

The Curbside Consult

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

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UPDATES IN RESEARCH

Use of Inhaled Steroids by Pregnant Asthmatic Women

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Background: In pregnant women there are two main prenatal risks of being an asthmatic, hypoxia and medications. Hypoxia decreases fetal blood oxygen, which may lead to abnormal growth. Asthma medications are blamed in some for reduced intrauterine growth. With this said, the mainstay of therapy for all patients with persistent asthma are inhaled steroids.

Purpose: The goal of this study was to study the effect of all inhaled steroids used during pregnancy on intrauterine growth.

Methods: In this prospective observational cohort study patients were selected based on exposure before outcomes were known. A total of 474 women were recruited and enrolled between July 1996 and January 2002 and were patients of allergists at the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology. Kaiser Permanente of California acted as the coordinating center and recorded the following information on patients at entry: age, parity, race, smoking, due date, asthma medications used since conception and acute asthma episodes since conception. If any of this data changed during pregnancy, it was reported. The following formula was used to calculate total pregnancy microgram doses: (number of puffs per day) X (number of days during pregnancy that the patient took that dose) X (micrograms per puff). From this the total beclomethasone equivalent dose was calculated for each individual inhaled steroid using the following conversion factors: triamcinolone, 0.5; flunisolide, 0.5; beclomethasone, 1.0; budesonide, 1.0; fluticasone, 2.0. A mean daily dose was then computed for each patient. SGA (small for gestational age) was defined as <10th percentile

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birth weight for age. The Pearson correlation coefficient was used to evaluate the relationship between total inhaled steroid use and birth weight.

Results: Then incidence of SGA was 7.1% (95% CI, 5.0% to 10.1%). Birth weight for the study population was similar to the reference population. Also, there was no relationship found between specific inhaled steroids and the incidence of SGA. There was an increasing trend of infants who were SGA with increasing doses of steroids, but these results weren't statistically significant.

Conclusions: With 95% certainty, this study shows that the incidence of SGA and impairment of uterine growth, in infants of mothers who utilized inhaled steroids during pregnancy, is of no concern. We can also conclude with reassuring data that the dose of inhaled steroids doesn't matter.

Take home message: Although there is concern that inhaled steroids may pose an undesired effect on intrauterine growth, it must be emphasized that this observation is based on the knowledge that oral steroids have been associated with reduced birth weight and that inhaled steroids have been found to delay growth in children. There is only one study that suggests the association of low birth weight and inhaled steroids, and there was no comparison group included. In conclusion, when indicated, inhaled steroids should be used during pregnancy for the management of persistent asthma.

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Comparison of Dextromethorphan, Diphenhydramine, and Placebo on Cough

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Background: One of the most common reasons parents take their child to a physician is because of a bothersome cough. Non-prescription medications containing dextromethorphan or diphenhydramine are readily available and often selected as cough suppressants. Currently, the American Academy of Pediatrics discourages use of dextromethorphan because of toxicity concerns and little evidence of its effectiveness. Due to hyperactivity and insomnia, diphenhydramine should be used cautiously in children less than six years of age. Previous studies have failed to show the benefit of using dextromethorphan or diphenhydramine over placebo; yet, in an attempt to lessen a child's cough and improve sleep, healthcare practitioners and parents still use non-prescription antitussives.

Objective: Compare dextromethorphan and diphenhydramine vs. placebo in treating nocturnal cough and facilitating improved sleep quality for a coughing child and his or her parent.

Study Design: The double-blinded, randomized cohort study evaluated 100 children's sleep quality and cough the night before and the night of a dose of dextromethorphan, diphenhydramine or placebo. Data was collected by having parents complete the same assessment form before and after treatment. To be included in the study the children (2-18 years old; median age 4.5 years) must have had a cough caused by upper respiratory infection (URI) lasting less than seven days. Patients with history of respiratory disease (e.g. asthma) or concurrent use of CYP450 inhibitors were excluded from the study. Medication dosing was based on label recommendations of diphenhydramine and dextromethorphan.

Results: On average, the children had been ill with an upper respiratory infection for four days. After the one night study, results indicated there was significant improvement in all groups on child's cough and sleep with a one-dose treatment compared to the night prior to treatment ($p < 0.0001$). However, there was no difference between dextromethorphan, diphenhydramine or placebo groups. Parents did report a statistically significant improvement in their sleep quality the night of their child's treatment. Few side effects were reported across all groups. Hyperactivity was the most common side effect in treatment groups with 14 of 100 children exhibiting hyperactivity, without a difference between groups. Drowsiness, nausea

and vomiting also occurred, again with no difference between groups.

