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St. Johns Wort May Alter Drug Levels

CONFERENCE COVERAGE

Synopsis: *St. Johns wort, the commonly used dietary supplement reported to have mild antidepressant effects, may cause a significant lowering of concomitant medication levels via induction of hepatic cytochrome P450 enzymes.*

Source: Roby CA, et al. St. Johns wort impact on CYP3A4 activity. New Clinical Drug Evaluation Unit Program, 39th Annual Meeting, June 1-4, 1999, Boca Raton, FL.

Dietary supplements are not subject to fda regulation and approval processes. Therefore, knowledge is greatly lacking regarding the drug interaction potential and safety of these compounds. As with other drugs and botanicals, inhibition or induction of cytochrome P450 enzymes is one of the most common causes of drug interactions. The current study was designed to assess the effect of St. Johns wort on hepatic cytochrome P450 3A4 activity in human subjects. Normal volunteers between the ages of 18 and 45 ingested 300 mg 0.3% hypericin-standardized reagent grade St. Johns wort three times daily for 14 days. This dose and preparation is concordant with general clinical use. All subjects were medication-free for at least three weeks prior to the study. Baseline and day 14 CYP3A4 enzyme activity was determined using 24-hour urinary excretion ratios of 6b-hydroxy cortisol/cortisol. Urine specimens were analyzed for 6b-hydroxy cortisol/cortisol and cortisol by HPLC. This is an appropriate in vivo assay because cortisol is metabolized primarily by the 3A34 enzyme. Comparison of baseline and day 14 ratio was performed using paired Student's t-test. After treatment with St. Johns wort, the 6b-hydroxy cortisol/cortisol ratio increased in 12 of 13 subjects who completed the study. Therefore, St. Johns wort appears to be a potent 3A4 inducer resulting in approximate doubling of cytochrome P450 3A4 activity. Concomitant use of St. Johns wort with medications that are eliminated via the CYP3A4 pathway may result in increased clearance of these compounds, which may manifest clinically as treatment failure with standard dosing regimens.

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INSIDE

COMMENT BY LAUREN B. MARANGELL, MD

Induction of hepatic cytochrome P450 enzymes, particularly 3A3/4, is a significant cause of therapeutic failure. This finding is of paramount importance because of the widespread use of St. Johns wort, generally by patients who are self-medicating without the physician's knowledge. The CYP3A3/4 system is responsible for metabolism of substantial numbers of known and unknown medications and endogenous substances. Any medication that is a substrate for this enzyme (i.e., uses this enzyme as a primary metabolic pathway) will be subject to increased metabolism (i.e., decreased blood levels if the patient is taking St. Johns wort). For example, estrogens and, therefore, many oral contraceptives are metabolized by this pathway. A woman who has been taking oral contraceptives with appropriate therapeutic results who then begins taking St. Johns wort may find that the oral contraceptives are no longer effective because the blood level has been decreased via the enzyme induction referred to above. A similar phenomenon occurs with other CYP inducers, such as barbiturates and carbamazepine. Other important 3A3/4 substrates are nifedipine, carbamazepine, cyclosporine, and macrolide antibiotics. Therefore, a patient who has been taking carbamazepine (Tegretol) for seizure control at Subsequent blood level monitoring breakthrough seizures following initiation of St. Johns wort treatment. Subsequent blood level monitoring will reveal a decreased carbamazepine level despite the patient's assurances that they have indeed been taking the medication in the same manner as usual. It is also worth noting that this type of drug interaction is not shared by any of the other antidepressants. Indeed, some antidepressants are known to increase blood levels concomitantly in administered medication. As it is wise to be hesitant with initial reports, the methodology appears reasonable and a second report presented at the same meeting demonstrated a trend toward the same finding. The second report (Taylor vH, and Kobak KA, NCDUE 1999) used a different assay, which was not as sensitive for CYP3A4 induction. As such these data, appear to warrant clinical attention. It is advised that physicians specifically ask patients about the use of over-the-counter supplements and warn patients who are taking 3A3/4 substrates not to initiate treatment with St. Johns wort. Several of the newer antidepressants can be used safely with medications that are 3A3/4 substrates without this type of pharmacokinetic interaction. Specifically, citalopram, sertraline, venlafaxine, and vupropion have been found not to affect the 3A3/4 system. ❖

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Depressed Adolescents Grown Up

ABSTRACT & COMMENTARY

Synopsis: *Adolescents who experience an episode of major depression are at markedly increased risk for subsequent episodes of depression, suicide attempts, and impaired functioning. Early identification and treatment is warranted.*

Source: Weissman MM, et al. Depressed adolescents grown up. *JAMA* 1999;281(18):1707-1713.

