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INSIDE

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Lumbar Spinal Surgery Versus Conservative Treatment

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Weill Cornell Medical Center

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

***Synopsis**: Surgery for a herniated lumbar disc with sciatica does not have a better long-term result than conservative therapy. However, surgical decompression for spondylolisthesis with symptomatic spinal stenosis results in better pain relief and functionality, than does conservative treatment.*

Sources: Peul WC , et al. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med* 2007;356;2245-2256.
Weinstein JN, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. *ibid* 2257-2270.
Deyo RA. Back surgery—who needs it? Editorial. *ibid* 2239-2243.

TWO ARTICLES, ONE DUTCH AND ONE AMERICAN, RECENTLY reported in the *New England Journal of Medicine*, provide further support to a growing body of literature that supports the notion that lumbar spine surgery should be undertaken for indications that are more limited than what is currently practiced in the United States.

In the Dutch paper by Peul et al, a prospective, 9-center, randomized study of early surgery vs. conservative treatment was undertaken to determine which strategy provided the better outcome for severe sciatica. Criteria for inclusion required radiologic confirmation of disc herniation in patients 18-65 years old, with incapacitating sciatica of 6-12 weeks duration, diagnosed by a neurologist. Exclusionary criteria included cauda equina syndrome, inability to counter gravity in any muscle tested, prior spine surgery, bony stenosis, spondylolisthesis, pregnancy, or other severe complicating disease. Surgery within 2 weeks of enrollment defined early surgery and comprised a minimal unilateral transflaval approach with nerve root decompression, annular

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fenestration, curettage, and removal of loose disc material, without performing subtotal discectomy. Patients randomized to conservative management were treated by their family physician, with pain medication as needed, and formal physical therapy if patients were fearful of mobilizing on their own. Surgery was offered if sciatica persisted for another 6 months, and earlier if pain increased or neurologic deficits developed. Primary outcome measures were the Roland (100 point) Disability Questionnaire for Sciatica, the Likert (7 point) self-rating scale for global recovery, and intensity of leg pain during 7 visits over the next 52 weeks. Secondary outcome measures included the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) scale, the Sciatica Frequency and Bothersome Index, and a 100-mm visual analog scale for health perception. Students t-test, Kaplan-Meier survival analysis, and Cox modeling were used for statistical analysis.

Among 283 patients who met inclusion criteria, 141 were randomly assigned to early surgery, but 16 improved before surgery was performed, leaving the remaining 89% to undergo surgery within a mean of 1.9 weeks. Among 142 patients initially assigned to conservative management, 55 (39%) underwent surgery after a mean of 18.7 weeks due to intractable pain. 3.2% of early surgery patients required repeat operations due to recurrence of pain. Pain relief and perceived recovery were faster in the surgery cohort ($P < 0.001$) but probability of perceived recovery at 1 year was 95% in both groups.

Management of lumbar spinal stenosis due to degenerative spondylolisthesis was the subject of the American paper, authored by Weinstein, et al. 607 patients with neurogenic claudication or radicular leg pain of at least 12 weeks duration, with radiographic evidence of spondylolisthesis on lateral lumbar X-rays and spinal stenosis on cross sectional imaging, were offered enrollment into a randomized (n = 304) or observational (n = 303) cohort, comparing standard nonsurgical care to decompressive laminectomy, with or without bilateral single level fusion with or without posterior pedicle-screw instrumentation. Multiple levels of stenosis was an exclusionary criteria but spondylolysis and isthmic spondylolisthesis were not. Primary outcome measures included the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) scale and the Oswestry Disability Index at 3, 6, 12, and 24 months following enrollment, whereas secondary outcome measures included the Stenosis Bothersome index, the Low Back Pain Bothersome scale, and patient-reported improvement and satisfaction with current status.

Among 304 randomized patients, 159 were assigned to surgery, of which 64% underwent operation by 2 years. Of 145 patients assigned to the nonsurgery treatment group, 49% had surgery by 2 years. Among 303 patients in the observational group, 173 chose surgery and 97% underwent the operation within 1 year. 130 chose nonsurgical treatment but by 2 years, 25% had surgery. Intention-to-treat analysis revealed no significant difference within the randomized cohort for primary outcome measures. As-treated analysis for both cohorts demonstrated a significant benefit from surgery, in both function and disability index, at 3 months, which increased, and then slightly decreased, at 1 and 2 years, respectively. Surgery, more so than conservative measures, provides significant pain relief and improved functionality for spinal stenosis due to degenerative spondylolisthesis.