Conclusion: Dextromethorphan and diphenhydramine are no more effective at providing relief from cough or improving sleep quality compared to placebo.

Take Home Message: Despite the lack of evidence for effectiveness of OTC cough medications compared to placebo, parents may still want a solution to their child's cough. If cough syrups are to be recommended, consider a less expensive single-ingredient antitussive. Remind parents to encourage their child to drink plenty of non-carbonated fluids as well as frequent hand washing to prevent the spread of infection.

Pediatrics. 2004;114(1):e85-e89

Efficacy and Safety of Statin Therapy in Children with Familial Hypercholesterolemia

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Background: Pre-pubertal children with familial hypercholesterolemia have impaired endothelial function leading to increased intima-media thickness (IMT) of the carotid arteries which can lead to coronary stenosis. Early initiation of statin therapy may be advantageous, however, the long-term use of statins in children with familial hypercholesterolemia has not been evaluated and only short-term tolerability and safety issues have been addressed.

Objective: Determine the 2-year efficacy and safety of pravastatin therapy in children with familial hypercholesterolemia given the effects of statin on endogenous cholesterol biosynthesis, growth and sexual development.

Study Design: A prospective, randomized, double blind, placebo controlled trial evaluating children ages 8 to 18 years old with heterozygous familial hypercholesterolemia and LDL-C greater than 155 mg/dL (to give a 99.6% chance of LDL receptor mutation). Children were excluded for homozygous familial hypercholesterolemia, hypothyroidism, and abnormal levels of muscle or liver enzymes. After three months of fat-restricted diet and physical activity, children with two fasting LDL-C samples of at least 155 mg/dL were randomized to receive either placebo or pravastatin. Children 14 years or older received 40 mg each evening, and participants less than 14 years old received 20 mg.

Lipids, lipoproteins, ALT, AST, and CPK were evaluated at baseline, at 3-month intervals during

year one, and at 6-month intervals during year two. Levels of sex steroids, gonadotropins, and variable of the pituitary-adrenal axis were measured at baseline and years one and two. Each participant's height, weight, body surface area, Tanner staging, and menarche or testicular volume was obtained at each visit. Patient compliance was monitored by tablet counting. A blinded physician evaluated all children every six months for two years. A blinded sonographer performed all IMT and a blinded image analyst read all ultrasonic images at study completion.

Results: Two-hundred and fourteen children with median age of 13 years were randomized to receive pravastatin (n=106) or placebo (n=108). In 96% of the children, a diagnosis was confirmed by mutation of the LDL receptor gene. Baseline characteristics of the groups were similar with respect to age, smoking frequency, blood pressure, sex distribution and menarche for girls.

Compared to baseline, IMT showed a trend of regression (p=0.049) with pravastatin compared to a trend of progression in the placebo group (p=0.28). The mean standard deviation change in

IMT between the two groups was significant (p=0.02). Pravastatin significantly reduced mean LDL-C compared to placebo (p<0.001). Children between the two groups showed no differences in growth, muscle or liver enzymes, endocrine function parameters, Tanner staging scores, onset of menses, or testicular volume. HDL-C, triglycerides, and lipoprotein (a) levels did not change significantly. Also, levels of dehydroepiandrosterone sulfate and cortisol were unchanged after two years of pravastatin therapy.

Conclusions: Pravastatin therapy induced significant regression of carotid atherosclerosis in children with familial hypercholesterolemia with no adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue. Although some of the safety outcomes may have been underpowered, statin influences on growth and maturation appear to be unlikely. Clinical Impact: Pravastatin appears to improve the lipoprotein profile in children with familial heterozygous hypercholesterolemia without causing significant adverse effects; however, longer-term studies on efficacy and safety need to be performed.

JAMA. 2004;292:331-337

NEW DRUG UPDATES

Xifaxan™ *rifaximin (Salix)*

Indication: Rifaximin is a derivative of rifampin indicated for the treatment of patients greater than or equal to 12 years of age with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*.

Mechanism of Action: Rifaximin inhibits bacterial RNA synthesis by binding to DNA-dependent RNA polymerase.

Dosage: The recommended dose is 200 mg three times a day for three days. Rifaximin may be taken with or without food.

