

**SPECIAL
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INTEREST:**

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Pharmacotherapy Update

LEBANON VAMC

PHARMACY

Editor Notes

Hello Lebanon VA readers! It's that time of year to break out the long sleeves and light weight coats as fall quickly approaches. In this edition of the *Pharmacotherapy Update*, a little something is included for everyone. So take a few minutes, find a cozy spot, and read up on your fall edition of the pharmacy newsletter.

First, resident Carolyn Snavely will review a recently approved drug for multiple sclerosis, Dalfampridine, including suggested criteria for its use. Our literature review section follows, written by current pharmacy student

Katie Kane. Katie reviews the TOM Trial and gives insight into proper testosterone treatment and use.



The Drug class review section on page 3 is a must read for everyone! Our new Pharmacy resident, Kristie Wahl, writes about the hottest fall topic, the

“high-dose” Flu Vaccine. We are already receiving an abundance of questions from patients and staff members about this approach to flu vaccination. On the lighter side, for your enjoyment, some pharmacy lightheartedness is located on page 5. Finally, new to the PBM, recent considerations for the safe and effective use of colchicine are located in our drug safety corner.

Carolynn Snavely, Pharm.D. and Dina Norris, Pharm.D., BCPS, Editors

New Drug Review: Dalfampridine (Ampyra®)

Multiple Sclerosis (MS) is a chronic, degenerative autoimmune disease affecting approximately 400,000 Americans. There are roughly 200 new diagnoses each week, more likely in women, who are diagnosed twice as often as men. The onset of the disease usually occurs between the ages of 20 to 40, but can also be diagnosed in much older adults. Multiple Sclerosis affects the central nervous system, more specifically the myelin, a fatty protective layer around the axon of the neurons essential for proper transmission of the nerve signals.

Symptoms vary depending on the location of the affected nerve fibers, but most commonly include fatigue, numbness, vision problems, loss of coordination, and difficulty walking.

Different types of MS exist, but most common is the relapsing/remitting form characterized by clearly defined attacks of worsening neurologic function followed by partial or complete recovery periods in which no disease progression occurs. These remissions may continue for months to years before symptoms return. The focus of cur-

rent treatment is to decrease the frequency of exacerbation episodes. Agents currently used include Interferon beta 1a (Avonex®, Rebif®), Interferon beta1b (Betaseron®), and glatiramer acetate (Copaxone®). When an inadequate response or intolerable effects occur, talizumab (Tysabri®) may be used. The latest MS drug approval, Dalfampridine (Ampyra®), is the first to be associated with an indication of improved walking, specifically demonstrated by an increase of walking speed.

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“While increasing a patient’s quality of life is always at the forefront of therapeutic planning, the risks and benefits of testosterone therapy must be heavily weighed.”

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Literature Review: The TOM Trial

Testosterone Replacement— Helpful or Harmful? By Katie Kane, Pharm. D. Candidate

In the geriatric male population, limited mobility is a common condition and is unfortunately a good predictor of disability, poor quality of life and death.¹ As men age, a decline in testosterone production occurs causing decreases in muscle mass and strength, as well as decreased bone density, resulting in a condition referred to as androgen deficiency in aging males (ADAM).² Our intuitive thought to treat this deficiency is to give exogenous testosterone because we know that testosterone helps build lean muscle mass, increase bone density and augment strength. However, many patients suffering from ADAM are over 65 years of age and no studies to date have included enough men in this age group to determine the safety and efficacy of testosterone therapy. Until the Testosterone in Older Men (TOM) trial, that is.

The TOM trial, a parallel group, randomized, placebo controlled, double blind study, set out to assess the safety and efficacy “of testosterone administration on lower extremity strength and physical function in men with low serum testosterone.”¹ TOM included men 65 years of age or older with total serum testosterone levels of 100-350ng/dL (measured in the morning; normal is 280-1100ng/dL³) with evidence of mobility limitations (walking 2 blocks or climbing 10 steps and scoring 4-9 on short physical performance battery). The trial excluded men with uncontrolled hypertension, unstable angina, patients with a history of MI within the past three months and those with NYHA Class III or IV heart failure, patients with hormone regulated cancers (prostate or other), severe sleep apnea, patients on glucocorticoid/anabolic steroid therapy, uncontrolled diabetes, hematocrit > 48% , BMI > 40kg/m² and patients with mobility issues related to a disease process. TOM was powered to 90% with an $\alpha = 0.05$ to detect a change in bilateral leg press strength assuming a 20% loss to follow up. Unfortunately, the trial was stopped prematurely due to increased cardiac adverse events in the testosterone group before enough patients to meet power were enrolled.