COMMENTARY

Low back pain is big business in the United States. It is the second leading cause of physician visits, the third leading cause for surgical procedures, and the fifth leading cause of hospitalizations, amounting to $24 billion annually in direct medical costs alone. It is crucial to know which patients truly benefit from surgical therapy. As emphasized in the accompanying editorial by Deyo, surgery appears beneficial for degenerative spondylolisthesis resulting in spinal stenosis, a condition predominantly of the elderly, but this benefit must be weighed against the increased risk of complications seen in this age group. Disc herniation, present in up to 40% of

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asymptomatic young adults (mean age 35 years), when accompanied by sciatica, responds to conservative management if the patient is not in intractable pain and can tolerate the time it takes to recover. Of note, even when surgery in the disc herniation group was delayed for months, the ultimate outcome was no different in the surgical vs. conservatively treated group. Surgery remains an important option in the choice of interventions for low back pain, but its indications and documented benefits are slowly being whittled away. ■

Intervertebral Disc Transplantation: Treatment in Motion

ABSTRACT & COMMENTARY

By Justin F. Fraser, MD, and John Boockvar, MD
Department of Neurological Surgery
Weill Medical College of Cornell University, New York, NY
Drs. Fraser and Boockvar report no financial relationships relevant to this field of study.

Synopsis: *A pilot study of human cervical disc transplantation has been shown to be surgically feasible, but requires further investigation.*

Source: Ruan D, et al. Intervertebral disc transplantation in the treatment of degenerative spine disease: a preliminary study. *Lancet* 2007; 369:993-999.

Anterior cervical discectomy and fusion is a standard procedure for the treatment of cervical herniated intervertebral discs and cervical spondylosis. However, while the procedure directly decompresses nerve roots and/or the spinal cord, it permanently alters spinal anatomy. In particular, cervical fusion reduces motion in at least one spinal segment. Traditionally considered benign, this modification to natural movement has been shown to accelerate adjacent disc degeneration. In an effort to reduce this effect, some investigators have studied the possibility of intervertebral disc transplantation to retain segmental motion while treating pathological discs in the cervical spine. Given initial success in animal models, Ruan et al. now publish their results of a pilot series of patients using composite allograft intervertebral disc transplantations from human donors. The stated aims of this trial were to demonstrate graft viability and stability, preservation of segmental mobility, and satisfactory clinical outcome.

The authors report outcomes of 5 patients in whom single-level anterior cervical discectomy was performed, and who received allograft disc transplants from previously healthy 20-30 year-old female victims of trauma. Four patients presented with cervical spondylotic myelopathy, and one presented with incomplete paraplegia from a traumatic cervical disc herniation. The surgery involved an endplate-disc-endplate transplantation, without internal fixation. All patients wore cervical collars for at least 2 weeks postoperatively, and were examined two months postoperatively, and every 3 months thereafter, with flexion-extension radiographs, and, at last follow-up, with MRI. Mean follow-up was 66 months, with all patients showing individual improvement in neurological status per Japanese Orthopedic Association (JOA) scale or Frankel grade. Two patients reported worse neck pain at last follow-up compared to preoperative assessment, and 2 patients had complications — one reported a 'foreign body sensation' in the throat that lasted 18 months postoperatively, and the second developed recurrent upper extremity numbness and radiculopathy at 20 months postoperatively, that required posterior unilateral foraminotomy. No patient had signs or symptoms of graft rejection, and no patient demonstrated evidence of graft migration. One patient had autofusion at the transplanted segment just posterior to the grafted disc. Three patients had hypointensity noted in the transplanted discs at last MRI follow-up similar to adjacent discs (so-called 'dark discs'), often indicative of early disc degeneration. With these results, the authors claim that "the motion and stability of the spinal unit is preserved after transplantation of fresh-frozen allogeneic intervertebral discs in human beings, despite signs of mild disc degeneration."