Pharmacokinetics: Rifaximin is considered a non-systemic antibiotic as less than 0.4% is absorbed after oral administration. In vitro studies have shown that rifaximin induces CYP3A4; however, due to its extremely limited systemic absorption clinically significant drug interactions are not expected.

Efficacy: Two randomized, double-blind, placebo controlled studies evaluated the efficacy of rifaximin. The causative agent in both studies was predominantly *Escherichia coli*. In the first study, the duration of diarrhea was significantly shorter in patients treated with rifaximin versus placebo (32.5 hours versus 58.6 hours respectively, P=0.0002). The second study supported these findings,

however, it showed that rifaximin is not effective in patients with fever and/or blood in their stool or whose diarrhea is caused by *Campylobacter jejuni*.

Safety Issues: Rifaximin is contraindicated in patients with a known hypersensitivity to rifamycin antibiotics. It should not be used in patients with diarrhea accompanied by fever or blood in the stool or in cases of diarrhea caused by pathogens other than *Escherichia coli*. Rifaximin should be discontinued if diarrhea worsens or persists for more than 48 hours and an alternate antibiotic considered. The most common side effects were flatulence, headache, abdominal pain, and rectal tenesmus; of which only headache occurred more commonly in the rifaximin treated group than the placebo group (9.7% vs. 9.2% respectively).

How Supplied & Cost: Rifaximin is supplied in 200 mg tablets. At the time of this publication, pricing information is unavailable

Place in Therapy: Rifaximin is the first non-systemic antibiotic approved for the treatment of travelers' diarrhea. It has been proven more effective than placebo, but it is unknown whether it is more effective for treating travelers' diarrhea than other, more conventional treatments such as fluoroquinolones or azithromycin. Nonetheless, it does provide the advantage of sparing systemic antibiotics from use in a predominantly noninvasive

infection. However, as most cases of travelers' diarrhea are self-limiting and require only fluid replacement, the CDC suggests that the use of any antibiotic be considered only if patients have had three or more loose stools in an eight-hour period.

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Apidra®

Insulin Glulisine (Aventis)

Indication: Insulin glulisine is a rapid-acting human insulin analog that may be used in both Type 1 and Type 2 diabetes to help control blood glucose levels.

Mechanism of Action: Insulin glulisine acts to decrease blood glucose levels by stimulating peripheral glucose uptake by both fat and muscle cells and inhibiting hepatic glucose production.

Pharmacokinetics: When given intravenously, insulin glulisine is equipotent with regular insulin. Intravenous administration results in half-lives of about 13 and 17 minutes, respectively. After subcutaneous dosing, insulin glulisine has a faster onset of action (19 minutes versus 24 minutes) and shorter duration of action (318 minutes versus 385 minutes) compared to regular human insulin when given in the abdomen. Subcutaneous absorption of insulin glulisine is only slightly faster in the abdominal versus the deltoid or thigh. Bioavailability was similar with each administration site and peak insulin levels are attained after about 50 minutes. Subcutaneous administration results in a half-life of about 42 minutes.

Efficacy: Pharmacokinetic and pharmacodynamic studies with insulin glulisine and Humalog demonstrated comparable times to peak plasma levels, time of onset and duration of action. When both agents were compared to regular human insulin, they both achieved peak plasma levels in about half the time and had a shorter onset and duration of action. Some of the insulin glulisine trials showed that patients used less overall insulin at the end of the study, but the decrease in insulin doses is not clinically significant. There are no head to head efficacy trials of insulin glulisine and Novolog, but instead trials to compare insulin infusion pump compatibility and catheter occlusion rates. There was no significant difference between the two insulins.

Safety Issues: As with other insulin products, insulin glulisine may cause hypoglycemia. Dosing must be adjusted according to each patient's insulin requirements. Renal impairment may lead to increased circulating levels of insulin. Other potential side effects include local and systemic allergic reaction. Insulin glulisine should be given

15 minutes before or within 20 minutes of starting the meal. It may also be used alone in an insulin infusion pump.

How Supplied & Cost: Insulin glulisine is available in 10 ml vials, 100 units/ml. It is a clear, colorless solution that is stable at room temperature for 28 days. Insulin glulisine may be mixed with NPH and is approved for use alone in insulin infusion pumps. The cost of insulin glulisine is not known at time of publication.

