Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Volume 19, Number 4 Pages 7-8 April 2014

Treatment to Reduce Genital HSV Shedding

Source: Wald A, et al. *N Engl J Med* 2014; 370:201-210.

Patients burdened with genital herpes often desire treatments to reduce the frequency of viral shedding, hoping to reduce the rate of transmission. Several antivirals are currently available to reduce viral shedding, each of which has demonstrated some efficacy, but none of which totally eliminates viral shedding.

Herpes simplex virus type 2 (HSV-2) comprises a substantial share of the causes of genital herpes infection. Although two decades ago HSV-2 was responsible for the vast majority of genital herpes infections, the prominent role of HSV-1 in genital herpes has been increasingly recognized since 2006. Clinically, outbreaks are indistinguishable, although nuances of difference between HSV-1 and HSV-2 do exist (e.g., frequency of outbreaks and severity of outbreaks being modestly less with the former).

Pritelivir (PRT) is the first member of a new class of antiviral agents active against both HSV-1 and HSV-2. The mechanism of action — inhibition of the viral helicase-primase complex — differs from currently available nucleosidase analogues.

Wald et al performed a double-blind, placebo-controlled trial among adults (n = 156) with a clinical history of genital herpes and confirmed HSV-2 seropositivity. Subjects performed daily self-swabbing for HSV PCR testing, as well as reporting on occurrences of HSV outbreaks (which had to be confirmed within 24 hours by clinic personnel).

Over the 28-day duration of the study, study subjects who received daily doses of PRT of 25-400 mg/day experienced a significant reduction in the number of days of viral shedding (43-87% reduction, depending on dose). Clinical outbreaks were also dramatically reduced (87% reduction). PRT was well tolerated, with no serious drug-attributable adverse effects. It is uncertain if and when PRT will find clinical utility because animal trials disclosed skin and hematologic abnormalities, albeit at much larger relative doses than used in humans. ■

The Continuing Saga of Vitamin D: Who, When, and Why Should We Use It

Source: Reid IR, et al. *Lancet* 2014;383: 146-155.

The greying of the population assures a continued prominence for osteoporosis and its consequences. The "story line" of vitamin D in relation to osteoporosis is fairly straightforward: As vitamin D levels decline to suboptimal levels (actual number of what constitutes "suboptimal" is still hotly debated), secondary hyperparathyroidism develops, resulting in accelerated bone loss. To date, clinical trials have not confirmed a fracture reduction benefit from vitamin D supplementation, and even the relationship between vitamin D status and bone mineral density (BMD) is plagued with inconsistencies. To further clarify the question of the relationship between vitamin D and BMD, Reid et al performed a meta-analysis of clinical trials that evaluated the effects of vitamin D on BMD.

The clinical trial results (23 studies, n = 4082) were quite mixed, with some showing BMD benefit, some detriment, and some neutral. In essence, the net small benefit suggested by some trial data was of dubious clinical significance. These results should be distinguished from data on vitamin D in combination with calcium supplementation; since many trials provide vitamin D in combination with calcium (calcium does increase BMD), it has been sometimes misconstrued that each component of the vitamin D/calcium combo contributed to better BMD. The authors suggest that vitamin D would be best suited for persons with vitamin D insufficiency, rather than for all persons at risk for osteoporosis. ■

Antidepressants and New Onset Diabetes

Source: Wu CS, et al. *J Clin Psychiatry* 2014;75:31-38.

The relationship between antipsychotic medication and diabetes has been well demonstrated and is widely recognized by clinicians. Unfortunately, the relatively limited selection of antipsychotics sometimes requires that in order to achieve symptom control, new-onset diabetes must be accepted as a consequence.

The population of individuals treated with antidepressants far eclipses those treated with antipsychotics. The earliest commonly used antidepressants, tricyclics, were associated with weight gain due to activity and the post-synaptic histamine receptor site, which of course could be diabetogenic.

Wu et al report on a case-control study based on the Taiwan National Health Insurance Research Database. Over the

1998-2009 interval, they compared use of antidepressants among patients with diabetes (n = 47,885) and controls (n = 95,770).

Overall, persons treated with antidepressants for at least 2 years were 20% more likely to develop diabetes. In particular, younger individuals were adversely affected: Persons < 44 years of age had more than a doubling of risk for new onset diabetes.