■ COMMENTARY

In their pilot series of human recipients of cervical disc transplantations, Ruan et al are pioneers in the clinical application of a novel treatment for cervical disc disease. They analyzed both clinical and radiographic outcome variables, studying neurologic outcome as well as biomechanical graft persistence and maintenance of mobility. With a mean follow-up of 66 months, the authors followed this pilot group of patients for a significant period. The study was successful in demonstrating that intervertebral disc transplantation is feasible without significant autoimmune response in the postoperative period. It also demonstrated that segmental motion could be preserved while qualitative improvement in neurological status

could be obtained through this methodology. As such, the results of the study support further clinical research to study the long-term safety and efficacy of this therapy in larger groups of patients.

However, some features of this study limit its clinical applicability. First, while the mean 66-month follow-up provided a significant interval to study clinical and postoperative radiographic outcome, it falls short of determining long-term transplant degeneration. The majority of patients (3 of 5) demonstrated early signs (loss of T2 hyperintensity within the nucleus of the disc transplant) of disc degeneration at last follow-up MRI. Given that the grafts were all obtained from previously healthy 20-30 year-olds, imaging reports that 3 of 5 transplants resembled the degenerative pattern of adjacent native discs in the recipients is a concerning finding. It suggests an accelerated pathway of degeneration in the grafts. Indeed, this finding requires more study.

A second limitation is the methodology for graft selection. While taken from previously-healthy 20-30 year-old females screened for transmissible diseases, and imaged with plain radiographs to "exclude bony abnormality and any obvious disc degeneration," the grafts were not visualized using MRI of their hosts. It would have been helpful to visualize the MR characteristics of the grafts prior to harvesting in order to have a baseline for future comparison and to rule-out grafts with early degenerative changes.

The third problem relates to the selection criteria for graft recipients. In a pilot study where the number will be small, minimization of controllable variables is important. The authors should not have included a patient with paraplegia from a traumatic disc herniation, as the pathophysiology is very different from that of chronic degenerative spondylotic myelopathy.

Finally, while the authors show technical success in performing disc transplantation safely, the results during follow-up are discouraging. One of five of the patients demonstrated autofusion at the transplanted level within 2 years of operation. Two of 5 patients reported worse neck pain at last follow-up compared to preoperative assessment.

In summary, Ruan et al. provide an intriguing pilot study that highlights a potential future modality for treating cervical disc disease while maintaining segmental motion. Disc transplantation may represent an alternative to artificial disc replacement, but raises important questions that must be addressed in future trials if disc transplantation is to become a tool in the armamentarium of physicians who treats spine disease. ■

The Rotigotine Patch for Early Parkinson's Disease

ABSTRACT AND COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg receives research support from Boehringer-Ingelheim.

Synopsis: *The rotigotine transdermal system (Neupro) is a safe and effective treatment for early Parkinson's Disease.*

Source: Jankovic J, et al. Transdermal Rotigotine: Double-blind, Placebo-Controlled Trial in Parkinson Disease, *Arch Neurol.* 2007; 64(5): 676-682.

Dopamine agonists have played a key role in the treatment of Parkinson's Disease (PD) for many years, but until recently were only available in the United States as oral medications that needed to be taken several times daily. This pharmaceutical-sponsored randomized, double-blind, multicenter, placebo-controlled trial examined the safety and efficacy of the rotigotine transdermal system (Neupro), a non-ergolinic dopamine agonist medication delivered via a 24-hour cutaneous patch, in the treatment of early PD. The primary outcome measure was the "20% responder rate," defined as the percentage of subjects who achieved a 20% reduction (improvement) in the sum of the activities of daily living (part II) and motor (part III) subsets of the Unified Parkinson's Disease Rating Scale (UPDRS).

A total of 277 subjects with early PD (5 years duration) who were not on dopaminergic therapy were randomized in a 2:1 ratio to receive either rotigotine (n=181) or placebo (n = 96). Subjects were recruited from fifty sites in the United States and Canada. There was a 3-week flexible-dose titration phase, followed by 24 weeks of maintenance therapy with either rotigotine or placebo. The maintenance dose of rotigotine was either 2, 4, or 6 mg/24 hours based on optimal clinical response (mean = 5.7 mg/24 hours).

