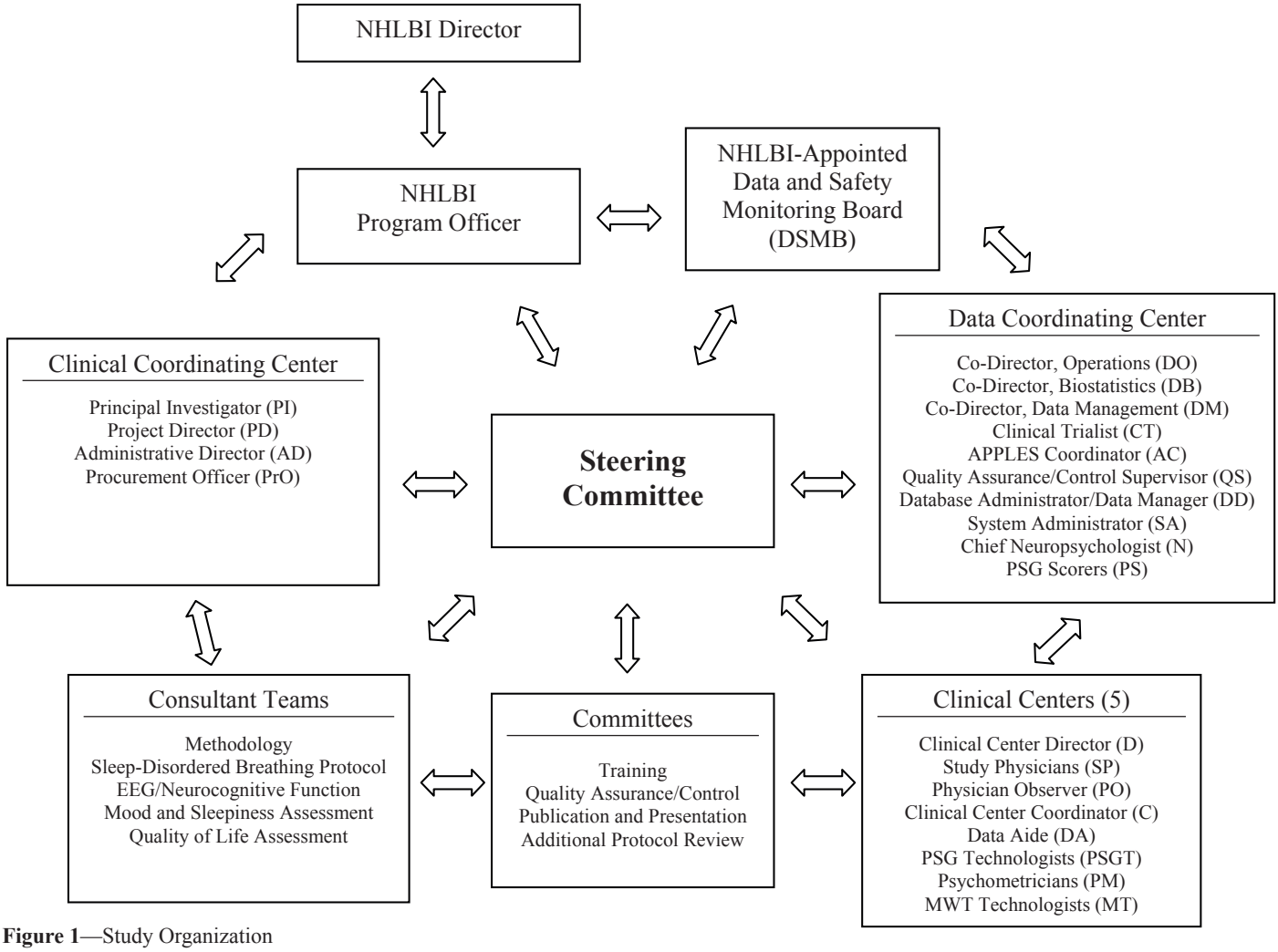

Figure 1—Study Organization

subjects with OSA to evaluate differences in patterns of cortical activation before and after CPAP therapy and to assess whether this pattern change is associated with improvement in the performance of specific neurocognitive tasks.

Two pilot studies with a total of 16 subjects (14 men and 2 women, aged 28-65 years) were completed at Stanford University in conjunction with SAM Technology and the San Francisco Brain Research Institute.[52] Eight subjects were assigned, in random order, to active CPAP and 8 to sham CPAP. All subjects gave informed consent to participate in the study, which was approved by the Stanford University Panel on Human Subjects in Medical Research. These pilot studies demonstrated the feasibility of the methods to be employed in APPLES and provided preliminary data used in power and sample-size calculations.

DESIGN, METHODS, AND PROCEDURES

Experimental Design

APPLES is an ongoing 2-arm, comparative, randomized trial. Subjects are being randomly assigned to the active-CPAP or sham-CPAP group at a 1:1 ratio in a permuted block design. Subjects are enrolled at the 5 APPLES Clinical Centers (Stanford University, Stanford, CA; University of Arizona, Tucson, AZ; St. Mary Medical Center, Walla Walla, WA; St. John's/St. Luke's Hospitals, Chesterfield, MO; and Brigham and Women's Hospital, Boston, MA). All subjects are assessed for 6 months on the arm to which they are assigned. Primary analyses will be conducted in accordance with the intention-to-treat principle.

Sample Size

We set the sample size to permit detection of treatment effects at least as large as those estimated from the pilot studies with 90% power, allowing for a Type I error rate of 5%. The results from the pilot studies for the Pathfinder Number Test (see Primary Outcomes section) set the sample size because this test requires the largest sample size among the 3 primary outcome measures. Allowing for 3 interim analyses and a 20% dropout rate that was estimated based on our clinical research experience and 2 prospective population studies measuring long-term CPAP adherence,[53, 54] our target is to randomly assign 1100 subjects.

Study Organization and Administration

The study's organizational structure is detailed in Figure 1. The Clinical Coordinating Center and the Data Coordinating Center are located at Stanford University.

Subject Inclusion and Exclusion Criteria

Data regarding the inclusion and exclusion criteria for subjects are listed in Table 2. To enhance the generalizability of our find-

Table 2—Inclusion and Exclusion Criteria

Inclusion Criteria

1. A diagnosis of OSA, as defined by the AASM Task Force[69] OSA diagnostic criteria, and a RDI ≥ 10 by polysomnography
2. Male or female sex
3. Age ≥ 18 y

