

# The Curbside Consult

## Updates in Pharmacotherapy Provided by the University of Minnesota Pharmaceutical Care Residency Program

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### UPDATES IN RESEARCH

#### A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women

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**Background:** Although aspirin therapy has been proven efficacious in the secondary prevention of cardiovascular disease (CVD) in both men and women, evidence supporting its use as primary prevention in women is limited. Five trials to date have evaluated the use of aspirin in primary prevention. Of the 2,402 vascular events that occurred in these trials, less than 180 involved women. Three of these trials evaluated men exclusively.

**Objective:** The objective of this study was to evaluate the use of low-dose aspirin in the primary prevention of CVD in healthy women.

**Study Design:** A randomized, double-blind, placebo-controlled trial evaluated 39,876 women 45 years of age or older with no history of coronary heart disease, cerebrovascular disease, cancer, or other major chronic illness. Exclusion criteria included a history of side effects to study medications; use of aspirin, anticoagulants, corticosteroids, NSAIDs (selective or nonselective) or individual supplements of vitamin A, E, or beta carotene more than once a week. Participants underwent a three-month trial-period to determine compliance with long-term therapy. A total of 19,934 were randomized to receive aspirin 100 mg every other day and 19,942 received placebo. Participants were followed for a mean of 10 years. Every 12 months participants were sent questionnaires addressing compliance, side effects, the occurrence of clinical end points, and risk factors. The primary endpoint was any major cardiovascular (CV) event, including nonfatal myocardial infarction (MI), nonfatal stroke, and death from CV causes.

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Secondary endpoints included the individual occurrence of fatal or nonfatal MI or stroke, ischemic stroke, hemorrhagic stroke, and death from CV causes.

**Results:** The aspirin and placebo groups had similar baseline characteristics. A total of 477 women in the aspirin group, and 522 in the placebo group experienced a major CV event. Aspirin was associated with a nine percent nonsignificant risk reduction (P=0.13). In the evaluation of secondary endpoints, there was a 24 percent significant reduction in the risk of ischemic stroke, and a 24 percent nonsignificant increase in the risk of hemorrhagic stroke in the aspirin group compared to the placebo group (P=0.009, P=0.31 respectively). Overall women in the aspirin group had a 17 percent significant reduction in the risk of any stroke compared to the placebo group (P=0.04). Aspirin was also associated with a 22 percent significant reduction in the risk of transient ischemic attack (P=0.01). Aspirin was not found to have a significant effect on the risk of fatal or nonfatal MI or death from CV causes. In a subgroup analysis of women 65 years of age or older, the aspirin group demonstrated a significant 34 percent reduction in the risk of MI (P=0.04), 30 percent reduction in ischemic stroke (P=0.05), and 26 percent reduction in a major CV event (P=0.008) as compared to placebo group. The risks of gastrointestinal bleeding, peptic ulcer development, easy bruising, and epistaxis were all significantly increased in the

aspirin group compared to the placebo group ( $P < 0.001$ ).

**Conclusions:** The results of this trial increase the existing data on the use of aspirin as primary prevention in healthy women. Aspirin therapy was associated with a nonsignificant reduction in the risk of major CV events, a significant reduction in the risk of total stroke and ischemic stroke, and no significant effect on the risk of MI or death from CV causes. In a subgroup of women 65 years of age or older, aspirin was found to significantly reduce the risk of major CV events, ischemic stroke, and MI. Aspirin therapy was associated with a significantly increased risk of bleeding and ulcers at all ages.

**Key Points:** The dosing of aspirin 100 mg every other day was a limitation in this study. In clinical practice aspirin is commonly dosed 81-325 mg daily for primary prevention. Therefore, based on this study it can only be inferred that aspirin 100 mg every other day does not reduce MI in women over ten years. Further studies are required to evaluate the efficacy of daily aspirin therapy in the primary prevention of CVD in women. Currently the American Heart Association guidelines for primary prevention recommend aspirin prophylaxis in all women with a ten-year risk of CVD of ten percent or more. Until further studies are available regarding daily aspirin dosing, these guidelines should still be followed in clinical practice. Aspirin therapy should also be strongly considered as primary prevention in women at high risk for ischemic stroke. Risk factors for stroke in women include age >65 years, family history of stroke, history of smoking, hypertension, dyslipidemia, diabetes, coronary disease, heart failure, claudication or atrial fibrillation. Stroke risk increases further in women with two or more risk factors. Due to its potential of increasing bleeding risk, aspirin therapy should be used cautiously and monitored closely in women with a history of bleeding.

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### **Daily versus As-Needed Corticosteroids for Mild Persistent Asthma**

*Jennifer Platt, Pharm.D. Student, Smiley's Clinic*

**Background:** Asthma guidelines recommend patients with mild persistent asthma use daily anti-inflammatory therapy. Studies have reported that this therapy can improve physiological measures of airway obstruction (peak expiratory flow [PEF] and forced expiratory volume in one second [FEV<sub>1</sub>]), quality of life, decrease the frequency and severity of symptoms and prevent the decline of pulmonary

function. Refill patterns suggest that many patients use their daily controller therapy on an as-needed basis rather than scheduled.

**Objective:** The objective of this study is to show if intermittent based therapy with corticosteroids is superior to daily therapy with corticosteroids for the treatment of mild persistent asthma.

