Clinical Briefs in Primary Care

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Evidence-based updates in primary care medicine

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Fixing Intractable Pruritus: Azathioprine

SOURCE: Maley A, Swerlick RA. *J Am Acad Dermatol* 2015;73:439-443.

When we can identify and remove the source of pruritus, we would like to do so. Unfortunately, sometimes the cause cannot be identified, as in recurrent urticaria, for which an inciting agent remains unconfirmed as often as half of the time. Additionally, there are times when a necessary or preferred treatment must be continued despite pruritis, as is sometimes the case with opioid analgesics. While traditional antihistamines often effectively relieve pruritus, the tricyclic antidepressant doxepin is actually many times more potent than other antihistamines and also effectively treats pruritus. However, since it is highly sedating at doses effective for pruritus, it generally is not used as a first line-treatment. Although systemic steroids are often effective, their side effect profile limits chronic use.

Based on the theory that pruritus may be an immunologically mediated phenomenon — corroborated by the frequency of pruritus relief through systemic steroid administration — Maley and Swerlick administered azathioprine to patients (n = 96) with intractable pruritus. Azathioprine inhibits T-cell and B-cell proliferation, leading to its role in prevention of organ transplantation rejection. Each of these patients had suffered long-term pruritus (mean = 53 months), and the mean pruritus score was 9.25 on a 10 point scale. Azathioprine was found to be highly effective: The post-treatment pruritus score came down from 9.25/10 to 1.63/10. Advantages of azathioprine include that it is once daily, inexpensive, and drug levels can be monitored. Disadvantages include consequences of immune suppression, including malignancy. While probably not a treatment to be commonly employed in the primary care setting, this retrospective study supports consideration of azathioprine when other efficacious treatments have been exhausted. ■

Dextromethorphan-Quinidine Combo for Alzheimer's Patients with Agitation

SOURCE: Cummings J, et al. *JAMA* 2015;314:1242-1254.

First-line management of agitation in persons with dementia is supposed to be non-pharmacologic. When this is insufficient to adequately manage agitation, atypical antipsychotics have been often used, but the recognition that such agents are associated with increased mortality has dampened enthusiasm for their use. A trial of citalopram was promising, but the adverse effect of potential QT prolongation remains a concern. The idea to use a combination of dextromethorphan and quinidine for agitation stems from the approval of this same combination for treatment of pseudobulbar affect. Pseudobulbar affect, which is sometimes colloquially called "emotional hyperlability syndrome," is typified by outbursts of exaggerated or inappropriate positive (e.g., laughing) or negative (e.g., crying) emotions. A patient might burst into uncontrolled sobbing because he or she discovered his or her shirt was not buttoned properly. Since agitation syndromes are also emotion-laden, might the combination of dextromethorphan and quinidine work here?

Cummings et al randomized patients assessed to have probable Alzheimer's disease and a history of agitation to the combination of quinidine and dextromethorphan or placebo for 10 weeks. Aggression scores were substantially improved compared to placebo. Adverse events leading to discontinuation were infrequent (5.3% on the quinidine-dextromethorphan combination, 3.1% on placebo). The combination of dextromethorphan and quinidine appears promising for management of aggression in Alzheimer's patients. ■

Difficult Choices in Long-term Osteoporosis Management

SOURCE: Leder BZ, et al. *Lancet* 2015;386:1147-1155.

The propriety of long-term bisphosphonate utilization (that is, > 5 years) has recently come into question subsequent to a clinical trial that compared bisphosphonate discontinuation at 5 years vs continuation for 10 years. Despite a decline in bone mineral density (BMD) in the cessation group, the actual hip fracture rate was no greater than in the group who continued bisphosphonate for 10 years. Since there are adverse effects and expense associated with treatment, many questions remain about how long to treat and which

agent(s) to utilize.

In the DATA (Denosumab and Teriparatide Administration) trial, postmenopausal women (n = 94) with osteoporosis were randomized to treatment with teriparatide (TER), denosumab (DEN), or both for 2 years. DATA-Switch is an extension of DATA, during which patients on monotherapy were switched (e.g., if on DEN for 2 years, switched to TER, and vice versa), and patients on dual therapy (DEN + TER) were switched to DEN monotherapy. The SWITCH phase of the trial lasted an additional 2 years. TER patients switched to DEN, and DEN + TER patients switched to DEN monotherapy continued to accrue more mass at the lumbar spine, distal radius, femoral neck, and total hip. Women who were switched from DEN to TER lost BMD at the distal radius, and showed losses of BMD in the femoral neck and total hip for the first 12 months, after which some gain in BMD occurred.