Exclusion Criteria

1. Prior treatment for OSA with CPAP or surgery (prior oral appliance usage is permitted as long as the subject has not utilized the oral appliance for at least 1 month prior to the diagnostic appointment)
2. An oxygen saturation < 75% for > 10% of the diagnostic sleep study. Additionally, if a subject has an oxygen saturation < 75% for > 25% of the first 4 h of the diagnostic sleep study, the subject will be excluded from further participation in the study.
3. A near-miss or prior automobile accident due to sleepiness within the past 12 months
4. Use of hypnotics, anxiolytics, sedating antidepressants, anticonvulsants, sedating antihistamines, stimulants, or other medications likely to affect neurocognitive function and/or alertness (Exclusionary medications are listed in the APPLES MOP).[72] For subjects on approved medications, a stable dosage for 2 months is required. If subjects are taking medications that are on the exclusionary list either chronically or on a PRN basis, they will be required to stop these medications for either a 2-week period or 5 half-lives of the medications, whichever is the longer period of these 2 alternatives.
5. Congestive heart failure (defined as a prior clinical diagnosis, an ejection fraction cutoff of 40%, or a clinical warning from a primary care physician or cardiologist); coronary artery disease unless stable for at least 6 months and considered by the Study Physician to have stable disease; or history of angina, myocardial infarction, or stroke. An abnormal screening electrocardiogram is also grounds for exclusion, at the discretion of the Study Physician.
6. Cardiac rhythm disturbance (defined as a 5-beat run of sustained ventricular tachycardia or bradycardia if < 30 beats per min for a 10-second run or previously undiagnosed and untreated atrial fibrillation or Mobitz II or third-degree heart block)
7. Respiratory disease requiring medications (may include patient with lung disease [e.g., asthma] if on stable medications for 2 months or subject is taking PRN medications—at the discretion of the Study Physician)
8. Chronic neurologic disorders affecting neurocognitive abilities or daily function
9. Cancer, unless in remission for more than 1 year and not taking exclusionary medications. An individual with a small basal cell carcinoma (without metastasis) that was excised with wide margins may be included at the discretion of the Study Physician.
10. Self-reported renal failure
11. Pregnancy anytime during a subject's participation in the study
12. Psychiatric illness, as defined by a DSM-IV axis I diagnosis, except for depression or mild anxiety. Depressed patients will be excluded only if using sedating medication, if they have not been on a stable dose of medication for 2 months, or if the Study Physician judges their depression to be poorly controlled or severe (HAM-D score > 24 or suicidal ideation and plan). Mildly anxious patients will be excluded if they are using sedating medication, if they have not been on a stable dose of medication for 2 months, or if the Study Physician judges their anxiety to be poorly controlled.
13. Narcolepsy, idiopathic hypersomnolence, DSM-IV chronic insomnia, restless legs syndrome, REM sleep behavior disorder, or any other sleep disorder specified in the APPLES MOP.[72]
14. Current use of diurnal or nocturnal supplemental oxygen
15. Significant vision, hearing, or coordination problems
16. Difficulty understanding or speaking English
17. Currently working night or rotating shifts
18. Consumption of > 10 caffeinated beverages per day (approximately 1000 mg per day)
19. Smokers whose habit interferes with the overnight PSG or with the battery of testing during the day
20. Consumption of > 2 alcoholic beverages per day
21. Any illicit drug usage or marijuana usage > 1/wk
22. Any individual in the household currently on CPAP or on CPAP in the past
23. A score ≤ 26 on the MMSE

AASM refers to the American Academy of Sleep Medicine; RDI, respiratory disturbance index; PRN, pro re nata, as needed; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-D, Hamilton Rating Scale for Depression; REM, rapid eye movement; MMSE, Mini Mental State Examination; for additional abbreviations, please refer to Table 1.

ings, APPLES does not have a minimum threshold for educational level or intelligence.

Visits and Procedures

The tests, measures, and procedures for each of the 9 or more separate study visits are listed in Table 3.

Clinical Evaluation

The clinical evaluation consists of informed consent, discussion of alternative treatments, baseline testing, screening questionnaires, and a clinical evaluation by a Study Physician.

Training Session 1

Training session 1 entails neurocognitive test training and the administration of psychological tests, screening questionnaires, and screening interviews.

Training Session 2

Training session 2 entails additional neurocognitive test training and the administration of psychological tests.

Diagnostic Polysomnography Visit

The diagnostic polysomnography (PSG) visit involves an overnight diagnostic sleep study, questionnaires, Maintenance of Wakefulness Test (MWT), and the neurocognitive test battery.

Table 3—APPLES Tests, Measures, and Procedures

Test, Measure, or Procedure	Type	Visit	Duration	Notes
History and physical	X, O	CE; 4M-CPAP	20 min	a,b[72]
Physician-verified medications and medication updates	X, O	CE; T1, T2; D-PSG; C-PSG; 2M-, 4M-, 6M-CPAP	10-15 min	c[72]
Mini Mental State Examination	X	CE or T1	10 min	d[79]
Judgment of Line Orientation	X	CE or T1	5 min	[80]
Clinical Screening Questionnaire	X	CE or T1	5-10 min	a[72]
Epworth Sleepiness Scale	X, S	CE or T1; D-PSG; C-PSG; 2M-, 4M-, 6M-CPAP	5 min	e[81-84]
Morningness-Eveningness Questionnaire	X	CE or T1	10 min	[85]
Sleep Habits Questionnaire	X	CE or T1	20 min	a[72]
Bedtime Questionnaire	A	D-PSG; C-PSG; 2M-, 6M-CPAP	5 min	a[72]
Morning Questionnaire	A	D-PSG; C-PSG; 2M-, 6M-CPAP	5 min	a[72]
Sleep logs	A	D-PSG; C-PSG; 2M-, 4M-, 6M-CPAP	20 min	f
Body Mass Index; hip, waist, neck circumference	A	CE or T1; D-PSG; C-PSG; 2M-, 4M-, 6M-CPAP	10 min	[72]
Blood pressure and pulse	A	CE; D-PSG; C-PSG; 2M-, 4M-, 6M-CPAP	20 min	g
Fasting glucose, hematocrit, electrolytes	A	D-PSG	10 min	[72]
Diagnostic PSG	X	D-PSG	7-9 h	h
CPAP Titration and Post-CPAP PSG	O	C-PSG; 2M-, 6M-CPAP	7-9 h	i
Encore® Pro SmartCard®	O	C-PSG		j
Wechsler Abbreviated Scale of Intelligence	GIF	T1 or T2 or D-PSG	30 min	[86-90]
Symbol Digit Coding*	A/P	T1, T2; D-PSG; 2M-, 6M-CPAP	5 min	k[91]
Pathfinder Number Test*	A/P	T1, T2; D-PSG; 2M-, 6M-CPAP	3 min	l[92, 93]
Visual Sequence Comparison*	A/P	T1, T2; D-PSG; 2M-, 6M-CPAP	5 min	m[94]
Shifting Attention Test Instruction Condition*	A/P	T1, T2; D-PSG; 2M-, 6M-CPAP	9 min	m[94]
Psychomotor Vigilance Task*	A/P	T1, T2; D-PSG; 2M-, 6M-CPAP	10 min	[95-97]
Buschke Selective Reminding Test*	L/M	D-PSG; 2M-, 6M-CPAP	20 min	[57-60]
Symbol Digit Coding Delayed Recall Task*	L/M	T1, T2; D-PSG; 2M-, 6M-CPAP	2 min	m[94]
Sustained Working Memory Test*	E/F	T1, T2; D-PSG; 2M-, 6M-CPAP	20 min	[8-17, 63, 66-68, 98, 99]
Paced Auditory Serial Addition Task*	E/F	T1, T2; D-PSG; 2M-, 6M-CPAP	15 min	[100]
Pathfinder Combined Test*	E/F	T1, T2; D-PSG; 2M-, 6M-CPAP	3 min	l[92, 93]
Shifting Attention Test Discovery Condition*	E/F	T1, T2; D-PSG; 2M-, 6M-CPAP	9 min	m[94]
Maintenance of Wakefulness Test*	S	D-PSG; 2M-, 6M-CPAP	20 min	n[72, 101, 102]
Stanford Sleepiness Scale*	S	D-PSG; 2M-, 6M-CPAP	2.5 min	[103, 104]
Fatigue Scale*	S	D-PSG; 2M-, 6M-CPAP	2.5 min	a
Mini International Neuropsychiatric Interview*	X, M	T1 or T2; 2M-, 6M-CPAP	65 min	o[105, 106]
Hamilton Rating Scale for Depression*	X, M	T1 or T2; 2M-, 6M-CPAP	30 min	p[107, 108]
Profile of Mood States*	M	D-PSG; 2M-, 4M-, 6M-CPAP	5 min	[109, 110]
Beck Depression Inventory*	M	D-PSG; 2M-, 4M-, 6M-CPAP	10 min	q[111-113]
Calgary Sleep Apnea Quality of Life Index*	Q	D-PSG; 2M-, 4M-, 6M-CPAP	20 min	[114-116]
Quality of Well-Being Scale, Self-Administered*	Q	D-PSG; 2M-, 4M-, 6M-CPAP	10 min	[117-120]
Functional MRI	O		30 min	r