**Study Design:** A double-blind, superiority trial randomized 225 patients including males and females between the ages of 18 to 65 years, a diagnosis of asthma, and a measured FEV<sub>1</sub> greater than or equal to 70% of the predicted value. The exclusion criteria included cigarette smoking, respiratory tract infection or corticosteroid use in the previous six weeks, and hospitalization or two or more emergency room visits for asthma in the previous year. All eligible patients were instructed to follow a therapy action plan if asthma symptoms worsened. This asthma action plan included the use of open-label budesonide and oral prednisone. After a four week run-in phase, if diary records and findings classified the patient with mild persistent asthma, patients were enrolled in the study. Patients were then randomly assigned to one of three treatment groups. Therapy consisted of either:

1. Twice-daily oral placebo and inhalation of 200 mcg of budesonide
2. Twice-daily oral zafirlukast (20mg) and inhalation of placebo
3. Twice daily oral and inhaled placebo (intermittent treatment) over one year.

At the termination of both the run-in and treatment phase, 10 to 14 days of intense combined therapy, prednisone 0.5 mg/kg/day, budesonide 800 mcg twice daily and zafirlukast 20 mg plus as needed albuterol, was employed to eliminate any easily reversed causes of airflow obstruction. The primary outcome was the change in morning PEF. Other outcomes included change in FEV<sub>1</sub> before and after bronchodilator use, frequency of asthma exacerbations needing prednisone therapy, asthma-related quality of life, symptom-free days, missed days from work or school and adverse events.

**Results:** Baseline characteristics of the patients were largely similar. The treatment groups contained between 34% and 43% males. The majority of the patients had low asthma symptoms, adequate asthma control with minimal symptoms (6 days symptom free in the past 14 days) and minor limitations in quality of life. The only minor difference was the number of minorities in each group: daily budesonide (18%), daily zafirlukast

(34%), and intermittent therapy (29%). Out of the 225 patients that underwent randomization, 199 completed the study. Six patients each withdrew from both the budesonide and intermittent treatment groups and 14 withdrew from the zafirlukast group. Loss to follow-up, pregnancy, side effects to study medications and dissatisfaction with asthma control were some of the reasons for withdrawal.

The study found no statistically significant difference between treatment groups for the primary outcome of change in morning PEF ( $P=0.90$ ). Daily budesonide therapy however did show a statistically significant difference in the following secondary outcomes over the other two groups: increased pre-bronchodilator FEV<sub>1</sub> ( $P=0.005$ ), decreased exhaled nitric oxide ( $P=0.006$ ), decreased eosinophils in sputum ( $P=0.007$ ), increase in the 20% fall of FEV<sub>1</sub> (PC<sub>20</sub>) ( $P<0.001$ ), decrease in symptoms correlated with asthma control ( $P<0.001$ ), and an increase in symptom free days ( $P=0.03$ ). Kaplan-Meier estimates of the time to a first exacerbation of asthma showed no significant difference among the groups ( $P=0.39$ ). The post-bronchodilator FEV<sub>1</sub> ( $P=0.29$ ) did not show a significant difference nor was there a significant difference among the groups in the amount of exacerbations. There was no difference in the amount of open-label budesonide use amongst the three treatment groups, but only the daily therapy group had no patient use greater than two 10-day courses during the study period. The frequency of adverse events or severe events did not differ significantly among the treatment groups. Of the seven patients that were hospitalized during the study, the findings suggest no correlation to the study, study medication or asthma.

**Conclusion:** The study was unable to show superiority of one treatment group over another with respect to the primary outcome of morning PEF. Patient reported outcomes such as number of symptom free days and asthma control score were favorable for the daily steroid therapy, but no difference was noted in the Quality of Life score. The authors argue that while this novel approach to asthma control did not demonstrate superiority, a larger non-inferiority trial with a more inclusive asthma patient population should be done to support the use of intermittent therapy in asthma control. As this study was designed as a superiority trial for mild persistent asthma, it can not prove equal efficacy between the treatment groups.

Clinically, providers should understand that patients adjust their therapy outside of the recommended therapy regimen. Health care providers should

continue to recommend and encourage the use of daily corticosteroid therapy for mild persistent asthma, but recognize the potential benefit of a symptom oriented asthma action plan that is customized for the individual patient.

*NEJM. 2005; 352(15)*

### **Vitamin E in the Primary Prevention of Cardiovascular Disease and Cancer: The Women's Health Study (WHS)**

*Kelly Schweim, Pharm.D., Fairview Crosstown Clinic*

**Background:** Current guidelines do not support vitamin E supplementation for cardiovascular disease (CVD) or cancer risk reduction. In fact, some studies have raised the question of possible adverse effects on total mortality with high doses of vitamin E. However, these studies have generally enrolled patients with CVD, CVD risk factors and/or those at high risk for cancer and, generally, address short-term therapy. There currently is no data from long-term studies evaluating vitamin E therapy in healthy patients.

**Objective:** The objective of the study was to test whether vitamin E supplementation for 10 years decreased risk of cardiovascular disease and cancer among healthy women.

**Study Design:** A randomized, double-blind, placebo-controlled trial evaluated the use of low-dose aspirin and vitamin E in healthy female health care professionals. Eligibility included age 45 years or older; no previous history of coronary heart disease, cancer, or other major chronic illnesses; and no use of vitamin A, E, or beta carotene more than once per week. After a three month run-in period with placebos to identify long-term compliers, 39,876 women enrolled in the study. Each year, patients received calendar packs of amber capsules (vitamin E 600 IU or placebo) and white pills (aspirin (ASA) 100 mg or placebo) that were to be taken on alternate days. Patients received questionnaires about compliance, adverse effects, occurrence of end-points, and risk factors every 6 months for the first year, then annually. Patients were followed for an average of 10.1 years. The primary end-points were a composite of first major cardiovascular event (nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular (CV) death) and total invasive cancer (except nonmelanoma skin cancer). Secondary end points were the individual CV events (total MI, total stroke, and CV death) and specific cancers in women (breast, lung and colon cancer). Information was also collected on coronary

revascularization procedures, transient ischemic attacks and total mortality.

