The Influence of CPAP on the Neurobehavioral Performance of Patients with Obstructive Sleep Apnea Hypopnea Syndrome: A Systematic Review

Joseph P. McMahon, MD; Brian H. Foresman, DO; Ronald C. Chisholm, PhD

ABSTRACT
Objective: To determine what is known about neurobehavioral outcomes in patients with the obstructive sleep apnea hypopnea syndrome following treatment with continuous positive airway pressure (CPAP).

Data Sources: Medline was searched. Abstracts presented at international meetings were searched and authors were contacted for additional trials. Bibliographies of the retrieved articles were reviewed.

Study Selection: We reviewed all prospective studies that included: 1) a target population with obstructive sleep apnea, 2) CPAP as a study intervention, 3) evidence that the CPAP level was titrated until the AHI was <5, and 4) standardized neurobehavioral outcomes appropriate for assessing sleep apnea.

Data Synthesis: Twenty-six studies contributed to this qualitative systematic review. Effect sizes were calculated and adjusted for small samples and multiple measurements. Studies were then scored according to the outcome of the study.

Conclusions: This qualitative systematic review supports the assertion that CPAP has a significant and positive impact on subjective sleepiness and depression when randomized controlled trials are considered, and on fatigue, generic health-related quality of life, vigilance, and driving performance when all prospective trials are considered. These parameters appear to be sensitive to treatment duration and compliance. These results should be considered when developing health policy and designing future clinical trials.

INTRODUCTION
The prevalence of the obstructive sleep apnea hypopnea syndrome (OSAHS), when defined as at least 5 apneas and hypopneas per hour of sleep accompanied by excessive daytime sleepiness, was 4% for males and 2% for females in a population of working adults 30 to 60 years of age.1 Perhaps more interesting is the finding that less than 10% of those who met the criteria for OSAHS sought medical attention.2 This would suggest that the majority of those with symptomatic OSAHS are currently undiagnosed. Defining the benefits of OSAHS treatment is of great interest to clinicians, researchers, health care agencies, and policy makers because of the magnitude of the population at risk.

The American Thoracic Society and American Sleep Disorders Association (ATS/ASDA) statement dealing with health outcomes research in sleep apnea3 identified neurobehavioral outcomes following continuous positive airway pressure (CPAP) therapy as an area that needed further evaluation. Neurobehavioral outcomes were defined as those that evaluated quality of life, general performance (psychomotor and cognitive function), neuropsychological assessment, and sleepiness. The therapeutic options for the management of OSAHS include weight loss,4,5 CPAP,6-9 bilevel positive airway pressure,10,11 mechanical advancement devices,12,13 and surgical procedures.14 Of these, nasal CPAP is most frequently used to treat OSAHS but its efficacy may be impaired by a low compliance rate.15-19

We performed a systematic review of prospective studies to investigate what is known about the neurobehavioral outcomes of patients with OSAHS following treatment with CPAP. The current study ex-
explores the published data and includes 26 prospective studies.

METHODS
The target population consisted of subjects with a diagnosis of obstructive sleep apnea defined as an Apnea-Hypopnea Index (AHI) >5 events per hour. The study intervention included CPAP—there needed to be evidence that the CPAP was titrated until the AHI was <5.

Outcomes of interest were consistent with the neurobehavioral classification described by the ATS/ASDA and included quality of life, psychomotor and cognitive function, neuropsychological assessment and subjective sleepiness assessment. All prospective studies, except case reports, were included.

Greater than 5 to 10 episodes of apnea or hypopnea per hour of sleep are considered beyond the broad limits of normal. CPAP treatment was defined as positive airway pressure delivered through a nasal mask, nasal prongs, or a full-face mask.

Literature Search
We used several complementary search strategies to retrieve potentially relevant articles. First, we conducted a MEDLINE search through June 1999. Three searches were conducted: 1) the target population (sleep apnea syndromes, sleep apnea, sleep apnoea, osa) was combined with (using an “and”) the target intervention (positive-pressure respiration, cpap, CPAP, positive airway pressure, positive airways pressure); 2) the target outcomes (cognition, affect, activities of daily living, quality of life, neuropsychological tests, depression, affective disorders, fatigue, hypersomnia) were combined with (using an “and”) the target intervention; and finally 3) the results of the first search were combined with the second search (using an “or”). All terms were explored and were limited to studies with English language abstracts and human adults (>18 years old). We also reviewed the reference lists of relevant articles, guidelines of the ATS/ASDA and the ASDA, and abstracts presented at national meetings to retrieve potentially relevant articles. Experts in the field were consulted about missing studies.