Place in therapy: Insulin glulisine may be used in both Type 1 and Type 2 Diabetes. It is very similar to other rapid acting agents (e.g. Humalog, Novolog) for mealtime administration and may be used as an alternative to these insulins. Insulin glulisine is an alternative to Novolog in insulin infusion pumps.

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Raptiva®

Efalizumab (Genentech)

Indication: Efalizumab is approved for use in patients with moderate to severe chronic plaque psoriasis who are candidates for systemic or phototherapy.

Mechanism of Action: Efalizumab is an immunosuppressive recombinant humanized IgG1 monoclonal antibody. It inhibits the intercellular adhesion of leukocytes to other cell types, like epithelial cells, thus inhibiting the activation and migration of T-cells to the skin. Activation of T-cells and migration to the skin significantly contributes to the lesions present in psoriasis. By inhibiting the initial activation of T-cells and their movement to the skin, the overall disease process of psoriasis is interrupted and further inflammation and plaque formation is stopped.

Dosage: An initial dose of 0.7 mg/kg subcutaneously is recommended followed by a dose of 1 mg/kg once weekly. A single dose should not exceed 200 mg. Higher doses (2 mg/kg/week) appear to be effective in patients that did not respond to the lower dose.

Pharmacokinetics: Initial response to weekly injections may be seen at two weeks. Steady state concentrations are reached after about four weeks. The half-life of the drug after subcutaneous administration is around 6 days. The exact mechanism of elimination is unknown.

Efficacy: Compared to placebo, patients receiving efalizumab more frequently experience a $\geq 75\%$ improvement in psoriasis. After discontinuing therapy, 33% of the patients that had received efalizumab maintained a 50% or more improvement. Relapse of disease usually occurred after one to two months. In patients whom resumed

treatment after relapse of psoriasis, 31% re-established a 75% improvement response.

Safety Issues: Efalizumab is contraindicated in patients with prior hypersensitivity to efalizumab or any murine or humanized monoclonal antibody preparation. Patients with a history of allergies, medication or other, or asthma are at an increased risk for sensitivity reactions; use caution before considering these patients as candidates for therapy. The safety and efficacy of this drug has not been established when used with phototherapy or other immunosuppressive therapies or in pediatric patients. Do not administer acellular, live or live-attenuated vaccines to patients on efalizumab. Also, efalizumab administration is not recommended in patients with clinically important infections. With the first dose of efalizumab, patients may experience headache, fever, nausea or vomiting. In general, the most common side effect is flu-like symptoms (headache, chills, fever, nausea, myalgia). More serious possible side effects include infection, malignancy, thrombocytopenia and worsening of psoriasis/variants. Platelet counts should be taken monthly initially, and every 3 months thereafter to monitor for thrombocytopenia.

How Supplied & Cost: Efalizumab is packaged as a kit that contains four trays. Each tray contains a single-use vial of sterile powder, designed to deliver 125 mg of drug, a single-use pre-filled diluent syringe containing 1.3 ml sterile water for injection plus other supplies necessary for proper administration. Once reconstituted it is stable for eight hours at room temperature. The powder must be stored in the refrigerator. The AWP of a one-month supply of efalizumab is \$1372.

Place in therapy: Efalizumab should be considered in patients with chronic moderate or severe plaque psoriasis that have not responded well to or do not tolerate conventional therapy of systemic steroids, PUVA, methotrexate, cyclosporine, or systemic retinoids. Additional studies will clarify its place in therapy.

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Cymbalta®

Duloxetine (Eli Lilly)

Indication: Duloxetine was approved for treatment of major depressive disorder on August 4, 2004 and for treatment of pain caused by peripheral diabetic neuropathy on September 3, 2004.

Mechanism: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). The mechanism of antidepressant action is unknown.

Dosage and Administration: For depression, the total daily dose should be 40-60 mg, dosed as 20 or

30 mg twice daily or 60 mg once per day. For neuropathic pain, the dose is 60 mg once a day. It can be given without regard to meals, but must be swallowed whole. It has not been approved for use in children.

Pharmacokinetics: The half-life of duloxetine is 12 hours. Duloxetine is well absorbed; the capsules contain enteric coated pellets to prevent degradation of the drug in the stomach. Duloxetine undergoes extensive metabolism to numerous metabolites. In vitro studies show both CYP2D6 and CYP1A2 are responsible for metabolism.

Efficacy: Patients should notice an improvement in depressive symptoms within one to four weeks. Some patients may have a reduction in pain after one week.