It is increasingly apparent that depression is often a recurrent disorder. This prospective, case-controlled study evaluated the subsequent risk of 73 subjects with adolescent-onset major depression (MDD) after 10-15 years of follow-up, compared to 37 control subjects without major depression at the time of initial evaluation. The depressed adolescents were identified at Columbia Presbyterian Hospital from 1977 to 1985. The diagnosis of depression was confirmed on two separate interviews, separated by two weeks. Subjects were not

included in the original sample if they had been taking medication that could produce depressive symptoms, or had significant medical problems or other psychiatric disorders. Healthy controls were recruited concurrently via advertisement. Interviewers who were blind to the initial diagnosis collected follow-up data. Collateral information was obtained from an adult who was knowledgeable about the subjects functioning during the follow-up period; in most cases this was the subject's parent. Copies of medical records were obtained and used to supplement the interview data. Data analysis was appropriate and controlled for covariate and potential confounds. At follow-up there were no significant demographic differences between the two groups. Subjects with adolescent-onset MDD had a significantly increased risk of MDD compared to healthy controls (> 2-fold), but not for other psychiatric disorders. There were no gender differences in the risk of subsequent MDD. At the end of the observation period, only 37% of subjects with adolescent-onset MDD survived without an episode of MDD, compared to 69% of the control subjects in the some period ($P < 0.05$). Seven suicides occurred in the adolescent-onset MDD subjects. In addition, 26.1% of the adolescent-onset MDD subjects and 5.4% of the controls made a first suicide attempt during the follow-up period. In total, 50.6% of the adolescent-onset MDD subjects made a suicide attempt over their lifetime to follow-up and 22% had made multiple attempts. Subjects with adolescent-onset MDD also had higher rates of medical hospitalizations ($P = 0.008$). In summary, adolescent-onset MDD is associated with continuity and specificity of MDD into adulthood with high rates of suicide attempts and psychosocial impairment.

COMMENT BY LAUREN B. MARANGELL, MD

Adolescent MDD was found to have a poor outcome and strong predictive value for subsequent episodes of MDD, but not other psychiatric disorders. These data are particularly striking given the methodological rigor of the study by a well-respected group of investigators. Although most depressed adolescents will not seek psychiatric treatment, there is tremendous opportunity for primary care practitioners to intervene when there is the suspicion of depression. As a reminder, physical symptoms without etiology, increased irritability, and loss of interest in usual activities should raise suspicion of adolescent depression. On a more optimistic note, Weissman and colleagues point out that although the subjects received state-of-the-art treatment for the time, currently effective treatments were not available at the time. Specifically, controlled trials have failed to demonstrate efficacy for the tricyclic antidepressants in adolescent depression. Treatments with demonstrated efficacy in clinical trials that include adolescent depression are the selective serotonin reuptake inhibitors[1] and newer time-limited therapies developed for adolescents. ❖

Reference

1. Emslie GJ, et al. Fluoxetine treatment of depressed children and adolescents. *Arch Gen Psychiatry* 1997; 54:1031-1037.

More New Treatments for Bipolar Disorder

ABSTRACT & COMMENTARY

Synopsis: *Olanzapine (Zyprexa), although currently marketed as an antipsychotic medication, may have a much broader spectrum of efficacy. The current controlled study demonstrates the efficacy of olanzapine in the treatment of acute mania with and without psychotic symptoms.*

Source: Tohen M, et al. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry* 1999;156: 702-709.