**Results:** Early in the trial, there appeared to be a benefit of vitamin E on major CV events, including MI, stroke and CV deaths. This benefit diminished over the course of the study and vitamin E supplementation was not significantly different from placebo at the conclusion of the trial. Overall, there was a non-significant 7% reduction in major CV events with Vitamin E. Analysis of the data by age subgroups revealed a significant 26% reduction in major CV events in women aged at least 65 on vitamin E (RR, 0.74; 95% CI, 0.59-0.93; P=0.009); primarily due to 34% reduction in MI and 49% reduction in CV death. Vitamin E had no effect on total MI (636 vs. 615; P=0.96), total stroke (241 vs. 246; P=0.82), coronary revascularization procedures, transient ischemic attack (TIA), cancer (1437 vs. 1428; P=0.87) or total mortality (636 vs. 615; P=0.53). Randomization to ASA did not significantly affect the occurrence of major CV events (235 vs. 245 events in subjects on ASA and

Vitamin E or ASA and placebo respectively, P = 0.55) or total invasive cancer (716 vs. 722 cases in subjects on ASA and Vitamin E or ASA and placebo respectively, P = 0.86).

**Conclusions:** The findings of this large, long-term study of vitamin E 600 IU every other day for 10 years in healthy, well-nourished women supports current guidelines stating that use of antioxidant vitamins is not justified for CVD risk reduction. The WHS showed no significant benefit of vitamin E on major cardiovascular events, total MI, total stroke, coronary revascularization procedures, TIA, cancer or mortality. However, the significant reduction of cardiovascular deaths in women over 65 years of age taking vitamin E differs from results of previous studies. Further studies need to be done to explore this new finding and to evaluate the use of vitamin E in men.

JAMA. 2005;294(1):56-65.

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## NEW DRUG UPDATES

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### **Lunesta™**

#### **Eszopiclone (Sepracor Inc.)**

*Karen Kottschade, Pharm.D., Bethesda Clinic*

**Indication:** Eszopiclone is a nonbenzodiazepine hypnotic indicated for the treatment of insomnia. It has been shown to decrease sleep latency and improve sleep maintenance. Eszopiclone is an isomer of the hypnotic medication zopiclone (Imovane) which has been available in countries outside the US for almost 20 years.

**Mechanism of Action:** The exact mechanism of action of eszopiclone is unknown. It is thought to interact with GABA-receptor complexes at binding domains close to, or allosterically coupled to, benzodiazepine receptors.

**Dosage:** A starting dose of 2 mg immediately before bedtime is recommended for non-elderly patients. The dose can be increased to 3 mg if indicated. Elderly patients (age  $\geq$  65) who have a hard time falling asleep should start with 1 mg while those having trouble staying asleep should start with 2 mg. The dose should not exceed 2 mg in the elderly due to prolonged elimination.

The dose of eszopiclone should be reduced to 1mg in patients with severe hepatic impairment. Doses should be decreased in patients who are

given potent CYP3A4 inhibitors like ketoconazole or patients taking other agents with known CNS-depressant effects. No dosage adjustment is necessary for renal impairment.

**Pharmacokinetics:** Eszopiclone is rapidly absorbed after oral administration. Time to peak plasma concentration is achieved within 1 hour of administration. Sleep effects of eszopiclone may be reduced if it is taken with a high fat meal. Eszopiclone is extensively metabolized by oxidation and demethylation. Based on *in vitro* data, CYP3A4 and CYP2E1 are involved in its metabolism. The half-life is approximately six hours and in elderly patients, the half-life is increased to nine hours. Up to 75% is excreted in the urine, primarily as metabolites.

**Efficacy:** Eszopiclone has been evaluated in both transient insomnia and chronic insomnia up to six months duration. The efficacy and safety of eszopiclone has been assessed in six trials; two of which have been published. In a two week trial that enrolled elderly patients (65-85 years old), a

significantly shorter sleep latency was seen with both the 1 mg and 2 mg dose compared to placebo ( $p \leq 0.012$  and  $p = 0.0003$  respectively). A significantly longer sleep time was also seen with the 2 mg dose ( $p = 0.0003$ ). In a six month trial, patients 21-69 years old were given 3 mg eszopiclone or placebo. Throughout the trial, there was a statistically significant decrease in sleep latency and increase in sleep maintenance and sleep duration compared to placebo. No comparative studies have been performed.

**Safety Issues:** Eszopiclone should be taken immediately before bedtime. Do not administer with alcohol. The most common reported side effects are unpleasant taste and headache. Tolerance was not observed over six months in clinical trials. Symptoms of withdrawal occurred in less than 2% of patients.

**How supplied & cost:** Eszopiclone is available in 1 mg, 2 mg, and 3 mg tablets. The cost of 30 tablets for all strengths is \$99 ([www.drugstore.com](http://www.drugstore.com)). Eszopiclone is a schedule IV controlled substance.

