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St. John's Wort Reduces Digoxin Levels

ABSTRACT & COMMENTARY

Source: Johne A, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther* 1999;66:338-345.

Due to the increasing popularity of alternative or natural treatments, St. John's wort (*Hypericum perforatum*) has become widely used in the treatment of depression. Despite being largely available as an over-the-counter drug, very little is known about the pharmacokinetics of its ingredients and/or its drug interactions. With a single-blind, placebo-controlled parallel design, the investigators studied the interaction between hypericum extract LI160 (the putative active ingredient in St. John's wort) and digoxin. The LI160 preparation contained 92 mcg of hypericin per 300 mg tablet of dried hypericum extract.

All subjects, who were instructed not to smoke or consume alcohol, coffee, tea, cola beverages, or drugs, received a loading dose of digoxin 0.25 mg twice daily for two days then once daily thereafter. After the achievement of steady state for digoxin on day five, healthy volunteers who were 22-33 years of age received digoxin (0.25 mg/d) either with placebo (n = 12) or with 900 mg/d LI160 (n = 13) for another 10 days. Digoxin concentration profiles on day five were compared with day six (single-dose interaction) and day 15 (10th day of co-medication).

The effect of a single dose of hypericum extract on digoxin kinetics did not achieve statistical significance, although the digoxin levels were slightly higher than the placebo group. After 10 days of co-medication, trough levels of digoxin were reduced by ~33% in the hypericum group. Maximum levels (Cmax) and the area under the curve of digoxin were similarly affected (reductions of 28% and 26%, respectively). These parameters were also significantly lower compared to those for the placebo arm. Cotreatment with hypericum did not affect the elimination half-life of digoxin, suggesting that a mechanism other than hepatic enzyme induction. The effect on

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digoxin seemed to be time dependent (maximum reduction not present until the 10th day). This fact, combined with the fact that the single-dose effect of hypericum coadministration did not reduce but rather raised digoxin levels, suggests that the mechanism was not due to an impairment of absorption by physicochemical binding of digoxin and hypericum in the gut.

COMMENT BY MICHAEL F. BARBER, PharmD

The current study is important for several reasons. First, the reduction of digoxin concentrations by hypericum is clinically significant since patients may lose efficacy of digoxin when St. John's wort (SJW) is taken concomitantly. Patients who claim that they have been adherent to their digoxin regimen may present with lower serum digoxin concentrations despite the fact that their dosage has not been changed. Alternatively, patients who have achieved therapeutic levels of digoxin while taking SJW may develop digoxin toxicity once they discontinue SJW.

Another important point about this finding is that this pharmacokinetic study illustrates the importance of studying both the acute and chronic effects of drug interactions. The acute effect of this combination, although not statistically significant, may have suggested to clinicians that SJW may raise serum digoxin levels, whereas the chronic administration showed an impressive reduction in serum digoxin levels. The findings of this study also suggest that SJW does not induce hepatic metabolism of digoxin. Marangell[1] has previously discussed that SJW is an inducer of CYP3A4, and can lower serum levels of substrates of that enzyme. However, hepatic metabolism of digoxin constitutes a relatively minor pathway. A large portion of digoxin metabolism takes place in the intestine. The intestinal degradation of digoxin may be mediated by P-glycoprotein, a product of the multiple-drug-resistance gene MDR1, which transports digoxin into the gut from the blood. Thus, the mechanism by which SJW reduces serum digoxin levels may be via induction of the P-glycoprotein transporter. This is consistent with several other CYP3A4-inducing drugs, such as rifampicin, which also induce the expression of P-glycoprotein.

Finally, the current study is yet another example of a drug interaction involving a non-prescription product. With the current increase in popularity of alternative, over-the-counter medications (particularly herbal "remedies"), clinicians should be aware of patients taking such products as well as the possible interactions between the products and prescription medications. ❖

Reference

1. Marangell LB. St. John's wort may alter drug levels. *Psychiatric Medicine in Primary Care* 1999;1(3):17-18.

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Nefazodone May Inhibit Metabolism of HMG-CoA Reductase Inhibitors

ABSTRACT & COMMENTARY

Source: Alderman CP. Possible interaction between nefazodone and pravastatin. *Ann Pharmacother* 1999;33:871.

