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INSIDE

A Puff of Prevention is Worth a Pound of ICU Care

ABSTRACT & COMMENTARY

Synopsis: *Inhaled corticosteroids are the most effective pharmacologic agents in reducing exacerbations in asthmatics.*

Source: Sin DD, et al. *JAMA*. 2004;292:367-376.

This paper is the product of a metanalysis. Sin and colleagues searched 3 major medical databases and consulted experts to identify trials evaluating pharmacologic treatment of asthma in adults. The review period was from January 1, 1980, until April 30, 2004. To be included in the analysis, trials had to be randomized, double-blind, include at least at 3 months of follow-up, and contain data about either exacerbations or change in forced expired volume in 1 second (FEV_1), or both. Abstract reports and trials with poor follow-up were excluded. In general, an exacerbation was defined as an episode requiring oral or parenteral corticosteroids, emergency visits, hospitalization, or decrease in morning peak expiratory flow rates (PEFR). The analyses were conducted using Review Manager (from the Cochrane Collaboration), and controlled for many variables, including sample size, disease severity, and concomitant drug therapy. A varying number of trials were identified for each of the drug categories under investigation, but the numbers of participants from pooled studies was well over 2000 for each comparison.

Compared with placebo or short-acting beta agonists, inhaled corticosteroids were more effective in reducing asthma exacerbations (by 55%) and improving FEV_1 (by 330 mL) than any other category of asthma medication. Long-acting beta agonists (LABA) reduced exacerbation rates by 25% and improved FEV_1 by 330 units. In patients with persistent asthma symptoms despite inhaled steroids, the addition of LABA to inhaled steroids further reduced exacerbations (by 26%) compared with inhaled steroids alone, and this was better than doubling the inhaled steroid dose. The leukotriene modifiers reduced exacerbation rates by 41% and improved FEV_1 by 250 units compared with placebo, but when directly compared with inhaled corticosteroids, these agents were inferior in reducing exacerbations or improving FEV_1. When compared with the LABA (in patients already

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taking inhaled steroids), leukotriene modifiers were not significantly different. Recombinant monoclonal anti-IgE therapy was associated with a 45% reduction in exacerbations and improved FEV_1 by 180 mL (in patients with positive allergy skin tests or other objective evidence of atopy). There are many caveats to this analysis, including the inability to evaluate long-term side effects of inhaled steroids (or any of the agents studied). Also of note is the fact that those studies evaluating LABA and steroids in combination included patients who were still symptomatic on steroids, so they cannot be generalized to steroid naïve patients. Those patients in the leukotriene modifier studies were proven to be allergic, and these results may not be generalizable to non-atopic asthmatic.

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COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Asthma is prevalent (5-12%),[1] expensive ($11 billion per year in the United States)[1,2] and deadly (4487 deaths in 2000).[3] For reasons that are incompletely understood, both the prevalence and the death rate from asthma are increasing,[1] despite a truly impressive expansion in our pharmacologic armamentarium and an NIH-backed health education effort.[4] About 20% of asthmatics consume 80% of the resources expended on asthma; these patients are more likely to die and have the most frequent exacerbations.[2,4] Thus, reduction in exacerbations is a critical aspect of therapeutic efficacy.

All of the drugs included in this metanalysis reduced the risk of exacerbations compared with placebo or short-acting beta agonists, but inhaled corticosteroids are clearly the most effective. Although the studies included in this metanalysis were not consistently long enough to compare long-term side effects of these agents with each other, inhaled beta agonists are associated with an increased risk of cardiac events,[5,6] which does not appear to be the case with other agents. On the other hand, inhaled steroids, especially at high doses, may be associated with bone demineralization, cataracts, glaucoma, and adrenal suppression.[7,8]

The studies reviewed did not include enough long-term data for Sin et al of this metanalysis determine whether any agent reduced asthma-related mortality, but other observational studies suggest that inhaled steroids, but not other agents.[9] In sum, as Sin et al put it, there is ". . . a wealth of evidence supporting the use of inhaled corticosteroids in low doses and first-line therapy for adult patients who require more than an occasional use of short-acting B2 agonistics for control of their disease."