The prevalence of bipolar disorder (manic depression) in primary care practice is 0.42%, and the lifetime prevalence in the general population of the United States ranges from 1.0-1.6%. Bipolar disorder is also associated with significant mortality risk, with approximately 25% of patients attempting suicide at some time during their lives and 11% of patients dying by suicide. All patients who present with depression should be asked if they have a history of manic episodes (i.e., bipolar disorder). Of depressed patients without a history of mania, approximately 12.5% have subsequent manic or hypomanic episodes when followed for 2-11 years.[1] Many primary care physicians encounter bipolar patients in their practice and are unsure how to manage them. For acute mania, these patients require a mood stabilizer (e.g., lithium, valproate, carbamazepine), short-term use of a benzodiazepine for agitation and insomnia, and short-term use of an antipsychotic medication for psychosis. For bipolar depression, patients need a mood stabilizer and use of an antidepressant for 3-6 months. Once in remission, patients need a mood stabilizer long-term for prophylaxis.

In the current study, Tohen and colleagues compare the efficacy of olanzapine, an atypical antipsychotic, vs.

placebo for acute bipolar mania. The introduction emphasizes that new medications are needed for bipolar mania for several reasons: 1) a substantial proportion of patients fail to respond to conventional mood stabilizers; 2) conventional mood stabilizers have common side effects that affect adherence; 3) conventional mood stabilizers have rare but potentially serious side effects that require monitoring (e.g., renal toxicity with lithium); and 4) typical antipsychotics (e.g., haloperidol [Haldol]) are also efficacious for bipolar mania, but have potentially serious side effects (e.g., tardive dyskinesia). The premise for trying olanzapine is the success of atypical antipsychotic medications (e.g., clozapine, olanzapine, risperidone) in open trials for the treatment of mania. Patients between the ages of 18 and 65 years were enrolled after being diagnosed with bipolar mania via a structured psychiatric interview; those with medical or substance etiologies for mania were excluded. After a 2 to 4 day medication washout period, patients were randomized to olanzapine 10 mg per day or placebo with dose adjustment as necessary; prn medication included a benzodiazepine for agitation or insomnia and benztropine for extrapyramidal side effects. Mania, quality of life, and side effects were assessed in an ongoing manner. A 50% decrease in manic symptoms was the a priori criterion for a positive response to medication. The sample size was 139 patients. Statistical analyses were done on an intent-to-treat basis; that is, data on all randomly assigned patients were included in the analysis (not just those who finished the study). At three weeks, olanzapine was superior to placebo in reducing mania, with 48.6% and 24.2% of patients meeting criteria for a positive response; olanzapine was equally effective in nonpsychotic and psychotic mania. The average olanzapine dose was about 15 mg/d. The olanzapine-treated patients also had improved physical functioning compared to the placebo-treated patients. More somnolence, dry mouth, dizziness, and weight gain occurred in the olanzapine group than the placebo group. No clinically significant extrapyramidal side effects or laboratory changes were noted. The dropout rates were 65.2% for placebo and 38.6% for olanzapine.

COMMENT BY DONALD M. HILTY, MD

This study suggests that atypical antipsychotic medications may be effective as mood stabilizers for the treatment of bipolar mania. An identical study is in progress to attempt to replicate the findings. In addition, studies comparing risperidone (another atypical antipsychotic medication) to placebo are in progress. While olanzapine is effective for the treatment of mania, nothing is known about how it directly compares to conventional mood stabilizers, its ability to prophylaxe against mania, or what factors predict a positive response to olanzapine relative to other mood stabilizers.

It is not yet clear how these findings will affect selection of medication by primary care physicians and psychiatrists. Lithium is perhaps the mood stabilizer most familiar to primary care physicians. Valproate is currently the most commonly prescribed mood stabilizer, surpassing lithium in recent years after gaining FDA approval for bipolar disorder in 1995. Finally, new anticonvulsants (e.g., lamotrigine and gabapentin) are being studied for the treatment of bipolar disorder and another recent study abstracted in this issue suggests a possible role for omega-3 fatty acids. A recent review article discusses the epidemiology, assessment, and management of bipolar disorder by psychiatrists in mental health settings,[2] and it is currently being adapted to a review article for primary care practice. ❖

References

1. Akiskal HS, et al. Switching from "unipolar" to bipolar II. *Arch Gen Psychiatry* 1995;52:114-123.
2. Hilty DM, et al. Bipolar disorder in adults: A review of recent literature. *Psychiatric Services* 1999;50:201-213.

