Clinical Briefs in Primary Care

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Evidence-based updates in primary care medicine

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Improving Sexual Function and Mood

SOURCE: Snyder PJ, et al. *N Engl J Med* 2016;374:7:611-624.

Male hypogonadism is best defined as a clinical syndrome (changes in libido, sexual function, mood, and strength) confirmed by subnormal testosterone. This definition dissuades clinicians from measuring testosterone in asymptomatic men and instituting treatment solely on the basis of low testosterone levels. On one hand, clinical trials of testosterone in asymptomatic men have not demonstrated salutary outcomes. On the other hand, numerous trials confirm improvements in symptoms of hypogonadism through testosterone replacement, albeit with some uncertainty about potential toxicity of testosterone replacement.

Snyder et al performed a double-blind, randomized, placebo-controlled 12-month trial of testosterone replacement (using testosterone gel) in symptomatic hypogonadal men (n = 790) ≥ 65 years of age. Testosterone replacement restored testosterone levels to the mid-normal range for young adult men. Testosterone replacement resulted in statistically significant improvements in sexual function, desire, mood, and depression. Testosterone replacement did not improve walking distance. Testosterone generally was well tolerated, although seven men in the testosterone treatment group developed a hemoglobin > 17.5 mg/dL (none in the placebo group). There was no signal for increased cardiovascular risk, although a much larger trial would be necessary to provide definitive evidence of cardiovascular safety. The authors did not observe any worsening of symptoms relevant to benign prostatic hyperplasia. Testosterone replacement provides several areas of potential symptomatic improvement for hypogonadal men, but ongoing monitoring for adverse events (such as polycythemia) is necessary. ■

Liraglutide Improves Non-alcoholic Steatohepatitis

SOURCE: Armstrong MJ, et al. *Lancet* 2016;387:679-690.

Hepatosteatosis indicates deposition of fat in the liver in the absence of inflammation. Steatohepatitis is the term for deposition of fat in the liver that is associated with inflammation and fibrosis, which ultimately can lead to end-stage liver disease if untreated. Indeed, it has been suggested that within the next five years, non-alcoholic steatohepatitis (NASH) may become the most common disorder leading to the need for liver transplantation worldwide. As is perhaps implied in the name, the most common NASH etiologies are diabetes and obesity. The prevalence of both continues increasing.

The Liraglutide Efficacy and Action in NASH trial was a double-blind, randomized 48-week study of liraglutide (titrated to 1.8 mg/d subcutaneous) vs. placebo (n = 52). All patients were confirmed by biopsy at baseline to have NASH, and were again biopsied at week 48. Specific biopsy-based outcomes included disappearance of hepatocyte ballooning (which indicates resolution of inflammation) without worsening fibrosis, liver function tests, and other hepatic biomarkers. The number of study subjects who attained resolution of NASH was more than four-fold greater in the liraglutide group than placebo (39% vs. 9%). Liraglutide is already recognized to be a generally safe and well-tolerated medication, including doses up to 3 mg/d subcutaneous in obese patients. These favorable outcomes should prompt a much larger trial to definitively determine the role of liraglutide in treatment of NASH. ■

Long-acting Anticholinergics and Beta Agonists for COPD

SOURCE: Calzetta L, et al. *Chest* 2016;149:1181-1196.

There has been some suggestion that the bronchodilation afforded by anticholinergic agents, commonly referred to as long-acting antimuscarinic agents (LAMA, e.g., tiotropium, umeclidinium) is at least as good as that provided by long-acting beta-agonists (LABA, e.g., salmeterol, formoterol). Additionally, there does not appear to be any tachyphylaxis associated with LAMA as has been seen with LABA. Since most patients with COPD experience disease progression, pharmacologic augmentation is the rule rather than the exception. Only recently have LAMA/LABA combinations become available. Is LAMA + LABA really better than either alone? And if so, is there a best LAMA/LABA combination?

Calzetta et al performed a systematic review and meta-analysis of controlled trials (n = 23,168) that addressed LAMA/LABA combination treatment compared to individual component (LAMA or LABA) monotherapy. As measured by trough FEV_1, dyspnea indices, and the St. George's Respiratory Questionnaire scores, LAMA/LABA consistently outperformed either monotherapy. Although there are a variety of different LAMA/LABA combinations, no particular combination emerged as distinctly superior. Combining LAMA with LABA provides meaningfully better symptomatic improvement than either agent alone. ■

Updated Guidelines on Acne Management

SOURCE: Zaenglein AL, et al. *J Am Acad Dermatol* 2016:74:945-973.

There are updated guidelines on the management of acne in adolescents and adults from the American Academy of Dermatology. A multidisciplinary team, which included representatives from dermatology, primary care, pediatrics, and an acne patient participant, generated the guidelines. While it's not possible to adequately summarize this lengthy document in a few words, several noteworthy principles merit sharing with all primary care clinicians who address acne in their practices.