We and others have previously described the important relationship between depression and cardiovascular disease (CVD). Many patients with CVD, therefore may be receiving multiple medications concomitantly, including antidepressants and cholesterol-lowering agents. This article discusses a possible drug interaction between nefazodone, an antidepressant, and pravastatin, an antilipemic agent.

The article describes a case involving a 74-year-old white man with a history of hypertension, ischemic heart

disease, and hyperlipidemia who was admitted to a hospital for an episode of major depression. The patient was initially treated with citalopram 30 mg/d, atenolol 100 mg/d, enteric-coated aspirin 100 mg/d, and pravastatin 20 mg/d. All admission laboratory values were within normal limits. The antidepressant regimen was subsequently changed to nefazodone 50 mg twice daily, which was initiated after a 36-hour washout period. Approximately 36 hours after the introduction of nefazodone, plasma creatine kinase (CK) was 877 U/L (normal range 0-190). Lactate dehydrogenase was also elevated at 307 U/L (normal range 115-200), as were aspartate aminotransferase (AST) at 58 U/L (normal range 0-30) and alanine aminotransferase (ALT) at 64 (normal range 0-30). The CK was sent for fractionation, which determined that CK-MB constituted only 1% of the total CK concentration. This ruled out cardiac causes, thereby suggesting rhabdomyolysis.

Nefazodone was discontinued, but CK remained elevated (275 U/L) for 14 days at which time pravastatin was discontinued. CK returned to normal (169 U/L) within three days after pravastatin was discontinued. All laboratory values remained normal for approximately one month after pravastatin was reintroduced. Subsequent treatment with the antidepressant venlafaxine did not precipitate any clinical problems.

COMMENT BY MICHAEL F. BARBER, PharmD

Nefazodone is an antidepressant that has a different mechanism of action than the SSRIs. Nefazodone is a relatively mild inhibitor of serotonin reuptake, but it seems to exert its antidepressive effect via 5-HT2 receptor antagonism. Nefazodone differs from the SSRIs not only in terms of adverse effects (with favorable rather than disruptive effects on sleep and lack of sexual dysfunction), but also in terms of pharmacokinetic drug interactions. Specifically, nefazodone is a relatively potent inhibitor of CYP3A4, a hepatic enzyme that is responsible for the metabolism of many drugs, such as terfenadine, astemizole, cisapride, and pimozide. While the above combinations of nefazodone and these agents can be fatal and must be avoided, drug interactions between nefazodone and other CYP3A4 substrates such as calcium channel blockers, macrolide antibiotics, anticonvulsants, and HMG-CoA reductase inhibitors are usually hypothetical since clinical data involving these combinations are often not available. Thus, the clinical significance of such hypothetical drug interactions is usually undetermined, leaving some question as to whether or not such combinations are relevant. The current report illustrates that the combination of nefazodone and the HMG-CoA reductase inhibitor pravastatin does in fact appear to result in a clinically important drug interaction. The impairment of the hepatic clearance of pravastatin by nefazodone presumably resulted in increased levels of pravastatin, causing rhabdomyolysis as evidenced by the large increase in CK levels. In this case, the offending agent was removed quickly after the CK increased; thus, the patient did not suffer any pain from skeletal muscle damage. It should also be noted that the dose of nefazodone used in this patient was relatively low, whereas higher doses may have resulted in an even more dramatic increase in CK. This finding was consistent with a report by Jacobsen et al, who reported myositis and rhabdomyolysis associated with the use of nefazodone and simvastatin.

In summary, clinicians should be aware of the drug interactions between CYP3A4-inhibiting antidepressants and HMG-CoA reductase inhibitors. Among antidepressants, nefazodone is the most potent inhibitor of CYP3A4; whereas fluvoxamine, and to a lesser extent fluoxetine, can inhibit this enzyme as well. Neither venlafaxine nor citalopram have not been shown to inhibit CYP3A4 to any appreciable effect. If such a combination is decided upon, patients should be monitored for toxic effects in order to allow for an early intervention before the problem can become severe. ❖

Hysterectomy and Sexual Functioning

ABSTRACT & COMMENTARY

Source: Rhodes JC, et al. Hysterectomy and sexual functioning. *JAMA* 1999;282:1934-1941.