**Place in therapy:** Eszopiclone is one of the first sleep agents not limited to short-term use as trials have been conducted up to six months in duration. It does not appear to have tolerance associated with its use and therefore has an advantage over benzodiazepines. Other nonbenzodiazepine medications, zolpidem (Ambien®) and zaleplon (Sonata®), have a different mechanism of action as they bind to the GABA-benzodiazepine receptor. Zaleplon has been shown to decrease sleep latency while zolpidem and eszopiclone have been shown to decrease sleep latency and efficiency. However, other than the indication for longer use, eszopiclone does not have any significant advantage over other non-benzodiazepine medications. The long half-life may mean carry-over effects to the next day, especially for elderly patients. Remember sleep medications treat the symptoms, but do not treat the underlying cause of the insomnia.

### **Byetta™**

#### **Exenatide (Amylin Pharmaceuticals)**

*Jody Lounsbery, Pharm.D. Student, Bethesda Clinic*

**Indication:** Exenatide is indicated as adjunct therapy in patients with type 2 diabetes (DM2) who are uncontrolled despite therapy with metformin and/or a sulfonylurea.

**Mechanism of Action:** Exenatide is the first drug known to mimic the peptide incretin. Exenatide enhances glucose-dependent insulin secretion, promotes insulin release in response to hyperglycemia, and slows gastric emptying.

**Dosage and Administration:** Exenatide should be started at 5 mcg subcutaneously within 60 minutes prior to the morning and evening meals and increased to 10 mcg after one month of therapy based on clinical response. Exenatide should not be administered after a meal.

**Efficacy:** In a randomized, double blind, placebo-controlled trial, DM2 patients treated with metformin and a sulfonylurea were randomized to one of four treatment arms. The exenatide-treated arms, A and B, were given 5 mcg BID and 10 mcg BID, respectively. Arms C and D were given placebo in equal volumes to active drug. The average baseline A1C was 8.5%. Patients were started on 5 mcg twice daily for an acclimation period of four weeks before the fixed dose was either increased to 10 mcg twice daily or left at 5 mcg twice daily. After 30 weeks, patients in both exenatide-treated arms exhibited statistically significant decreases in A1C,  $-0.8 \pm 0.1\%$  (10 mcg),  $-0.6 \pm 0.1\%$  (5 mcg), and  $+0.2 \pm 0.1\%$  (placebo) ( $p < 0.0001$  compared to placebo). The percentage of patients with a baseline A1C  $> 7\%$  achieving an A1C  $\leq 7\%$  was 30% in the 10 mcg arm and 24% in the 5 mcg arm compared to 7% in the placebo arm ( $p < 0.0001$  for pairwise comparisons). Both exenatide-treated arms had statistically significant weight loss,  $-1.6 \pm 0.2$  kg from baseline in each exenatide arm compared to  $-0.9 \pm 0.2$  kg in the placebo arm ( $p \leq 0.01$ ). In a similar study with metformin-treated patients, the percentage of patients with a baseline A1C  $> 7\%$  who achieved an A1C  $\leq 7\%$  was 40% in the 10 mcg arm and 27% in the 5 mcg arm vs. 11% with placebo ( $p < 0.01$  for pairwise comparisons). Both exenatide-treated arms had significant weight loss,  $-2.8 \pm 0.5$  kg (10 mcg) ( $p < 0.001$ ), and  $-1.6 \pm 0.4$  kg (5 mcg) ( $p < 0.05$ ), compared to  $-0.3 \pm 0.3$  kg in the placebo arm. For all of the comparisons above, the 5 mcg and 10 mcg doses were only compared to placebo, not to each other.

**Safety:** Exenatide is not recommended to be used as a substitute for insulin and should not be used in patients with type 1 diabetes. The use of exenatide has not been studied concomitantly with thiazolidinediones, meglitinides, insulin, D-phenylalanine derivatives, or alpha-glucosidase inhibitors. Exenatide is not recommended for use in patients with severe renal impairment (creatinine

clearance < 30 mL/min). The use of exenatide is associated with gastrointestinal (GI) side effects, most notably nausea, and should be avoided in patients with severe GI disease. When exenatide was used in combination with metformin, there was no increase in the incidence of hypoglycemia compared to placebo. However, when exenatide was used in combination with a sulfonylurea, there was an increase in the incidence of hypoglycemia compared to placebo. To reduce the risk of hypoglycemia, reducing the dose of a sulfonylurea may be considered.

**How Supplied and Cost:** Exenatide is supplied as a 250 mcg/mL solution in a prefilled pen. Pens are

available for 60 doses in either 5 mcg per dose (1.2 mL) or 10 mcg per dose (2.4 mL). The monthly cost of exenatide is approximately \$180.00 for the 5 mcg pen and \$210.00 for the 10 mcg pen.

**Place in Therapy:** Exenatide is a unique adjunct to metformin and/or sulfonylurea therapy in patients with DM2 who are not achieving adequate glycemic control. Weight loss is an added benefit of using exenatide. A long-acting release formulation is in Phase II clinical trials. This formulation of exenatide could allow for once-weekly to once-monthly dosing. Due to the high cost, use of exenatide will be limited until comparative studies with insulin and oral agents shows superior efficacy

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## NEW FORMULATIONS AND INDICATIONS

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### **Requip® (Ropinirole, GlaxoSmithKline)**

#### ***Approved for Restless Leg Syndrome***

*Karen Kottschade, Pharm.D., Bethesda Clinic*

**Indication:** Ropinirole is the first and only medication to gain approval for treatment of restless leg syndrome (RLS). It is approved for use in moderate to severe RLS.