Article Selection
Subjects with central sleep apnea, Cheyne Stokes respiration, upper airways resistance syndrome, or obstructive sleep apnea as a consequence of neuromuscular, cardiac, or renal disease were excluded from this review. Treatment with bilevel positive airway pressure was excluded. Physiologic measures of sleepiness such as the multiple sleep latency test and the maintenance of wakefulness test were also excluded.

Data Extraction and Synthesis
A qualitative assessment of patient population, study design, treatment duration, and neurobehavioral outcome was performed. Disagreement was resolved by consensus.

Neurobehavioral test classification was based on the ATS/ASDA statement on health outcomes in sleep apnea research and included the categories sleepiness, quality of life, psychomotor and cognitive function, and neuropsychological assessments. In the ATS/ASDA statement paper, psychomotor and cognitive function tests include reaction time tests, vigilance tests, driving performance, finger tapping, and list recall, and neuropsychological assessments include standardized instruments to assess mood, anxiety, depression, memory, learning, and integrative functions. This classification system posed a problem because learning and integrative function appeared to overlap into both categories. Therefore, for this review, learning and integrative functions were considered part of psychomotor and cognitive function, which was renamed “Performance Assessment,” and the category neuropsychological was renamed “Psychological Assessment.”

We calculated an effect size for each neurobehavioral outcome for which complete assessment was possible. Due to the small sample sizes and multiple measurements in the majority of the studies, we represented the
effect size as “+” (a statistically significant difference favoring the treatment group), “0” (no significant difference), or “-” (a statistically significant difference favoring the control group). The entire study was then classified based on the overall number of individual assessments it contained as either: 1) supporting statistical improvement (+ >0); 2) failing to detect a statistical improvement (+ <0); or 3) producing no conclusion.

RESULTS

Literature Search

Nine hundred twenty-six articles were retrieved from the computerized search. Ten additional articles were retrieved following review of the references of relevant articles (n=9) and review of scientific meeting abstracts (n=1). Table 1 provides a summary of the article selection process.

Following the phase 1 screening process, 65 abstracts were identified as meeting the phase 1 inclusion criteria. The 871 abstracts were excluded for the following reasons: the study population did not have OSAHS (n=221); the study intervention did not include CPAP (n=180); the study outcome was other than neurobehavioral (compliance n=32, physiological n=112, technical n=45, biochemical n=28); the article was a case report, letter, or editorial (n=110); or other (n=143). Articles may have been rejected for more than one reason.

Sixty-five articles were evaluated during phase 2, and 28 articles were identified as meeting inclusion criteria. Articles were excluded for the following reason(s): OSAHS was not defined by either an AHI, respiratory disturbance index (RDI) or apnea index (AI) >5 (n=10); CPAP titration was not used to determine the optimal level of CPAP required to “normalize” the AHI/ RDI/AI (n=11); the instrument used to measure the neurobehavioral outcome was not described (n=14); or the neurobehavioral state was not measured prior to and following CPAP therapy (n=22).

Twenty-eight articles were evaluated during phase 3, and 2 articles were rejected for the following reasons: the manuscript did not contain new data that had not been previously published elsewhere (n=1), and it was not possible to calculate the effect size from the data provided in the article (n=1). Therefore, 26 separate trials were finally considered in the review.

Study Characteristics

Table 2 summarizes study characteristics included in this systematic review. All studies were prospective, and the majority used a single cohort design in which the neurobehavioral outcome was measured in the same cohort before and after CPAP intervention. Four studies utilized a parallel cohort design. Of these, 3 studies used a comparison cohort with OSAHS who were not treated with CPAP, and a fourth study used a comparison cohort without OSAHS. Four studies used a single cohort in which either a placebo or CPAP was applied and afterward the alternative therapy was evaluated. In these studies the sequence of the interventions was randomized. Finally, 3 studies utilized a randomized control design with 1 using nasal strips, 1 with weight loss combined with improved sleep hygiene, and 1 used sub therapeutic CPAP.