*These tests comprise the test battery. Subjects are limited to 2 caffeinated beverages (approximately 200 mg of caffeine) within 1 hr of awakening on the morning of the test battery and are only allowed to smoke during specified breaks. Bold font denotes a primary outcome measure.
In the Type column, X refers to screening; S, sleepiness; A, ancillary; GIF, general intellectual function; A/P, attention and psychomotor function; L/M, learning and memory; E/F, executive and frontal-lobe function; M, mood and psychological; Q, quality of life; O, Other.
In the Visit column, CE refers to clinical evaluation; T1 and T2, training sessions 1 and 2; D-PSG, diagnostic polysomnography visit; C-PSG, continuous positive airway pressure (CPAP) titration visit; 2M-, 4M-, 6M-CPAP, 2-month, 4- month, and 6-month post-CPAP follow-up visits. For additional abbreviations, please refer to Table 1.
In the Notes column, relevant references are shown as superscripted numbers, and letters refer to the following notes:

a. Test, measure, or procedure developed specifically for the Apnea Positive Pressure Long-term Efficacy Study (APPLES) by the APPLES Team
b. An abbreviated version of the history and physical is administered at the 4M-CPAP.
c. The physician-verified review of medications is administered by a Study Physician and the medication update is completed by staff at every subsequent visit for assessing changes in medications (including frequency and/or dosage changes) between visits.
d. A total score ≤ 26 excludes the subject from participation in APPLES.
e. A total score ≥ 18 or an endorsement of 3 on the drowsy-driving question results in immediate further evaluation of the subject by the Physician Observer (PO).

Table 3—continued

f. Each subject is asked to complete a 1-week sleep log prior to the visits, and each subject must spend at least 7 h in bed for the 3 nights prior to each follow-up session.
g. Orthostatic blood pressure and pulse procedures were adapted from the Sleep Heart Health Study protocol.
h. The subject must spend between 7 and 9 h in bed and have a respiratory disturbance index (RDI) ≥ 10. The subject is excluded from the study with an oxygen saturation < 75% for > 10% of the diagnostic sleep study or < 75% for more than 25% of the first 4 h. Attempts are made to record at least 1 hour of sleep in the supine position.
i. Prior to C-PSG, each subject will become familiar with CPAP through at least 20 min of a CPAP habituation exercise. For the C-PSG, 2M-CPAP, and 6M-CPAP visits, the subject must spend between 7 and 9 h in bed, and attempts are made to record at least 1 hour of sleep in the supine position. Pressure may be modified at the 2M- and 6M-CPAP visits.
j. The SmartCard® is placed in the CPAP machine at the C-PSG visit, and subsequent cards are mailed at 2-wk intervals and collected at each visit up to and including the 6M-CPAP visit.
k. CogScreen® computer analogue of the Digit Symbol Substitution Test (DSST)
l. Pathfinder Number and Pathfinder Combined are the CogScreen® computer analogues of the Trail Making Test Part A and Trail Making Test Part B.
m. Test developed by CogScreen®
n. Four 20-min trials at 10:00 AM, 12:00 noon, 2:00 PM, and 4:00 PM. A trial will be ended after 20 minutes or after 3 consecutive 30-second epochs of any stage of sleep, whichever occurs first. Once a trial is terminated, the room lights are turned on and the subject is asked to open his or her eyes, stay seated in bed, and remain awake until the 20 min of the trial have elapsed.
o. Any subject with an Axis I psychiatric diagnosis other than depression, dysthymia, or mild anxiety (social phobia or generalized anxiety disorder) is excluded from participation. Low, medium, or high suicide risk on the suicide module results in immediate further evaluation of the subject by the PO.
p. A total score ≥ 24 results in exclusion, and a score of ≥ 1 on the suicide module results in immediate further evaluation of the subject by the PO.
q. A score of 1, 2, or 3 on the suicide question results in immediate further evaluation of the subject by the PO.
r. Functional magnetic resonance imaging scans while the subjects are performing tests of neurocognitive function are obtained from a subset of APPLES subjects at baseline and post-CPAP to assess changes in cortical activation.

CPAP Titration Visit

The CPAP titration visit occurs within 4 ± 3 weeks after the diagnostic PSG and includes an overnight CPAP titration PSG study and the administration of questionnaires.

Two-month Post-CPAP Follow-up Visit

The 2-month post-CPAP follow-up visit represents a follow-up overnight CPAP titration PSG study, with questionnaires, psychological tests, MWT, and the neurocognitive test battery. During this visit, the subject uses his or her own CPAP device (active or sham), which is also true for the 6-month post-CPAP follow-up visit. CPAP pressures may be adjusted during these visits for those in the active-CPAP condition if necessary.

Four-month Post-CPAP Follow-up Visit

The 4-month post-CPAP follow-up visit consists of questionnaires and a follow-up appointment with a Study Physician that includes a physical examination and discussion of CPAP adherence, protocol compliance, safety issues, and changes in medications.

Six-month Post-CPAP Follow-up Visit

The 6-month post-CPAP follow-up visit uses the same sleep study, tests, and questionnaires as the 2-month post-CPAP visit.

Additional Follow-up Visit

An additional follow-up visit allows the subject to discuss any issues or problems, especially with respect to CPAP adherence and safety issues. Subjects are encouraged to contact the staff with any questions; at times, subjects may request an extra visit to resolve a problem. CPAP pressure is not adjusted ad-hoc, only at the 2-month, 4-month, and 6-month post-CPAP visits; a non-blinded Study Physician must approve any change in pressure.

Exit Interview

The exit interview gives the subject an opportunity to start active CPAP (for subjects who had been in the sham group) or continue active CPAP (for those in the active group), or to pursue other OSA treatment options. Prior to being informed of his or her treatment condition, the subject is asked to judge to which treatment condition he or she was assigned; this information will allow us to assess whether the therapy blind was maintained. Subjects are compensated as they complete study visits, up to a total of $500 if all visits are completed.