**Mechanism of Action:** Ropinirole is a dopamine agonist with high *in vitro* specificity at the D3 and D2 dopamine receptor subtypes. The exact mechanism of action in restless leg syndrome is unknown. It is theorized that patients with RLS have a decrease in dopamine function in the striatum and dopamine agonists improve symptoms by increasing dopamine. Time to peak concentration is reached approximately 1-2 hours after ingestion or at 2.5 hours if the drug is taken with food. It is extensively metabolized via CYP1A2 to inactive metabolites. The half-life is approximately 6 hours. Excretion is reduced by 30% in patients > 65 years old.

**Dosage and Administration:** The suggested starting dose is 0.25 mg/day and should be administered one to three hours before bedtime. The dose may be increased after 2 days to 0.5 mg daily and then may be increased in 0.5 mg intervals weekly as needed up to 4 mg/day.

**Effectiveness:** Ropinirole was found to be effective for RLS in three randomized, double-blind placebo controlled studies in adults diagnosed with moderate to severe RLS. The studies measured effectiveness of the drug using the International Restless Leg

Syndrome Scale, a patient-rated scale that measures different aspects of RLS including severity

of muscle movement and discomfort, sleep disturbance, mood and overall effect on quality of life. The Clinical Global Impression-Global Improvement scale, an investigator-rated improvement score, was also used. All three studies demonstrated a statistically significant difference between the treatment group receiving ropinirole and the group receiving placebo. Long-term efficacy up to 36 weeks has also been studied and shown to have a significantly lower rate of relapse. To date, no adequate comparative studies have been reported.

**Safety:** Augmentation of RLS may occur with ropinirole but is less common than with levodopa. Rebound may also occur with ropinirole use. Side effects include nausea, headache, vomiting, orthostatic hypotension, somnolence, syncope and falling asleep during activities of daily living. Somnolence and falling asleep with daily activities is more common in those using the medication for Parkinson's than for RLS. Inform patients about syncope and postural hypotension, especially when increasing the dose. Use caution in severe hepatic or renal dysfunction, and in use with other CNS depressants or psychoactive agents due to the potential increase in sedation. Other dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on withdrawal or significant dosage reduction after long-term use.

**How Supplied:** Ropinirole is available in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 5 mg tablets. The price is about \$49 for most tablet strengths (www.drugstore.com).

**Place in Therapy:** When treating a patient with RLS, treat iron deficiency first if present as iron deficiency has been associated with RLS. A dopamine agonist is a good starting choice for patients with RLS. The non-ergot dopamine agonists, ropinirole or pramipexole (Mirapex®), have less nausea and vomiting associated with their use as compared with ergot derivative dopamine agonists such as pergolide and thus are the preferred agents. Pramipexole also has studies supporting its use in RLS but has not gained FDA approval. The price of ropinirole may be a limitation for some patients. Consider carbidopa/levodopa for these patients but be aware that carbidopa/levodopa use has been associated with more rebound and augmentation than dopamine agonists.

### **Bidil®**

#### **Isosorbide dinitrate and hydralazine (NitroMed)**

*Konping Khang, Pharm.D.*

*West Side Community Health Service*

**Indication:** Isosorbide dinitrate/hydralazine (ISDN-H) is indicated for the treatment of heart failure in black patients as an adjunct to standard therapy.

**Mechanism of Action:** The exact mechanism for ISDN-H's effect on heart failure is unknown. Isosorbide dinitrate effects arterial and venous dilation through the release of nitric oxide, activating guanyl cyclase which relaxes vascular smooth muscle. Hydralazine dilates arterial smooth muscle and enhances isosorbide's action by inhibiting nitric oxide destruction.

**Dosage:** ISDN-H is initially dosed at one tablet three times daily and titrated to a maximum tolerated dose not to exceed two tablets three times a day. A dose of one-half tablet daily can be used in patients experiencing side effects.

**Efficacy:** In the A-HeFT trial 1,050 self-identified black patients with NYHA class III or IV heart failure were randomized to placebo or ISDN-H 120/225 mg per day. Over 94% of study subjects had NYHA class III heart failure. Patients were taking diuretics (90%), beta blockers (74%), angiotensin-converting enzyme inhibitors (70%), digoxin (59%), carvedilol (55%), spironolactone (39%), and angiotensin receptor blockers (17%). The primary endpoint was a composite score of death from any cause, first

hospitalization for heart failure during 18 month follow up, and change in quality of life as measured by the Minnesota Living with Heart Failure questionnaire at six months. The composite score in the ISDN-H group was significantly better than placebo (-0.1 vs -0.5, p=0.01, range of possible values -6 to +2). Secondary endpoints included individual analyses of components of the composite score. There was a 43% relative reduction in mortality (6.2 vs 10.2, p=0.01), a 39% reduction in time to first hospitalization (16.4 vs 24.4, p=0.001), and improved quality of life in the active treatment group (p=0.02).

**Safety issues:** ISDN-H is contraindicated in persons hypersensitive to any component of the product, closed angle glaucoma, head trauma or cerebral hemorrhage, severe anemia, mitral valve rheumatic heart disease, and concurrent use of phosphodiesterase-5 inhibitors (e.g. sildenafil and tadalafil). It may induce a lupus-like syndrome and require dosage adjustment in severe renal failure. Use cautiously in patients with pulmonary hypertension, volume depletion, hypotension, and right ventricular infarctions. In the A-HeFT trial, the most common adverse effects in the ISDN-H group were headache (47.5%) and dizziness (29.3%).