Male patients accounted for approximately 85% of the combined study population. The CPAP duration across the studies had a range of 1 night to 1 year with a mean (SD) of 4.9 (4.1) months. The neurobehavioral outcomes most often measured were performance assessment and psychological assessment.

Performance Assessment

Nineteen studies evaluated performance assessment. They measured 14 different parameters of performance...
assessments as defined by the intent of the authors. Thirty-six different instruments were used to evaluate these parameters.

Six of the 19 studies used a comparison group other than the pre CPAP treatment state. Two of the 6 studies demonstrated an overall significant improvement in performance assessment. Seven of the 13 single cohort studies demonstrated a significant performance assessment improvement. No decline in performance assessment was reported following the addition of CPAP treatment.

**Psychological Assessment**

Nine studies evaluated the impact of CPAP on psychological assessment. Eleven different instruments were used to assess psychological status and, in addition, the

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Reference Number</th>
<th>Study Design</th>
<th>Subjects (% Male)</th>
<th>Comparison Group</th>
<th>AHI Mean (SD)</th>
<th>CPAP Duration (Months)</th>
<th>Neurobehavioral Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derderian (88)</td>
<td>23 Parallel Cohort</td>
<td>7 (100)</td>
<td>Untreated SAHS</td>
<td>40.7 (5.5)</td>
<td>2</td>
<td>Psy</td>
<td></td>
</tr>
<tr>
<td>Findley (89)</td>
<td>24 Single Cohort</td>
<td>6 (83)</td>
<td>Self Pre-treatment</td>
<td>83 (20)</td>
<td>3.5</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Ramos (92)</td>
<td>25 Single Cohort</td>
<td>5 and 23 (97)</td>
<td>Self Pre-treatment</td>
<td>61.1 (21.8)</td>
<td>11</td>
<td>Psy</td>
<td></td>
</tr>
<tr>
<td>Bedard (93)</td>
<td>26 Single Cohort</td>
<td>10 (100)</td>
<td>Self Pre-treatment</td>
<td>65.4 (21)</td>
<td>6.6(1.4)</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Engleman (93)</td>
<td>27 Parallel Cohort</td>
<td>21 and 16</td>
<td>Untreated SAHS</td>
<td>57(28) &amp; 49(28)</td>
<td>6(4.6)</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Kribbs (93)</td>
<td>28 Single Cohort</td>
<td>15 (93)</td>
<td>Self Pre-treatment</td>
<td>56.6 (24.8)</td>
<td>2.5(1.7)</td>
<td>Psy; Per; S; QoL</td>
<td></td>
</tr>
<tr>
<td>Minemura (93)</td>
<td>29 Single Cohort</td>
<td>14 (100)</td>
<td>Self Pre-treatment</td>
<td>40 (20)</td>
<td>11(9)</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Engleman (94)</td>
<td>30 Randomized Crossover</td>
<td>32 (81)</td>
<td>150 mg Ranitidine</td>
<td>28</td>
<td>1</td>
<td>Psy; Per; S; QoL</td>
<td></td>
</tr>
<tr>
<td>Borak (96)</td>
<td>31 Single Cohort</td>
<td>16 (100)</td>
<td>Self Pre-treatment</td>
<td>67 (16)</td>
<td>12</td>
<td>Psy; Per</td>
<td></td>