Optional Follow-up Visits Upon Completion

Optional follow-up visits upon completion of the study may occur if the subject agrees to further participation. For these visits, the subject is asked to complete any or all of the questionnaires, interviews, procedures, or tests. The frequency and duration of the follow-up is at the discretion of each Clinical Center.

Primary Outcomes

The primary outcomes are 3 neurocognitive measures, each representing 1 of 3 different neurocognitive domains: (1) attention and psychomotor function, (2) learning and memory, and (3) executive and frontal-lobe function. The primary outcomes are described below and listed (along with the secondary outcomes) in Table 3.

The Pathfinder Number Test

The Pathfinder Number Test assesses attention and psychomotor function, requiring the subject to scan, locate, and connect numbers in sequence. The Pathfinder Number is the computer

analogue of the Trail Making Test Part A. An association between performance on the Trail Making Test Part A and OSA severity has been reported.[55,56]

The Buschke Selective Reminding Test

The Buschke Selective Reminding Test is a measure of verbal learning and memory that can distinguish between short-term and long-term memory components.[57,58] The APPLES version consists of a series of 12 unrelated words presented over 6 selective reminding trials or until the subject is able to recall the entire list on 3 consecutive trials.[59,60] A delayed-recall trial is given with forewarning 30 minutes after the completion of the test. The Buschke Selective Reminding Test has been used to demonstrate a learning deficit in patients with moderate to severe OSA.[61]

The Sustained Working Memory Test

The Sustained Working Memory Test assesses executive and frontal-lobe function by requiring the subject to compare the spatial position of a stimulus with the position of the stimulus that occurred on a previous trial, pressing one button if the spatial position was the same as that on the previous trial or a second button if it differed. In the easiest version of the task, subjects compare each stimulus to the stimulus that immediately preceded it. In a higher difficulty (increased working-memory load) level, subjects compare the position of the current stimulus with that presented 2 trials previously. Behavioral and electroencephalographic (both background electroencephalographic and event-related potential) parameters are extracted from the resulting data. These measures are combined to yield a composite score indicating the degree of change from pretreatment baseline. Studies have demonstrated that this method is sensitive to changes in alertness induced by pharmacologic agents[62-65] or by sleep deprivation,[8,66] and neuroimaging studies have indicated that this task activates dorsolateral and medial frontal lobe areas, as well as superior parietal cortex and other brain regions.[67,68]

Polysomnography

PSG consists of monitoring of the electroencephalogram (C_3-A_2 or C_4-A_1, O_2-A_1 or O_1-A_2), electrooculogram (ROC-A_1, LOC-A_2), chin and anterior tibialis electromyograms, heart rate by 2-lead electrocardiogram, snoring intensity (anterior neck microphone), nasal pressure (nasal cannula), thoracic and abdominal movement (inductance plethysmography bands), and oxygen saturation (pulse oximetry). Similar PSG equipment (Respironics® Alice® 4 or Alice® Host) and identical nasal cannulae and inductance bands are used at all Clinical Centers. Additional electrodes necessary for the MWT and neurocognitive test battery the following day are also applied with the above montage. These extra electrodes are placed on the face (RUE and RLE) for detecting vertical eye movements during the MWT and on the scalp (P_3, P_4, F_3, F_4, T_5, T_6, FP_1, FP_2, F_z, FP_3) for obtaining additional electroencephalographic data during the neurocognitive test battery. Administration guidelines regarding the overnight PSG (e.g., time in bed, oxygen saturation cutoff values) and MWT are described in Table 3. OSA is diagnosed in APPLES subjects using American Academy of Sleep Medicine Task Force (1999) OSA diagnostic criteria,[69] with the exception that a respiratory disturbance index or apnea-hypopnea index (apneas + hypopneas per hour of sleep) of 10 or more obstructed breathing events per hour of sleep is our PSG criterion for OSA. The use of this elevated cutoff value reduces the number of equivocal or false-positive cases of OSA in our sample. Modified American Academy of Sleep Medicine Task Force criteria[69] are also utilized to classify the obstructive respiratory events as apneas/hypopneas and to classify OSA severity: 10.0 to 15.0 events per hour of sleep (mild), 15.1 to 30.0 events per hour of sleep (moderate), and more than 30 events per hour of sleep (severe). Site personnel review the PSG record to determine whether the subject meets the APPLES PSG criteria for OSA, and this is confirmed by the Data Coordinating Center Central PSG Reading Center. The subject is informed of his or her diagnosis, treatment options for OSA are discussed, and the subject is asked if he or she agrees to further participate in the study. All PSG records are subsequently scored, both manually and visually, at the Data Coordinating Center Reading Center (minimum of 8 registered PSG Technologists) using Rechtschaffen and Kales criteria for sleep staging[70] and the American Academy of Sleep Medicine Task Force criteria for scoring abnormal respiratory events.

Randomization

The Biostatistics component of the Data Coordinating Center directs the randomization procedure. Randomization is performed using permuted blocks, with strata defined by sex, race/ethnicity, and OSA severity. This randomization design minimizes confounding of subpopulations with treatment assignment (active versus sham CPAP). A Data Coordinating Center computer randomly assigns each subject using a unique subject identification code once the Database Administrator/Data Manager confirms that all inclusion and exclusion criteria are met.

Continuous Positive Airway Pressure

A CPAP titration study is conducted for subjects in both the active- and sham-CPAP treatment arms in which the PSG Technologist manually but remotely adjusts the subject's CPAP pressure throughout the night. In addition, all subjects are asked to wear CPAP (while awake) for at least 20 minutes prior to the study to become accustomed and habituated to using the CPAP device while sleeping. A CPAP mask, a connecting hose, and a Respironics® REMstar® Pro CPAP system (with a heated humidifier) are subsequently set up for each subject. A Respironics® Encore® Pro SmartCard® is programmed to monitor CPAP adherence. The sham-CPAP device closely simulates the airflow through the exhalation port and the operating noise of the active-CPAP device. Prior studies[71] using a functionally similar sham-CPAP device revealed that oxygen saturation, end-tidal CO_2, and mean temperature and humidity measured at the CPAP mask were the same with active versus sham-CPAP. These earlier studies also found no significant differences in sleep parameters or the number of abnormal respiratory events between the sham-CPAP group and a no-treatment group in 10 men with OSA.

Special Considerations

Protocol and Treatment Adherence

The APPLES Data Coordinating Center quality assurance/quality control program monitors subject and staff adherence to the protocols of the APPLES Manual of Operations.[72] All protocol deviations and violations are reported to the Data Coordinating

Center. Protocol deviations and violations are directly managed by the Quality Assurance/Quality Control Supervisor but may require consultation with the Project Director, Principal Investigator, and/or the Data Coordinating Center Co-Directors. Protocol deviations and violations are regularly submitted in a report to the Steering Committee and the Data and Safety Monitoring Board A special advisory committee (APPLES Biostatisticians, a Study Physician, and the Database Administrator/Data Manager) makes recommendations to the Steering Committee when it is unclear whether an event should be classified as a deviation or a violation and when a question arises related to the outcome of an event (e.g., merits subject disqualification from APPLES).