Safety Issues: The most common adverse effects are nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating. Duloxetine may increase blood pressure, therefore, this should be monitored prior to initiation and periodically throughout treatment. Withdrawal symptoms (dizziness, nausea, headache, paresthesia, vomiting, irritability, and nightmares) have been noted, particularly when abruptly discontinued. Upon discontinuation, tapering the dose gradually is recommended. Like other antidepressants, the duloxetine label also carries the warning to closely monitor patients for clinical worsening and suicide risk. Concomitant use with monoamine oxidase inhibitors (MAOIs) is contraindicated. Avoid use in patients with uncontrolled narrow-angle glaucoma, any hepatic insufficiency, substantial alcohol use, or end stage renal disease. Duloxetine should be okay in mild renal dysfunction. As with other drugs effective for major depressive disorder, care should be taken when prescribing for patients with a history of seizure disorder, as these patients were excluded from the clinical trials. There is potential for drug interactions with medications that inhibit CYP1A2 or CYP2D6 (ex: some quinolone antibiotics and quinidine). It is unlikely that duloxetine affects the metabolism of CYP1A2 substrates, but does moderately inhibit CYP2D6. Therefore, when prescribing with desipramine, nortriptyline, amitriptyline, imipramine, phenothiazines, and Type 1C antiarrhythmics (propafenone, flecainide) do so with caution. The dose of the tricyclic may need to be reduced if co-administered. There is also a potential for interaction with drugs that affect gastric acidity. There was no significant effect when given with famotidine or aluminum and magnesium containing antacids, however, administration with proton pump inhibitors has not been studied.

Special Safety Comment: One week after the FDA put out a warning for the use of antidepressants in children (February 2004), a 19 year old female

participating in a duloxetine trial committed suicide. She was considered a healthy patient (not diagnosed with depression) and had been off of duloxetine for four days after receiving higher than approved doses. Eli Lilly has stated that they did not believe duloxetine was the cause for the woman's suicide. This tragedy brought additional attention to four suicides of depressed patients in earlier clinical trials. Eli Lilly pointed out that this was out of more than 8500 patients treated with duloxetine, 4142 which were depressed.

How Supplied and Cost: Available in 20, 30, and 60 mg capsules. AWP is \$2.85 per 60 mg capsule.

Anticipated Place in Therapy: Duloxetine is expected to compete primarily with Effexor XR® (another SSNRI) and has been priced

comparatively. A potential advantage to duloxetine will be treating the physical pain sometimes associated with depression. Duloxetine is the first medication approved by the FDA for treatment of pain associated with diabetic peripheral neuropathy. It will compete with Neurontin® and the tricyclic antidepressants for this indication, but should be less expensive than Neurontin®. Duloxetine has also been studied for stress urinary incontinence and was recently given approval by the European Union. Duloxetine for urinary incontinence will be marketed under the brand name Yentreve® and is expected to obtain approval from the FDA during the first half of 2005.

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THERAPEUTIC THOUGHTS

Implications of Recent Clinical Trials for the NCEP ATP III Guidelines

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Key Point: Upon review of recent clinical trials, recommendations for treating hyperlipidemia consist of lower LDL-C goals as therapeutic options.

Background: The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) in 2001 issued a set of evidence-based guidelines to manage cholesterol. Since that time, five new major clinical trials produced results that have the potential to change the way we treat cholesterol. The trials include the HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, and PROVE IT-TIMI 22*.

Prior to the publication of results from these trials, epidemiologic data revealed a log linear relationship between LDL-C levels and relative risk for coronary heart disease (CHD). The log-linear relationship suggests that for every 30 mg/dL change in LDL-C, the relative risk for CHD is changed proportionally by 30%; however, data from previous clinical trials failed to show this relationship in high risk patients with an LDL-C in ranges lower than traditional target endpoints.

Purpose: This report incorporates the results of five major clinical trials to confirm the benefits of cholesterol lowering therapy outlined in ATP III and provide recommendations for modification of the ATP III treatment algorithm.