**How supplied & cost:** ISDN-H is supplied as an orange, scored tablet containing isosorbide dinitrate 20 mg and hydralazine 37.5 mg. A cost of \$324 a month is estimated to maintain target dosing at 2 tablets three times daily. The drug's company, NitroMed, has reported that through their "payment-assistance program," they will make BiDil available free of charge to patients with no insurance coverage whose annual household incomes are up to three times the poverty level. For all others without insurance coverage, the program expects to make BiDil available for \$25 per prescription. Generic isosorbide dinitrate and hydralazine dosed similarly as separate tablets would cost approximately \$57 a month.

**Place in therapy:** ISDN-H may be used as adjunctive treatment in black patients with heart failure who are already receiving angiotensin-converting enzyme inhibitors, beta blockers, diuretics, cardiac glycosides, and aldosterone antagonists as standard treatment of heart failure.

## Crestor® Post-Marketing Analyses

Jennifer Mihm, Pharm.D.

Paynesville Area Healthcare System

**Key Point:** The safety of Crestor® (rosuvastatin) has been questioned since its approval in August 2003. Recently, the scrutiny has intensified after a negative post-marketing analysis.

**Background:** In March of 2004, the Public Citizen Health Research Group petitioned the Food and Drug Administration (FDA) to immediately remove Crestor® from the market, citing concerns over unacceptable rates of rhabdomyolysis, renal failure, and renal insufficiency as compared to other statins. This petition led to two separately conducted analyses of rosuvastatin's safety.

**Analysis 1:** The petition by Public Citizen prompted the FDA to complete a review of pre-marketing and post-marketing clinical trials with Crestor® in addition to reviewing reports concerning Crestor® in the FDA's Adverse Event Reporting System (AERS) database.

**Analysis 2:** Independent investigators conducted a post-marketing analysis of Crestor® solely utilizing the FDA's AERS database. Rates of Crestor® associated adverse event reports were compared to atorvastatin, simvastatin, pravastatin, and cerivastatin associated adverse event reports per one million prescriptions. Baycol® (cerivastatin) was removed from the market in 2001 due to unacceptable rates of muscle toxicity, however, was still included in the study to serve as a reference of a statin with an unfavorable safety profile. The adverse event reports were reviewed for the time period of October 2003 through September 2004 in addition to reviewing adverse event report rates during each drug's initial year on the market. The primary analysis examined the combined endpoint of adverse event reports of rhabdomyolysis, proteinuria, nephropathy, or renal failure.

**Purpose:** The purpose of both analyses was to determine whether Crestor® carries an increased risk of muscle or kidney damage as compared to other statins.

### Conclusions:

**Analysis 1:** The FDA responded to Public Citizen Health Research Group with a 36 page letter in

March 2005 detailing their reasons for denying the petition for removal of Crestor® from the market

based on their analysis of pre-marketing, post-marketing, and AERS data. In their letter to Public Citizen, the FDA concluded that Crestor® poses a risk of muscle toxicity similar to other statins on the market and that it does not pose a risk of serious renal injury. Furthermore, the FDA notes that proteinuria caused independently of rhabdomyolysis, a finding initially thought to be unique to rosuvastatin, is a benign, transient condition that can occur with all statins.

**Analysis 2:** After a review of adverse event reporting rates, rosuvastatin was found to be significantly more likely to be linked to the combined endpoint of rhabdomyolysis, proteinuria, nephropathy, or renal failure than atorvastatin, simvastatin, or pravastatin for the time period of October 2003 through September 2004 ( $p < 0.001$  for all). Comparisons were unable to be made against cerivastatin as it was no longer on the market at this time. Rosuvastatin had significantly greater numbers of adverse event reports concerning the combined endpoint than did atorvastatin or pravastatin for each drug's initial year on the market. It did not have a significantly greater number of reports than did simvastatin during its first year. Lastly, it had significantly fewer reports than did cerivastatin during its initial year. The authors conclude that statins other than rosuvastatin should be considered first line and that patients receiving rosuvastatin be closely monitored for adverse effects. This study has several limitations. The AERS database is not designed to allow for valid comparisons of adverse event rates between drugs as reported rates do not equal actual event rates, they do not demonstrate causality, and they are subject to the reporter's bias. Furthermore, the reporting for Crestor occurred during a time when public recognition of statin-induced rhabdomyolysis, coupled with negative publicity, was greater than in the first years for the statins it was compared against. Finally, adverse event reports were very low for all statins studied (with the exception of cerivastatin), calling into question whether the statistically significant findings convey clinical significance.

**Clinical Impact:** The FDA and independent investigators reached starkly different conclusions concerning rosuvastatin's safety relative to other statins. Both parties agree, however, that the risk of

muscle and kidney damage from rosuvastatin can be minimized by following appropriate dosing guidelines including 1) starting at 5 mg daily and not exceeding 10 mg daily in patients with severe renal impairment (CrCl < 30 ml/min), 2) starting at 5 mg daily in Asian patients, 3) limiting therapy to 5 mg daily in patients taking cyclosporine, 4) limiting therapy to 10 mg daily in patients taking gemfibrozil, and 5) avoiding the initiation of therapy in a Crestor® naïve patient at 40 mg per day.

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*Circulation.* 2005;111:3016-3021

### **Clinical Outcomes in Antihypertensive Treatment of Type 2 Diabetes, Impaired Fasting Glucose Concentration, and Normoglycemia**

*Stephanie Cone, Pharm.D. St. Cloud VAMC*

**Key Point:** Controversy exists for the optimal first-step agent for treating hypertension to reduce the risk of cardiovascular disease (CVD) in patients with diabetes mellitus (DM) or impaired fasting glucose (IFG) who have little or no existing renal damage.