</tr>
<tr>
<td>Cassel (96)</td>
<td>32 Single Cohort</td>
<td>59 (100)</td>
<td>Self Pre-treatment</td>
<td>38.9 (3.4)</td>
<td>12</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Meurice (96)</td>
<td>33 Single Cohort</td>
<td>8 (100)</td>
<td>Self Pre-treatment</td>
<td>0.75</td>
<td>12</td>
<td>Per; S</td>
<td></td>
</tr>
<tr>
<td>Valencia-Flores (96)</td>
<td>34 Single Cohort</td>
<td>37 (78)</td>
<td>Self Pre-treatment</td>
<td>46.7 (32.4)</td>
<td>0.067</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Engleman (97)</td>
<td>35 Randomized Crossover</td>
<td>16 (75)</td>
<td>150 mg Ranitidine</td>
<td>11(4)</td>
<td>1</td>
<td>Psy; Per; S; QoL</td>
<td></td>
</tr>
<tr>
<td>Feuerstein (97)</td>
<td>36 Single Cohort</td>
<td>10 (100)</td>
<td>Self Pre-treatment</td>
<td>53.5 (24)</td>
<td>6.5 (1.3)</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Krieger (97)</td>
<td>37 Single Cohort</td>
<td>547 (100)</td>
<td>Self Pre-treatment</td>
<td>61.3 (25)</td>
<td>12</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>George (97)</td>
<td>38 Parallel Cohort</td>
<td>18 and 17(100)</td>
<td>Untreated without SAHS</td>
<td>73 (28.9)</td>
<td>9.2(4.2)</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Bolitschek (98)</td>
<td>39 Parallel Cohort</td>
<td>16 and 67</td>
<td>Untreated SAHS</td>
<td>47.8(18.4)</td>
<td>3</td>
<td>QoL</td>
<td></td>
</tr>
<tr>
<td>Engleman (98)</td>
<td>40 Randomized Crossover</td>
<td>23 (91)</td>
<td>Placebo tablet</td>
<td>43 (37)</td>
<td>1</td>
<td>Psy; Per; S; QoL</td>
<td></td>
</tr>
<tr>
<td>Kotterba (98)</td>
<td>41 Single Cohort</td>
<td>15 (100)</td>
<td>Self Pre-treatment</td>
<td>36.9 (23.8)</td>
<td>6</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Meurice (98)</td>
<td>42 Single Cohort</td>
<td>9(100)</td>
<td>Self Pre-treatment</td>
<td>60.4(22.8)</td>
<td>0.7</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Naegele (98)</td>
<td>43 Single Cohort</td>
<td>10(100)</td>
<td>Self Pre-treatment</td>
<td>53.5(24)</td>
<td>6.5</td>
<td>Per</td>
<td></td>
</tr>
<tr>
<td>Redline (98)</td>
<td>44 Randomized Control</td>
<td>97 (52)</td>
<td>Nasal Strips</td>
<td>13.3 (9.8)</td>
<td>2.5 (0.67)</td>
<td>Psy; S</td>
<td></td>
</tr>
<tr>
<td>Ballester (99)</td>
<td>45 Randomized Control</td>
<td>105 (88)</td>
<td>Sleep hygiene/weight loss</td>
<td>56 (20)</td>
<td>3</td>
<td>S; QoL</td>
<td></td>
</tr>
<tr>
<td>D’Ambrosio (99)</td>
<td>46 Single Cohort</td>
<td>29 (79)</td>
<td>Self Pre-Test</td>
<td>77 (9)</td>
<td>2</td>
<td>QoL</td>
<td></td>
</tr>
<tr>
<td>Engleman (99)</td>
<td>47 Randomized Control</td>
<td>34 (62)</td>
<td>Placebo Tablet</td>
<td>10 (3)</td>
<td>1</td>
<td>Psy; Per; S; QoL</td>
<td></td>
</tr>
<tr>
<td>Jenkinson (99)</td>
<td>48 Randomized Control</td>
<td>107 (100)</td>
<td>Subtherapeutic CPAP</td>
<td>33 (CI 6-72)</td>
<td>1</td>
<td>S; QoL</td>
<td></td>
</tr>
</tbody>
</table>