NCEP Subcommittee Summary of Recommendations for ATP III Modification:

- Therapeutic lifestyle changes (TLC) remains essential to cholesterol management

- In ATP III high-risk patients, the minimal LDL-C goal is <100 mg/dL
 - An LDL-C goal of < 70 mg/dL is a therapeutic option, especially for those at very high risk.
 - If LDL-C is \geq 100 mg/dL, a LDL-lowering drug is indicated simultaneously with TLC.
 - If baseline LDL-C is <100 mg/dL, LDL-lowering drug use to achieve a LDL-C <70 mg/dL is a therapeutic option.
 - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with a LDL-lowering drug. When triglycerides are \geq 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal of 30 mg/dL higher than the LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10-20%), the recommended LDL-C goal is <130 mg/dL
 - A LDL-C goal < 100 mg/dL is a therapeutic option.
 - When LDL-C is 100-129 mg/dL, at baseline or with TLC, initiation of an LDL-C lowering drug is a therapeutic option to achieve LDL-C < 100 mg/dL.
- Any person at high risk or moderately high risk who has lifestyle related risk factors is a candidate for TLC regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that the intensity of such therapy be able to achieve at least a 30-40% reduction of LDL-C.
- For those in lower-risk categories, newer trials do not suggest any changes to goals or cutoffs for therapy.

Conclusion: The results of these studies support previous epidemiologic data that suggested lower LDL-C results in lower risk of coronary heart disease. However, these studies cannot be taken as the last

word in cholesterol management; rather, they provide therapeutic options. While there is some clinical evidence showing the benefit of lower LDL-C target goals, these studies were not without inconsistencies. For example, the HPS trial explored a subgroup of patients with LDL-C levels < 100 mg/dL based on direct LDL-C levels rather than levels based on the Friedewald equation, which ATP III uses. The subgroup LDL-C levels would have been higher if they would have used the Friedewald equation. In PROVE IT, patients taking atorvastatin 80 mg had a LDL-C that was, on average, 33 mg/dL lower compared to patients taking pravastatin 40 mg. After two years, the composite cardiovascular endpoint was reduced only 16% with atorvastatin compared to pravastatin, rather than the anticipated 33% based on previous epidemiologic results. In the 72% of patients with LDL-C levels < 125 mg/dL at the start of therapy, the trend toward atorvastatin benefit was not statistically significant.

Clinical Impact: Based on results from more recent trials, the use of lipid-lowering medications to achieve LDL-C goals lower than those previously set by ATP III may result in even greater risk reduction. However, the ability to lower LDL-C levels to < 70 mg/dL depends on the patient's baseline LDL-C at drug initiation and the safe use of both TLC and higher doses of HMG CoA Reductase Inhibitors alone or in combination with other lipid lowering agents (fibrates, ezetimibe, or nicotinic acid).

If the LDL-C level of < 70 mg/dL is obtainable, this certainly appears to be an option to help high risk patients achieve lower cardiovascular risk. Because of the relative safety of LDL lowering agents and the recommendation to use these medications prudently to reduce risk 30-40% rather than just reach an LDL goal, a LDL-C <70 mg/dL can become a realistic goal for some patients. Studies have not revealed the LDL-C level at which no further lowering of LDL-C results in no additional risk reduction. Additional trials are exploring the question of "how low LDL should go?" With the results of clinical trials in this area of interest on the horizon, potential ATP IV guidelines may be updated with lower established LDL-C goals both for those at high risk (CHD or CHD risk equivalent) and for those at moderately high risk (2+ risk factors and 10-year risk 10-20%).

Circulation. 2004;110:227-239.

*HPS=Heart Protection Study, PROSPER = Prospective Study of Pravastatin in the Elderly at Risk, ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Trial, ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm, PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22

SSRI Use in Children and Adolescents: "Should We Be Worried?"

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Key Point: The FDA Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee meet jointly on September 13 and 14, and recommended a "black box" warning on the use of antidepressants in patients 18 or younger due to suicide risks.

Background: Controversy on the use of SSRIs in children and adolescents began in June of 2003 when the British government issued a strong warning against the use of paroxetine in British patients under age 18 and declared all SSRIs except fluoxetine unsuitable for use in depressed youth. The UK Committee on Safety of Medicines issued an interim report in September 2003 describing two areas of "continuing concern and scientific debate" that include suicidal behavior associated with SSRI treatment and withdrawal effects on stopping these drugs. As a result of the UK's warning, in March 2004, the FDA urged ten companies to add warning labels to their antidepressants stating both pediatric and adult patients should be monitored closely, especially during drug therapy initiation and dosage changes.