Each year, more than half a million women in the United States decide to have a hysterectomy for the treatment of gynecologic conditions. There is understandable concern about the effects of hysterectomy on sexual functioning. Existing data, mostly from small retrospective samples, indicates that 13%-37% of women report a deterioration in sexual functioning, 16%-47% report no change, and 34%-70% report improvement in sexual functioning.

The current study is a two-year prospective study. As part of the Maryland Women's Health Study, measures of sexual functioning were assessed prior to hysterectomy and at 6, 12, 18, and 24 months post-operatively. The sample included both large urban and small rural hospitals. The majority of women in the study were referred by gynecologists at the time of surgical posting (66%) or from their office (33%); 1% of patients were self-

referred. Of 1604 patients contacted, 81% agreed to participate. The main reason for declining was too little time to complete the in-home interview before hysterectomy. Sexual functioning was evaluated as follows:

1. an open-ended inquiry as to the "frequency of sexual relations over the past month";
2. a 6-point Likert scale from "all of the time" to "none of the time" for dyspareunia, orgasm, and vaginal dryness;
3. an 8-point Likert scale from "every day" to "not at all" for libido;
4. a 4-point Likert scale from "very strong" to very mild" for strength of orgasm.

Compared to all hysterectomy patients in the state of Maryland, study participants were younger (43.3 vs 44.6 years), had a shorter length of stay (3.4 vs 3.8 days), lower hospital charges, and were more likely insured by an HMO. Table 1 summarizes statistically significant results.

Table

Sexual Functioning Before and After Hysterectomy

Function	Baseline	12-Month Follow-up	24-Month Follow-up
Having sexual relations	70.5%	77.6%	76.7%
Sexual relations/month	2.3	3.1	2.9
Any dyspareunia	40.8%	18.4%	14.9%
Frequent dyspareunia	7.6%	4.3%	3.6%
Orgasms experienced	62.8%	72.4%	71.5%
Strong orgasms	44.6%	58.4%	57.3%
No vaginal dryness	37.3%	46.8%	46.7%
Low libido	10.4%	6.3%	6.2%

Only prehysterectomy dyspareunia and depression (after adjustment for age) predicted dyspareunia after hysterectomy. Prehysterectomy lack of orgasm, increasing age, and bilateral oophorectomy (after adjustment for age), and depression (after adjustment for age) predicted lack of orgasm after hysterectomy. Prehysterectomy vaginal dryness and depression (after adjustment for age) predicted vaginal dryness after hysterectomy. Finally, low libido and depression (after adjustment for age) before hysterectomy predicted low libido after hysterectomy. The primary limitation of the current study is short period of time between the interview and hysterectomy (a time during which sexual functioning may have been negatively affected by anxieties about the upcoming surgery).

COMMENT BY DONALD M. HILTY, MD

The results of this large prospective study are very encouraging, and challenge previous findings from smaller, retrospective studies. There are potential biological and many psychological mechanisms (relief, reduced fear of pregnancy, freedom from vaginal bleeding) that could account for the observed improvements in sexual function after hysterectomy. It is also possible that women simply feel better after hysterectomy and that sexual functioning improves along with overall health status and quality of life. In the current study, prehysterectomy depression predicted worse sexual functioning after hysterectomy buy the study did not evaluate mood post-operatively. Further evaluation of this issue is warranted. In any event, these data are encouraging for the many women that are contemplating this procedure. ❖

Risperidone for Behavioral Disturbance Associated with Dementia

ABSTRACT & COMMENTARY

Source: De Deyn PP, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999;53:946-955.

AGGRESSION AND OTHER BEHAVIORAL SYMPTOMS OF dementia (e.g., agitation, pacing) psychosis create stress for caregivers and often adversely effect the patient's quality of life. Many patients with dementia ultimately require pharmacologic intervention to manage disruptive behaviors. Neuroleptics are often effective, but conventional neuroleptics are associated with extrapyramidal symptoms (EPS) and anticholinergic effects, particularly in older patients. Open trials of atypical antipsychotics (e.g., risperidone, olanzapine) appear promising in this population.

