Clinical Briefs in
Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

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Reducing Drug-induced Xerostomia with Sorbet

Source: Crogan NL. *Ann Long Term Care* 2015;23:17-21.

Xerostomia, or dry mouth, is common in senior citizens, partially because of disorders that are directly associated with xerostomia (e.g., Sjogren syndrome, HIV, hepatitis C, diabetes) and, additionally, because numerous pharmacologic treatments seniors receive produce "drying" effects: anticholinergics (e.g., antimuscarinic OAB drugs, tricyclic antidepressants), sympathomimetics (e.g., milnacipran, atomoxetine), or diuretics. Although for some geriatric patients, xerostomia is merely an irksome symptom, for others it leads to impaired nutrition as well. Pharmacologic treatments (e.g., cholinergic agonists), while having some degree of efficacy, have their own adverse effect profile. Is there a simpler, kinder way to address the problem?

As part of a quality improvement program, Crogan performed a study in cognitively intact nursing home residents (n = 22) who scored positively on a xerostomia index and were consuming medications known to induce xerostomia. They directly measured the food intake and wasted food that had been provided in the facility dining room from these subjects, comparing results from the 7 days prior to intervention to results 6 weeks after intervention.

The active intervention was provision of 2 ounces of sugar-free lemon-lime sorbet prior to lunch and dinner for 6 weeks. Measured outcomes included fluid intake during meals — with decreased fluid intake suggesting less dry mouth — calorie intake, and body weight.

Pre-meal sorbet was associated with a (mean) 22% increase in food intake, and 81% of participants either maintained or gained weight. Provision of pre-meal sorbet may improve nutrition among seniors treated with medications that produce xerostomia. ■

The Ongoing Search for Biomarkers that Provide Early Identification of Cognitive Impairment

Source: Wang T, et al. *J Clin Psychiatry* 2015;76:135-141.

Messenger RNA (mRNA) markers are used for identification of a variety of pathologic processes, most recently including malignant melanoma. Although the labels "BACE1" and "miRAN107" likely hold little meaning for most clinicians, investigators have found that diminished levels of these particular biomarkers may help identify persons with cognitive impairment, specifically in Alzheimer's disease.

The low levels of such biomarkers in cerebrospinal fluid (CSF) as a correlate of dementia — as well as identification of their diminution being associated with tissue deposition of amyloid — strengthens the case considering their etiologic role in dementing disorders. Because of the relative inaccessibility of CSF, however, it is fortunate that biomarker plasma levels of BACE1 and miRAN107 reflect CSF levels.

In a study of elderly patients with either Alzheimer's disease (n = 97), mild cognitive impairment (n = 116), or normal cognitive function (n = 81), investigators identified a nearly four-fold lower plasma level of BACE1 and miRAN107 in mild cognitive impairment (as well as Alzheimer's disease) compared to healthy controls. The authors are hopeful that these biomarkers may ultimately help us identify mild cognitive impairment early, as well as discriminate Alzheimer's disease from other forms of dementia. ■

Bipolar Disorder is Associated with New-onset CVD

Source: Goldstein BI, et al. *J Clin Psychiatry* 2015;76:163-169.

Although perhaps not widely recognized, bipolar disorder (BPD) is associated with an excessive risk of cardiovascular disease (CVD). Not only is CVD more prevalent, but it occurs as much as a decade earlier than comparators without BPD. Some of this risk is attributed to utilization of pharmacotherapies that are known to be diabetogenic (e.g., mood stabilizers), but this is insufficient to fully explain the observed increased CVD risk.

To better clarify risk of CVD in BPD patients, an analysis was performed of persons in the NESARC epidemiologic survey (National Epidemiologic Survey on Alcohol and Related Conditions). The population studied included persons with BPD (n = 1439), major depressive disorder (n = 4396), and controls (n = 26,266). The incidence of CVD was compared in two survey "waves," the first performed in 2001-2002 and the next performed in 2004-2005.

Even within this very short window of observation, the odds ratio for new-onset CVD among persons with BPD was over

2.5 compared to controls. In contrast, persons with major depressive disorder did not have an incidence of CVD that differed meaningfully from controls.

These concerning data show a nearly three-fold increased risk of new-onset CVD in persons with BPD, despite being controlled for commonly recognized risk factors (e.g., age, smoking, HTN, obesity). Equally alarming is the observation that the mean age of CVD onset in BPD patients was 14-17 years earlier than controls! Clinicians should heighten their vigilance for addressing CVD risk factors among persons with BPD. ■

Chronobiology and Insulin Glargine

Source: Porcellati F, et al. *Diabetes Care* 2015;38:503-512.