At the end of the maintenance phase, the rotigotine-treated group had a significantly greater 20% responder rate than the placebo group (48% vs 20% of subjects, $P < 0.001$). Several secondary endpoints, including the percentage change in the sum of the UPDRS part II and III scores (-15.1% vs. 7.3%, $P < 0.001$) and the percentage of patients who demonstrated clinical improvement on the Clinical Global Impression Scale (57% vs. 30%, P

< 0.001) were also improved in the rotigotine vs. placebo group. The sum of the UPDRS part II and III scores improved by about 4 points in the rotigotine group vs. a 1.3 point worsening in the placebo group ($P < 0.05$). The most common adverse event was application site reaction (usually mild or moderate in severity), which occurred in 44% of patients who received rotigotine vs. 12% of those who received placebo. Other common adverse effects included nausea (41% vs. 17% in the placebo group) and somnolence (33% vs. 20% in the placebo group).

COMMENTARY

The recently FDA-approved rotigotine patch is a welcome new addition to the armamentarium of treatment options for early Parkinson's disease. The mechanism of action of rotigotine is comparable to that of oral dopamine agonists, but the 24-hour transdermal patch is a novel delivery system that allows for treatment of patients who cannot take oral medications, can be administered independent of mealtimes, and has the potential to increase patient adherence. The absolute improvement in UPDRS scores was small but significant, and clinically relevant as reflected by the Clinical Global Impression Scale. Physicians who use this medication should be aware of the high frequency of application site reactions, and that transdermal administration does not eliminate the nausea that commonly occurs with this class of medications. Further studies are needed to determine whether the more continuous dopamine receptor stimulation provided by this medication may reduce susceptibility to motor complications such as wearing off and dyskinesias.

Treatment of Neurosarcoidosis

ABSTRACT AND COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Safdieh reports no financial relationships relevant to this field of study.

Synopsis: *Patients with high-risk neurosarcoidosis who receive combination therapy with corticosteroids and additional immunosuppressive agents seem to have favorable outcomes.*

Sources: Scott TF, Yandora K, Valeri A, et al. Aggressive Treatment for Neurosarcoidosis : Long-term Follow-up of 48 Treated Patients. *Arch Neurol* 2007;64:691-696

Neurological involvement is encountered in approximately 5% of cases of systemic sarcoidosis. Both the central and peripheral nervous systems can be involved. The more common central nervous system manifestations include cranial neuropathies, chronic meningitis, myelopathy, and intraparenchymal lesions. Due to the relative rarity of neurosarcoidosis, there have been no randomized, controlled, treatment trials published. Corticosteroids are generally used as first-line agents in symptomatic neurosarcoidosis. The role of alternative immunosuppressive agents has traditionally been limited to corticosteroid refractory cases, or in those patients who cannot tolerate corticosteroid treatment. In this retrospective study, the treatment response of 48 patients with neurosarcoidosis is reviewed. The practice of the authors is to use combination therapy with corticosteroids plus additional immunosuppressive agents at diagnosis, in patients who are considered to be high-risk for progression. High-risk patients were defined as those with intracranial lesions, hydrocephalus, myelopathy, seizures, or encephalopathy. Patients who were not considered to be high-risk were treated with corticosteroids alone. Alternative immunosuppressive agents used in this study included methotrexate, azathioprine and cyclophosphamide. Adverse events in the combination group were generally mild and included moderate leukopenia in 2 patients, mild leukopenia in 6 patients and elevated liver function tests in 11 patients.

In the study, 26 of the 48 patients were deemed high-risk and treated with combination therapy. Of the high-risk patients, 69% improved, 15% remained stable, and 15% worsened. Of the 19 standard risk patients treated with corticosteroids alone, 35% improved, 55% remained stable, and 10% worsened. Additionally, retrospective assignment of disability scores demonstrated a significant decline in disability over the course of treatment with combination immunosuppressive therapy, but not in the group treated with corticosteroids alone. However, the group treated with corticosteroids alone had lower disability scores at baseline.

