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The essential monthly primary care update

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Detection of Alzheimer's Disease and Dementia in the Preclinical Phase

Source: Palmer K, et al. *BMJ*. 2003; 326:245-247.

Alzheimer's disease (AD) is the most common form of dementia in America, but often escapes clinical attention until symptoms compromise quality of life, activities of daily living, or safety. Interventions might be enhanced by early detection of AD, but little investigation of early detection techniques has been done.

Palmer and colleagues evaluated 1435 persons aged 75-95 years who were without dementia at baseline. All persons underwent evaluation at baseline, 3 years, and 6 years with 3 different tools; subjects were asked, "Do you currently have any problems with your memory?" Additionally, each subject underwent mini-mental status examination, and neuropsychological testing assessed cognitive function.

At follow-up, almost 20% of survivors had dementia. All 3 screening tools, if positive, increased relative risk of AD. Having a memory complaint at baseline doubled the relative risk of subsequent dementia, and cognitive impairments increased relative risk of dementia by 2- to 5-fold.

Although using all 3 tools had a high predictive value if positive, the tools are too insensitive for routine employment, since only 18% of persons who ultimately developed dementia were identified using this 3-step process. That we can identify, with some reliability, a subgroup of persons likely to progress to dementia is promising. For broader applicability, more sensitive screening tools will be required. ■

Shoe Design and Plantar Pressures in Neuropathic Feet

Source: Praet S, et al. *Diabetes Care*. 2003;26:441-445.

Clinicians have tried a variety of maneuvers to reduce the incidence and effect of neuropathic foot ulcers in an attempt to reduce their subsequent morbidity. Since a substantial proportion of diabetics will ultimately develop distal sensory neuropathy and be at risk of foot ulcers, learning which type of footwear might help minimize the consequences of this neuropathy is of great importance. The most commonly used orthopedic shoe for diabetic neuropathy is the "rocker bar" variety (RB shoe), others suggest that a simple extra depth shoe, which is typically less expensive, more cosmetically pleasing, and more readily accessible, may be equally effective.

Praet and colleagues studied 10 diabetic women suffering from peripheral sensory neuropathy, but without evidence of foot deformity or ulceration. Women were tested in 3 categories of shoes: Category A were simple popularly styled traditional shoes, category B were extra depth shoes, and category C were specially crafted (based upon plaster casts of feet) shoes with rocker bottoms.

Overall, only the RB shoes effectively reduced forefoot pressure more than traditional "over the counter" footwear. Praet et al acknowledge that choosing footwear for any one individual diabetic remains a difficult choice and that shoe-specific pressure measurements in different types of footwear may be the best alternative for some patients, especially for those who balk at use of the less cosmetically acceptable RB shoes. ■

TSH in Assessment of Hypothyroidism

Source: Meier C, et al. *BMJ*. 2003; 326:311-312.

Although there is good agreement that thyroid stimulating hormone (TSH) is the most appropriate indicator of hypothyroidism, it is little understood whether absolute levels of TSH correlate either with degree of tissue effect of hypothyroidism, or levels of thyroid hormone. Meier and colleagues used a composite of clinical score, ankle reflex time, CK, and total cholesterol as markers of what they term "thyroid hormone action at the tissue level." They then correlated TSH with thyroid hormone levels and tissue parameters.

The correlation of tissue parameters and TSH was weak. This review suggests that there is a poor correlation between levels of TSH and clinical or metabolic severity of hypothyroidism. Meier et al have no quarrel with the sensitivity and diagnostic accuracy of TSH to discern the presence or absence of hypothyroidism. Rather, they hypothesize that once TSH is maximally stimulated, no further increase will occur, despite progressively greater degrees of hypothyroidism. Meier et al suggest that thyroxine treatment should be guided by clinical signs and thyroid hormone concentrations, rather than solely by TSH concentration. ■

Oral Vitamin D3 Supplementation on Fractures and Mortality

Source: Trivedi DP, et al. *BMJ*. 2003;326:469-472.