Treatment adherence is an important factor for CPAP; even 1 night without CPAP can reverse virtually all of the sleep and daytime alertness gains derived from CPAP usage.[73] Studies have demonstrated that CPAP-related education and close monitoring of subjects with OSA significantly improved CPAP adherence.[74] Every subject in APPLES is encouraged to contact the Clinical Center for any CPAP-related problems that occur throughout the study; nonblinded personnel address these problems. Subjects are contacted by staff twice within a week of starting CPAP to ensure adequate CPAP use (defined as ≥ 4 hours use per night) and to manage any problems that may initially develop. Additional phone calls or an office visit may be scheduled if the subject is experiencing difficulty adjusting to CPAP or is using CPAP for less than 4 hours per night.

CPAP adherence is assessed objectively using the REMstar® Pro CPAP system equipped with an Encore® Pro SmartCard® port. The adherence data are automatically transferred to the SmartCard®, and the subject mails the cards to the Clinical Center approximately every 2 weeks. In the event that the SmartCard® data reveals less than 4 hours of CPAP usage, subjects are contacted by Clinical Center staff to discuss CPAP nonadherence and methods to increase usage.

Blinding Issues

Site personnel are blinded, with the exception of those whose duties prevent them from being blinded. The nonblinded personnel are limited to the Clinical Center Coordinators, the PSG Technologist conducting the active- or sham-CPAP titration study, and the Database Administrator/Data Manager (who has no contact with subjects). Specific rules of interaction have been developed to prevent unblinding of the subject by the Coordinators and PSG Technologists.

Safety Issues

It is recognized that there is always an inherent risk to subjects in placebo-controlled trials.[75] The potential safety risks for untreated OSA necessitated limiting the treatment-period duration; despite this concern, patients generally use CPAP for their entire lifetime, so some may argue that this study should not be considered "long-term." However, regardless of the terminology, the major potential safety risk to participants in APPLES derives from the delay in any OSA treatment for up to 7 months in subjects randomly assigned to sham CPAP. Potential risks for untreated OSA include drowsiness-related accidents, OSA-linked exacerbation of mood disorders and suicidality, high blood pressure, stroke, myocardial infarction, heart failure, and sudden death due to cardiac arrhythmia. Safety monitoring for APPLES subjects is of paramount importance because the risks associated with the usage of sham CPAP are not well defined. The APPLES safety plan is divided into 4 components: (1) staff safety training—staff are trained to recognize high-risk behaviors often associated with OSA; (2) subject baseline health assessment—history and physical examination, electrocardiogram, blood tests, urine pregnancy test, mental status, and mood assessments are conducted to evaluate baseline risk, to screen subjects, and to serve as a comparator to identify and interpret any changes in the subject's health during the study; (3) subject safety education—starting with the informed consent process, specific standardized educational topics include the risks and avoidance of drowsy driving, drowsiness effects on daily living, and CPAP care and use; and (4) subject monitoring—to reduce the likelihood of high-risk behaviors that may be associated with sleep deprivation, 3 specific areas are monitored by study staff: drowsy driving, psychological disorders, and suicidal ideation.

Epworth Sleepiness Scale score cutoffs are used to assess drowsy-driving risk. Cutoff points for the Mini International Neuropsychiatric Interview modules on depression, anxiety, and suicidality; Hamilton Rating Scale for Depression; and Beck Depression Inventory are used to assess risks associated with psychological disorders and suicidal ideation.

A Physician Observer plays an important role in APPLES safety monitoring. The primary responsibilities of this independent, blinded "safety officer" are to evaluate all adverse events, to determine whether a subject is at unacceptably increased risk while in the study, and to decide whether the subject should continue participation or be discontinued in order to seek a treatment modification. The Physician Observer has 3 scheduled contacts with each subject (1 month, 3 months, and 5 months after the initiation of CPAP), during which the following general topics are explored: hospitalizations/doctor visits, accidents/near-miss accidents, mood/suicidal ideation, treatment-related problems, and any other problems. The Data Coordinating Center monitors all safety data and summarizes these data in regular safety reports. Additionally, the Data and Safety Monitoring Board conducts a periodic evaluation of patient safety by blinded treatment group and at each interim analysis.

In the event of a serious adverse event, irrespective of whether it is related to therapy, key APPLES personnel at the Clinical Center, Data Coordinating Center, and Clinical Coordinating Center; Steering Committee; National Heart, Lung, and Blood Institute Program Officer; Data and Safety Monitoring Board; Institutional Review Board of the Clinical Center (as appropriate); and the Institutional Review Board of the Data Coordinating Center are notified within 72 hours if the event is life threatening or fatal and within 15 calendar days for all other serious adverse events. An adverse event that does not meet criteria for a serious adverse event is reported to the Data and Safety Monitoring Board at conference calls and face-to-face meetings.

Data Management

Data Collection and Transfer

Research data collected and then transferred to the Data Coordinating Center are in 3 forms: (1) primary data input, which consists of raw data passed from the subject directly to a computer, either by electrodes attached to the subject and connected to the computer or by the subject performing a task on the computer

(e.g., PSGs, MWTs, and the majority of the neurocognitive test battery); (2) data recorded and stored in peripheral devices, which are transferred to a computer via a special interface device (e.g., Encore® Pro SmartCard® CPAP adherence data); and (3) forms and questionnaires, which are recorded on paper and subsequently entered into the database.

Processing of data at the Data Coordinating Center is through an integrated data management system that includes registration, encryption, tracking, storage, cleaning, and querying of subject data. Input to the database from the Clinical Centers is primarily via the password-protected APPLES Web site. A specialized mechanism has been designed to link a unique Subject ID number with all entered and imported data from the Clinical Centers. Further, tracking of subject data is performed using the linked Web site interface/SQL Server database. The Clinical Centers access this Web site to create new subjects and to enter data for existing subjects. Large data files, such as those from PSGs and MWTs, are uploaded to the file transfer protocol server by the Clinical Centers and imported into the database by the Data Coordinating Center.

Data Review and Quality Control

The Data Coordinating Center is responsible for developing and implementing quality control and for ensuring that data-collection procedures for all sites are uniform and of the highest quality. Several front-end quality assurance/quality control procedures are implemented to ensure data quality: (1) a double data-entry system automatically identifies and requests resolution for any unmatched data entries by Data Aides at the Clinical Centers; (2) a field-type error-detection protocol flags incorrect field-type entries and will not allow blank entries; (3) data-entry ranges are restricted by preset inner bounds and outer bounds that are encoded in the Web site via Java Script, which provides immediate feedback to Data Aides at the Clinical Centers through messages if the bounds are exceeded; and (4) safety and exclusion flags alert Data Aides at the Clinical Centers if certain responses qualify as safety concerns or exclusions (e.g., an Epworth Sleepiness Scale total score ≥ 18).