As the use of SSRIs in children and adolescents evolved into a major public concern, the FDA in conjunction with Columbia University researchers conducted an analysis of 25 studies involving eight different antidepressants and 4,000 children and adolescents. The analysis showed that patients who were given any of the antidepressants were about 1.8 times more likely to have suicidal thoughts or behavior than patients who were given a placebo. The analysis also revealed that most suicidal tendencies occurred in the studies with the highest proportion of patients who had a history of suicidal attempts and/or behaviors prior to enrollment. There were no successful suicides during any of the studies. Further complicating the assessment, the risk varied widely not just from drug-to-drug but between studies of the same drugs. In short, this intensive analysis demonstrated that patients less than 18 years old on antidepressants had some risk of suicidal tendencies; and patients in the fluoxetine studies had fewer problems than those on the other agents.

Using the UK General Practice Research Database from 1993 through 1999, the Boston Collaborative Drug Surveillance Program conducted a matched case-control study to evaluate the correlation of antidepressant use and suicidal ideations. Their main objective was to determine the relative risks of

nonfatal suicidal behavior in patients starting treatment with fluoxetine, paroxetine, and amitriptyline compared to dothiepin (a tricyclic antidepressant available in the UK). This study included 159,810 patients of all ages, of which only 4% were ages 10 to 19 years. Participants had to be on only one of the antidepressants and received at least one prescription for the drug within 90 days before their index date (the date of suicidal behavior or ideation for cases and the same date for matched controls). The study revealed that "the risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin." The authors further concluded that the risk of suicidal behavior is increased in the first month after starting antidepressants due to drug treatment not being immediately effective. The risk of suicidal behavior is higher in patients initiating therapy compared to those who have been receiving therapy for some time. Finally, the researchers concluded that there is no substantial difference in effect of the four drugs on people aged 10 to 19 years.

In contrast to recent concerns, the American Academy of Child and Adolescent Psychiatry (AACAP) supports the use of SSRIs as a drug therapy option in depressed children and adolescents and believes SSRIs can be effective in treating this population. In addition, a recent American College of Neuropsychopharmacology (ACN) Task Force Report (which reviewed over 2000 clinical trials, epidemiological studies, and toxicology studies in autopsies) did not find evidence for a link between SSRIs and increased risk of suicide in children and adolescents. Their review revealed no significant increases in suicidal ideations and no suicidal deaths. Furthermore, autopsy reviews of 49 suicidal adolescents exhibited similar results as 24% of the

victims which were taking antidepressants had no trace of SSRIs in their system at the time of their death. This suggests that medication non-adherence could be a significant risk factor contributing to adolescent suicides. A 2003 World Health Organization (WHO) epidemiological study showed a significant reduction in the youth suicide rate in over 15 countries (averaging about 33% reduction), with the initiation of SSRI treatment. This provides reassurance that SSRIs are effective at reducing the risk of suicide in this patient population.

As of the September 13th hearing, FDA officials concurred that 2-3% of children and adolescents exhibit suicidal ideations during antidepressant therapy, therefore enforcing the addition of a black-box warning for the use of antidepressants in individuals 18 years or younger. The recommendation of banning the use of all antidepressants in children and adolescents was denied due to the fact that it would leave clinicians with limited options for the 10% of the pediatric patients who have depression.

Clinical Impact: Since the risks and benefits of SSRI use in children and adolescents remain unclear, clinicians should use these agents with caution and should follow the committee's consensus on the use of antidepressants in pediatric patients. The recommendations are as follows:

- 1) Fluoxetine is the only antidepressant approved for use for depression in patients less than 18 years old.
- 2) Clinicians and parents should monitor individuals carefully for signs of suicidal ideations throughout therapy but *particularly during the first few weeks of treatment* due to evidence suggesting that the incidence of suicidal tendencies is increased during this period.

References available on request.

Miscellaneous News

Menopause Home Tests

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Paynesville Area Health Care System

There are currently two types of home tests available for testing menopause in women, urine tests (Menocheck, Estroven Menopause Monitor) and saliva tests (Hormone Profile I, Saliva Hormone Test Kit).

The urine test is the only FDA approved home menopause test. This test measures Follicle Stimulating Hormone (FSH) excretion in the urine by detecting FSH levels >25 mIU/ml. These tests are relatively inexpensive at \$20.00 per kit, and detect FSH accurately 90% of the time. Women

who are experiencing menopausal symptoms can use this test as a screening, but the test in itself is not diagnostic of menopause. Diagnosis of menopause typically requires consultation with a physician and further lab testing in addition to FSH levels. Patients should only use this test if they are experiencing menopausal symptoms and should follow up with their primary physician for further evaluation and diagnosis. Women using birth control or hormone replacement therapy will receive inaccurate results from this test. Patients should also be instructed to follow packaging directions carefully to ensure accurate results.