So, how often does this happen? In an Internet survey of asthma treatment in Sweden, Jenson found that short-acting beta-agonists were used by 67% and inhaled steroids by 59% of those with daily symptoms.[10]

The reasons for our failure to optimally treat asthma are probably multiple, but chief among them is the difficulty in maintaining burdensome treatment to prevent a bad outcome. Use of antihypertensives or lipid-lowering agents are cases in point; compliance with these agents is relatively poor, despite strong evidence that they prevent bad outcomes, and despite the fact that they are pills, which are much less cumbersome to use than are inhaled medications. Our patients don't want to use an inhaler (or multiple inhalers) daily or several times a day when they are asymptomatic. But the data are clear that we need to work harder to try to get our asthmatics to do this,

especially if they have exacerbations. The risk and cost of a single exacerbation generally outweighs the burden of daily preventive therapy. ■

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LDL—Lower Is Better but How Low Should We Go?

SPECIAL FEATURE

By Harold L. Karpman, MD

MANY RISK FACTORS CONTRIBUTE TO THE COMPLEX metabolic process which leads to atherosclerosis development. In an atherogenic environment, oxidized LDL infiltrates the vascular intima resulting in inflammation, endothelial dysfunction and eventually in the development of significant atherosclerosis even in those individuals with "normal" LDL levels (ie, 90-130 mg/dL.[4] At least 7 statin mega-trials (with control LDL levels of 120-180 mg/dL and treatment LDL values of between 100-140 mg/dL) demonstrated remarkable reductions in CHD events and in all cause mortality.[5-11] The National Cholesterol Education Program Adult Treatment Panel-III targeted the optimal low-density glycoprotein (LDL) level for patients with established coronary artery disease or coronary heart disease (CHD) risk equivalents (ie, diabetes, peripheral or cerebral vascular disease, and/or predicted 10-year CHD risk of > 20%) at < 100 mg/d.[1] The European guidelines for this group of patients recommended a target LDL of < 115 mg/dL.

O'Keefe and colleagues[3] reviewed published reports regarding the hunter-gatherer populations that existed before the introduction of agriculture and animal husbandry 10,000 years ago and which revealed no evidence for atherosclerosis even in individuals living into the seventh and eighth decades of life.[12,13] These populations had total cholesterol levels of 100-150 mg/dL and LDL cholesterol levels estimated to be 50-75 mg/dL. Even today, the LDL levels of healthy neonates are in the 30-70 mg/dL range and healthy, wild adult primates usually have LDL levels of 40-80 mg/dL; in fact, modern humans are currently the only adult mammals, excluding some domesticated animals, with a mean average LDL level over 80 mg/dL and a total cholesterol over 160 mg/dL.[12,13]

Multiple, prospective, randomized controlled trials have demonstrated that the rate of angiographic progression of atherosclerosis was closely related to the chronic LDL level and that the threshold for progression appears to be at an LDL level at or above approximately 67 mg/dL (*see Figure 1*).[14-20] More recently, an intra coronary ultrasound study even demonstrated atherosclerotic regression when LDL levels were reduced to a mean level of 79 mg/dL.[20] More than 100,000 patients have been randomized to statin therapy in CHD event reduction trials which have clearly demonstrated a direct relationship between the level of on-treatment LDL values and the absolute risk of CHD events.[5-11] The LDL level at which the cardiovascular event rate is predicted to approach zero is 57 mg/dL for primary prevention (*see Figure 2*) and 30 mg/dL for secondary prevention (*see Figure 3*). Inflammation and endothelial dysfunction have both been shown to be improved if the LDL is lower to < 80 mg/dL.[20] Finally, statin therapy with improved LDL levels have been associated with reductions in the incidence of symptomatic peripheral vascular disease, stroke, dementia, macular degeneration, aortic stenosis, and osteoporosis, and, as result, some investigators have suggested that statins be considered for routine use in individuals over the age of 55 years.[21]

