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Orlistat in Overweight Patients with Type 2 Diabetes

Source: Miles JM, et al. *Diabetes Care*. 2002;25:1123-1128.

Recently, it has been acknowledged that metformin (MET), in contrast to insulin secretagogues or insulin supplementation, is weight neutral or even associated with weight loss. Unfortunately, most DM2 patients are, or will be, on more than one medication, which may complicate weight management.

Of the 2 medications currently available for long-term management of obesity, both sibutramine and orlistat (ORL) have been shown to provide statistically significant weight reduction in DM2. Whether such effects might extend to persons specifically receiving DM2 treatment with metformin has not been previously studied. In particular, since both MET and ORL are associated with GI symptoms, the tolerability as well as efficacy of this combination merits clarification.

In this study, ORL (n = 249) or placebo (n = 254) was administered t.i.d to patients on stable doses of MET. Some patients were also receiving sulfonylureas (SFU) in addition to MET. Insulin, thiazolidinedione, or alpha-glucosidase treatments were exclusionary from the study. Patients were treated for 1 year.

ORL was associated with clinically important, as well as statistically significant improvements in A1c (mean = 0.9 decrease); LDL, triglycerides, and blood pressure were all favorably affected in comparison to placebo. Mean weight loss was 4.7 kg on ORL (vs 1.8 kg, placebo). Although GI complaints were more frequent in the ORL group, withdrawal due to adverse events was actually more frequent in the placebo group. In overweight diabetics on MET, ORL is well tolerated and effective for multiple factors pertinent to diabetic control. ■

Sleep Attacks in Patients Taking Dopamine Agonists

Source: Homann CN, et al. *BMJ*. 2002;324:1483-1487.

The term "sleep attack" is defined as ". . . an event of overwhelming sleepiness that occurs without warning or with a prodrome sufficiently short or overpowering to prevent protective measures." It has already been recognized that dopaminergic drugs, such as those commonly used in Parkinsonism (eg, levodopa, ropinirole, bromocriptine), are associated with somnolence and motor vehicle accidents (MVA). Identification of the frequency of sleep attacks is relevant to risk reduction.

Homann and colleagues identified 20 publications that included suspect events (n = 124), further dividing them into definite, probable, and possible sleep attacks. Ten of 17 events occurring during driving lead to MVA; however, numerous attacks happened even during ambulatory activities, such as walking or standing.

In this review, as many as 30% of patients receiving dopamine agonists for Parkinson's disease (PD) had sleep attacks, regarded by Homann et al as a class phenomenon, rather than due to a specific agent. Additionally, dose reduction was not reliably associated with remission of sleep attacks, and of course could risk lesser symptom control of PD. It has been recommended that persons taking pramipexole and ropinirole not drive. Short of not driving, it is uncertain which measures should be exercised for Parkinson's patients taking other dopaminergic medications. Indeed, there remains some controversy about the existence of sleep attacks distinct from simple somnolence. The descriptions in this communication argue for the definition of sleep attacks as a separate entity. ■

Probiotics in Prevention of AAD

Source: D'Souza AL, et al. *BMJ*. 2002;324:1361-1364.

The consequences of antibiotic-associated diarrhea (AAD) are potentially far ranging. Though thoughtful antibiotic selection and application can reduce the frequency of AAD, numerous clinical situations will require antibiotics for which the likelihood of AAD is known to be significant. Probiotics (PRO) are microorganisms with therapeutic potential—some nonpathogenic organisms appear to inhibit the growth of pathogens. *Saccharomyces boulardii*, a nonpathogenic yeast, has been reported to destroy the receptor site for *C difficile* toxin A and B through a protease enzyme.

In this report, 9 double-blind, placebo-controlled trials were analyzed. Agents used included *S boulardii*, lactobacilli, and enterococcus. In each of the trials, the PRO was administered concomitantly with the antibiotics. Antibiotics studied included amoxicillin, clindamycin, and multi-drug regimens.

Concomitant PRO administration was associated with an approximately 60% reduction in odds ratio for AAD. PRO are well tol-

erated, without known serious adverse effects, and though they transiently colonize the gut, upon cessation of therapy they are generally rapidly cleared from the GI microbial population. This meta-analysis indicates PRO may offer valuable reductions in the frequency of AAD, and further study is suggested. ■

Botulinum Toxin for Wrist and Finger Spasticity

Source: Brashear A, et al. *N Engl J Med*. 2002;346:395-400.