The "indication" labeling for insulin glargine (Lantus) simply says, "Administer subcutaneously once daily at any time of day, but at the same time every day." Some patients and clinicians prefer morning administration, some prefer evenings, and some even prefer twice-daily injections, although the latter is clearly off-label. The important question is, then, does it make any difference *when* you give insulin glargine, or is it just personal preference?

The pharmacokinetics and pharmacodynamics of insulin glargine were studied in 10 subjects with type 2 diabetes who had already been receiving insulin glargine as part of their therapeutic regimen. Subjects were randomized in a crossover design to dose insulin glargine at either 10 a.m. or 10 p.m., with dose optimization attained during a 2-week period to achieve fasting blood glucose (FBG) ≤ 100 mg/dL without experiencing nocturnal hypoglycemia (glucose < 72 mg/dL).

Several interesting results were noted. First, the actual dose needed for optimization of FBG was slightly greater when glargine was administered at 10 a.m. than 10 p.m. Second, morning administration of glargine had less glucagon-suppression effect in the second half of the 24-hr cycle than evening administration had in the second half of its 24-hr cycle. Evening administration also limited lipolysis more than morning, resulting in lower levels of plasma fatty acids.

The differences between morning and evening glargine administration demonstrated here are quite modest, but do suggest that overall, evening administration may be superior in reference to some dysregulations seen in type 2 diabetes, such as glucagon and fatty acids. ■

Dual Add-on Therapy for Type 2 Diabetes When Metformin is Not Enough

Source: Rosenstock J, et al. *Diabetes Care* 2015;38:376-383.

The current (2015) American Diabetes Association guidance for progression of treatment when A1c goals are not attained with metformin implies stepwise initiation of additional monotherapies. But would it make sense to consider dual add-on?

Rosenstock et al studied patients with type 2 diabetes (T2DM) whose A1c was 8.9% at baseline on monotherapy with metformin. Subjects were randomized to add a DPP4 inhibitor (saxagliptin), an SGLT2 inhibitor (Dapagliflozin), or both, and were followed for 24 weeks.

All three regimens were successful to reduce A1c from baseline, and it probably comes as no surprise that the addition of two drugs (DPP4 inhibitor *and* SGLT2 inhibitor) to metformin outperformed the addition of either monotherapy. The addition of an SGLT2 to metformin demonstrated substantially better A1c reductions than the addition of a DPP4 inhibitor (-0.9% vs -0.59%), but the three-drug combination was far more effective, providing a -1.5% A1c reduction.

The simultaneous addition of two drugs to metformin monotherapy is probably an uncommon step for clinicians, who are more accustomed to progressive monotherapeutic step advancements. The fact that there were no episodes of major hypoglycemia during the 6 months of the trial is reassuring that similar therapeutic steps may be safely taken in practice settings where patients continue to have an elevated A1c on metformin. Because of the very potent A1c reduction, however, it is equally important to select patients with a sufficiently elevated A1c on metformin (at least 8.9%) so that the addition of dual add-on treatment does not lead to problematic hypoglycemia. ■

Might Long-term Dual Antiplatelet Therapy Be Better? Not

Source: Elmariah S, et al. *Lancet* 2014; 385:792-98

Risk reduction provided by dual antiplatelet therapy (DAT) in the short-term interval (3-12 months) after coronary stenting is well established, and published guidelines provide consistent advice about appropriate duration of such therapy. In essentially every large randomized trial that has compared DAT to monotherapy, bleeding risks go up to a sufficient level that it counterbalances any risk reduction in reference to cardiovascular events. Indeed, two major mega-trials comparing DAT to monotherapy in stable patients with established vascular disease failed to demonstrate beneficial reduction in stroke (the MATCH trial) or stable coronary disease (the CHARISMA trial), but did find more bleeding risk.

Elmariah et al performed a meta-analysis of randomized, controlled trials employing DAT post coronary stenting to compare "short duration therapy" (i.e., ≥ 6 months) or aspirin alone with longer treatment.

Based on data from 14 clinical trials (n = 69,644), they found no evidence of improved outcome associated with longer duration treatment. While this may appear disappointing, one rationale for the investigation was the finding in the large DAPT Study (Dual Antiplatelet Therapy Study, n = 11,648) that non-cardiovascular deaths were actually increased if DAT was extended beyond 12 months, which was not confirmed in the meta-analysis. ■

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Executive Editor: Leslie Coplin.
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Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: leslie.hamlin@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

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