The newer, more potent, statin drugs are capable of reducing LDL cholesterol safely and tolerably in most patients thus making a target LDL of 50-70 mg/dL a practical goal, but, how low is too low? Since the cumulative experience with statin therapy has demonstrated impressive cardiovascular benefits that are directly proportional to the degree of LDL lowering with no increase in adverse events and, since on the other hand cholesterol is an essential component of the cell membrane and a needed precursor for bile acid, steroid hormones, and vitamin D

synthesis, there must be a physiologically ideal range of blood cholesterol and LDL levels above and below which adverse health consequences might be expected. Patients with heterozygous hypobetalipoproteinemia with cholesterol levels as low as 80 mg/dL and LDL levels as low as 30 mg/dL live long lives presumably due to the absence of atherosclerosis and have no increase in adverse effects.[22]

Finally on July 13, 2004, most newspapers nationwide published a report issued by a panel from the National Institutes of Health's National Cholesterol Education Program which recommended that reduction of LDL cholesterol to < 70 mg/dL is a "therapeutic option" (ie, a reasonable clinical strategy) on the basis of available clinical evidence. Furthermore, they extended this therapeutic option recommendation to patients at very high risk who even have achieved the previously recommended goal of a baseline LDL < 100 mg/dL.[23]

In summary, although an LDL level of 50-70 milligrams/dL may seem excessively low by recent American standards, it appears to be precisely the correct or normal range for individuals living the lifestyle and eating the diet for which we are genetically adapted and it would appear to be the goal that we should achieve in order to prevent the progression and even to promote regression of coronary atherosclerosis. ■

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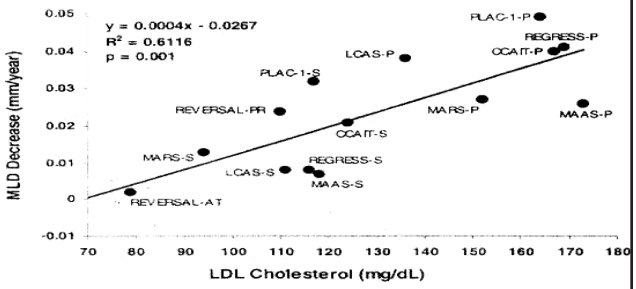
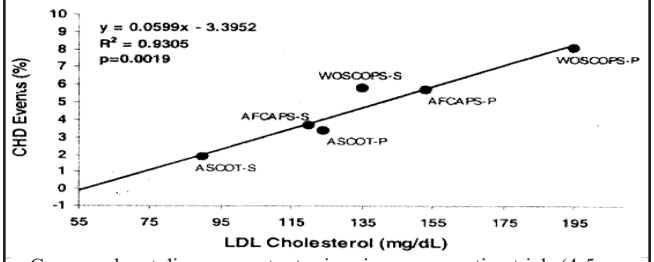
Figure 1



Atherosclerosis progression varies directly with low-density lipoprotein cholesterol. This regression line indicates that atherosclerosis does not progress when LDL is 67 mg/dL or below.

All Figures adapted from O'Keefe, JH, et al. Jour Am Coll of Card. 2004;43:2142-2146.

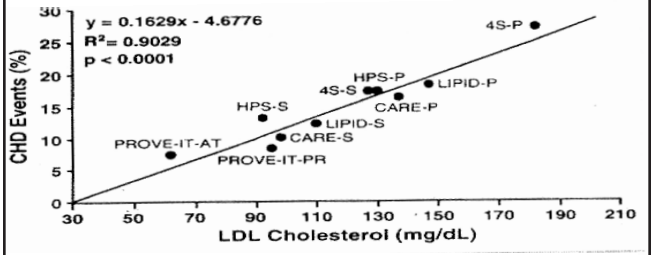
Figure 2



Coronary heart disease event rates in primary prevention trials (4-5 years duration) are directly proportional to the on-treatment low-density LDL cholesterol levels. The event rate is predicted to approach 0 at an LDL level of about 57 mg/dL.

Adapted from O'Keefe, JH, et al. Jour Am Coll of Card. 2004;43: 2142-2146.

Figure 3



Coronary heart disease event rates in secondayr preventino trials (5 years in duration except the PROVE-IT study, which was 2 years) were directly proportional to low-density LDL cholesterol levels. The event rateis predicted to approach 0 at LDL of 30 mg/dL.

