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Mirtazapine for Concurrent Depression and Anxiety

ABSTRACT & COMMENTARY

***Synopsis**: This small open study suggests that the antidepressant mirtazapine (Remeron) may be effect in patients with both depression and generalized anxiety disorder.*

Source: Goodnick PJ, Puig A, DeVane CL, et al: Mirtazapine in major depression with comorbid general anxiety disorder. *J Clin Psychiatry* 1999;60:446-448.

A HIGH PROPORTION OF PATIENTS WITH DEPRESSION HAVE COMORBID anxiety disorder, which is associated with increased severity, poorer outcome, and increased risk of suicide . Selective serotonin reuptake inhibitors (SSRIs), nefazodone (Serzone), venlafaxine (Effexor XR), and tricyclic antidepressants (e.g., imipramine) have been shown efficacious for these comorbid disorders. Mirtazapine (Remeron) is a relatively new antidepressant that enhances both noradrenergic and serotonergic transmission while simultaneously antagonizing postsynaptic 5-HT2 and 5-HT3 receptors. Post synaptic 5HT2 antagonism may limit activation and contribute to its anxiolytic and sleep-enhancing properties. Post synaptic 5HT3 antagonism is a pharmacologic target for treating nausea. For example, odansetron (Zofran) is a post synaptic 5HT3 antagonist.

In the current study, 10 patients with major depression comorbid with general anxiety disorder, and without any other Axis I diagnosis, received mirtazapine 15mg QHS for one week, 30mg QHS for three weeks, and then 45mg QHS for four weeks. Assessments were carried out at baseline, 1, 2, 4, and 8 weeks of therapy, including the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

There was significant improvement in scores on all rating scales used with improvement noted after the first week of therapy and continuing to improve over the eight-week period. A 50% reduction

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in the HAM-A score from baseline occurred for three patients after one week, five patients after four weeks, and all 10 patients at eight weeks. The most common adverse events were sedation in four patients (mostly occurring early) and blurred vision in two patients. Side effects common to SSRIs (e.g., sexual dysfunction, insomnia, gastrointestinal distress, diarrhea, and agitation) were not noted with mirtazapine.

COMMENTARY BY DONALD M. HILTY, MD

It appears that mirtazapine (Remeron) is a viable option for depression with anxiety, although the current findings must be replicated with a suitable double-blind placebo-controlled design and with a larger number of subjects. SSRIs and nefazodone are the treatment of choice for these patients in the primary care setting, though with further trials this may well be reconsidered. Mirtazepine may have a valuable place in the treatment of these patients because, like nefazodone, it avoids many typical side effects of SSRIs because it antagonizes post synaptic 5HT-2. Its most significant side effects appears to be sedation and weight gain, both of which can be of marked severity in some patients early in treatment. Interestingly, in open trials the sedation appears less at 30mg QHS than 15mg QHS; many psychiatrists start at the higher dose accordingly. ❖

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Depression and Platlet Reactivity

ABSTRACT & COMMENTARY

***Synopsis**: This study provides direct evidence for enhanced in vivo platelet reactivity and platelet product release (e.g., PF-4 and B-TG) in depressed patients with ischemic heart disease.*

Source: Laghrissi-Thode F, Wagner WR, Pollock BG, et al: Elevated platelet factor 4 and B-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry* 1997;42:290-295.

As reviewed in the last issue of, clinical depression has recently been recognized as an independent risk factor for cardiac mortality in patients six, 12, and 18 months after myocardial infarction (MI).[1-2] This remains true even after controlling for other post-MI risk factors, such as left ventricular dysfunction, complex arrhythmias, and history of prior MI [3].

The underlying mechanism(s) of this increased mortality in depressed patients post-MI have not fully elucidated. This study investigated the hypothesis that patients suffering from ischemic heart disease (IHD) and depression concurrently may have abnormal platelet activation resulting in an increased risk of thrombosis. Platelets activated at the interface with a vessel wall injury accelerate the local formation of thrombin and release a variety of endogenous products from their storage granules, including platelet factor 4 (PF-4), B-thromboglobulin (B-TG), and serotonin. PF-4, a protein synthesized by megakaryocytes, was originally recognized by its ability to neutralize the anticoagulant activity of heparin.

Interestingly, platelets have been proposed as a model for central nervous system presynaptic nerve terminals, including serotonin terminals. Serotonin is a weak agonist of platelet aggregation compared to thrombin, but markedly amplifies platelet reactions to other agonists (adenosine 5'-diphosphate, thromboxane A2, catecholamines, or thrombin).