The Data Coordinating Center conducts several independent back-end quality assurance/quality control procedures: (1) The Data Coordinating Center Database Administrator/Data Manager checks all computer or hardcopy files for correct formatting, missing or duplicate data, valid ranges, and internal consistency; (2) the Data Coordinating Center conducts statistical quality control using univariate and multivariate outlier detection (i.e., methods to detect abnormal or outlying data); (3) for data manually entered by the Clinical Center into the Web site, the Data Coordinating Center conducts random pulls of up to 5% of the original source document data and compares these to database entries; (4) Data Coordinating Center staff conducts annual site audits of data integrity and data-handling procedures of the Clinical Centers; (5) the Data Coordinating Center uses specialized quality assurance/quality control queries to screen the database for errors; (6) inter-rater reliability assessments are conducted for PSGs and MWTs blindly scored by the Data Coordinating Center PSG Technologists, and the Data Coordinating Center is responsible for further quality assurance/quality control procedures for these data; (7) for the Hamilton Rating Scale for Depression quality control, a sampling of the audiotapes recorded during the interviews are sent to the Data Coordinating Center and Psychometricians at the Clinical Centers are asked to independently score a standardized videotaped Hamilton Rating Scale for Depression interview for interrater reliability assessment on a biannual basis; and (8) the Data Coordinating Center has procedures for assessing its own performance, such as periodic evaluation of data collection and flow, data processing and analysis time, and procedures to minimize data errors.

Data Confidentiality, Security, and Storage

Procedures are in place to monitor HIPAA (Health Insurance Portability and Accountability Act) compliance in all study procedures performed at each Clinical Center. Each subject is assigned a unique Subject ID number upon enrollment by the Data Coordinating Center that is used on all APPLES data. Multilevel security access, password protection, and file locking protect the security and confidentiality of subject databases in both Data Coordinating Center and Clinical Center computers. Confidential subject-identifying information remains at the Clinical Centers in secure files. Additionally, all study personnel sign a statement of confidentiality. The Data Coordinating Center serves as the primary central repository for all collected data, and the Clinical Center computers, Data Coordinating Center server, and file transfer protocol server are backed up on hourly, daily, and weekly schedules using different storage media and on-site and off-site servers. All data transfers utilize secured protocols.

Primary Data Analyses

One of the roles of the Data Coordinating Center is to conduct statistical analyses in preparation for publication. The Type I error rate for all statistical tests is set at 0.05. Baseline characteristics of study subjects will be summarized with descriptive statistics (i.e., means, standard deviations).

The primary endpoint of APPLES is the effect of CPAP on neurocognitive function. The primary outcome measures for the study are the Pathfinder Number Test, Buschke Selective Reminding Test, and Sustained Working Memory Test. We will compare the slope over time of the active-CPAP group with that of the sham group for each of the 3 primary outcome measures using generalized estimating equations, in which, under the null hypothesis, the difference in slopes is expected to be equal to 0. Secondary analyses will be conducted and detailed in subsequent reports.

Interim analyses will be conducted when 25%, 50%, and 75% of the subjects recruited have completed their 6-month post-CPAP visit. Stopping rules will permit early termination of the trial if the estimated treatment difference is sufficiently large. Specifically, stopping boundaries at interim have been set using a 2-sided Type-I error spending function,[76] which approximates boundaries of O'Brien and Fleming.[77] An O'Brien–Fleming-type procedure is less likely than other stopping rules (e.g., Pocock[78]) to cause stopping during early stages of the study, thereby reserving most statistical power for end-of-study hypothesis testing. In addition, results of interim safety analyses assist the Data and Safety Monitoring Board in comparing risks due to motor vehicle accidents or cardiovascular disease between sham- and active-CPAP groups.

Procedures for Minimizing Possible Biases and Limitations

Internal Validity

Treatment selection is unbiased because subjects are randomly assigned to active or sham CPAP. In addition, the double blind coupled with procedures to maximize retention will mitigate these sources of potential bias.

External Validity

Use of 5 sites that are dissimilar in locale, patient populations, practice setting, and physician specialty increase generalizability of the study. The study protocol was designed to parallel the standards of practice for the diagnosis and treatment of OSA in clinical sleep medicine.

Test Selection

The test battery was composed by teams of experts specializing in each area under study (neurocognitive function, mood, sleepiness, and quality of life). The likelihood that the tests are not valid or reliable has been reduced by the careful selection of the tests by these experts following an extensive literature review.

Controls

Data sets are available from healthy normal controls for all of the tests selected for this study, including our primary neurocognitive outcome measures. These data serve as standards of comparison for the subsequent analyses and interpretation of data from the active- and sham-CPAP groups.

Detectable Placebo

Questioning of the subjects from the pilot studies revealed that they were unsure whether they received active- or sham-CPAP devices. To a patient with OSA who is naïve to CPAP use, the active- and sham-CPAP devices are practically indistinguishable. During the exit interview, the subjects are asked whether they believe they were assigned to the active- or sham-CPAP condition to assess whether the therapy blind was maintained.

Recruitment

The APPLES Web site provides a live enrollment and randomization report available to the Steering Committee and Quality Assurance/Quality Control Committee so that they may track subject recruitment study wide and by site. Specific enrollment and randomization targets are monitored by the Data Coordinating Center, and predetermined corrective measures are implemented to achieve study targets.

Dropouts

Education and close monitoring of subjects with OSA while they are enrolled in the study, especially while they are on CPAP, are paramount to the study because these practices have been shown to minimize dropouts and significantly improve CPAP adherence.[74] The use of newer technologies such as the Respironics® SmartCard® enables frequent and accurate assessment of CPAP adherence, allowing Clinical Center personnel to rapidly identify and remedy the source of any potential reduction in treatment adherence.

DISCUSSION

APPLES is a long-term study designed to test the effectiveness of CPAP therapy. Upon completion, it will be the largest clinical trial in the field of sleep medicine. The primary goal of APPLES is to test the hypothesis that CPAP therapy results in significant, stable, and long-term benefits to patients with OSA. APPLES is evaluating this hypothesis by administering a comprehensive, yet novel, test battery containing measures of neurocognitive function, mood, sleepiness, and quality of life to a large group of subjects with OSA who are assigned to either active- or sham-CPAP therapy in a randomized, double-blinded design for a 6-month period. The major safety risk of the study is the lack of any OSA treatment during the 7 months after enrollment for subjects randomly assigned to the sham-CPAP group; however, the potential risks of untreated OSA are minimized by intensive safety monitoring throughout this time period. The most important potential outcomes of the study are to assess the long-term clinical benefit of CPAP therapy in the domains of neurocognitive function, mood, sleepiness, and quality of life. We anticipate that APPLES will provide health-care practitioners and the general public with evidence for the efficacy or inefficacy of CPAP therapy on the important consequences of this prevalent sleep-related breathing disorder.

ACKNOWLEDGEMENTS

APPLES is funded by the NHLBI (HL68080). The APPLES pilot studies were supported by grants from the American Academy of Sleep Medicine and the Sleep Medicine Education and Research Foundation to Stanford University and by the NINDS (N44NS002394) to SAM Technology. Respironics®, Inc. supplied the active- and sham-CPAP devices and equipment.