Adapted from O'Keefe, JH, et al. Jour Am Coll of Card. 2004;43: 2142-2146.

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Better Diagnosis of Celiac Disease

ABSTRACT & COMMENTARY

Synopsis: *An NIH Consensus Panel has announced new recommendations for the diagnosis of Celiac Disease using new serologic testing. This disorder is easily treated, but the diagnosis may be delayed for many years due to the nonspecific nature of the symptoms. Celiac disease has a frequency that is 10 times previous estimates.*

Source: Mitka M. *JAMA*. 2004;292:913-914.

CELIAC DISEASE IS AN IMMUNE-MEDIATED DISORDER with chronic inflammation of the small intestinal mucosa resulting in atrophy of intestinal villi and malabsorption. Symptoms include diarrhea, abdominal cramping, pain and distention, very similar to irritable bowel syndrome. Once considered to a rare condition, Celiac Disease affects about 1% of the US population and may manifest in childhood or as adults. The average delay in diagnosis is 10 years!

Celiac Disease should be considered in any patient with chronic GI symptoms described above. New serologic tests which have a high sensitivity and specificity are: antihuman tissue transglutaminase IgA and endomysial antibody immunofluorescence IgA. Confirmation of positive testing may be done by biopsy of the proximal small bowel. Definitive diagnosis comes from a resolution of symptoms when the patient is placed on a gluten-free diet.

Gluten is a dietary protein present in wheat, barley and rye. Patients and their family may want to consult a dietician for specifics on the necessary dietary changes, or consult various internet sources. The main substitution rice based grains for those above, and rice breads and other products have become widely available.

The NIH consensus statement is available at: http://consensus.nih.gov/cons/118/118cdc_intro.htm.

COMMENT BY JOSEPH E. SCHERGER, MD, MPH

Not mentioned in this article is the frequency of Celiac Disease in the elderly, which may be a variant of the autoimmune disorder. My introduction to this phenomenon was my father, who during his 70s developed diarrhea, bloating, and gas, which completely resolved on a gluten free diet. He is doing well at 87. Since then I have had a series of elderly patients develop the same condition and they are grateful for the diagnosis and treatment which allows them to remain socially active. These GI complaints are embarrassing and may limit eating out and other social activities. Information about gluten-free diets has become common among seniors. While the development of an autoimmune condition may be possible, I have explained to patients that certain enzyme systems atrophy or wear out with age. We certainly know this to be true with lactose intolerance, which worsens with age.

This NIH consensus statement states that while the definitive diagnosis comes from a trial of a gluten free diet, endoscopy with biopsies of the proximal small intestine should be done after serologic testing. Despite the certainty that comes from a tissue diagnosis, I doubt that most primary care physicians will feel that invasive testing is necessary when the history, serologic testing and a dietary challenge all point to the diagnosis. Most importantly, think of Celiac Disease in patients with chronic diarrhea, bloating, pain, and gas.

Pharmacology Update

Duloxetine Hydrochloride Capsules (Cymbalta)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA HAS APPROVED DULOXETINE FOR THE treatment of depression and the management of the pain associated with diabetic peripheral neuropathy. The drug is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) similar to venlafaxine (Effexor). Duloxetine is marketed by Eli Lilly and Company as Cymbalta.

Indications

Duloxetine is indicated for the treatment of major depressive disorder (MDD). Effectiveness has not been studied in hospitalized patients with MDD.[1]

Duloxetine is also indicated for the management of pain associated with diabetic peripheral neuropathy.

Dosage

The recommended dose for depression is 40 mg (20 mg twice daily) to 60 mg daily (60 mg once daily or 30 mg twice daily). It may be taken without regard to meals. The recommended dose for neuropathy is 60 mg daily. The capsule contains enteric-coated pellets therefore it should be swallowed whole, not chewed or crushed nor sprinkle on food or liquid. It is not recommended for patients with liver dysfunction or patients with end stage renal disease.[1]

Duloxetine supplied as 20 mg, 30 mg, and 60 mg capsules.

