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***Our Mission:*** Helping to prepare Iowa's health practitioners to care for our growing population of elders. *E-NEWS* is one of our methods of teaching through technology.

Each month, *E-NEWS* delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month's *E-NEWS* focuses on MANAGEMENT OF NEUROPATHIC PAIN.

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## MANAGEMENT OF NEUROPATHIC PAIN

**In this issue of the *E-NEWS*, you will find abstracts for:**

- A study that assesses the pain-relieving effects of high-rate repetitive transcranial magnetic stimulation (rTMS) on neuropathic pain.
  - A study that examines the efficacy of mexiletine therapy for neuropathic pain.
  - A study that compares psychological and physical function in neuropathic pain and nociceptive pain and discusses the implications for cognitive behavioral pain management programs.
  - A study that explores the incidence rates and treatment strategies of neuropathic pain in the general population.
  - A study that evaluates the potential benefit of adding oxycodone to gabapentin therapy in persons with diabetic neuropathy.
  - An article that reviews pharmacological treatment of neuropathic pain in older adults.
  - A study that investigates electrical stimulation of the primary motor cortex within the central sulcus for intractable neuropathic pain.
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- André-Obadia N, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. *Neurology*. 2008 Sep 9;71(11):833-40.

OBJECTIVES: To assess, against placebo, the pain-relieving effects of high-rate repetitive transcranial magnetic stimulation (rTMS) on neuropathic pain. METHODS: Double-blind, randomized, cross-over study of high-rate rTMS against placebo in 28 patients. The effect of a change in coil orientation (posteroanterior vs lateromedial) on different subtypes of neuropathic pain was further tested in a subset of 16 patients. Pain relief was evaluated daily during 1 week. RESULTS: High-frequency, posteroanterior rTMS decreased pain scores significantly more than placebo. Posteroanterior rTMS also outmatched placebo in a score combining subjective (pain relief, quality of life) and objective (rescue drug intake) criteria of treatment benefit. Changing the orientation of the coil from posteroanterior to lateromedial did not yield any significant pain relief. The analgesic effects of posteroanterior rTMS lasted for approximately 1 week. The pain-relieving effects were observed exclusively on global scores reflecting the most distressing type of pain in each patient. Conversely, rTMS did not modify specifically any of the pain subscores that were separately tested (ongoing, paroxysmal, stimulus-evoked, or disesthetic pain). CONCLUSIONS: Posteroanterior repetitive transcranial magnetic stimulation (rTMS) was more effective than both placebo and lateromedial rTMS. When obtained, pain relief was not specific of any particular submodality, but rather reduced the global pain sensation whatever its type. This is in accord with recent models of motor cortex neurostimulation, postulating that its analgesic effects may derive in part from modulation of the affective appraisal of pain, rather than a decrease of its sensory components.



- Carroll IR, Kaplan KM, Mackey SC. Mexiletine therapy for chronic pain: survival analysis identifies factors predicting clinical success. *J Pain Symptom Manage*. 2008 Mar;35(3):321-6.

Mexiletine, a sodium channel blocker, treats neuropathic pain but its clinical value has been questioned due to its significant side effects and limited efficacy. We hypothesized that ongoing therapy with mexiletine would have limited patient acceptance, but that an analgesic response to intravenous (IV) lidocaine (a pharmacologically similar drug) would identify patients most likely to choose ongoing therapy with mexiletine. We identified a cohort of 37 patients with neuropathic pain who underwent IV lidocaine infusions at our institution and were subsequently prescribed mexiletine. Time until discontinuation of mexiletine was used as the primary endpoint. Time until discontinuation is a clinically relevant, discrete, objective endpoint gaining acceptance as a metric for assessing clinical performance of drugs with significant side effects and limited efficacy. We used the techniques of survival analysis to determine factors that predicted continued therapy with mexiletine. Median time to discontinuation of mexiletine was only 43 days. A stronger analgesic response to IV lidocaine significantly predicted continued acceptance of mexiletine therapy. Decreasing age and male gender also predicted continued acceptance of mexiletine therapy. Analyzing time to mexiletine discontinuation uncovers important limitations in mexiletine's clinical performance missed by studies with conventional endpoints, such as change in pain score. Despite claims of efficacy, acceptance of mexiletine therapy is poor overall. Test infusions with lidocaine identify patients most likely to continue mexiletine therapy. Further work is needed to confirm these results and evaluate the relative acceptance of mexiletine vs. other treatments of neuropathic pain.



- Daniel HC, Narewska J, Serpell M, Hoggart B, Johnson R, Rice AS. Comparison of psychological and physical function in neuropathic pain and nociceptive pain: implications for cognitive behavioral pain management programs. *Eur J Pain*. 2008 Aug;12(6):731-41.

Research has increased our understanding of the psychological and physical functioning associated with persistent pain and has facilitated the development of cognitive behavioral pain management programs to help improve people's physical function and decrease their distress in the presence of persistent pain. The majority of this research has focused on nociceptive pain or pain of mixed etiology. There has been less focus on these aspects of neuropathic pain. It is possible that differences exist in the function and difficulties associated with nociceptive and neuropathic pain. These differences may be associated with our clinical observation that some people with neuropathic pain have difficulty applying some aspects of the theory and practice of cognitive behavioral pain management. The purpose of this study was to compare a single neuropathic pain condition

(post-herpetic neuralgia) with a persistent pain of nociceptive origin (low back pain) and determine whether differences exist in: (1) physical and psychological function; (2) factors that increase difficulties; (3) responses to pain; (4) beliefs about pain and (5) problems experienced. The results suggest that the differences between the two groups were not on the major variables of pain, mood, cognition and physical function. The main differences were in factors that increase pain, people's responses to pain, their beliefs about diagnosis and the cause of pain and the problems they reported as a result of experiencing pain. The implications of our findings for the development of cognitive behavioral pain management programs for people with neuropathic pain are discussed.