Despite recent enhanced clinician and public awareness, prevention and treatment goals for osteoporosis (OSPS) remain inadequately fulfilled. A variety of lifestyle and pharmacologic tools have been applied to OSPS management, including Vitamin D (VitD) supplementation, with some, albeit inconclusive, success.

This trial was a pilot study using VitD (cholecalciferol) supplementation in a British senior citizen population (age range, 65-85) solicited by mail (n = 2686) to participate in a placebo-controlled trial lasting 5 years. Unusual in this trial was the dosing methodology, which administered a single 100,000 IU VitD capsule once every 4 months for 5 years—not once daily, but once (total capsules administered in 5 years = 15). Participants were instructed to take the capsule they received in the mail immediately upon receipt, and respond by mail on a form indicating that they had indeed taken the medication.

Compared to placebo, the treatment group had a 22% lower rate for first fracture (any site) and a 33% lower hip, wrist, forearm, or vertebrae fracture rate. The parathyroid hormone concentrations did not differ significantly between active VitD and placebo, despite a 40% higher VitD level in the former.

Ultimately, the 100,000 IU dose of VitD is approximately equivalent to 800 IU per day, which has been used in other trials. However, the convenience, lack of toxicity, and monetary savings (in the United Kingdom, 3 capsules of 100,000 IU vitD costs less than 1 pound) provide intriguing stimuli for a larger trial. ■

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Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

Source: Rowbotham M, et al. *N Engl J Med*. 2003;348:1223-1232.

Neuropathic pain (NPP) is often described as "opioid resistant," based upon some limited human and animal studies. On the other hand, parenteral opioid analgesia has produced success in NPP. Although data on postherpetic neuralgia indicate a degree of efficacy with opioid analgesia, other NPP syndromes are not well studied in prospective, blinded studies.

Because of the ethical boundary of administering placebo to patients suffering chronic pain, a study was performed comparing 2 different dosing levels of levorphanol, a potent mu-opioid agonist, for patients (n = 100) suffering chronic NPP, in a double-blind fashion. Patients were administered either 0.15 mg or 0.75 mg capsules, and allowed to titrate up to as many as 7 capsules 3 times daily (levorphanol has a 6-8 hour duration of analgesia). The primary outcome of the study was degree of pain reduction; secondary outcome was time to pain relief. The study period was 8 weeks duration.

As perhaps might be intuitive, high-strength levorphanol reduced pain to a significantly greater degree than in the lower-strength group, despite the option available to patients of up-titrating their medication dose. Encouragingly, both groups did report levorphanol efficacy (pain reductions, 21% and 36%). Contrary to popular wisdom, tolerance to opioid analgesia was not evidenced. Additionally, the magnitude of pain reduction in the high-strength group was similar to that achieved with other more traditionally used NPP tools like tricyclic antidepressants and gabapentin.

Clinicians who have excluded opioid analgesia as an effective tool in NPP may need to consider these data in their decision process. ■

Tacrolimus Ointment vs. Topical Corticosteroids in Atopic Dermatitis

Source: Ellis C, et al. *J Am Acad Dermatol*. 2003;48:553-563.

For several decades the mainstay of management of atopic dermatitis (AD) has been corticosteroids (CSD), usually administered topically. When AD is mild-moderate, low, and mid-potency, CSD often suffices, but more severe disease may require high-potency agents, or even systemic therapy. Since CSD can produce both local effects like skin atrophy and systemic effects such as hypothalamic-pituitary suppression, chronic administration requires a degree of caution. Recently, a class of topical immunomodulator agents (IMA), exemplified by tacrolimus (Protopic) and pimecrolimus (Elidel), has been offered for clinical use as an alternative to CSD and appears to be equally efficacious. There are no serious side effects of IMA, and they have been demonstrated to be both safe and effective in children as young as 2 years, with minimal side effects.

For patients with moderate-to-severe AD, the cost of treatment was similar for either high-potency CSD and IMA for a 4-week treatment regimen. For short-term treatment (2 weeks), IMA is more cost effective than CSD because there is less requirement for secondary interventions. If lower potency and less costly CSD are used efficaciously, the cost efficacy of IMA becomes less favorable. The combination of safety, efficacy, and cost has important therapeutic implications for the role of IMA in AD. ■