Potential Advantages

Duloxetine is the first drug approved for the management of diabetic peripheral neuropathy. It is also reported to be effective in relieving painful physical symptoms in depressed patients. Improvements in pain severity were associated with higher remission rates.[2]

Potential Disadvantages

Duloxetine has been associated with increased risk of mydriasis. Therefore it should be avoid in patients with uncontrolled narrow angle glaucoma. Common side effects associated with duloxetine are nausea, somnolence, insomnia, headache, dry mouth, constipation, dizziness, and diarrhea.[1,3] These tend to be more common earlier in therapy.[3] Increase in blood pressure, symptoms of urinary hesitation, sexual dysfunction in males, and elevation of serum transaminase levels have also been reported. Other frequent (at least 1/100) side effects observed during premarketing evaluations include gastritis, irritability, lethargy, nervousness, nightmare, restlessness, dysuria, night sweats, pruritus, and rash.[1] Duloxetine is metabolized by CYP1A2 and CYP2D6. Potent inhibitors of these isoenzymes result in increase levels of duloxetine. Duloxetine is also a moderate inhibitor of CYP2D6 and intermediate between paroxetine and sertraline.[4] Due to the risk of serious ventricular arrhythmias and sudden death the co-administration of thioridazine and duloxetine in contraindicated.[1]

Comments

Duloxetine is a SSNRI with high affinity for these transporters and with little affinity for other central nervous system neural transmitters.[5] Efficacy in MDD was shown in randomized placebo controlled studies of 8-9 week duration[1,2,5,6] The primary end point was the 17-item Hamilton Depression Rating Scale (HAMD-17). In comparative trials with placebo and an active control, Duloxetine 40 mg was found to similar to paroxetine 20 mg in terms of response rate and remission rate although the primary goal of the study was not to compare active treatments,[7] However, in a long-term open-label (n = 1279) the drug was reported to be effective, safe, and well tolerated.[3] Mechanistically, duloxetine is most similar to venlafaxine. There are currently no published comparative trials between these SSNRIs. Venlafaxine is metabolized by CYP2D6 while duloxetine is metabolized by 2D6 and 1A2 isoenzymes. Side effects of duloxetine appear to be similar to venlafaxine and other SSRIs. The efficacy of duloxetine for the management of diabetic neuropathy was established in 2 randomized 12-week, controlled studies in about 1000 non-depressed subjects.[8] Fifty eight percent (58%) achieved a 30% reduction in pain compared to 34% for placebo. Duloxetine is being investigated for treating urinary incontinence.[9] Duloxetine is priced similar to venlafaxine.

Clinical Implications

Duloxetine is the first drug to be approved for the management of diabetic peripheral neuropathy. It is not known how it compares with other drugs (ie, antidepressant, anticonvulsants) currently being used for this condition with limited success.

Duloxetine joins the crowded antidepressant market with several SSRIs and one other SSNRI. It is most similar to venlafaxine with no clear clinical advantage over other antidepressants. ■

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CME Questions

13. With regard to asthma exacerbations:

a. All pharmacologic agents for the treatment of asthma reduce their frequency, but corticosteroids are most effective.
b. All pharmacologic agents for the treatment of asthma reduce their frequency, but long-term beta agonists are most effective.
c. All pharmacologic agents for the treatment of asthma reduce their frequency, but corticosteroids have the worst side effects.
d. Only long-acting beta agonists reduce their frequency.
e. Only long-acting corticosteroids reduce their frequency.

14. Which of the following statements is true regarding the diagnosis of Celiac Disease?

a. Celiac Disease is a congenital condition and the diagnosis is usually made by the age of 5.
b. Celiac Disease is an immune mediated condition and the diagnosis requires a biopsy of the small intestine.
c. The most common symptoms of Celiac Disease are diarrhea, abdominal cramping, pain and distention.
d. Since there are no laboratory tests for Celiac Disease, the diagnosis can only be made by biopsy or a trial of a gluten free diet.

Answers: 13 (a); 14 (c)

By Louis Kuritzky, MD

Functional Decline in Peripheral Arterial Disease

Peripheral arterial disease (PAD) may be stratified in severity by the ankle-brachial index (ABI), measured by dividing the ankle systolic BP by the brachial systolic BP. Normally, this number is 1 or greater. Progressive atherosclerotic disease reduces the index, with a number < 0.9 considered indicative of PAD.