L-Tryptophan for Premenstrual Depression

ABSTRACT & COMMENTARY

Synopsis: *This study compares the efficacy of L-tryptophan vs. placebo in the treatment of premenstrual dysphoric disorder (PMDD). L-tryptophan was significantly superior to placebo in relieving mood and physical symptoms associated with PMDD.*

Source: Steinberg S, et al. A placebo-controlled clinical trial of L-tryptophan in premenstrual dysphoria. *Biol Psychiatry* 1999;45:313-320.

In this study, the dietary supplement l-tryptophan was compared to placebo in the treatment of premenstrual dysphoric disorder (PMDD). Eighty women were recruited by referral from the obstetrics and gynecology department or by self-referral from a newspaper advertisement. Following a two-month evaluation period, eligible patients received randomized treatment for three months. The active treatment consisted of 2 mg of L-tryptophan three times a day for 17 days, from the time of ovulation to the third day of menstruation. A self-rating visual analog scale (VAS) was used to assess

irritability, tension, dysphoria, mood swings, headache, bloating/edema, and breast tenderness. Other self-rating scales were used to assess effect, life events, and adjustment. A psychiatrist completed an observer rating scale. The maximum luteal phase VAS-mood score over the three treatment cycles was used as the principal outcome measure. This was felt to capture the most extreme disturbance of mood over the three cycles.

Of the original 80 women recruited, 63 completed the study, 32 in the L-tryptophan group and 31 in the placebo group. Analysis of the data showed a significant difference (P = 0.004) for the patient-rated VAS-mood scores for symptoms of dysphoria, mood, tension, and irritability for the group treated with L-tryptophan compared to placebo. The mean reduction from baseline in the VAS-mood score was 34.5% for L-tryptophan compared to 10.4% for placebo. The significant reduction in the mood scores occurred in the first month with no further improvement in successive treatment months. L-tryptophan did not show significant benefit for the symptoms of headache, edema, or breast sensitivity. However, no significant difference was found between the two treatment groups when assessed by a clinician.

No symptoms of eosinophilia myalgia syndrome were noted in the current study. Previous use of a presumably contaminated batch of L-tryptophan has been associated with the eosinophilia myalgia syndrome.

COMMENT BY LUCY J. PURYEAR, MD

Premenstrual dysphoric disorder (PMDD) affects between 3-5% of women during their reproductive years. Symptoms include irritability, dysphoria, and sleep disturbance along with physical symptoms including breast tenderness, headache, and bloating. Symptoms begin in the late luteal phase of the menstrual cycle and remit with the onset of menses. Symptoms are severe enough that they interfere with daily functioning and cause difficulty in relationships and social and occupational functioning. During the rest of the menstrual cycle, there are no mood or physical symptoms and functioning returns to normal baseline.

Treatment for PMDD has included exercise, diet, and nutritional supplementation, gonadotropin-releasing hormone agonists, and antidepressants. Studies have demonstrated a greater efficacy with the serotonergic antidepressants, including fluoxetine, sertraline, paroxetine, citalopram, and clomipramine, compared to noradrenergic agents. This study is useful in that it uses a serotonin precursor, L-tryptophan, providing additional evidence for the importance of serotonin in the treatment of PMDD.

When evaluating women for PMDD it is important to rule out other psychiatric disorders, such as unipolar depression, bipolar depression, dysthymia, and anxiety disorders, all of which can worsen premenstrually. First line treatment for PMDD continues to be the serotonergic antidepressants. GNRH agonists have difficult side effects and can not be taken long term due to their causing a hypoestrogenergic state.[1] Other non-pharmacologic treatments such as calcium, caffeine reduction, diet, and exercise show efficacy in some women and may be useful as adjunctive agents or for women with mild to moderate symptoms. This study supports the serotonergic hypothesis for PMDD and L-tryptophan may be a useful treatment for some women with mild to moderate symptoms. ❖

Reference

1. Halbreich U. Gonadal hormones and antihormones, serotonin and mood. *Psychopharmacol Bull* 1990; 26(3):291-295.

Omega-3 Fatty Acids May Help Mood

ABSTRACT & COMMENTARY

Synopsis: *This double-blind, placebo-controlled study found that the addition of high-dose omega-3 fatty acids in the form of fish oil improved the clinical course of patients with unstable bipolar disorder.*

Source: Stoll A, et al. Omega-3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-412.