At baseline, the testosterone group contained statistically significantly more African American men ($p = 0.04$), men on antihypertensive therapies ($p=0.04$) and a higher percentage of patients who had a diagnosis of hyperlipidemia or were on statin therapy ($p=0.03$). The testosterone group experienced more “cardiac disorders” ($p<0.001$) during therapy with a maintained greater incidence during the three month observation phase where no testosterone was administered. Of the cardiovascular related adverse events, the testosterone group experienced 82% of the events (23 of 28 events) and 87.5% (7 of 8) of the atherosclerotic related events. Men with testosterone levels in the highest quartile (>1000ng/dL) had an increased risk of cardiovascular related events (HR 2.4, $p=0.05$) than did their placebo counterparts. “The risk of CV events remained significantly greater among men in the testosterone group after adjustment for age group, body-mass index, smoking status, HDL level and presence of diabetes, hyperlipidemia, and hypertension.”¹

Although the trial was not able to be completed, efficacy outcomes were computed with the data at the time the trial was discontinued. Treatment with testosterone gel was shown to increase leg press strength ($p=0.004$) and chest press strength ($p=0.002$). However, the clinical significance of increased leg press or chest press strength is debatable. There was no statistical difference found in stair climbing power or walking speed between the two groups.

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Because this trial was halted prematurely, and the number of adverse events was small, the differences between the two groups (in regards to the significance of adverse events) may be an over-estimation. However, there is no denying that there is a definite link between exogenous testosterone administration and an increase in cardiovascular related events; especially when the difference remained after adjustments were made for possible cofounders (i.e. BMI, smoking status, etc). Although the trial evaluators listed the use of testosterone in the geriatric population as a weakness (as it differed from most previous trials involving testosterone), many of the patients seen in practice at the VA are often > 65 years of age. The applicability of this data to our patient population here at the VA is relatively perfect.

The results of this trial leave practitioners in limbo. While increasing a patient's quality of life is always at the forefront of therapeutic planning, the risks and benefits of testosterone therapy must be heavily weighed. The Endocrine Society, in their clinical practice guidelines for testosterone therapy, recommends the use of testosterone in the geriatric population on a case by case basis and only in those patients who have "consistent symptoms and signs, and unequivocally low serum testosterone levels."² The Endocrine Society also recommends against the use of "case-finding instruments" such as questionnaires and offering all men testosterone therapy without a "low testosterone level on more than one occasion and clinically significant symptoms of androgen deficiency."²

References:

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High Dose Flu Vaccine

By: Kristie Wahl, Pharm.D.

Flu season is fast approaching; starting in October, peaking during the months of January and February, and tapering off by May. Each year the question is raised, how do we best prepare for flu season? This year, the Centers for Disease Control recommend vaccinating patients as soon as the vaccines become commercially available as a way to ensure the maximum amount of patients receive the vaccine¹. Along with these recommendations come many questions from both patients and healthcare workers.

With each new season we ask ourselves, who is at risk for influenza-related complications? According to data from years past, pregnancy, children, adults over the age of 65, and patients with asthma, neurological disorders, chronic obstructive pulmonary disorder, heart failure, cystic fibrosis, sickle cell, diabetes, liver or kidney disease, human immunodeficiency virus, and cancer are all at an increased risk for influenza-related complications. More importantly, approximately 90% of deaths each year attributed to influenza complications occur in patients 65 years of age or older¹. This further highlights the importance of being vaccinated yearly.

What will this year's influenza vaccine offer? The 2010-2011 influenza vaccine will contain 15 micrograms of inactivated hemagglutinin of H3N2, influenza B, and H1N1 strains combined in one single dose. In addition to this standard vaccine recommended for all patients 6 months of age or older, there will be a new high-dose influenza vaccine recommended for patients 65 years of age and older. This vaccine will contain 60 micrograms of each of the three strains, which is four-times the standard dose.

Why give four-times the dose and why recommend it to patients 65 years of age or older specifically? A phenomenon exists in the elderly known as immunosenescence. Immunosenescence is characterized by a decrease in humoral and cellular immunity accompanied by age related changes in T-cell subsets. In other words, elderly patients have a decreased immune response to antigens². Studies have shown that with standard doses of vaccines, elderly patients mount lower titers as compared to younger individuals when given the same dose. In theory, lower titers could correlate to higher chances of infection despite being vaccinated.