Participants in this randomized double-blind study were 55 years or older, institutionalized, and diagnosed with dementia. Patients were excluded if they had other psychiatric disorders, ECG or lab abnormalities, or clinically relevant neurologic disease. After a one-week washout period, patients were randomized in a double-blind fashion to placebo, risperidone, or haloperidol. Medication was started at 0.25 mg bid, increased every four days if indicated to 1 mg bid; if the patient suffered no side effects and symptoms persisted, the dose could be increased to 2 mg bid. Lorazepam was allowed concurrently. Patients were evaluated at the time of screening, baseline, and weeks 1, 2, 4, 6, 8, 10, and 12. Efficacy measurements included the BEHAVE-AD (25 items;

symptoms clusters of psychosis, activity, aggression, diurnal disruption, mood, and anxiety/phobias; 4-point severity scale) and the Cohen-Mansfield Agitation Inventory (CMAI; 29 items; 7-point severity scale). The primary endpoint was defined a priori as the percentage of patients with 30% reduction on the BEHAVE-AD at week 12. EPS was measured by structured examination and Mini Mental Status Examination (MMSE) scores were also serially measured.

A total of 371 patients (56% women) with dementia of the Alzheimer type (67%), vascular dementia (26%), or mixed dementia (7%) were enrolled. The participants had a median age of 81 years, a median duration of institutionalization of four months, and a median time of 4.3 years between onset of dementia and trial entry. Baseline BEHAVE-AD, CMAI, and MMSE scores were 16, 26, and 8, respectively, indicating severe dementia and agitation. A total of 223 (68 risperidone, 81 haloperidol, and 74 placebo) completed the trial, with 70 days as the mean duration of treatment, and 1.2 mg as the mean dose of medication; there were no significant between-group differences. Adverse effects were reported by 76.5%, 80%, and 72.8% of patients in the risperidone, haloperidol, and placebo groups; only somnolence was higher in the treatment groups compared to the placebo group (18% greater with haloperidol and 12.2% greater with risperidone).

The percentage of patients who achieved 30% reduction in the BEHAVE-AD in the risperidone, haloperidol, and placebo groups was 55%, 63%, and 47%, respectively, at endpoint and 72%, 69%, and 61% at week 12. The risperidone group showed significantly greater improvement than placebo in the mean BEHAVE-AD total score at week 12, with the effect seen as early as week two and sustained for the duration; likewise, CMAI scores were significantly reduced. The treatment effect with risperidone was seen for patients with Alzheimer and vascular types of dementia. The haloperidol group showed significant improvement in the BEHAVE-AD aggression score, but not in the total score for completers, compared to placebo. Interestingly, the BEHAVE-AD total score was significantly lower for the haloperidol group compared to placebo when the data were analyzed with respect to all endpoints (i.e., treatment completers and non-completers). The haloperidol group, but not the risperidone group, had significantly more EPS than the placebo group. Lorazepam use in the three groups was similar. An ANOVA model revealed the change in aggression was explained partially by a direct treatment effect and partially by a change in psychosis. Limitations included the arbitrary criteria used to judge response, the concurrent use of lorazepam, and the high response rate in the placebo group.

COMMENT BY DONALD M. HILTY, MD

Demented patients with behavioral disturbances are difficult to treat. Psychosocial interventions include ongoing orientation to the environment, minimizing changes in routine, minimizing interruptions of sleep, and staff education. Medications are often necessary, but the response to trials is modest (e.g., 30%-40%, in contrast to a rate of 60+% for antidepressants for patients with major depression). Medications currently under evaluation for behavioral disturbance associated with dementia include divalproex, buspirone, and atypical antipsychotics. These options appear to be advantageous in terms of side effect profile compared to typical neuroleptics. This study indicates that risperidone is well-tolerated and has a direct treatment effect for these patients (and not just an effect via reduced psychosis). It is unclear why the conflicting results occurred with the haloperidol group. More data are needed to confirm the results of this study. ❖

Treating Erectile Dysfunction in Diabetic Men

ABSTRACTS & COMMENTARY

Sources: Rendell MS, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: A randomized controlled trial. *JAMA* 1999;281(5):421-426; Lipshultz LI, Kim ED. Treatment of erectile dysfunction in men with diabetes. Commentary. *JAMA* 1999;281(5):465-466.