The need for additional therapeutic modalities for the treatment of bipolar disorder (manic-depression) is particularly compelling because current treatments, such as lithium and valproate, are not effective in all patients, have a relatively high side effect burden, and are teratogenic. Omega-3 fatty acids are naturally occurring lipids most commonly found in cold water fish. Omega-3 fatty acids appear to attenuate intracellular signal-transduction pathways in a manner similar to lithium and valproate, which were discovered serendipitously. Based on this mechanistic commonality, Stoll and colleagues designed a controlled pilot study to assess the efficacy of omega-3 fatty acids as a potential treatment. This was a four-month parallel-group, placebo-controlled, double-blind study in which outpatients with bipolar disorder were randomized to receive either omega-3 fatty acids or placebo, in addition to their ongo-

ing usual treatment. Omega-3 fatty acids ethyl esters were administered in gelatin capsules that contained 440 mg of eicosapentaenoic (EPA) acid and 240 mg of docosahexanoic acid (DHA), or olive oil ethyl esters (the placebo). Each subject received 14 capsules per day, for a total daily dose of 9.6 grams of omega-3 fatty acids in the active group. The product was obtained from the Fish Oil Test Materials Program, which was a joint program of the National Institutes of Health and the National Marine Fisheries Service. Subjects with evaluable data, based on a priori criteria, consisted of 30 patients with the diagnosis of bipolar disorder (type I or type II) who had experienced a manic or hypomanic episode in the past year. The fact that all subjects had a fairly recent episode of mania or hypomania enriches the cohort because this subgroup is at a higher risk for relapse. The randomization produced a comparable distribution of men and women, concomitant medications, and baseline mood states in the omega-3 and placebo groups. A Kaplan-Meier survival analysis, where survival is defined as remaining well enough to stay in the study (i.e., not requiring a medication change to treat mania or depression), was used as the primary outcome measure. As per this analysis, the omega-3 group had a significantly longer period of remission than the placebo group ($P = 0.002$). In addition, for every other outcome measure, the omega-3 group performed better than the placebo group. In a subgroup of eight patients who were receiving no other concomitant medications, the omega-3 group also demonstrated a significantly better outcome than the control group. The omega-3 fatty acids were well tolerated. Mild gastrointestinal upset and a "fishy taste" were the most common side effects.

COMMENT BY LAUREN B. MARANGELL, MD

Although the current study suffers from several limitations, these data, if replicated, are of clinical and theoretical import. One important point is that these substances are substantially less toxic than other available treatments and are not teratogenic. However, the current data are too preliminary to warrant widespread use, or monotherapy treatment, except perhaps in patients with very mild illness, or extenuating circumstances. The fact that omega-3 fatty acids are natural substances is appealing to many patients, which may increase acceptance of treatment. As with other natural substances, physicians must educate patients to avoid self-medication. At this time, it is not clear what the appropriate dose or preparation is for optimal treatment. Commercial fish oil preparations are a combination of EPA and DHA and vegetable-derived sources of DHA are available. Although the current study was not designed to assess acute antidepressant effects, the data suggest a trend toward improved depression ratings warranting further evaluation of these compounds for the treatment of depression. ❖

Nefazodone for Panic

CONFERENCE COVERAGE

Synopsis: *This double-blind, placebo-controlled trial found that nefazodone (Serzone) was effective and well tolerated for the treatment of panic disorder.*

Source: Cassano G, et al. A multicenter, double-blind comparison of nefazodone and placebo in the treatment of panic disorder. New Clinical Drug Evaluation Unit Program, 39th Annual Meeting, June 1-4, 1999, Boca Raton, FL.

Nefazodone (serzone) is a combined serotonin norepinephrine reuptake inhibitor, with post-synaptic 5HT2 antagonism. Nefazodone is currently indicated in the United States for treatment of depression. As with selective serotonin reuptake inhibitors (SSRIs), nefazodone may have a spectrum of efficacy that extends beyond the treatment of depression. This 12-week, double-blind, flexible dose study of outpatients with DSM-IV diagnosed panic disorder was conducted at 23 European centers. Patients who had at least two panic attacks during the two-week placebo run were randomized to either nefazodone or placebo. Nefazodone was initiated at 50 mg bid followed by a flexible-dose titration, with an allowable dose range of 100-600 mg per day. A total of 274 patients were randomized. The primary efficacy rating was based on the number of full panic attacks within two weeks as determined at the 10 week end point. At end point, nefazodone treated patients exhibited significantly ($P < 0.05$) greater improvement than the control group. Similar results were evident on other outcome measures, such as mean reduction in the number of panic attacks from baseline, and the number of patients with a 50% reduction in panic attacks from baseline. At end point, the mean nefazodone dose was 453 mg per day. Nefazodone was well tolerated, with only 4% discontinuation for adverse events compared to 7% of the placebo patients. Common adverse events in the nefazodone-treated patients were dizziness and somnolence, which is consistent with the use of this drug in the treatment of depression.