Observational studies from prior decades may have given the impression that PAD is a relatively static disorder, with as few as 15-30% of subjects experiencing symptom progression over intervals as long as 10 years. However, the lack of discernible symptomatic worsening might actually reflect a reduction in activities which induce symptoms, rather than lack of disease progression.

McDermott and colleagues studied subjects older than age 55 (n = 676) with PAD as demonstrated by ABI < 0.9. Functional status over time was measured by means of the 6-minute walk performance, usual-pace walking velocity, and fastest-pace walking velocity.

The presence of PAD, whether symptomatic or not, was associated with decrements in the 6-minute walk performance over time. For symptomatic PAD patients, performance declines were proportional to the degree of baseline ABI. Even amongst asymptomatic persons with PAD, the likelihood of ultimately being unable to walk was almost 4-fold greater than persons without PAD. Previous guidance that minimized the importance of disease progression may have overlooked and seriously underestimated the functional consequences of even asymptomatic PAD. ■

McDermott MM, et al. JAMA. 2004;292:453-461.

Topical Capsaicin for Chronic Pain

Topical analgesics, such as capsaicin (CAP), methylsalicylate, and transdermal lidocaine, are agents which are applied topically for a local effect, as opposed to agents applied topically for a systemic effect (eg, transdermal fentanyl). Topical analgesics have recently enjoyed greater application in primary care, perhaps to some degree due to the endorsement of agencies such as the American College of Rheumatology, whose guidelines include CAP as foundation therapy for osteoarthritis of the knee.

Mason and colleagues performed a metaanalyses of double-blind placebo controlled trials of CAP used for neuropathic pain (6 trials; n = 656) or musculoskeletal pain (3 trials, n = 368). Clinical success was defined as approximately a 50% reduction in pain. Adverse effects monitored included local adverse events and withdrawal due to adverse events.

CAP was superior to placebo for both pain syndromes. For example, the mean number of persons achieving at least 50% reduction in neuropathic pain at 4 weeks was 57% vs 42% with placebo, and similar results were seen in musculoskeletal syndromes.

The rate of adverse events leading to withdrawal was 13% in CAP subjects (3% in placebo). Overall, 54% of patients experienced some adverse local event in 4-8 week trials. Although the positive effects of CAP are modest, some patients achieve substantial benefit, and CAP treatment may reduce the need for concomitant systemic pharmacotherapy. ■

Mason L, et al. BMJ USA. 2004;4: 349-358.

Topical Tacrolimus Therapy for Vitiligo

Vitiligo (VIT) is a disorder characterized clinically by one or more skin sites of depigmentation caused by loss of melanocyte activity. Demonstrated etiologies include genetic factors, autoimmune disorders, and viral infections, although in most cases the underlying pathology remains elusive. Recently, the role of blood and cutaneous cytokine expression in VIT has received increasing attention, resulting in recognition of alterations in interleukin and tumor necrosis factor alfa in these patients.

Tacrolimus (TAC) is a topical immunomodulator currently used to treat atopic dermatitis. Its putative primary mechanism is immune modulation by inhibition of T-cell activation, resulting in decreased proinflammatory cytokine production and release. Based upon favorable results from a small pilot study in VIT, Grimes et al performed this trial of TAC in subjects with VIT.

All subjects (n = 19) applied TAC as 0.1% ointment twice daily for 24 weeks. In addition, they used sunscreen (SPF 30 with Parsol 1789) each morning. VIT disease severity was assessed on a 6-point scale.

The degree of repigmentation varied with tissue site, with greatest success on the face and neck (68% experiencing greater than 75% repigmentation). Cytokine expression (which was elevated at baseline) showed a significant decrease over time with use of TAC. Tacrolimus shows promise as a therapeutic tool for VIT. ■

Grimes PE, et al. J Am Acad Dermatol. 2004;51:52-61.

In Future Issues: **Should All Hypertensive Patients Older Than Age 60 Be Treated?**