Psy = Psychological Assessment; Per = Performance Assessment; S = Sleepiness; QoL = Quality of Life
performance on numerous subscales was reported separately. The Hospital Anxiety and Depression Scale was the most frequently used assessment tool.\textsuperscript{30,35,40,47} The Profile of Mood was administered in 2 studies\textsuperscript{23,28} but was used differently in each. In one, only results on 2 subscales were assessed, while in the other study all 6 subscales and an overall total score were assessed and analyzed. The remaining 9 instruments were not used in more than 1 study.

Six of the studies used a comparison group for CPAP treatment other than the pretreatment state. Three\textsuperscript{23,30,44} demonstrated an overall significant improvement in psychological performance, while 2 were inconclusive.\textsuperscript{35,47} Depression and anxiety were the subscales of psychological assessment most frequently measured. Five of 8 studies demonstrated a statistically significant improvement in performance on a depression scale, and 1 of 6 studies on an anxiety scale. No study reported a decline in psychological performance following treatment with CPAP.

Sleepiness
Eight studies reviewed the impact of CPAP on subjective sleepiness. Four instruments were used to measure sleepiness: 1) the Epworth Sleepiness Scale (a measure of the propensity to fall asleep), 2) the Stanford Sleepiness Scale (a subjective evaluation of sleepiness), 3) the UTWIST Mood Adjective checklist, and 4) the Psychomotor Vigilance Task. The Epworth Sleepiness Scale was used in 6 studies; the Stanford Sleepiness Scale and the UTWIST Mood Adjective checklist were each used in two.

The Epworth Sleepiness Scale demonstrated a statistically significant improvement in 5 studies, the Sanford Sleepiness Scale in two and the Psychomotor Vigilance Task in one. Only 1 study\textsuperscript{13} failed to demonstrate an improvement in subjective sleepiness with any scale. This study used a randomized crossover design with 16 subjects with a mean AHI of 11 and the follow up evaluation at 1 month. No study reported a worsening of subjective sleepiness following the administration of CPAP therapy.

Quality of Life
Quality of life was assessed in 9 studies. Four different instruments, the Nottingham Health Profile Part 2 (NHP-P2), the Sickness Impact Profile, the Munich Life Questionnaire, and the Medical Outcome Study SF-36, were utilized in these studies. The Nottingham Health Profile Part 2 was the instrument used most frequently. Six studies used a comparison group for CPAP treatment other than the pretreatment self state.\textsuperscript{30,35,39,40,47,48}

Three studies demonstrated an overall statistical improvement in quality of life, two demonstrated no impact on subscales of the SF-36, and four were inconclusive. One study,\textsuperscript{35} which failed to show an improvement in quality of life, noted that in a subset analysis that the quality of life improved significantly in the group with greater CPAP compliance (5 ± 0.6 hours versus 1.1 ± 0.2 hours, p<0.05). No study reported a significant decline in quality of life following CPAP treatment.

DISCUSSION
CPAP efficacy has been the focus of statement papers,\textsuperscript{3} review articles,\textsuperscript{50} and numerous clinical investigations. Such publications have a profound impact on clinical practice and research. Systematic reviews address a sharply defined clinical question, summarize the data, and therefore help refine research hypotheses and goals. We performed this systematic review to frame what is known about the neurobehavioral performance of patients with obstructive sleep apnea following CPAP therapy.

A systematic review may be qualitative or quantitative. A qualitative review summarizes the results of the primary studies but does not combine the results for statistical analysis. A quantitative review, also referred to as a meta-analysis, uses statistical methods to combine the results of primary studies, provided primary study design heterogeneity does not complicate the successful integration of data. Three forms of heterogeneity:\textsuperscript{51} 1) diverse study designs, 2) numerous instruments used to measure response to therapy, and 3) broad duration of CPAP therapy, prevented integrating the primary study data into a quantitative review. This current systematic review is, therefore, a qualitative review summarizing, but not integrating, the data presented in the 26 studies included in this review.

Sleepiness was the most consistently evaluated of the 4 outcome parameters researched. The evidence suggested that self-reported sleepiness improves following therapy. Sleepiness failed to significantly improve in 1 study\textsuperscript{35} of patients with “mild disease.” These same authors later published a study in which the AHI and treatment duration were similar to the former study but with twice the number of participants. This subsequent study did demonstrate improved sleepiness following CPAP treatment,\textsuperscript{47} suggesting that the first study lacked sufficient power to detect a change.

This review suggests health-related quality of life (HRQOL) may improve following CPAP therapy, and that the improvement is sensitive to both compliance.
and duration. The primary studies measured overall (generic) HRQOL. Generic HRQOL instruments are expected to be less sensitive to changes in HRQOL attributable to OSAH treatment, than would disease specific instruments such as the Functional Outcomes of Sleep Questionnaire and the Calgary Sleep Apnea Quality of Life Index. Failure to detect a significant improvement had a treatment duration of 1 month, whereas those detecting improvement had a treatment of 1 month or more. This suggests that changes in HRQOL may be sensitive to treatment duration. It is also evident that improvement in HRQOL is sensitive to CPAP compliance. Engleman performed a subgroup analysis and noted that HRQOL improved significantly in the group with greater compliance (mean use of CPAP for 5 ± 0.6 hours), compared to the noncompliant group (mean use of CPAP of 1.1 ± 0.2 hours). Redline also noted that greater compliance was associated with a greater likelihood of treatment response. Finally, using a generic measure of HRQOL, Engleman noted that better CPAP compliance resulted in a greater treatment effect size though this did not reach statistical significance.