The second test is the saliva test. This non-FDA approved test purports to measure a combination

of hormones including estrogen, progesterone, testosterone, DHEA, cortisol, and androstenedione. This test can be purchased on the Internet and will cost consumers \$60-\$165. This testing method should not be recommended to patients.

In conclusion, when recommending a home menopause test to a patient, the urine test is the less expensive and FDA approved option.

Low Dose Hormone Therapy

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In 2002, when the Women's Health Initiative announced that it was prematurely ending the combined conjugated estrogen and medroxyprogesterone acetate arm of the study in postmenopausal women because the benefits of therapy no longer outweighed the risks of therapy, many health care providers and patients became concerned about the risks associated with using hormone therapy. Over the last few years, in response to these concerns, new lower dose estrogen and estrogen/medroxyprogesterone therapies have been developed. The result has been several new products including, most recently, Prempro® 0.3mg/1.5mg, Premarin® 0.3mg, and Menostar® 0.014mg. Low dose hormone therapy is considered to be <0.625 mg conjugated estrogens,

<1.0 mg estradiol, <0.05 mg transdermal estradiol, <0.625 mg esterified estrogens, < 0.625/2.5 conjugated estrogen/ medroxyprogesterone. The following chart contains a listing of current low dose hormone therapy products available today.

Low dose hormone therapy is efficacious in reducing hot flashes; however, it may take longer to achieve the same level of improvement recognized with standard dose hormone therapy. Low dose hormone therapy is efficacious in retaining bone mass density, however, improved bone mass density is understood to be dose related, with standard hormone therapy providing the greatest retention of bone density. Low dose therapy used for this indication should also include the use of supplemental calcium with vitamin D. Low dose therapy also improves vulvovaginal atrophy, though it is unclear how this compares to standard hormone therapy.

Finally, low dose hormone therapy shows a decreased incidence of breakthrough bleeding when compared to standard hormone therapy. It is still too soon to tell if low dose hormone therapy is safer than traditional standard dosing with respect to breast cancer and cardiovascular risk, however, it is still advisable to recommend the lowest dose of therapy needed to control menopausal symptoms, for the shortest duration necessary.

Low Dose Hormone Therapy

Product	Active Ingredient	Dosage Form	Dosage Strength	Cost (1 month)	Dosing	Indications*	Additional Information
Prempro	Conjugated Estrogen/ Medroxyprogesterone	Tablet	0.3mg/1.5mg 0.45mg/1.5mg	\$35.99 \$35.99	Daily	HF, VVA, OPP	Consider alternatives for OPP.
Premarin	Conjugated Estrogens	Tablet Tablet	0.3 mg 0.45mg	\$27.99 \$29.99	Daily	HF, VVA, OPP	Consider alternatives for OPP.
Estrace	Estradiol	Tablet	0.5mg	\$19.81	Daily	HF, VVA	
Menest	Esterified Estrogen	Tablet	0.3mg	\$14.90	Daily	HF, VVA, OPP	Consider alternatives for OPP.
Menostar	Estradiol	Patch	0.014mg/24h	Pricing NA	Weekly	OPP	Menostar: women w/ uterus need progestin 14 days every 6-12 mo. ² Make sure adequate Ca and Vit D intake. ² Consider alternatives for OPP.
Vivelle	Estradiol	Patch	0.025 mg/24h 0.0375mg/24h	Pricing NA \$29.99	2x Weekly	OPP HF, VVA	
Vivelle Dot	Estradiol	Patch	0.025mg/24h 0.0375mg/24h	Pricing NA \$35.30	2x Weekly	OPP HF, VVA	
Alora	Estradiol	Patch	0.025mg/24h	\$34.23	2x Weekly	OPP	
Climara	Estradiol	Patch	0.025mg/24h 0.0375mg/24h	\$35.14 \$35.14	2x Weekly	HF HF	
Esclim	Estradiol	Patch	0.025mg/24h 0.0375mg/24h	\$44.89 \$42.39	2x Weekly	HF, VVA, OPP HF, VVA, OPP	
Climara Pro	Estradiol and levonorgestrel	Patch	0.045mg/ 0.015mg	\$36.99	Weekly	HF	

*Indications: HF (Hot Flashes), VVA (Vulvovaginal Atrophy), OPP (Osteoporosis Prevention)