REFERENCES

1. National Institute of Neurological Disorders and Stroke (National Institutes of Health). Brain Basics: Understanding Sleep. Available at: http://www.ninds.nih.gov/disorders/sleep_apnea/detail_sleep_apnea.htm. Accessed: June 9, 2006.
2. Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. Am Rev Respir Dis 1988;138:337-40.
3. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829-36.
4. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. Sleep;20:1077-85.
5. Weiss JW LS, Anand A. Cardiorespiratory Changes in Sleep-Disordered Breathing. Philadelphia: WB Saunders; 2000.
6. Engleman HM, Kingshott RN, Martin SE, Douglas NJ. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 2000;23 Suppl 4:S102-8.
7. Decary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 2000;23:369-81.
8. Gevins A, Smith ME. Detecting transient cognitive impairment with EEG pattern recognition methods. Aviat Space Environ Med 1999;70:1018-24.
9. Gevins A, Smith ME, Le J, et al. High resolution evoked potential imaging of the cortical dynamics of human working memory. Electroencephalogr Clin Neurophysiol 1996;98:327-48.
10. Gevins A, Smith ME, Leong H, et al. Monitoring working memory load during computer-based tasks with EEG pattern recognition

methods. Hum Factors 1998;40:79-91.
11. Gevins A, Smith ME, McEvoy L, Yu D. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb Cortex 1997;7:374-85.
12. Gevins AS, Bressler SL, Cutillo BA, et al. Effects of prolonged mental work on functional brain topography. Electroencephalogr Clin Neurophysiol 1990;76:339-50.
13. Gevins A, Smith ME. Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. Cereb Cortex 2000;10:829-39.
14. Gevins A, Cutillo B. Spatiotemporal dynamics of component processes in human working memory. Electroencephalogr Clin Neurophysiol 1993;87128-43.
15. McEvoy LK, Smith ME, Gevins A. Test-retest reliability of cognitive EEG. Clin Neurophysiol 2000;111457-63.
16. McEvoy LK, Smith ME, Gevins A. Dynamic cortical networks of verbal and spatial working memory: effects of memory load and task practice. Cereb Cortex 1998;8:563-74.
17. Smith ME, McEvoy LK, Gevins A. Neurophysiological indices of strategy development and skill acquisition. Brain Res Cogn Brain Res 1999;7:389-404.
18. Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. Sleep. 1987;10:254-62.
19. Fix AJ, Golden CJ, Daughton D, Kass I, Bell CW. Neuropsychological deficits among patients with chronic obstructive pulmonary disease. Int J Neurosci 1982;16:99-105.
20. Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1982;142:1470-6.
21. Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd DG, Suratt PM. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest 1986;90:686-90.
22. Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 1991;13:950-64.
23. Valencia-Flores M, Bliwise DL, Guilleminault C, Cilveti R, Clerk A. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. J Clin Exp Neuropsychol 1996;18:197-210.
24. Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure vs placebo continuous positive airway pressure on sleep quality in obstructive sleep apnea. Chest 1999;116:1545-9.
25. Fietze I, Quispe-Bravo S, Hansch T, Rottig J, Baumann G, Witt C. Arousals and sleep stages in patients with obstructive sleep apnoea syndrome: Changes under nCPAP treatment. J Sleep Res 1997;6128-33.
26. Borak J, Cieslicki JK, Koziej M, Matuszewski A, Zielinski J. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. J Sleep Res 1996;5:123-7.
27. Feuerstein C, Naegele B, Pepin JL, Levy P. Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. Acta Neurol Belg 1997;97:96-107.
28. Montplaisir J, Bedard MA, Richer F, Rouleau I. Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. Sleep 1992;15(6 Suppl):S17-9.
29. Bedard MA, Montplaisir J, Malo J, Richer F, Rouleau I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 1993;15:330-41.
30. Kotterba S, Rasche K, Widdig W, et al. Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. J Neurol Sci 1998;159:45-50.
31. Naegele B, Pepin JL, Levy P, Bonnet C, Pellat J, Feuerstein C. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 1998;21:392-7.
32. Kingshott RN, Engleman HM, Deary IJ, Douglas NJ. Does arousal frequency predict daytime function? Eur Respir J 1998;12:1264-70.
33. Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. Am J Respir Crit Care Med 1996;153:1328-32.
34. Sforza E, Krieger J. Daytime sleepiness after long-term continuous positive airway pressure (CPAP) treatment in obstructive sleep apnea syndrome. J Neurol Sci 1992;110:21-6.
35. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353:2100-5.
36. Derderian SS, Bridenbaugh RH, Rajagopal KR. Neuropsychologic symptoms in obstructive sleep apnea improve after treatment with nasal continuous positive airway pressure. Chest 1988;94:1023-7.
37. Yamamoto H, Akashiba T, Kosaka N, Ito D, Horie T. Long-term effects nasal continuous positive airway pressure on daytime sleepiness, mood and traffic accidents in patients with obstructive sleep apnoea. Respir Med 2000;94:87-90.
38. Yu BH, Ancoli-Israel S, Dimsdale JE. Effect of CPAP treatment on mood states in patients with sleep apnea. J Psychiatr Res 1999;33:427-32.
39. Munoz A, Mayoralas LR, Barbe F, Pericas J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J 2000;15:676-81.
40. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. J Sleep Res 1997;6:199-204.
41. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:461-7.
42. Kingshott RN, Vennelle M, Hoy CJ, Engleman HM, Deary IJ, Douglas NJ. Predictors of improvements in daytime function outcomes with CPAP therapy. Am J Respir Crit Care Med 2000;161:866-71.
43. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862-65.
44. Hoffstein V, Viner S, Mateika S, Conway J. Treatment of obstructive sleep apnea with nasal continuous positive airway pressure. Patient compliance, perception of benefits, and side effects. Am Rev Respir Dis 1992;145:841-5.
45. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. Lancet 1994;343:572-5.
46. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:495-501.
47. Lojander J, Kajaste S, Maasilta P, Partinen M. Cognitive function and treatment of obstructive sleep apnea syndrome. J Sleep Res 1999;8:71-6.
48. Hack M, Davies RJ, Mullins R, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. Thorax 2000;55:224-31.
49. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. Ann Intern Med 2001;134:1015-23.
50. Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of

obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. BMJ 1997;314:851-60.
51. Stradling J. Sleep apnoea and the misuse of evidence-based medicine. Lancet 1997;349:201-2.
52. Kushida CA, Kuo T, McEvoy L, Gevins A, Guilleminault C, Dement WC. Apnea Positive Pressure Long-Term Efficacy Study (APPLES): Preliminary Studies. Sleep 2004;27(Suppl):A181-2.
53. Krieger J, Kurtz D, Petiau C, Sforza E, Trautmann D. Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. Sleep 1996;19(9 Suppl):S136-43.
54. McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:1108-14.
55. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992;152:538-41.
56. Yesavage J, Bliwise D, Guilleminault C, Carskadon M, Dement W. Preliminary communication: intellectual deficit and sleep-related respiratory disturbance in the elderly. Sleep1985;8:30-3.
57. Buschke H. Selective reminding for analysis of memory and learning. J Verbal Learn Verbal Behav 1973;12:543-50.
58. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24:1019-25.
59. Hannay HJ, Levin HS. Selective reminding test: an examination of the equivalence of four forms. J Clin Exp Neuropsychol 1985;7:251-63.
60. Hannay J, ed. Experimental Techniques in Human Neuropsychology. New York: Oxford University Press; 1986.
61. Naegele B, Thouvard V, Pepin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18:43-52.
62. McEvoy LK, Smith ME, Fordyce M, Gevins A. Characterizing impaired functional alertness from diphenhydramine in the elderly with performance and neurophysiologic measures. Sleep 2006;In Press.
63. Gevins A, Smith ME, McEvoy LK. Tracking the cognitive pharmacodynamics of psychoactive substances with combinations of behavioral and neurophysiological measures. Neuropsychopharmacology 2002;26:27-39.
64. Chung SS, McEvoy LK, Smith ME, Gevins A, Meador K, Laxer KD. Task-related EEG and ERP changes without performance impairment following a single dose of phenytoin. Clin Neurophysiol 2002;113:806-814.
65. Ilan AB, Smith ME, Gevins A. Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology (Berl) 2004;176:214-22.
66. Smith ME, McEvoy LK, Gevins A. The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. Sleep 2002;25:784-94.
67. Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 1997;5:49-62.
68. Jansma JM, Ramsey NF, Coppola R, Kahn RS. Specific versus nonspecific brain activity in a parametric N-back task. Neuroimage 2000;12:688-97.
69. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
70. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. University of California Los Angeles: Brain Information Service/Brain Research Institute; 1968.
71. Farre R, Hernandez L, Montserrat JM, Rotger M, Ballester E, Navajas D. Sham continuous positive airway pressure for placebo-controlled studies in sleep apnoea. Lancet 1999;353:1154.
72. Apnea Positive Pressure Long-Term Efficacy Study (APPLES) Manual of Operations: NHLBI-APPLES; 2003.
73. Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis 1993;147:1162-8.
74. Chervin RD, Theut S, Bassetti C, Aldrich MS. Compliance with nasal CPAP can be improved by simple interventions. Sleep 1997;20:284-9.
75. Chadwick D, Privitera M. Placebo-controlled studies in neurology: where do they stop? Neurology 1999;52:682-5.
76. Lan K, DeMets D. Discrete Sequential Boundaries for Clinical Trials. Biometrika 1983;70:659-63.
77. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
78. Pocock SJ. Randomised clinical trials. Br Med J 1977;1:1661.
79. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
80. Benton AL, Hamsher K, Varney NR, Spreen O. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983.
81. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
82. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376-81.
83. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 1993;103:30-6.
84. 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 ResMar 2000;9:5-11.
85. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97-110.
86. Wechsler Abbreviated Scale of Intelligence. San Antonio: The Psychological Corporation; 1999.
87. Axelrod BN. Validity of the Wechsler Abbreviated Scale of Intelligence and other very short forms of estimating intellectual functioning. Assessment 2002;9:17-23.
88. Hays JR, Reas DL, Shaw JB. Concurrent validity of the Wechsler Abbreviated Scale of Intelligence and the Kaufman Brief Intelligence Test among psychiatric inpatients. Psychol Rep 2002;90:355-9.
89. Hilsabeck RC, Schrager DA, Gouvier WD. Cross-validation of the two- and three-subtest short forms of the Wechsler Memory Scale-Revised. Appl Neuropsychol 1999;6:247-51.
90. Hilsabeck RC, Schrager DA, Gouvier WD. External validation of the equivalence of two computational formulas for a WAIS-R seven-subtest short form. Appl Neuropsychol 1999;6:239-42.
91. Wechsler D. Wechsler Adult Intelligence Scale-Revised. San Antonio: The Psychological Corporation; 1981.
92. Army Individual Test Battery: Manual of directions and scoring. Washington: War Department, Adjutant General's Office; 1944.
93. Reitan R, Wolfson D. The Halstead-Reitan Neuropsychologic Test Battery: Theory and Clinical Interpretation. Tucson: Neuropsychology Press; 1993.
94. Kay GG. CogScreen: Professional Manual. Odessa, Florida: Psychological Assessment Resources; 1995.
95. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods Instrum Comput 1985;17:652-5.
96. Dinges DF. Probing the limits of functional capacity: the effects of sleep loss on short-duration tasks. In: Broughton RJ, Ogilvie RD, eds. Sleep, Arousal, and Performance. Boston: Birkhauser; 1992:177-88.
97. Kribbs NB, Dinges DF. Vigilance decrement and sleepiness. In: Harsh J, Ogilvie R, eds. Sleep Onset Mechanisms. Washington:

American Psychological Association; 1994:113-25.
98. Gevins A. The future of electroencephalography in assessing neurocognitive functioning. Electroencephalogr Clin Neurophysiol 1998;106:165-72.
99. Gevins A, Smith ME, McEvoy LK, Leong H, Le J. Electroencephalographic imaging of higher brain function. Philos Trans R Soc Lond B Biol Sci 1999;354:1125-33.
100. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 1977;44:367-73.
101. Mitler MM, Gujavarty KS, Browman CP. Maintenance of Wakefulness Test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol 1982;53:658-61.
102. Doghramji K, Mitler MM, Sangal RB, et al. A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol 1997;103:554-62.
103. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology 1973;10:431-6.
104. Herscovitch J, Broughton R. Sensitivity of the Stanford Sleepiness Scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. Sleep 1981;4:83-91.
105. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22-57.
106. Sheehan DV, Lecrubier Y. M.I.N.I.: Mini International Neuropsychiatric Interview. English Version 5.0.0: Tampa: University of South Florida; 1992.
107. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
108. Marder SR. Psychiatric Rating Scales. Vol 1. 6th ed. Baltimore: Williams & Wilkins; 1995.
109. McNair DM, Lorr M, Droppleman L. Profile of Mood States. Boston: Boston University School of Medicine; 1981.
110. Nyenhuis DL, Yamamoto C, Luchetta T, Terrien A, Parmentier A. Adult and geriatric normative data and validation of the profile of mood states. J Clin Psychol 1999;55:79-86.
111. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory. 2nd ed. San Antonio: The Psychological Corporation; 1993.
112. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
113. Lasa L, Ayuso-Mateos JL, Vazquez-Barquero JL, Diez-Manrique FJ, Dowrick CF. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. J Affect Disord 2000;57:261-5.
114. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. Am J Respir Crit Care Med 1998;158:494-503.
115. Flemons WW, Remmers JE. The diagnosis of sleep apnea: questionnaires and home studies. Sleep 1996;19(10 Suppl):S243-7.
116. Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. J Allergy Clin Immunol 1997;99:S750-6.
117. Kaplan RM, Ganiats TG, Sieber WJ, Anderson JP. The Quality of Well-Being Scale: critical similarities and differences with SF-36. Int J Qual Health Care 1998;10:509-20.
118. Kaplan RM. An outcomes-based model for directing decisions in women's health care. Clin Obstet Gynecol 1994;37:192-206.
119. Kaplan RM. Value judgment in the Oregon Medicaid experiment. Med Care 1994;32:975-88.
120. Andresen EM, Rothenberg BM, Kaplan RM. Performance of a self-administered mailed version of the Quality of Well-Being (QWB-SA) questionnaire among older adults. Med Care 1998;36:1349-60.