In the current study, Laghrissi-Thode F et al evaluated three groups: healthy controls (n = 17), non-depressed patients with IHD (n = 8), and depressed patients with

IHD (n = 21). Criteria for ischemic heart disease was defined by any of the following in the three months prior to the study: 1) MI; 2) coronary artery bypass graft; 3) angioplasty; or 4) angiographic evidence of luminal narrowing of a major coronary artery or one of its primary branches. Severity of IHD was assessed by the results of coronary angiography; cardiac function was assessed by the left ventricular ejection fraction. The Structured Clinical Interview for DSM-III-R was used to diagnose depression and exclude other diagnoses, and the Hamilton Depression Rating Scale was used to rate the severity of depression. PF-4 and B-TG were markedly elevated in the patients with both depression and IHD compared to the other groups. No association was found between measures of platelet activation and angiographic results, left ventricular ejection fraction, age, sex, or race.

★ **COMMENTARY BY DONALD M. HILTY, MD**

Further research is needed to investigate if alterations of the serotonin (5-HT) system in depressed patients with IHD contribute to PF-4 and B-TG elevations and if this phenomenon is reversed by successful treatment of depression. Unpublished data from the same author indicates that a selective serotonin reuptake inhibitor - paroxetine (Paxil) - lowered similarly elevated levels of PF-4 and B-TG from four to eight times to approximately two times the level of controls and patients with IHD; interestingly, a tricyclic antidepressant - nortriptyline (Pamelor) - did not lower the levels at all.

Depressed patients without ischemic heart disease also appear to have abnormal platelet reactivity.[4] Depressed patients (n = 12), compared to healthy controls (n = 8), exhibited increased platelet activation at baseline and following orthostatic challenge, using monoclonal antibodies sensitive to detecting phase-specific stages of platelet activation.

Unquestionably, the evidence to date necessitates the screening for depression in patients with cardiovascular disease and implementing treatment if there is evidence of depression. To date, no single antidepressant or class of antidepressants has documented superiority in terms of efficacy in patients with cardiac disease.

Editor's note: A review of relevant side effects and drug interactions specifically relating to the use of antidepressants in patients with cardiac disease appeared in the June 1998 Psychiatric Medicine in Primary Care, pp. 36-37. ❖

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Special Feature

Medical Complications of Atypical Antipsychotics

By Michael F. Barber, Pharm.D.

THERE HAVE BEEN SIGNIFICANT ADVANCES IN THE PAST decade in the treatment of psychotic disorders, especially schizophrenia. Specifically, atypical antipsychotics, which block the serotonin-2 (5-HT2) receptor more potently than the dopamine-2 (D2) receptor, are effective treatments for psychoses while producing fewer extrapyramidal side effects (e.g. tremor, rigidity). These drugs include risperidone (Risperdal), olanzapine (Zyprexa) and quetiapine (Seroquel). Additionally, atypical antipsychotics have rapidly gained popularity as treatments for other psychiatric conditions, including bipolar disorder, complicated or resistant depression, mood lability of various etiologies, and agitation. As a result, primary care physicians are likely to treat patients who are receiving atypical antipsychotics, despite the low number of patients with schizophrenia seen in a general medical setting.

Most adverse effects of the atypical antipsychotics have been well documented and are predictable, based on the pharmacology of these agents. Examples of such effects include orthostatic hypotenion and nasal congestion resulting from alpha adrenergic antagonism, dry mouth, blurred vision, and constipation from cholinergic blockade, and sedation from histamine blockade. Recently there have been increasing numbers of reports of secondary medically important adverse effects of atypical antipsychotics. These include hyperprolactinemia and impaired glucose tolerance.

While it is well documented that all conventional antipsychotics (e.g. haloperidol) elevate serum prolactin levels, most atypical antipsychotics have minimal effects on prolactin. Clozapine, olanzapine, and quetiapine have

all been shown to cause transient, modest increases in prolactin, generally within the normal range, which are probably clinically insignificant.[1] Risperidone, however, is much less "atypical" in this regard, causing clinically significant increases in serum prolactin levels, roughly similar in magnitude to the conventional antipsychotics.[2] This characteristic of risperidone is consistent with its propensity to cause extrapyramidal side effects in dose dependent fashion. Put simply, risperidone effectively loses its "atypical" profile at doses above 6 mg/day. Galactorhea may also occur with even low doses of risperidone, although the incidence is not known. The increase in prolactin induced by risperidone and the conventional antipsychotics may result in several clinically important medical complications such as menstrual disturbances, infertility, sexual dysfunction, gynecomastia, and galactorrhea. Most of these adverse effects are personal in nature and may be embarrassing for patients to discuss with their physicians. In fact, a study of schizophrenic patients by Windgassen et al.[3] reported that most patients failed to report such side effects whereas close clinical observations and direct questioning revealed an incidence of galactorrhea in nearly half of the female cohort.