For mild acne, recommended first-line treatments include benzoyl peroxide, topical retinoids, and topical antibiotics (clindamycin preferred), with topical dapsone considered an alternative. Topicals may be used as monotherapy, dual, or even triple combination, except for topical antibiotics, which are not recommended as monotherapy due to emergence of bacterial resistance. For moderate acne, monotherapy is not considered first line; rather, dual or even triple combination topicals (benzoyl peroxide, antibiotics, retinoids), oral antibiotics plus dual/triple topicals, or (for women) oral contraceptives and spironolactone are options. Although not a usual treatment, isotretinoin becomes a consideration when moderate-to-severe acne has not responded to first-line treatments. Systemic antibiotics (e.g., doxycycline, TMP/SMX, azithromycin, cephalexin) are useful in moderate-to-severe acne, and are recommended to be used in combination with benzoyl peroxide and topical retinoids (but not in combination with topical antibiotics). Tetracycline is the preferred antibiotic class. The new guidelines provide a useful template on which to plan management of acne at all levels of severity. ■

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Sublingual Desensitization Against House Dust Mites

SOURCE: Virchow JC, et al. *JAMA* 2016;316:1715-1725.

As many as half of asthmatics are sensitized to house dust mites (HDM). Decades of implementation of subcutaneous allergy desensitization have demonstrated two important facts: 1) subcutaneous desensitization can improve asthma in some patients, and 2) although serious adverse reactions to subcutaneous desensitization are rare, asthmatics are the group in which such reactions most often occur. Because of the time and effort necessary to achieve allergen desensitization, only a small minority of asthmatics currently participate in any form of allergen desensitization.

Sublingual immunotherapy is a newer format for allergen desensitization. It can be performed at home and may be preferred by patients who are avoidant of injectable desensitization, but data on asthmatic exacerbations previously has not been studied. Adult asthmatics (n = 834) were randomized to a single sublingual HDM tablet (or placebo) each morning for 18 months. Inclusion required that asthma not be well controlled on inhaled steroids (ICS) or combination inhaled products. Beginning at month 12 of the study, ICS dosing was reduced by half, and at month 15, patients discontinued ICS entirely. The primary endpoint was time to first asthma exacerbation during the ICS-withdrawal phase of the study. HDM sublingual tablets reduced the risk of moderate/severe asthma exacerbations by approximately 30% compared to placebo. HDM was well tolerated, and no serious adverse systemic events occurred. Among the minor adverse effects, oral pruritus was most commonly reported (20% of the high dose HDM treatment group vs. 3% placebo), but all reports of oral pruritus occurred at initiation of treatment onset, and all had disappeared by day five of the clinical trial. Sublingual HDM desensitization is a promising tool for asthmatic patients not well controlled on ICS. ■

Treatment Selection for Older Adults with Atrial Fibrillation

SOURCE: Garwood CL, Chaben AC. *Ann Longterm Care* 2016;24:31-39.

Risk of stroke in patients with atrial fibrillation (AF) is predicted well by the $CHADS_2$ or CHA_2DS_2-VASc scores. Anticoagulant treatment should be celebrated since clinical trials document a ≥ 60% reduction in stroke, as well as a ≥ 25% mortality reduction compared to placebo. The addition of four so-called novel anticoagulants (NOACs) in recent years for AF requires that clinicians become more astute about individualizing anticoagulant choices, because there are factors that may have a substantial effect on which agent is best for a particular patient. Newer agents may appear at first glance to have enough superiority over warfarin that they generally should be preferred; to the contrary, it has been shown that for warfarin patients who are consistently (at least 66% of the time) within the desired therapeutic range, the risk-reduction performance of warfarin and the novel anticoagulants is essentially the same.

Additionally, compliance may turn out to be more important for patients taking novel anticoagulants than warfarin. For instance, missing a NOAC dose has a much more prompt and greater effect on risk reduction than missing a single dose of warfarin. Twice-daily dosing required for dabigatran and apixaban might be problematic for some but can be solved by utilizing rivaroxaban or edoxaban instead. Many warfarin patients find that dietary modulation is difficult for them and welcome NOACs, which are free of food interactions. Finally, regular blood monitoring required for warfarin is burdensome for some patients; some cost-effectiveness studies have opined that NOACs, despite their much greater up-front costs at the time of purchase, are no more expensive than warfarin over the long term because clinician visits, international normalized ratio monitoring, and travel for these events are eliminated. The decision to begin anticoagulant therapy is a very important one. The diversity of choices now requires closer attention to individual patient characteristics and preferences to ensure best outcomes. ■