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Metabolic Effects of Topiramate in Obese Diabetics

Rosenstock J, et al. *Diabetes Care.* 2007;30(6):1480-1486.

Almost 90% of persons with type 2 diabetes (DM2) are overweight or obese. Weight loss in DM2 consistently results in meaningful favorable changes in lipids, glucose, and insulin resistance. Hence, the clinical community embraces tools which can enhance weight loss in this population.

Unfortunately, currently available weight-loss tools (eg, orlistat, sibutramine) are limited by modest long-term impact, tolerability, and cost. Diet and exercise are highly effective as demonstrated in clinical trials, but most patients do not enjoy the advantage of a "team" approach available in such trials, and, as a result, fail to achieve and maintain weight loss goals.

In clinical trials of immediate-release topiramate (TOP-IR) for migraine, weight loss has been consistently identified, in the absence of any dietary or exercise intervention. Similarly, TOP-IR has demonstrated weight loss in trials of DM2, but has had tolerability issues. Controlled release topiramate (TOP-CR) has been developed for greater ease of administration (qd vs b.i.d.) and lesser adverse effect profile.

DM2 subjects (n = 111) were randomized to diet and exercise with or without TOP-CR; approximately ¾ of both groups were also on metformin. At 16 weeks, endpoints favored the group with TOP-CR: weight loss (6.0 kg vs 2.5 kg), A1C (6.7 vs 7.1), and BP (117/74 vs 124/77). Unfortunately, because of the profile of adverse events—43% of participants on TOP experienced central nervous system or peripheral nervous system effects—it is unlikely that current formulations of TOP will have a role in metabolic management of diabetes. ■

Clues Differentiate Toenail Onychomycosis from Look-alikes

Walling HW, Sniezek PJ. *Am Acad Dermatol.* 2007;56:945-948.

It is tempting to initiate pharmacotherapy when the appearance of a pathologic nail suggests onychomycosis (ONYC). However, systemic treatments for ONYC require a protracted course of therapy, at substantial expense, with potential toxicity, leading to expert advice which suggests not initiating treatment unless the presence of fungus has been confirmed, eg, by KOH examination, fungal culture, or both.

A variety of other disorders may mimic ONYC, including psoriasis, lichen planus, and post-traumatic dystrophy. Seeking to discern factors which correlate with the presence of ONYC, Walling et al reviewed characteristics of 150 cases of ONYC confirmed by PAS staining.

The factors that best correlated with confirmed fungal infection included male gender, age over 64, concurrent tinea pedis, and involvement of the third or fifth digit. Dystrophic changes of the great toe were the most commonly noted finding, but only in half of cases of dystrophic changes of the great toe was fungus confirmed. Female gender was a negative predictor.

Because current methodologies for confirmation of fungal infection are imperfect, cases which test negative for fungi but are associated with positive correlation factors should be considered for repeat testing. ■

Comparing Medical and Surgical Management of Sciatica

Peul WC, et al. *N Engl J Med.* 2007;356:22452256.

Low back pain (LBP) remains one of the most commonplace and costly disabilities affecting working Americans. Although there is some controversy about appropriate indications for surgery, the presence of persistent sciatica (SCI)—peripheral pain that indicative of a lumbar or sacral nerve compression—is commonly used as a selection criterion for consideration of surgical intervention. There is little data to compare outcomes for persons with SCI treated with conservative treatment vs surgery. Some guidelines suggest that surgical treatment be considered for persons with SCI persistent after 6 weeks of conservative therapy.

Subjects (n = 283) with SCI rated as severe due to incapacitating pain were enrolled in this trial if symptoms persisted 6-12 weeks, and were randomized into early surgery (within the next 2 weeks) or conservative management. A small percent of persons assigned to surgery (11%) experienced resolution within the 2-week waiting period for surgery. Because of persistent or worsening symptoms, 39% of the group randomized to conservative treatment underwent surgery. Outcomes of the trial included degree of functional disability, intensity of leg pain,

and overall perceived degree of recovery, as assessed periodically over 1 year.

Symptom relief was more prompt in the surgical group. However, at 1 year the degree of functional recovery, as well as the other outcomes measured was the same in both groups.