Erectile dysfunction (ed) affects approximately half of American men (52%) between 40-70 years of age. Diabetics suffer from it at a significantly greater rate. At least one study indicates that 28% of diabetic males suffer complete erectile incapacity, a rate almost three times greater than in the general population. The immediate mechanisms of ED consist largely of impaired penile hemodynamic functions secondary to the damage of microvascular and microneural structures in the region. Normally, nitric oxide (NO) generated in the region triggers and sustains the erectile activities of these tissues.

Sildenafil (Viagra) taken orally in 50 or 100 mg tablets acts to increase NO activity in the corpus cavernosum, thereby enhancing erectile activity. Rendell and colleagues evaluated the drug's improvement in a double-blind study of 268 biologically matched diabetics with ED, ranging from 33-76 years of age. Following a four-week no-treatment phase, 132 randomized diabetic men

were assigned to placebo and 136 were demographically matched to receive sildenafil. Approximately 80% of both the placebo and treated groups had type 2 diabetes.

The following averaged numbers emphasize the similar functional conditions of both the treated and nontreated numbers: age, 57 years (mostly 45-64); length of ED, 5.5 years; duration of diabetes, 12.1 years; type 2 diabetes, 81%; hypertension, 52%; ischemic heart disease, 26%; medications for hypertension, 54%; for cardiac, 12%; and antidepressants, 5%. Required were: stable, controlled diabetes for at least three months; plasma glucose level less than 300 mg/dL; and a stable female partner. Excluded were: patients with anatomic genital deformities; sexual disorders; severe psychiatric problems; serious systemic disease; severe hypertension; active diabetic retinopathy; severe autonomic neuropathy; diabetic ketoacidosis within 36 months; and regular use of nitrates.

Median length of treatment was 85 days for both groups. Median numbers of agent doses were 31 (range, 3-81) sildenafil and 25 (range, 2-83) placebo. Most treatment men (93%) took 100 mg sildenafil tablets, whereas 96% of the placebo patients took the largest available blank.

Outcomes at the 12-week termination of the study included the following: S = sildenafil receivers, P = placebo receivers. All quoted differences between S and P were significant at the $P < 0.001$ level.

1. Measurably improved erections: S = 56%.
2. Percent of successful erections during the last four weeks of treatment: S = 48%; P = 12%.
3. Numbers achieving at least one successful attempt at intercourse: S = 61%; P = 22%.
4. Ability to achieve erections at end of study compared with outset: S = 78%; P = 25%.
5. Functional improvement in maintaining erection at end of study compared to the start: S = 93%; P = 14%.

Adverse reactions occurred mainly among the sildenafil recipients as follows: transient headache 11%; dyspepsia 9%; mild respiratory symptoms 6%. Cardiac events occurred in 3% with sildenafil and 5% with placebo, but none were severe. Only 4% of the S group discontinued the drug vs. 8% in the P group.

COMMENT BY FRED PLUM, MD

Erectile dysfunction and related sexual impairments are bringing misery to more than half the American males older than age 40. Although many of the difficulties relate to psychiatric origins, neurological impairment with or without associated neuro-arteriolar disease contributes measurably to such patients' despair. Urologists have an important position in treating urinary tract and kidney diseases, but only a few have a strong knowledge of autonomic function/dysfunction and how to identify or approach the nervous system's visceral regulations. Other physicians of various disciplines may make a difference in these men's lives by investigating the patient's sexual function and to evaluating their need for treatment. Rendell et al indicate that sildenafil can bring at least a measure of erectile effectiveness to males with diabetes, but this is pharmacologically just a start. Greater understanding of the pathophysiology of normal and abnormal erectile function along with the development of new treatments can derive from greater attention, ingenuity, and treatment by neurologists. (*Dr. Plum is Professor and Chairman of the Department of Neurology and Neuroscience at the Weill Medical College of Cornell University, New York.*) ❖

Special Feature

More on Omega-3 Fatty Acids and Psychiatric Disorders

By Jerry Cott, PhD

It has been suggested that depletion of omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), impairs membrane function and may be of etiological importance in depression, aggression, schizophrenia, and other mental and neurological disorders.[1-4]