Of note, in this study, CSF angiotensin-converting enzyme levels were obtained in 12 patients and elevated in only 2. The most common symptoms of neurosarcoidosis in this cohort included cranial neuropathy, headache, ataxia, cognitive complaints, and paresthesias. Other less common symptoms included weakness, peripheral neuropathy, seizures and endocrine dysfunction. The majority of biopsy proven cases were demonstrated by lymph node or lung biopsy. Ten patients were diagnosed based on brain or meningeal biopsy. The mean time from onset of symptoms to diagnosis of neurosarcoidosis was 37 months.

COMMENTARY

The authors suggest that high risk neurosarcoidosis patients should be treated more aggressively than standard risk patients. Although the follow-up data that they present suggests that patients on combination therapy do quite well, the lack of a control group consisting of corticosteroid monotherapy in high-risk patients significantly limits the conclusions of their findings. However, this is an important study that describes the clinical presentation, diagnostic testing, and follow-up of neurosarcoidosis, contributing a large number of cases to the literature about a relatively rare disorder. Overall, the study confirms that neurosarcoidosis is a treatable disorder, and most treated patients stabilize or improve. In addition, the study notes that CSF angiotensin-converting enzyme has a low sensitivity and its absence does not rule out the diagnosis of neurosarcoidosis.

Optokinetic Therapy for Hemianopic Alexia

ABSTRACT & COMMENTARY

By Erik J. Kobylarz, MD, Ph.D.

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, Cornell University

Dr. Kobylarz reports no financial relationship relevant to this field of study.

Synopsis: *Improved reading skills in patients with hemianopic alexia can be achieved by having patients practice reading a right-to-left scrolling text.*

Source: Spitzyna GA, et al. Optokinetic therapy improves text reading in patients with hemianopic alexia: a controlled trial. *Neurology.* 2007 May 29;68(22):1922-1930.

Spitzyna and colleagues evaluated the efficacy of optokinetic therapy for alexia in patients with right-sided homonymous hemianopia. Essential visual information required for efficient reading to help guide reading fixations is lacking in patients with acquired right-sided homonymous hemianopia, particularly that involving foveal or peri-foveal vision. Patients with hemianopic alexia (HA) saccade more frequently when reading a line of text than do normal subjects, but utilize an inefficient ocular motor strategy when doing so. Two hypotheses were tested in this study: 1) Practice with a visual rehabilitation method that induced small-field optokinetic nystagmus (OKN) would improve reading speeds in patients with HA when compared to sham visual rehabilitation therapy. 2) OKN-inducing therapy would preferentially affect reading saccades into the blind hemifield.

Dr. Alexander Leff at the National Hospital for Neurology and Neurosurgery in London, England, and colleagues designed a physical rehabilitation method which induces small-field optokinetic nystagmus (OKN) by using horizontally scrolling text moving from right to left (so-called "Times Square presentation"). This technique has been shown to increase text reading speeds in normal subjects. The authors wished to compare the efficacy of this method, which induces OKN eye movements, versus a non-reading task that also induces saccadic eye movements for the treatment of HA. An additional objective was to identify if any therapy-induced effects on reading saccades were direction-specific.

Nineteen patients with hemianopic alexia were entered into this study. In most of the patients a posterior cerebral artery territory stroke (infarct or hemorrhage) was the causative lesion, but some patients had head injuries or tumors. All of the patients had a fixed homonymous field defect for a period of at least 3 months. This was a two-armed study with two therapy blocks in each arm. Group 1 practiced reading right-to-left moving text (MT) every day for 2 4-week blocks. Group 2 had sham therapy, consisting of "spot-the-difference" non-reading tasks (viewing children's puzzles), for the first four weeks, followed by MT for the second 4 weeks.

Group 1 showed significant improvements in mean reading speed (18%) following each of the two therapy blocks. However for Group 2 there was no significant improvement (5%) during the first block, but after crossing over to MT therapy, they subsequently demonstrated a 23% improvement. Spitzyna et al also report that MT therapy was associated with a direction-specific effect on saccadic amplitude for rightward, but not leftward reading saccades. The authors conclude that OKN-inducing therapy preferentially affects reading saccades in the direction of the induced (involuntary) saccadic component. They do not propose a neurophysiologic mechanism for this effect, but observed that after OKN therapy patients are able to make larger amplitude reading saccades into their blind field, which can improve their reading ability.