COMMENT BY LAUREN B. MARANGELL, MD

As with most placebo-controlled trials for a new indication, this study was supported by Bristol-Myers

Squibb, manufacturer of nefazodone. The overall design was appropriate and the study used an adequate sample size. Other medications that are effective for the treatment of panic disorder are the tricyclic antidepressants, particularly imipramine, SSRIs, monoamine oxidase inhibitors, and benzodiazepines. The tricyclic antidepressants were previously first-line agents but due to an increased side-effect burden and lethality in overdose, these agents are now second-line to the SSRIs. The SSRIs are effective in many patients but are sometimes not tolerated due to either acute or longer-term side effects (i.e., sexual dysfunction). Monoamine oxidase inhibitors are traditionally the therapy of last resort, given the risk of potentially lethal drug and food interactions. Benzodiazepines are often appropriate for acute use, and are sometimes recommended while the patient is being stabilized on an antidepressant for longer-term control of panic symptoms. Benzodiazepines are less desirable for long-term use. Benzodiazepines should be avoided in patients with substance abuse problems. Given the possible limitations of currently available treatments in at least some patients, the current data, particularly if replicated, will offer an additional therapeutic alternative for patients with panic disorder. ❖

Folate and Memory in the Elderly

ABSTRACT & COMMENTARY

Synopsis: *Folic acid, but not necessarily B_{12}, may be important for maximal episodic memory functioning in very old age.*

Source: Hassing L, et al. Further evidence on the effects of vitamin B_{12} and folate levels on episodic memory function: A population-based study of healthy, very old adults. *Biol Psychiatry* 1999;45:1472-1480.

The relationship between vitamins and memory has been frequently studied, but often with inconclusive or contradictory results. The current study examined the separate and combined effects of serum vitamin B_{12} and folic acid on episodic memory functioning in very old age. Episodic memory deals with the conscious recall of information about a particular place and time. Episodic memory appears to be much more sensitive to disruption from a variety of causes. Normal aging is associated with decline in both episodic memory and vitamin status. Because B_{12} and folic acid are vitamins thought to be important to normal brain functioning, the current study attempted to assess the relationship between these two vitamins, both independently and together, in a cohort of healthy, older adults (90-101 years of age). Four study groups were selected—normal B_{12}/normal folic acid, low B_{12}/normal folic acid, normal B_{12}/low folic acid, and low B_{12}/low folic acid. Cutoff levels were 180 pmol/L for vitamin B_{12} and 13 nmol/L for folic acid. Potential participants included 379 subjects in Stockholm, Sweden. Patients with dementia, major depression, or other impairments that would confound study evaluation (e.g., language difficulties) were appropriately excluded. A health screening was undertaken in order to exclude patients who suffered from other illnesses that might confound the ability to evaluate the relationship between vitamin status and cognitive functioning (e.g., thyroid dysfunction). All blood analyses were performed by the same laboratory. There were no differences with regard to age or education between the four study groups. Memory tasks included face recognition, immediate word recall, object recall, delayed word recall, and word recognition. In general, the results showed no effects of vitamin B_{12} level in any of the memory tasks or interaction between vitamin B_{12} and folic acid. However, folic acid level exhibited a clear relationship to some of the memory tasks. Specifically, low levels of folic acid were associated with decreased performance in object recall and word recall. In contrast, there were no vitamin-related effects on any of the recognition tasks. The present study replicates previous findings that folic acid may be more critical than vitamin B_{12} to memory functioning in late life and extends those findings into very old age.