**Background:** Patients with type 2 DM often also have hypertension, which results in a high risk for CVD and end-stage renal disease. Currently, angiotensin-converting enzyme inhibitors (ACEIs) are recommended as first-line hypertension therapy in patients with DM and proteinuria. However, for patients with DM who have little or no existing renal damage, there is less certainty of the optimal first-choice agent. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind clinical outcomes trial on the effect of different initial antihypertensive regimens preventing fatal CHD and nonfatal MI (primary outcomes), all cause mortality, fatal and nonfatal stroke, combined coronary heart disease, and combined cardiovascular disease (secondary outcomes). Of the 42,418 ALLHAT participants, 33,357 subjects were randomly assigned to receive amlodipine, lisinopril, or chlorthalidone as first-step antihypertensive therapy. The step 1 therapy dose was titrated if lowering of blood pressure was not achieved. Open-label atenolol, clonidine hydrochloride, or reserpine was added as step 2 therapy if needed, and hydralazine hydrochloride was considered step 3. Baseline glucose levels were only available for 31,512 of the subjects, and based on specified criteria these participants were classified as having DM, IFG, or normoglycemia (NG). An intention-to-treat analysis of the outcomes from these subjects was presented.

**Purpose:** To analyze treatment response of first-step antihypertensive therapy with a thiazide-type diuretic compared with a calcium channel blocker (CCB) or an ACEI in the following three baseline glycemic strata: DM, IFG, and normoglycemia, and to determine whether treatment with a CCB or ACEI decreases clinical complications compared with a diuretic.

**Conclusion:** The addition of a diuretic to DM patients assigned amlodipine or lisinopril was the most common addition, however, over time an increasing percentage of each treatment group took an agent from one of the other two classes used as first-step therapy. At year-1, the average number of antihypertensive medications was 1.4. This increased to two at the year-5 visit, with the DM group having a slightly higher average compared with the IFG or NG groups. Following is a summary of the study results across the three treatment groups.

- In the DM and NG participants, those who were assigned chlorthalidone as first-step therapy were treated with significantly fewer antihypertensive medications compared to those assigned to amlodipine or lisinopril.
- Throughout follow-up, systolic blood pressure in the DM group assigned to chlorthalidone was significantly lower compared with amlodipine (1 to 2 mmHg lower) or lisinopril (2 to 3 mmHg lower). However, diastolic blood pressure was significantly lower in DM subjects assigned to amlodipine compared with chlorthalidone (approximately 1 mmHg lower).
- IFG participants showed no significant difference in systolic or diastolic blood pressure across all three treatment groups.
- Differences in systolic BP between chlorthalidone and lisinopril among all three glycemic strata, and between chlorthalidone and amlodipine in IFG and NG groups, were greater in black participants compared to nonblack participants.
- In any of the three glycemic strata for those assigned to chlorthalidone, there was no significant difference in incidence of fatal CHD and nonfatal MI compared with lisinopril. The same is true for those assigned to chlorthalidone compared with amlodipine in the DM and NG groups.
- Within the IFG stratum, fatal CHD and nonfatal MI was significantly more common in those assigned to amlodipine compared with chlorthalidone.

- For secondary outcomes, there was no significant difference in the incidence of total mortality or end-stage renal disease within the three glycemic strata for those assigned to chlorthalidone compared with amlodipine or lisinopril.
- For those assigned to chlorthalidone vs. lisinopril within any of the three glycemic strata, there was no significant difference in the incidence of combined CHD. Stroke incidence and combined CVD was significantly more common in NG participants assigned to lisinopril vs. chlorthalidone.
- In the NG group, the incidence of heart failure was significantly higher for those assigned to amlodipine or lisinopril compared with chlorthalidone, and heart failure was higher in

the DM participants assigned to amlodipine compared with chlorthalidone.

**Clinical Impact:** The authors of this study conclude that no evidence of superiority exists for the use of lisinopril or amlodipine vs. chlorthalidone as first-step antihypertensive therapy among patients with DM, IFG, or NG. The chlorthalidone efficacy pattern was similar compared with amlodipine and lisinopril among all three glycemic strata. It is hard to generalize efficacy for the different drug classes (CCB, thiazide-diuretics, ACEI) used based on the results of one drug from each class. However, diuretics remain less expensive drugs and the results from the ALLHAT suggest their consideration as first-step anti-hypertensive therapy in patients with DM or IFG without renal damage.

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## MISCELLANEOUS NEWS

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### **Menactra™ (Sanofi Pasteur, Inc.), Conjugated Meningococcal Vaccine Licensed** *Keri Hager, Pharm.D. Student, Univ. of Minnesota*

Menactra™, the new tetravalent meningococcal conjugate vaccine (MCV4) was approved in 2005 for use in 11-55 year-olds after it demonstrated noninferiority to the previously approved meningococcal vaccine, MPSV4. MCV4 is administered intramuscularly (versus MPSV4, which is given subcutaneously), and each 0.5 mL single dose contains 4 mcg each of capsular polysaccharide from serogroups A, C, Y, and W-135 conjugated to 48 mcg of diphtheria toxoid.

The previous vaccine (MPSV4) is a bacterial polysaccharide vaccine. Bacterial polysaccharides (e.g. capsule of *N. meningitidis*) are T-cell independent. They stimulate B-cells, but not T-cells, and therefore do not elicit a memory response. The response to these types of antigens are not long-lasting or characterized by anamnestic response after subsequent antigen challenge. Therefore, they do not confer long-lasting immunity or cause a sustainable reduction of nasopharyngeal carriage of *N. meningitidis*. The new vaccine has bacterial polysaccharides conjugated to a protein carrier that contains T-cell epitopes. Therefore the response is T-cell dependent, which leads to a large primary response and substantial anamnestic response upon re-exposure.