While there are no long-term data available on the sequelae of antipsychotic-induced hyperprolactinemia, there may be an increased risk for certain medical complications. Since elevated prolactin levels result in impaired secretion of leutinizing hormone and follicle stimulating hormone, antipsychotic-induced hyperprolactinemia may result in estrogen deficiency in female patients. Presumably, this could further lead to increased risks for cardiovascular disease as well as decreased bone mineral density and osteoporosis. Further, there is some evidence for a link between chronic hyperprolactinemia and breast cancer.[4]

If a patient develops prolactin-related adverse effects secondary to risperidone or other antipsychotics, the risks of continuing therapy must be weighed against the benefits of maintenance antipsychotic treatment. Since the atypical antipsychotics (other than risperidone) are less likely to cause prolactin-related adverse effects, perhaps the patient could be switched. Switching agents is often best accomplished with the use of a cross-taper and, in general, a psychiatrist should be involved when it is necessary to switch antipsychotic medications.

In addition to their effects on prolactin, antipsychotics may also alter glucose metabolism.[5] Again, while this effect has been known to occur with the older 'conventional' antipsychotics, the atypicals agents clozapine and olanzapine have been associated with impaired glucose tolerance in published reports.[6-8] Further, there are two documented cases of diabetic ketoacidosis associated with clozapine use in patients who were also receiving lithium.[9,10] Many of these instances occurred in patients with a pre-existing diagnosis of diabetes mellitus; however, impaired glucose tolerance often occurred in patients without such diagnosis. In most cases, patients were found to have risk factors for the development of type 2 diabetes. Thus, it is possible that the use of antipsychotics may be the precipitating factor in exacerbating diabetes in predisposed patients.

The cause of impaired glucose metabolism induced by antipsychotics is unknown. Since atypical antipsychotics are known to cause weight gain [11], it is possible that this could lead to insulin resistance in predisposed patients. Yazici et al.[12] have reported that clozapine increases mean levels of blood glucose, insulin, and C-peptide, suggesting that antipsychotic use may lead to insulin resistance. In addition to the weight gain caused by the antihistaminic and antiserotonergic properties, Wirshing et al suggest that antipsychotics may decrease pancreatic beta-cell responsiveness via serotonin-1A antagonism; however, this has not been investigated. It is well documented that chronically poor glucose control leads to significant medical morbidity. Additionally, it is important to note that abnormal glucose metabolism may increase the risk for the development of tardive dyskinesia.[13,14]

The management of impaired glucose control secondary to antipsychotics is not clearly established. It would seem appropriate to treat patients with education, dietary restrictions, and oral hypoglycemics. Alternatively, psychiatric consultation may be warranted to determine whether the offending antipsychotic should be discontinued or switched.

In summary, there are many medically important side effects of atypical antipsychotics that have largely gone unnoticed until recently. The primary care physician should be aware of the potential of these agents to cause such complications as hyperprolactinemia and impaired glucose. This should lead to better monitoring and more appropriate treatment of these conditions. Psychiatric consultation may be quite helpful where indicated, since the best treatment may be the discontinuation of the antipsychotic agent. ❖

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Special Feature

SAMe: Cautious Optimism

By Andrew L. Stoll, MD

Sadenosylmenthionine, or SAMe, has received recent publicity as an effective and "natural" antidepressant with few, if any, side effects. SAMe is an endogenous compound that functions as a methyl donor in many cellular process. [1] It is not an essential dietary supplement, since humans can synthesize SAMe from readily available precursors. [2] Reports on the antidepressant activity of SAMe date back more than 30 years. A recent media account [3] report that more than 12 controlled trials of SAMe in depression have been conducted. However, a Medline search revealed only three small double-blind controlled trials. [4,5,6] The same media article reported that more than 40 "clinical studies" of approximately 1,400 patients have been published. Again, a Medline search revealed at most 10 open-label trials of SAMe in depression. Notwithstanding these discrepancies, a critical review of the literature indicates that SAMe is likely an effective antidepressant.