COMMENT BY LAUREN B. MARANGELL, MD

This study, which used a methodology of comparison groups, as opposed to a correlational analysis, showed a possible relationship between serum folic acid levels and recall in the extremely old. The fact that this type of analysis was more likely to detect an association may indicate that there is a critical level above which the relationship is less apparent. Memory difficulties are frequent complaints in primary care practice. The most common reversible cause of memory impairment is major depression. Other important conditions include thyroid disease, substance abuse, and medications. The roles of B_{12} and folate have been implicated for quite some time. Although the current study does not address the therapeutic role of folate supplementation, these data support evaluating serum folate levels in elderly patients with memory complaints. As long as other potentially reversible causes of memory decline are evaluated, folate supplementation may be of benefit. ❖

Bupropion for Adult Attention Deficit Disorder

CONFERENCE COVERAGE

Synopsis: *Bupropion is superior to placebo in attenuating ADHD symptoms in adults.*

Source: Wilens TE, et al. New Clinical Drug Evaluation Unit Program, 39th Annual Meeting, June 1-4, 1999, Boca Raton, FL.

Attention deficit hyperactivity disorder (ADHD) commonly persists into adulthood. Given the understandable reticence to use lifelong stimulant medication, and the dilemma of giving stimulants to patients with comorbid substance abuse, alternate medications are needed. The current study is a double-blind, placebo-controlled, randomized, six-week trial comparing bupropion SR (Wellbutrin SR) (up to 200 mg bid) to placebo in adults with DSM-IV diagnosed ADHD. Subjects consisted of 38 adults who completed the six-week trial. Subjects were excluded if they had diagnoses of an eating disorder, seizure disorder, bipolar disorder, or substance abuse. Bupropion SR was initiated at 100 mg per day and titrated in weekly intervals to a target dose of 400 mg per day. Subjects' mean age was 38.3 ± 11 years. Using a predetermined cutoff of 30% or more reduction in ADHD symptoms to denote response, 75% improved on bupropion SR, compared to 37% on placebo ($P = 0.012$). Similarly, using the Clinical Global Impression (GCI) scores of much to very much improved, 62% met response criteria on bupropion SR, compared to 11% on placebo ($P = 0.005$). The bulk of improvement in ADHD symptoms occurred after week four. There was no significant effect on anxiety or depression. Average daily dose at week six was 362 mg of bupropion SR. The most common adverse effect reported in those receiving bupropion SR was insomnia (38%). However, this did not result in withdrawal from the study. The delay in full therapeutic effect may represent a combination of time to titration and possibly a delayed onset of action.

COMMENT BY LAUREN B. MARANGELL, MD

Bupropion (Wellbutrin) is currently marketed in the United States for the treatment of depression, and under the trade name Zyban for smoking cessation. As opposed to most other antidepressants, bupropion inhibits the reuptake of norepinephrine, and to a lesser degree, dopamine. Therefore, there is a similarity in neurotransmitter targets between bupropion and the more commonly used psychostimulants. Although the current study has methodological limitations, including a small sample size, the fact that this was a randomized placebo-controlled trial is noteworthy. Bupropion may be a first-choice medication for patients who have both depression and ADHD, when the physician wants to avoid the use of a controlled substance. As in the treatment of depression, bupropion should be avoided in patients who are at increased risk of seizures or have an active eating disorder. Patients who fail to respond to bupropion may have an improved response with subsequent treatment with psychostimulants. (*This study was supported by Glaxo-Wellcome, the manufacturer of bupropion.*) ❖

CME Questions

13. Natural substances that may be helpful in treating bipolar disorder are:
a. St. Johns wort.
b. valerian root.
c. omega-fatty acids.
d. saw palmetto.

14. Tryptophan is a precursor of:
a. serotonin.
b. norepinephrine.
c. dopamine.
d. acetylcholine.

15. Newer treatments that may be effective for bipolar disorder include all of the following *except*:
a. olanzapine.
b. omega-3 fatty acids.
c. lamotrigine.
d. alprazolam.

16. Adolescents with major depression are at higher risk for:
a. subsequent major depression.
b. suicide attempts.
c. increased medical hospitalizations.
d. All of the above

17. St. Johns wort may:
a. increase levels of other drugs.
b. decrease levels of other drugs.
c. does not affect drug levels.
d. has fewer drug interactions than other antidepressants.

In Future Issues:

Cardiovascular Disease and Depression