POST-STROKE SPASTICITY IN THE HANDS and wrists is potentially particularly disabling in that it may complicate basic essential daily activities like dressing, washing, and eating. There is a paucity of information about the role of botulinum toxin (BOT) on functional outcome in post-stroke spastic disorders.

Brashear and colleagues studied patients (n = 126) with post-stroke spasticity of the upper extremity. In addition to an overall global assessment, functional disability outcomes measured were hygiene, dressing, limb position, and pain. Each patient selected one of these 4 end points as their personal "principal target," though all parameters were measured for all subjects. Most patients selected "dressing" as the principle target, but more than one quarter chose limb position. Patients received a single set of 4-5 injections in wrist and finger muscles, or placebo. Outcomes were measured at 4, 6, 8, and 12 weeks.

More than twice as many persons who received BOT than those who received placebo achieved improvement in their primary target. For functional disability, BOT recipients' improvements (at least 1 point on an 8-point scale) were again superior to placebo (83% vs 53%). The physician's global assessment score was significantly higher for BOT at all follow-up visits. No serious adverse events were seen in either group.

Statistically significant and clinically meaningful improvements in upper extremity function are seen as early as 1 week after BOT injections and are maintained for at least 12 weeks. ■

Exercise in People with Fibromyalgia

Source: Richards SCM, Scott DL. *BMJ*. 2002;325:185-187.

THE TREATMENT OFFERED FOR fibromyalgia (FMG)—typically consisting of analgesics, NSAIDs, and antidepressants, alone or in combination—often provides suboptimal efficacy. Although some trials of exercise have suggested a favorable effect on FMG, their widespread applicability to the ambulatory setting has been limited by underpowered study groups and provision of specialized exercise plans administered in hospitals by health professionals with special expertise in this field.

Richards and Scott investigated the effect of aerobic exercise (treadmill walking or exercise bicycles) or stretching/relaxation activities. Twice-weekly classes of aerobic activities began with two 6-minute sessions and were advanced as tolerated to 2 25-minute sessions over a 12-week observation period. The primary outcome was self-rated global impression, rated on a 7-point scale, with 1 being "very much worse" and 7 being "very much better." Only persons with a score of 6 or greater were considered responders.

The 108 participants were highly disabled at baseline, with a mean SF-36 score greater than 3 SD below normal, and two thirds were receiving disability benefits.

At 3 months, a statistically significantly greater portion of exercise subjects were responders than relaxation subjects (35% vs 18%). This beneficial effect was still measurable at 12 months. A substantial number of individuals were noncompliant: specifically, only 53% of subjects attended at least one third of the exercise classes. Accordingly, the authors do suggest that future investigation should evaluate methods to enhance compliance with exercise, given the favorable effects demonstrated in this trial. ■

Risk of Diabetes Among Patients with Schizophrenia

Source: Koro CE, et al. *BMJ*. 2002; 325:243.

THE ADVENT OF NEWER ANTIpsychotic agents for schizophrenia has broadened the clinician's therapeutic palette, with the additional benefit of fewer extrapyramidal adverse effects. Nonetheless, this pharmacotherapeutic evolution has introduced a different panel of adverse effects, such as weight gain, dyslipidemia, glucose perturbations, and cardiac toxicities. This study draws upon a very large database from 400 British general practice sites, including 3.5 million patients. The primary outcome was the quantification of risk of new onset diabetes in schizophrenic subjects who received newer antipsychotics, ie, olanzapine and risperidone.

Cases were defined as having been newly diagnosed with the diabetes at least 3 months after the beginning of the study period. Comparators were controls that did not have a diagnosis of diabetes. Study subjects were further classified as those receiving "conventional" antipsychotics or "newer" antipsychotics (olanzapine, risperidone).

Among 19,637 persons with schizophrenia from the study population, 451 cases of incident diabetes were discerned. Compared with matched controls, the odds ratio for diabetes among users of olanzapine was increased almost 6-fold, and was more than 4-fold greater than patients who had received "conventional" agents. There was no significant increase in risk for persons who took risperidone. Koro and colleagues conclude that the metabolic consequences of antipsychotics merit consideration by clinicians. ■

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