The American diet is low in omega-3 fatty acids, which are long-chain PUFAs found in plant and marine sources. Fish oil is very high in the PUFAs, DHA, and eicosapentaenoic acid (EPA). DHA can also be extracted from golden algae (Schizochytrium sp.). Alpha linolenic acid and other omega-3 fatty acids can be found in the seed oil of flax (Linum), black currant (Ribes), and Cannabis. Neuronal membranes contain high concentrations of DHA as well as arachidonic acid (AA); both of these essential fatty acids are crucial components of the phospholipid bilayer (each comprises approximately 25% of the phospholipid content).[5] Neurotransmitter receptors lie embedded in the matrix of this membrane and their three-dimensional conformation is dependent on the fatty acids which give structure to the membrane.[6]

There is intriguing indirect evidence to support the possibility that lowered blood levels of certain fats may result in behavioral disturbances. Rapid lowering of blood lipids by HMG-CoA reductase inhibitors is associated with a large number of psychiatric disor-

ders; 15% of psychiatric drug reactions were attributed to statins in a national Norwegian database.[7] Reactions included aggression, nervousness, depression, anxiety, and sleeping disorders. Additional data are accumulating that suggest an association between PUFAs and serotonin, a neurotransmitter important in determining mood. Severely depressed patients have lower levels of the serotonin metabolite 5HIAA in CSF. Both cholesterol lowering therapies and low cholesterol levels have been associated with an increased risk of suicide;[8-10] the prevailing theory holds that low cholesterol levels lower serotonin turnover. However, drug and diet therapies to lower cholesterol also alter essential fatty acid levels. Since essential fatty acid levels predict CSF 5-HIAA levels, and cholesterol does not,[11,12] cholesterol levels may be a surrogate marker for changes in essential fatty acids.

Depression

It has been theorized that adequate long-chain PUFAs, particularly DHA, may reduce the development of depression just as they may reduce coronary artery disease.[2] There appears to be an inverse relationship between the prevalence of major depression and the amount of fish consumed per capita worldwide.[13] Patients with major depression have an increased ratio of AA to EPA in their plasma[14,15] and erythrocytes.[14-16] It was recently reported that fatty acid composition of phospholipid in erythrocyte membranes (thought to mirror neuronal membranes) of depressive patients showed significant depletions of total omega-3 PUFA, particularly DHA.[17]

Postpartum Depression

Depletion of maternal omega-3 fatty acids has been noted during pregnancy.[18] The physiology of pregnancy involves the mobilization of PUFAs from maternal stores to the fetus, and supplementation with essential fatty acids may ensure adequate supplies for the needs of the mother and the developing fetus.[19,20] Hornstra et al demonstrated that maternal essential fatty acids, especially DHA, progressively decrease during pregnancy.[21] These decreased levels of DHA in plasma and erythrocytes may remain low for some time postpartum, particularly in lactating women. Thus it is possible that brain levels also are low during late pregnancy and the early postpartum period and that this maternal DHA depletion may contribute to postpartum depression.

Breast Milk and Infant Formula

Breast milk, unlike infant formula, has relatively high concentrations of DHA and EPA.[22] The World Health Organization recommends that DHA and EPA be added to infant formulas. European infant formulas are routinely fortified with these fatty acids, but to date the FDA has not allowed the addition of either DHA or EPA to infant formulas sold in the United States. These omega-3 fatty acids are crucial in the development of the fetal and neonatal brain and nervous system.[19] Intellectual development may also suffer in infants deprived of these fatty acids. A recent study found that infants who received formula supplemented with long-chain PUFAs during their first four months performed better at 10 months of age on a problem-solving test than infants given the unsupplemented formula.[23] *(Dr. Cott is a pharmacologist at the National Institute of Mental Health.)* ❖