COMMENTARY

A variety of visual search and navigation tasks have been utilized in an attempt to improve ocular motor efficiency (Pambakian et al. 2005). Only a few groups have focused on using such methods for the treatment of reading difficulties associated with HA (Kerkhoff, 2000). This study is novel in that it is the first to demonstrate the effectiveness of specific eye movement based

therapy in patients with hemianopic alexia in the context of a therapy controlled trial; they compared the treatment group with patients receiving sham therapy to induce saccadic eye movements. These results indicate that moving text therapy for inducing rightward optokinetic nystagmus can help reading efficiency in patients with hemianopic alexia.

Although rehabilitation for static visual defects is a controversial topic in the field of neuro-ophthalmology, to their credit, this group has utilized saccade training by means of OKN therapy in an attempt to train HA patients to read more effectively, thus improving their quality of life. It appears that MT therapy improves the reading ability in HA patients by augmenting the saccade amplitude towards the blind right hemifield. However, further studies are warranted to determine the exact neurophysiologic mechanism(s) by which the improvement in reading with OKN therapy occurs, as well as how to optimize its therapeutic effect (e.g., text movement velocity and direction, frequency and duration of therapy). The authors have made a Web-based version of this therapy available without cost on-line, which is certainly commendable. ■

Additional Reading

Kerkhoff G. *J Neurol Neurosurg Psychiatry*. 2000 Jun;68(6):691-706.

Pambakian A, et al. Rehabilitation strategies for patients with homonymous visual field defects. *J Neuroophthalmol*. 2005 Jun;25(2):136-142. Review.

Does Sleep Deprivation Aggravate Chronic Pain?

ABSTRACT & COMMENTARY

By Charles Pollak, MD

Synopsis: *Disturbance of sleep continuity, but not simple sleep deprivation, impairs pain inhibition and increases spontaneous pain.*

Source: Smith MT, et al. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007. 30: 494-505.

ANYONE WITH A TOOTHACHE KNOWS HOW DIFFICULT it can be to sleep. The same is true for back pain, fibromyalgia, or cancer pain, perhaps providing one reason why insomnia is common in the elderly. Less well known is the opposite effect, the augmentation of pain by sleep disturbance. Experiments designed to demonstrate that insomnia, for example, increases pain have indeed given inconsistent results. The present experiment, by contrast, clearly demonstrates that impairment of sleep continuity, though not simple sleep deprivation, impairs pain inhibition (to be explained) as well as increasing spontaneous pain.

The investigation was restricted to women, because female sex is associated with pain sensitivity and higher rates of chronic pain. A parallel investigation in males is in progress. Thirty-five women averaging 25 years of age participated. All were good sleepers and were healthy and did not abuse alcohol or other substances. They did not complain of pain or use analgesics. They were also screened for sleep disturbances, daytime sleepiness, psychiatric disorders, and acute pain. During the initial screening, they wore wrist actigraphs to provide measures of sleep and the circadian rhythm. During 7 subsequent experimental days, sleep was polygraphically recorded to rule out sleep disorders and track multiple sleep parameters.

Pain was induced by applying pressure to the belly of the trapezius muscle, masseter muscle and brachioradialis. The pressure pain threshold was again measured while immersing a hand in ice water (cold pressor task), and the increase in pain threshold was recorded (diffuse noxious inhibitory control or DNIC). An increase in the pressure threshold during cold pressor reflects normal pain-inhibitory processes. In addition to DNIC, the spontaneous occurrence of any potentially painful symptoms was recorded each night.

Subjects were randomly assigned to one of 3 groups: control, forced awakening (FA) or restricted sleep opportunity (RSO). All subjects slept undisturbed for the first 2 nights. Controls slept undisturbed for up to 8 hours on each of the remaining 5 nights. FA subjects were forcibly awakened for either 20 minutes or 60 minutes on each of 3 consecutive nights. This was followed by 36 hours of continuous wakefulness, then by a night of recovery sleep. The night of total sleep deprivation was intended to maximize the possibility of identifying an effect of sleep deprivation on pain inhibition.

The RSO subjects were deprived of sleep by delaying their bedtime while keeping a fixed wake time. The amount of delay was yoked to the amount of sleep achieved by the subjects in the FA group. After partial sleep deprivation, the RSO and FA subjects were deprived of sleep for 36 hours and were then allowed a night of recovery sleep.