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Clinical pharmacists Corner: 2010 New Pharmacy Residents

Left: PGY2 Administrative Resident Lee Fiebet
Center: PGY1 Residents (left to right) Kristie
Wahl, Vy Bui, Carolynn Snavelly

Right: PGY2 Monica Bowen
Recently Married! (Previously Gehret)

**Featured last newsletter

**Lebanon VAMC Pharmacy
Pharmacy (719)
Phone: 717-272-6621 ext 5444**

Any comments or
ideas for future issues,
email:
dina.norris@va.gov

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Lee Fiebert, PharmD

Education: Pharm.D., St. John's University College of
Pharmacy and Allied Health Professions

• PGY1 Pharmacy Practice Residency, Long Island Jewish Medical Center

Clinical area of interest: Medication Safety

Hometown: Massapequa Park, NY

Fun Fact: Loves Pomeranians

Kristie Wahl, PharmD

Education: University of Connecticut

Clinical area of interest: Primary Care

Hometown: The small little town of Gardner, MA

Fun Fact: I can shoot a can of peanuts from 15 feet away with a hand gun 7 out of 10 times in the same hole

Vy Bui, PharmD

Education: VCU/MCV School of Pharmacy

Clinical area of interest: Ambulatory Care

Hometown: Springfield, VA

Fun Fact: I can shoot a can of peanuts from 15 feet away with a hand gun 7 out of 10 times in the same hole

Carolynn Snavelly, PharmD

Education: Philadelphia College of Pharmacy

Clinical area of interest: Ambulatory Care

Hometown: Prescott, AZ

Fun Fact: In spring of 2008, broke USP's softball doubles record

Drug Safety Notice: National Pharmacy Benefits Management New Considerations for the Safe and Effective Use of Colchicine

By: Carolynn Snavelly, Pharm.D.



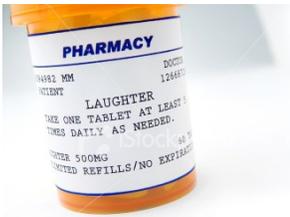
Colchicine, a drug that has been used for gout treatment for over 70 years, has finally received FDA approval by the name of Colcrys®. In a randomized, double-blind, placebo-controlled clinical trial of Colcrys®, 185 patients received low dose (1.2 mg, followed by 0.6 mg 1 hr later) or high dose (1.2 mg, followed by 0.6 mg every hr for 6 hours) colchicine or placebo. 38% of low dose, 33% of high dose, and 16% of placebo resulted in a greater than 50% reduction in pain at 24 hours. The most common adverse events included diarrhea, nausea and vomiting. 19% of the high dose group reported their adverse event as severe vs. none of those in the low dose or placebo group. Due to the results of the trial, the FDA recommends the low dose regimen for treatment of gout flairs.

Provider Recommendations

1. Colchicine should not be used in patients with renal or hepatic impairment who are also receiving inhibitors of P-glycoprotein (P-gp) or strong inhibitors of CYP3A4. The dose should be reduced in patients requiring treatment with moderate inhibitors of CYP3A4
2. Since there are a number of potential interactions with colchicine, providers should refer to FDA approved labeling for specific dose recommendations and information on additional drug interactions.
3. Although colchicine has not been adequately studied in patients 65 years and older, the choice of dose should take into account the potential for a greater incidence of reduced renal function, co-existing diseases, multiple medications, ect.
4. The dose of colchicine used for treating acute gout flares should be (1.2 mg [2 tablets], followed by 0.6 mg [1 tablet] one hour later).
5. Patients receiving colchicine should be instructed to inform their providers before taking any new medications including herbal or natural products or over the counter medications.

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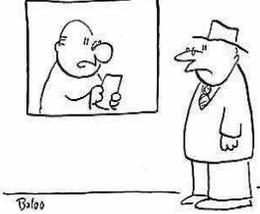
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PHARMACY PHUNNIES

A man goes into a drugstore and asks the pharmacist if he can give him something for the hiccups. The pharmacist promptly reaches out and slaps the man's face. "What did you do that for?" the man asks. "Well, you don't have the hiccups anymore, do you?" The man says, "No, but my wife out in the car still does!

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"Maybe we'd better check with your doctor— this seems to be a prescription for a watermelon and a pair of suspenders."

A nice, calm and respectable good looking lady went into the pharmacy, walked right up to the pharmacist, looked straight into his eyes, and said, "I would like to buy some cyanide." The pharmacist asked, "Why in the world do you need cyanide?" The lady replied, "I need it to poison my husband." The pharmacist's eyes got big and he exclaimed, "Lord have mercy, I can't give you cyanide to kill

your husband! That's against the law! I'll lose my license! They'll throw both of us in jail! All kinds of bad things will happen. Absolutely not! You CANNOT have any cyanide!" The lady reached into her purse and pulled out a picture of her husband in bed with the pharmacist's wife. The pharmacist looked at the picture and replied, "Well now, that's different. You didn't tell me you had a prescription.