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of young

adolescents (11-12 years of age) with MCV4 at their pre-adolescent health-care visit. If not previously vaccinated, ACIP recommends vaccination with MCV4 before high school entry (~15 years of age). The goal is to have routine vaccination of all adolescents beginning at age 11 by 2008.

Populations considered high risk for meningococcal disease include: college freshman living in dormitories, microbiologists routinely exposed to isolates of *N. meningitidis*, military recruits, persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic, particularly if contact with the local population will be prolonged, persons with terminal complement component deficiencies, persons with anatomic or functional asplenia, and possibly persons who are HIV-positive. In these at-risk populations, those 11-55 should receive one dose of MCV4, and those 2-10 or >55 should receive MPSV4.

MCV4 is licensed based on safety and short-term immunogenicity data. These data alone are insufficient in predicting efficacy and herd immunity. Additional studies are needed to evaluate efficacy, impact on nasopharyngeal carriage of *N. meningitidis*, and indirect effects on disease rates among those unvaccinated.

### **SSRIs and Adult Suicide**

*Stacy Ann Olson, Pharm.D., Smiley's Clinic*

After a literature review of the use of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants in pediatric and adolescents with

major depressive disorder and other psychiatric disorders, the FDA, in October 2004, ordered that antidepressants have a “black box” suicide warning to alert health care providers of the increased suicidality in children and adolescents (<18 years old) treated with these agents. The association between antidepressants and suicidality in the youth has further led the FDA to investigate whether there was a similar risk of suicidal thoughts or ideations with adults taking antidepressants.

To date, no conclusive evidence exists proving or disproving the association between antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), and increased adult suicide. Large meta-analyses were done on randomized controlled clinical trials, but because suicide is rare, these studies were not designed to detect the association. Observational studies, which are designed to detect rare events, also failed to identify any relationship between SSRIs and adult suicide. There is some evidence that SSRIs possibly increase non-fatal self harm, but the data is unconvincing.

At present, we know that SSRIs have proven efficacy in treating adult depression. It is also known that depression is correlated to increased suicide. Without evidence proving an association between increased suicide risk and adult use of SSRIs and until new clinically significant data surfaces, SSRIs should still be recommended for treatment of adult depression. Adults taking SSRIs should be closely monitored for symptoms of worsening depression, which can lead to suicidal behavior. Some of these symptoms include uncharacteristic changes in anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity and mania.

### **Viagra® and Blindness**

*Stacy Ann Olson, Pharm.D., Smiley's Clinic*

The pharmaceutical manufacturers of the erectile dysfunction medications Viagra®, Cialis®, and Levitra® have been ordered by the Food and Drug Administration to include warnings within the package labeling about rare cases of sudden vision loss. In 2000, Dr. Howard Pomeranz, an ophthalmologist at the University of Minnesota, reported the first case of blindness in a man who took Viagra®. Since, the FDA has been investigating case reports of blindness, otherwise known as non-arteritic anterior ischemic optic neuropathy (NAION), in men taking Viagra®. This past March, the Journal of Neuro-Ophthalmology published another study by Dr. Pomeranz detailing the possible blindness-Viagra® link. Following the study's publicity, the FDA responded by proposing changes to the Viagra® label, but they continue to investigate whether there is a connection.

Pfizer Inc., which makes Viagra, claims that within 103 clinical studies of Viagra® consisting of 13,000 participants the side effects of sudden blindness did not appear. Outside of these clinical trials, Pfizer states that reports of NAION or blindness have been rare. Pfizer also claims that the population of men taking Viagra® often has other medical conditions which put them at an elevated risk for developing NAION. High blood pressure, high cholesterol, diabetes, smoking, and obesity have been associated with NAION.

Of the 23 million individuals worldwide using Viagra®, less than 200 cases of blindness or NAION have been reported to date. Public awareness of the possible link of blindness and Viagra® has resulted from the rare cases. Regardless, either Viagra®, Cialis®, or Levitra® are still considered first line options for treating erectile dysfunction in patients not taking medications containing nitrates and without an allergy to the medication.

#### **First-Time Generics May – July 2005 [www.fda.gov/cder/ogd/approvals](http://www.fda.gov/cder/ogd/approvals)**

<b>Generic Drug Name</b>	<b>Brand Name</b>	<b>Strengths Available</b>
desmopressin acetate tablets	DDAVP	0.1 and 0.2 mg
isoniazid injection	Nydrazid	100 mg/mL; 10 mL
methimazole tablets	Methimazole	15 mg
alclometasone dipropionate cream	Aclovate	0.05%
fexofenadine hcl capsules	Allegra	60 mg
doxycycline tablets and capsules	Monodox	150 mg
pyridostigmine bromide tablets	Pyridostigmine Br	30mg
rifampin and isoniazid capsules	Rifamate	300/150 mg
carbidopa and levodopa tablets	Sinemet	10/100, 25/100, 25/250 mg
doxycycline hyclate tablets	Periostat	20 mg
doxycycline hyclate capsules	Periostat	20 mg
fenofibrate tablets	Tricor	54, 160 mg
ceftriaxone injection	Rocephin	10 gm/vial
foscarnet sodium injection	Foscavir	24 mg/mL; 250, 500 mL