The mechanism(s) by which antidepressants impart increased risk for diabetes are not clear. For instance, the above-mentioned weight gain with tricyclic antidepressants was not reflected in a greater incidence of diabetes than that seen with newer antidepressants (e.g., SSRIs, SNRIs). Recent studies have shown that other commonly used medications are associated with increased risk for new onset diabetes, including statins and thiazide diuretics. The frequency of prescription of antidepressants merits enhanced clinician vigilance for the development of diabetes. ■

GERD Medications and B12 Deficiency

Source: Lam JR, et al. *JAMA* 2014;310:2435-2442.

The consequences of vitamin B12 (B12) deficiency most commonly include neurologic (CNS and peripheral nervous system) and hematologic (megaloblastic anemia). Because the progression of symptoms and signs related to B12 deficiency can be subtle, yet extremely burdensome to patients, clinicians must maintain a high level of vigilance for circumstances in which B12 deficiency can predictably occur, such as alcoholism and malnutrition.

Use of proton pump inhibitors (PPIs) and histamine-type 2-receptor antagonists (H2RA) is widespread in the United States. In 2012, more than 150 million prescriptions were written for PPIs alone. These numbers underestimate use since OTC versions of PPIs are also available.

Absorption of B12 requires that it first be cleaved from its food protein source on entering the GI tract. Gastric acid is required to release B12 from food. Since PPIs and H2RAs reduce gastric acidity, it should come as no surprise that they might be associated with greater risk for B12 deficiency.

A case-control study using the population of the Kaiser Permanente Northern California Healthcare system provided the opportunity to compare PPI/H2RA use among persons confirmed to have B12 deficiency (n = 25,956) vs controls (n = 184,199).

Receiving a PPI prescription for ≥ 2 years was associated with a 65% increased odds ratio of B12 deficiency. Similarly, receipt of H2RA treatment for that same interval was associated with a 25% increased risk.

The benefits of PPI and H2RA treatment are often substantial. That B12 deficiency is more likely to occur when using long-term GERD treatments should not discourage their use, but rather, increase clinician vigilance for the possibility of B12 insufficiency, especially when potentially appropriate symptoms or signs appear. ■

Dietary Fish Intake and New Onset Diabetes

Source: Virtanen JK, et al. *Diabetes Care* 2014;37:189-196.

The cornerstones of diabetes prevention are healthy diet and maintenance of desirable weight. The most focus of diet has been the role of caloric restriction to improve glycemia in overweight and obese individuals. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) provides an opportunity to evaluate the potential role of diet and new onset diabetes in Finnish men.

The observational data from KIHD included measurement of omega-3 polyunsaturated fatty acids (PUFAs) by dietary history. Long-chain omega-3 PUFA levels are considered to be a reliable indicator of the level of fish consumption in the diet.

Over an interval of almost 20 years, there was a linear inverse relationship between omega-3 PUFAs and incident type 2 diabetes. Men in the highest quartile of omega-3 PUFA enjoyed a 33% lesser likelihood of incident diabetes, adjusted for other risk factors. The mechanisms by which omega-3 PUFAs exert a protective effect on incident diabetes are not fully understood, especially since studies that examine fish (or fish oil supplements) have not detected any direct impact on glucose metabolism. On the other hand, because higher fish intake is associated with lesser adiposity, avoiding the diabetogenic effects of obesity may be an important contributor. ■

The Metabolic Impact of Low-Dose Thiazide Diuretics

Source: Mukete BN, Rosendorff C. *J Am Soc Hypertens* 2013;7:454-466.

Hyperglycemia and hypokalemia are well-recognized consequences of thiazide diuretic (TZD) therapy. Both adversities appear to be dose-related, and since we currently generally use low-dose TZD for treatment of hypertension (the most common indication for TZD therapy), it is useful to identify its impact on metabolic parameters.

Mukete and Rosendorff performed a meta-analysis on clinical trial data of 17,947 subjects in whom potassium (K+) and glucose measurements were taken. Overall, the mean changes in both parameters compared to other treatments were modest: an increase of glucose of only 1.4 mg/dL and a decrease in K+ of 0.27 mEq/L.

The largest hypertension trial ever performed was the ALLHAT trial, which found that compared to the calcium channel blocker amlodipine or the ACE inhibitor lisinopril, diuretic therapy was associated with a small but statistically significant increased risk for new onset diabetes (8.1% vs 9.8% vs 11.6%, respectively). Although looking at mean changes of metabolic parameters, especially restricting the view to only low-dose thiazides, looks relatively reassuring, the fact that some outliers will still experience clinically relevant hypokalemia or hyperglycemia mandates our continued vigilance for both consequences during the course of long-term treatment. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.
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