Two outcomes of psychological assessment—fatigue and depression—responded favorably to CPAP therapy. Three studies reported a significant improvement in fatigue following 2 months or more of CPAP treatment. The outcome depression significantly improved in several studies. While failing to do so in a few, there was no difference with respect to therapy duration, subject number, or study design from those that did and did not detect an improvement in depression. The impact of CPAP on other outcomes of psychological assessment such as anxiety is not clear, in large part due to the diverse ways these parameters were evaluated.

Performance assessment was addressed as either 1) driving performance, or 2) cognition, vigilance, or 4) attention capacity. There was significant improvement in simulated driving performance and the number of automobile accidents and near accidents following CPAP therapy. Vigilance when evaluated a priori demonstrated a significant improvement following CPAP therapy.

Finally, memory efficiency—long-term memory or short-term memory—failed to significantly improve following CPAP therapy. This may not be unexpected given that a large population-based study did not detect an association between OSAHS and memory deficit. The more complex functions such as memory and executive function are felt to be more affected by hypoxemia. The level or duration of pretreatment hypoxemia endured by the subjects in these studies is unknown.

This review may be viewed as having limitations that may bias the conclusions in favor of “CPAP therapy having no impact on neurobehavioral outcome in OSAHS.” First, the effect is reported as either “significant or not” instead of in standard deviation units (effect size). Significance tests are intended solely to address the viability of the null hypothesis that a treatment has no effect, whereas the effect size estimates the magnitude (mild, moderate, large) of the treatment effect. In this review, studies with treatment effects of 0.6 or greater (data not shown) for the most part demonstrated a statistically significant improvement in test performance and as a result were designated as a “+” effect. The cases in which a large effect size did not correlate with statistical significance involved studies inadequately powered to reach statistical significance. Therefore, in a few cases in which a moderate to large treatment effect size was detected, but the change did not reach statistical significance, these were reported as “no change.” Second, this review did not combine data as would be done in a quantitative review. The possibility exists that studies with inconclusive results, when analyzed separately, would have attained significance if evaluated in aggregate. Third, this review cannot address the impact that sleep fragmentation, arousals, and hypoxemia have on neurobehavioral performance, as this information could not be abstracted from the reported data. Finally the robustness of the results might be called into question because studies other than randomized controlled trials were included. If the seven randomized trials were the only trials considered, the conclusions would require slight modification. There would be less evidence that CPAP has a significant impact on generic health-related quality of life, there would be more support for CPAP having a significant impact on depression, and finally fewer psychological and performance assessment studies would be available for analysis. In addition, recent randomized trials have shown improved quality of life, but otherwise support the above conclusions.

This qualitative systematic review supports the assertion that CPAP has a significant and positive impact on: 1) subjective sleepiness, and 2) depression when randomized controlled trials are considered and additionally on 3) fatigue, 4) generic health-related quality of life, 5) vigilance, and 6) driving performance when all prospective trials are considered. These parameters appear to be sensitive to the duration of (>1 month) and
compliance with therapy. These results should be considered when developing health policy and designing future clinical trials.

ACKNOWLEDGMENTS
We would like to thank our translators: Ms. Inge Morris (German), Dr. Yasuo Sekine (Japanese), and Dr. Irmina Gradus-Pizlo (Polish).

REFERENCES


The mission of the Wisconsin Medical Journal is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

The WMJ (ISSN 1098-1861) is the official publication of the Wisconsin Medical Society and is devoted to the interests of the medical profession and health care in Wisconsin. The managing editor is responsible for overseeing the production, business operation and contents of WMJ. The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic or organizational articles. Although letters to the editor are reviewed by the medical editor, all signed expressions of opinion belong to the author(s) for which neither the WMJ nor the Society take responsibility. The WMJ is indexed in Index Medicus, Hospital Literature Index and Cambridge Scientific Abstracts.

For reprints of this article contact the WMJ Managing Editor at 866.442.3800 or e-mail wmj@wismed.org.

© 2003 Wisconsin Medical Society