Speed of pain relief may be critical in some cases. If pain management can be satisfactorily achieved without surgical intervention, it appears that conservative treatment offers similar overall outcomes. ■

Step-Down Therapy for Controlled Mild Persistent Asthma

The American Lung Association Asthma Clinical Research Centers. *N Engl J Med.* 2007;356:2027-2039.

For persistent asthma, clinical guidelines recommend low-dose inhaled corticosteroids (LDIC) as initial maintenance therapy. If asthma is well controlled with this treatment, it is suggested that clinicians pursue "step-down therapy," ie, try to reduce the intensity of pharmacotherapy without incurring an increase in asthma symptomatology.

To test the viability of two different step-down regimens, 500 patients with mild persistent asthma that was well controlled on fluticasone 100 mcg b.i.d. were randomized to try either montelukast 5-10 mg once daily or fluticasone 100 mcg + salmeterol 50 mcg once daily. The "control" population continued to receive 100 mcg fluticasone b.i.d. Treatment failure was defined as including any of: hospitalization or acute care asthma visit, need for systemic increased steroids (oral or inhaled), 20% decrease from baseline FEV1, 35% decrease from baseline peak expiratory flow, or frequent use of rescue beta-agonist.

During 4 months of followup, treatment failure occurred in the same number of individuals who stepped down to fluticasone + salmeterol (20%) as those who continued on "full dose" inhaled steroid. On the other hand, 30% of the subjects stepped down to montelukast experienced treatment failure.

Use of montelukast for step-down therapy is associated with greater risk of treatment failure than step-down to once daily fluticasone + salmeterol. ■

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Risk-Management for Persons at High Risk of GI Bleeding

Chan FKL, et al. *Lancet.* 2007;369:1621-1626.

Persons with a history of ulcer bleeding are at great risk of rebleeding if a traditional NSAID is administered: as much as 19% over 6 months. Current guidelines suggest that appropriate steps for risk reduction in such individuals include utilization of a COX-2 inhibitor instead of an NSAID or combining a proton pump inhibitor (PPI) with an NSAID. Trials of such interventions are encouraging, and have shown bleeding rates as low as 5% over 6 months.

Whether combining a PPI with a COX-2 inhibitor would reduce risk still further was the hypothesis question of this trial by Chan et al. Subjects admitted for GI bleeding (n = 273) due to an ulcer on NSAIDs (all of whom were helicobacter negative) were randomized to celecoxib 200 mg b.i.d. plus placebo or esomeprazole 20 mg b.i.d. and followed for 1 year. The primary endpoint was recurrent bleeding within 13 months of study enrollment.

NONE of the study subjects who received celecoxib + esomeprazole experienced a GI bleed, compared with 8.9% of subjects treated with celecoxib alone. The authors suggest that this data should provide evidence to support recommending celecoxib in combination with a PPI for optimum risk reduction in persons at high risk of GI bleeding. ■

Group visits: Assessment of Patient Acceptance

Kawasaki Lm, et al. *Am J Managed Care.* 2007;13:257-262.

Group visits (GVIS) have appeal from a variety of vantage points, both patient and provider related. In an era of pressing time constraints and often shrinking resources, GVIS offers some respite. "High-profile" disorders, such as hypertension, diabetes, obesity, and dyslipidemia—which occupy a compelling place due to both epidemiologic presence and significant consequences—lend themselves well to consideration of GVIS. Clinician advocacy has an important role in development and utilization of GVIS, but patient acceptance is at least as important.

Kawasaki, et al conducted a survey by a single trained interviewer using a scripted interview of 296 persons with hypertension. After describing what a GVIS was, subjects were asked whether they would be willing to attend such a visit. Subsequently, those who said "no," were queried as to whether incentives, such as a monetary compensation for parking/transportation, more time with their physician, or less visit waiting time, would induce them to change their mind about GVIS.

With no mention of incentives, 68% of respondents were willing to participate in GVIS. Willingness did not vary across ethnicity, age, or gender.

After incentive offering, an additional 37% responded affirmatively to GVIS, with economic subsidy being the least common reason chosen.

These data suggest that patients are receptive, at least in principle, to GVIS, and that individuals with an initially tepid response might warm to the idea if incentives to greater address their personal needs are included. ■