Ultimately, the greatest improvements in BMD were seen in women who were assigned initially to DEN + TER and then switched to DEN monotherapy. Hopefully, we will see similar trials in the future to guide us in switching between bisphosphonates and alternative agents such as denosumab. ■

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ACE Inhibitors vs ARBs for Hypertension

SOURCE: Kaplan NM. *J Am Soc Hypertens* 2015;9:582-583.

Recommendations from the panel assigned to develop Eighth Joint National Committee hypertension guidelines indicate that angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) (as well as thiazide-type diuretics and calcium channel blockers) are all appropriate initial therapies for hypertension in the general non-black population. For persons with chronic kidney disease and hypertension, this same document suggests ACE inhibitors or ARBs, without distinction. But should we consider ACE inhibitors and ARBs essentially interchangeable? An editorial review of this issue in the *Journal of the American Society of Hypertension* suggests otherwise, preferring ACE inhibitors over ARBs both in the general population and persons with diabetes.

The endorsement for ACE inhibitors over ARBs by this editorialist does not stem from a large randomized trial comparing the two. Rather, meta-analyses of a large number of hypertension trials has shown that whereas ACE inhibitors consistently reduced cardiovascular mortality, including myocardial infarction, ARBs do not demonstrate the same convincing risk reduction, especially for myocardial infarction. Since a large randomized trial comparing ACE inhibitors to ARBs is highly unlikely in the near future, if at all, this data review would support using ACE inhibitors preferentially over ARBs in most patients with hypertension. ■

Uric Acid as a Predictor of Hypertension

SOURCE: Leiba A, et al. *J Am Soc Hypertens* 2015;9;600-609.

Currently accepted laboratory standards indicate that the upper limit of "normal" for uric acid levels is 7 mg/dL in men and 6 mg/dL in women. Uric acid has been recognized as a cardiovascular risk factor for more than 3 decades, thanks to data from the Framingham study. Nonetheless, whether uric acid causes — or is simply associated with — adverse cardiovascular outcomes is uncertain. Additionally, even if the association of uric acid with cardiovascular disease is determined to be causal, it will remain necessary to definitively prove that reductions in uric acid improve outcomes (without undue risk).

Using analysis from the largest HMO in Israel, healthy adults aged 40-70 years (n = 118,920) had baseline uric acid levels obtained in 2002, and were subsequently followed for 10 years. During this interval, almost one-quarter of these had a new diagnosis of hypertension recorded. The risk of hypertension in women and men began to increase well within the "normal" range. Compared to a uric acid of 2-3 mg/dL, even uric acid of 3-4 mg/dL were 15% more likely to become hypertensive; higher "normal" uric acid (5-6 mg/dL) was associated with a 66% increased incidence of hypertension. Results were similar for men. The authors suggested that our currently defined levels of "normal" for uric acid may have to be reconsidered. ■

Between-arm Differences in BP Predict Peripheral Arterial Disease

SOURCE: Singh S, et al. *J Am Soc Hypertens* 2015;9:640-650.

Although there is little evidence to support this practice, it has been suggested that when there is a measureable difference in blood pressure (BP) between arms, the arm with the higher BP should be considered the reference or actual BP. A number of different authors have pointed to a relationship between interarm BP discrepancy and adverse cardiovascular events, but the methods with which BP was obtained in many studies call into question whether any such relationship is valid. Specifically, it has been demonstrated that when BP is obtained simultaneously in both arms, the results often differ from BP obtained sequentially in both arms, with the former being more accurate. Unfortunately, much of the literature on inter-arm BP difference has been generated using sequential arm BP measurement.

Singh et al reviewed data from trials that only examined studies performed with simultaneous inter-arm BP measurement. They determined that an inter-arm systolic BP difference of as little as 10 mmHg was associated with a doubling of the risk for peripheral arterial disease. Although a trend for increased mortality and cardiovascular disease was noted when inter-arm systolic BP difference was > 10 mmHg, the results were not statistically significant. ■