References

1. Hibbeln JR, et al. Are disturbances in lipid-protein interactions by phospholipase-A2 a predisposing factor in affective illness? *Biol Psychiatry* 1989;25:945-961.
2. Hibbeln JR, Salem N Jr. Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy. *Am J Clin Nutr* 1995;62:1-9.
3. Hillbrand M, et al. Investigating the role of lipids in mood, aggression, and schizophrenia. *Psychiatr Serv* 1997;48:875-876.
4. Hibbeln JR, et al. Do plasma polyunsaturates predict hostility and depression? *World Rev Nutr Diet* 1997;82: 175-186.
5. Mahadik SP, Evans DR. Essential fatty acids in the treatment of schizophrenia. *Drugs Today* 1997;33:5-17.
6. Mitchell DC, et al. Why is docosahexaenoic acid essential for nervous system function? *Biochem Soc Trans* 1998;26:365-370.
7. Buajordet I, et al. Statins—the pattern of adverse effects with emphasis on mental reactions. Data from a national and an international database. *Tidsskr Nor Laegeforen* 1997;117:3210-3213.
8. Muldoon MF, et al. Lowering cholesterol concentrations and mortality: A quantitative review of primary prevention trials. *BMJ* 1990;301:309-314.
9. Neaton JD, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;152: 1490-1500.
10. Golomb BA. Cholesterol and violence: Is there a connection? *Ann Intern Med* 1998;128:478-487.
11. Hibbeln JR, et al. Essential fatty acids predict metabolites of serotonin and dopamine in CSF among healthy controls, early and late onset alcoholics. *Biol Psychiatry* 1998;44:235-242.
12. Hibbeln JR, et al. A replication study of violent and non-violent subjects: CSF metabolites of serotonin and

dopamine are predicted by plasma essential fatty acids. *Biol Psychiatry* 1998;44:243-249.
13. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998;351:1213.
14. Maes M, et al. Fatty acid composition in major depression: Decreased omega-3 fractions in cholesteryl esters and increased C20:4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 1996;38:35-46.
15. Adams PB, et al. Arachadonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996;31(suppl): S157-S161.
16. Edwards R, et al. Omega-3 polyunsaturated fatty acids in the diet and in the red blood cell membranes of depressed patients. *J Affect Disord* 1998;48:149-155.
17. Peet M, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 1998;43:315-319.
18. Otto SJ, et al. Maternal and neonatal essential fatty acid status in phospholipids: An international comparative study. *Eur J Clin Nutr* 1997;51:232-242.
19. Holman RT, et al. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. *Proc Natl Acad Sci* 1991;88:4835-4839.
20. Al MD, et al. Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. *Br J Nutr* 1995; 74:55-68.
21. Hornstra G, et al. Essential fatty acids in pregnancy and early human development. *Eur J Obstet Gyn Reprod Biol* 1995;61:57-62.
22. Willatts P, et al. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 1998;352:688-691.

Attention CME Subscribers

Due to an American Health Consultants editorial error, a mistake was made in the numbering of CME questions for *Psychiatric Medicine in Primary Care* that affects how you should enter your answers to some of the CME questions. For the current CME testing period, answers to questions No. 36 through No. 39 from the August issue should be entered entered into spaces No. 1 through 4 on the answer sheet. Likewise, answers to questions No. 40 through No. 43 in the September issue should be entered into spaces No. 5 through No. 8 on the answer sheet. Answers to questions No. 43 through No. 45 in the October issue should be entered into spaces No. 9 through No. 11 on the answer sheet. Beginning with the November issue, the numbering of the CME questions correctly corresponds with the numbering on the scantron form.

We regret the error and inconvenience. This explanation will be inserted in the January issue when the CME scantron forms are mailed. If you have questions please call Glen Harris at (404) 262-5461. ❖

CME Questions

16. Which of the following is a predictor for a woman's inability to experience orgasm after hysterectomy?
a. Increasing age
b. Lack of orgasms before hysterectomy
c. Prehysterectomy depression
d. Bilateral oophorectomy
e. All of the above

17. Sildenafil (Viagra) is helpful for the treatment of erectile dysfunction in males with diabetes.
a. True
b. False

18. Which of the following statements is true regarding the use of risperidone for patients with behavioral disturbance associated with dementia?
a. The starting dose is usually 1-2mg BID.
b. It has as much EPS as is seen with haloperidol.
c. It is known to work synergistically with lorazepam.
d. It appears to work even if the patient does not have psychosis.

19. The combination of drugs that inhibit 3A3/4 and HMG-CoA reductase inhibitors may result in the impairment of hepatic clearance with possible rhabdomyolysis, as evidenced by the large increase in CK levels.
a. True
b. False

20. Which of the following is true?
a. St. John's wort, taken in conjunction with digoxin, may result in the reduction of digoxin concentrations.
b. St. John's wort, taken in conjunction with digoxin, may result in reduced efficacy of digoxin.
c. Patients who have achieved therapeutic levels of digoxin while taking St. John's wort may develop digoxin toxicity once they discontinue St. John's wort.
d. All of the above

In Future Issues:

The DHEA Controversy