FA and RSO subjects demonstrated 50% reductions in total sleep time and increases in nonpainful somatic

symptoms during partial sleep deprivation. Sleep deprivation had no effect on pain thresholds. During partial sleep deprivation, however, the FA group showed a significant loss of pain inhibition and an increase in spontaneous pain. Neither of the other 2 groups showed changes in pain inhibition or spontaneous pain during partial sleep deprivation.

COMMENTARY

This is an elaborately designed, well controlled investigation of the effect of two kinds of sleep deprivation on pain perception. Remarkably, simple sleep deprivation, (shortened opportunity for sleep) had no effect on pain perception, but reduction of sleep to the same degree by means of an interspersed nocturnal awakening markedly reduced pain inhibition (DNIC). Why should it matter whether subjects are permitted to sleep a little longer before being awakened for the day (the RSO condition) or, instead, are permitted to sleep for the same total time after a interval of wakefulness (FA condition)? The authors have not shared any speculative explanations for this, their central finding.

If it can be confirmed, the finding may be of great clinical significance. As pointed out by the authors, the impairment of sleep continuity by pain can have a self-reinforcing, perpetuating effect that supports a possible pathophysiologic role of sleep disturbance in chronic pain. If we only knew how to do it (other than by means of analgesic drugs), it follows that insomnia should quickly be remedied in the patient with chronic pain. ■

CME Question

25. Choose the correct statement

A) Surgery provides significant pain relief and improved functionality for spinal stenosis due to degenerative spondylolisthesis
B) Probability of perceived recovery at 1 year is 95% following lumbar discectomy for severe sciatica, compared to 55% with nonsurgical conservative management
C) Conservative measures provides significant pain relief and improved functionality for spinal stenosis, more so than does surgery
D) Two of the above statements are correct
E) None of the above statements are correct

26. In the above study, the most common adverse effect of the rotigotine patch was:

A) Nausea
B) Headache
C) Somnolence
D) Application site reaction

27. The following statement is true about allogeneic cervical disc transplantation.

A) Disc transplantation has been compared to discectomy and fusion in clinical trials.
B) Disc transplantation has been shown to have excellent long-term results.
C) Disc transplantation has been compared to artificial disc implantation in clinical trials
D) Disc transplantation is experimental and requires further investigation.

28. Which of the following is the most common nervous system manifestation of neurosarcoidosis?

A) ataxia
B) headache
C) cranial neuropathy
D) seizures
E) endocrine dysfunction

29. Optokinetic therapy results in all of the following EXCEPT:

A) a significant alteration of leftward saccades.
B) significantly improved reading speed in patients with hemianopic alexia.
C) increased amplitude of rightward saccades.
D) an increase in reading speed in normal subjects.
E) significantly improved therapeutic results as compared to "spot-the-difference" visual tasks.

30. Pain inhibition refers to

A) Reduction of pain by noxious stimulus at a remote site.
B) Interference of pain with activities of daily living.
C) Reduction of the pressure pain threshold by cold pressor task

Answers: 25. (a) 26. (d) 27. (d) 28. (c) 29. (a) 30. (a)

Correction: Question 22 in the June issue was suppose to appear in the July issue. It appears as question 30 this month.

Upcoming Symposium

4th Annual Update Symposium on Clinical Neurology and Neurophysiology, February 18-19, 2008, Tel Aviv, Israel. Presented by Weill Cornell Medical College, Department of Neurology, and Tel Aviv University, Adams Brain Supercenter. For more information visit our website at: www.neurophysiology-symposium.com

In Future Issues:

Update on Alzheimer's Disease

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4. discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness.

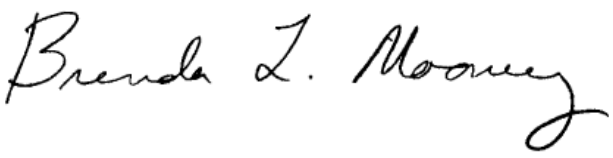
Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 24 months from the date of publication. The target audience for this activity is principal investigators and clinical trials nurses.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5525. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,



Brenda Mooney
Senior Vice-President/Group Publisher
AHC Media LLC

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■