- Dieleman JP, Kercklaan J, Huygen FJ, Bouma PA, Sturkenboom MC. Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*. 2008 Jul 31;137(3):681-8.

Incidence rate estimates of neuropathic pain are scanty and mostly address single types whereas the scope of the disease is wide. We aimed to calculate the incidence rates of neuropathic pain conditions in the Dutch general population and to assess treatment strategies in primary care. The study population included persons registered for at least one year in the Integrated Primary Care Information (IPCI) database between 1996 and 2003. Neuropathic pain was ascertained and classified by systematic review of computerized longitudinal medical records. Incidence rates (IR) were calculated, and the treatment for pain was compared to age and gender matched controls. Among 362,693 persons contributing 1,116,215 person years (PY), we identified 9135 new cases of neuropathic pain (IR: 8.2/1000 PY, 95%CI: 8.0-8.4). Mononeuropathy and carpal tunnel syndrome were the most frequent types with 4.3 and 2.3 cases/1000 PY followed by diabetic peripheral neuropathy and post-herpetic neuralgia at 0.72 and 0.42/1000 PY. Neuropathic pain was 63% more common in women than in men and peaked between the ages 70 and 79. More than 50% of cases received pain medication within 6 months after diagnosis, mostly consisting of NSAIDs or aspirin. Anticonvulsants and tricyclic antidepressants were only used by 4.8 and 4.7% of cases. Neuropathic pain is a rather frequent condition with an annual incidence of almost 1% of the general population and affecting women and middle-aged persons more often. The treatment mostly consisted of regular analgesics suggesting that pharmacological treatment of neuropathic pain is suboptimal.



- Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain*. 2008 Aug;12(6):804-13.

BACKGROUND: Neuropathic pain remains one of the most challenging pain syndromes; under-diagnosed, poorly managed and associated with significant co-morbidity. With standard therapeutic treatments, responders rarely exceed 50% pain relief and the majority suffer from residual pain. Titration to optimum dose is often limited by dose-related adverse events. AIMS: This randomized, double-blind, placebo-controlled study assessed the potential benefit of adding oxycodone (OxyContin tablets) to gabapentin. The primary endpoint was to evaluate the analgesic efficacy of co-administration of gabapentin and prolonged-release oxycodone, whilst also evaluating the use of escape medication, sleep quality and global assessment of pain. METHODS: Three hundred and thirty eight patients with moderate to severe painful diabetic neuropathy despite receiving their maximum tolerated dose of gabapentin, had oral prolonged-release oxycodone or placebo tablets added to their therapy for up to 12 weeks. RESULTS: Oxycodone-gabapentin reduced pain score by 33% from baseline to end of treatment. The overall treatment effect was greater with oxycodone-gabapentin than with placebo-gabapentin ( $P = 0.007$ ). Oxycodone-gabapentin also significantly improved pain relief vs gabapentin alone ( $P = 0.003$ ). Oxycodone-gabapentin co-administration was associated with less escape medication use ( $P = 0.03$ ) and fewer nights of disturbed sleep ( $P < 0.05$ ). Discontinuations due to lack of therapeutic effect were much lower (14% vs 54%) with oxycodone-gabapentin. The commonly seen opiate-induced adverse events were not exacerbated by the combination of oxycodone and gabapentin. CONCLUSIONS: This study provides the first evidence that co-administration of prolonged-release oxycodone and existing gabapentin therapy has a clinically meaningful effect in painful diabetic neuropathy.



- Haslam C, Nurmikko T. Pharmacological treatment of neuropathic pain in older persons. *Clin Interv Aging*. 2008;3(1):111-20.

Interest and research into the mechanisms and treatment of neuropathic pain have increased during recent years, but current treatment is still far from satisfactory (Dworkin et al 2003; Attal et al 2006). The European Federation of Neurological Societies (EFNS) Task Force recently published guidelines for the pharmacological treatment of neuropathic pain (Attal et al 2006). However, no particular consideration is given as to how the recommendations are applicable to the elderly population. This paper will review the guidelines in relation to this population and evaluate the existing evidence relating to the use of these drugs in older persons.



- Hosomi K, Saitoh Y, Kishima H, Oshino S, Hirata M, Tani N, Shimokawa T, Yoshimine T. Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. *Clin Neurophysiol*. 2008 May;119(5):993-1001.

**OBJECTIVE:** To assess the pain-relieving effects of motor cortex electrical stimulation (MCS) within the central sulcus and the predictive factors retrospectively. **METHODS:** Thirty-four patients with intractable neuropathic pain underwent MCS; 19 patients had cerebral lesions, and 15 had non-cerebral lesions. In selected 12 patients, test electrodes were implanted within the central sulcus and on the precentral gyrus. Twelve patients received both MCS and repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex. **RESULTS:** Pain reduction of > or =50% was observed in 12 of 32 (36%) patients with > or =12 months follow-ups (2 patients were excluded because of short follow-up). In 10 of the 12 patients who received test electrodes within the central sulcus and on the precentral gyrus, the optimal stimulation was MCS within the central sulcus. In 4 of these (40%) patients, positive effects were maintained at follow-ups. The pain reduction of rTMS significantly correlated with that of MCS during test stimulation. **CONCLUSIONS:** The test stimulation within the central sulcus was more effective than that of the precentral gyrus. In the selected patients, chronic stimulation within the central sulcus did not significantly improve long-term results. **SIGNIFICANCE:** The present findings suggest that an intra-central sulcus is one of the favorable targets for MCS.



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*Next Month's Issue:*

Preview of the 2009 Geriatric Lecture Series

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