Continued from page 1: Drug Review: Dalfampridine

Dalfampridine is a potassium channel blocker that has been shown in animal studies to increase conduction of action potentials in demyelinated axons. Currently two clinical trials have shown the efficacy of Dalfampridine with the primary outcome measured by walking speed in a timed 25-foot walk. Patients received 10 mg of dalfampridine twice daily, with or without immunomodulatory therapy. A statistically significant percentage of patients in the AMPYRA arm improved walking speed compared to placebo in both studies (34.8% vs. 8.3% and 42.9% vs. 9.3%). It is important to note more than one-half of patients did not experience a significant benefit from dalfampridine use. For those that did respond, this correlates with a slightly increased walking speed of 0.51 feet/second in the dalfampridine group versus 0.10 feet/second in the placebo group.

The incidence of urinary tract infection (12%) was the most common adverse event throughout the trials. Other frequently reported adverse events included insomnia (9%) dizziness (7%), headache (7%), nausea (7%), asthenia (7%), back pain (5%), and balance disorder (5%). Most importantly, the risk of dose related seizures are the greatest concern with Dalfampridine use. Dalfampridine is contraindicated with any history of seizures and should be discontinued if a patient experiences a seizure during use. Seizure risk is increased in patients with renal dysfunction as dalfampridine is approximately 90% excreted unchanged in the urine. Therefore, dalfampridine is contraindicated in patients with moderate to severe renal impairment or creatinine clearance of < 50 mL/min. Although there are no adequate well-controlled studies of dalfampridine, it is currently classified as a pregnancy category C. Safety and efficacy has not been established in patients younger than 18 years of age. Dalfampridine is supplied as a 10 mg extended-release tablet. FDA approved dosing is 10 mg twice a day, taken approximately 12 hours apart.

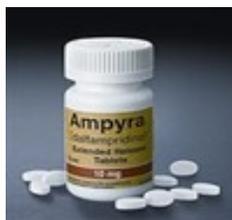
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VHA Pharmacy Benefits Management Dalfampridine Criteria for Use

Exclusion Criteria
Moderate to severe renal impairment (CrCl<50 ml/min)
Previous or current history of seizure disorder
Unstable disease (ie; dose change in DMARD therapy within the past month or evidence of relapse in the past month)



Inclusion Criteria: All must be fulfilled
Diagnosis of MS by the McDonald Criteria http://www.mult-sclerosis.org/DiagnosticCriteria.html
Documented difficulty with walking as defined by a functional measure i.e.; Timed 25 Foot Walk Test, MSWS-12, Subject/Caregiver Impression of Change, Clinician Impression of Change, ect)

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**As with all influenza vaccines, it is important to remember not to give the flu vaccine to patients with a severe allergy to chicken eggs, a reaction to a flu vaccine in the past, Guillain-Barre syndrome within six weeks of a previous flu vaccine, children under 6 months of age, or people with moderate to severe illness accompanied by a fever. **

Continued from page 3: Fluzone

This concept prompted Sanofi Pasteur to create a high-dose influenza vaccine intended for patients 65 years of age and older to boost titer levels and hopefully boost influenza protection. On December 23, 2009 the FDA approved the high-dose Fluzone® offering four-times the antigen dose for patients 65 years of age and older. Early clinical trials did show increased titers with a higher frequency of non-serious adverse effects which include pain, swelling, redness of the injection site along with headache, muscle aches, fever, and malaise. At this time however, there are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone® High-dose compared to standard-dose Fluzone® in individuals 65 years of age and older³. This poses the questions, should all patients greater than 65 receive the high-dose influenza vaccine and if there are not enough vaccine for all patients in this age group, which patients should preferentially receive the high-dose vaccine?

At this time there are no specific recommendations from the CDC or Advisory Committee on Immunization Practices (ACIP) on which vaccine is preferred in this age group. A 3-year study looking at the effectiveness of high-dose versus standard-dose is ongoing at this time with completion estimated sometime in 2012. The results of this study should answer some of the posed questions. For now, if patients inquire, they should be informed that the most important preventative measure to take is to receive a vaccine in general but at the same time they should be informed of the higher frequency of adverse effects seen with the high-dose vaccine and no data at this time can definitively conclude the superiority of one vaccine over the other.

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- CDC resources page. Seasonal Influenza. Centers for Disease Control Web site. <http://www.cdc.gov/flu/about/disease/>. Accessed September 15, 2010.
- Foster SL, Moore WP. High-dose influenza vaccination in the elderly. *JAPhA*. 2010;50(4):546-547.
- Fluzone® package insert. Swiftwater, PA: Sanofi Pasteur Inc; July 2010.

Look-alike Influenza Vaccine: High-Dose Flu Vaccine and Seasonal Influenza Fluzone® products Manufactured by Sanofi Pasteur.

SIMILAR PACKAGING — DIFFERENT COLOR!