However, these enthusiastic reports have wholly ignored several real dangers associated with the use of SAMe. The most serious hazard associated with SAMe is the extremely high rate of induction of mania in bipolar patients. This is highly significant in primary care practice, where antidepressant agents are widely prescribed. While only approximately one in 10 depressed persons in the community at-large have bipolar disorder, the rate of bipolar disorder may be as high as one in four depressed patients who seek treatment. Thus, without careful screening for a history of bipolar symptoms, many cases of mania associated with the use of SAMe can be expected. While all antidepressants can induce mania in susceptible patients, SAMe appears to induce mania more rapidly and at a much higher frequency than conventional prescription antidepressants. For example, less than 25% of bipolar patients receiving SSRIs over one year can be expected to "switch" into mania. For SAMe, the rate of mania induction is at least 50% within two-three weeks.

Another concern associated with SAMe has been the instability of the molecule and problems with tablet dissolution in some commercial preparations used in some of the early controlled trials of SAMe in depression5. Due to the unregulated nature of the dietary supplement industry, concern over the integrity, stability, and bioavailability of SAMe preparations appropriately persist. Finally, SAMe has never undergone the rigorous safety testing required for prescription medications, and although the existing data suggests that SAMe appears safe in short-term trials, no long-term data exists.

The usage of SAMe is fairly straightforward. SAMe is indicated as monotherapy in mild unipolar major depression, should the clinician and patient choose this agent over conventional prescription antidepressants or other natural mood-elevating substances, such as St John's wort or omega-3 fatty acids. In moderate or

severe depression or where suicidal ideation or safety is an issue, SAMe could be used as an adjunct to more standard prescription antidepressant therapies. SAMe is generally contraindicated in patients with bipolar disorder, or in seemingly unipolar depressed patients under age 25,where the rate of occult bipolar disorder is quite high.

There are at least seven retail distributors of SAMe products made by only several manufacturers. Currently available preparations usually contain 200 mg SAMe per capsule or tablet. The proper dosage of SAMe for major depression is not clear, but ranges from 400 to 1600 mg per day, given in a BID schedule. SAMe is very expensive, and insurers generally will not pay for this dietary supplement. The cost of SAMe generally ranges from $2 to $5 per day at 400 mg/day all the way up to $8 to $20 per day at 1600 mg/day. Thus, the price of SAMe could be prohibitive for many patients.

In summary, SAMe may be a safe and effective antidepressant agent or adjunct in selected patients with unipolar depression. However, SAMe should be avoided in patients with bipolar disorder or a suspected bipolar diathesis. ❖

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Estrogen Supplementation in Perimenopausal Women

ABSTRACT & COMMENTARY

Synopsis: *Estrogen supplementation of hypoestrogenic perimenopausal women attenuated blood pressure, cortisol, and catecholamine responses to acute psychological challenge.*

Source: Komesaroff PA, et al. *J Clin Endocrinol Metab* 1999;84:606-610.

The present study tested the hypothesis that estradiol reduces cortisol and catecholamine responses to stress. Twelve women within two years of their last menses with hot flashes were designated as being perimenopausal. Women with known cardiovascular disease, including hypertension, were excluded. These women were then randomized to 12 weeks of estradiol valerate, 2 mg daily by mouth, or placebo. Outcome variables that were determined before and after estradiol use included cortisol, adrenocorticotropic hormone (ACTH), epinephrine, norepinephrine, blood pressure, and heart rate. Estradiol levels rose from about 35 pg/mL to 250 pg/mL, which is well above physiological levels. After estradiol supplementation, the increases in both systolic and diastolic blood pressure in response to mental stress were reduced, and cortisol, ACTH, epinephrine, and norepinephrine responses were attenuated.

COMMENT BY SARAH L. BERGA, MD

There are several mechanisms by which estrogen protects against cardiovascular disease. One of these is thought to be reduced endocrine and vascular reactivity to psychological challenge. Indeed, estrogen exerts direct effects upon the vessel wall and vasomotor tone. Previous studies by Komesaroff and colleagues found that estrogen supplementation of perimenopausal women enhanced basal nitric oxide release from the vessel wall and reduced norepinephrine-induced vasoconstriction. In the present model, Komesaroff et al extend their previous work by asking whether estrogen supplementation alters cardiovascular and endocrine responses to psychological challenge.

The use of a challenge paradigm has advantages over studies in which a given vasoconstrictor agent is directly infused. Multiple factors regulate vasomotor tone and cardiovascular reactivity, and psychological challenge is thought to activate all or many of these mechanisms, including cortisol and catecholamine release. Further, basal endocrine and cardiovascular parameters do not adequately reflect what happens when an individual is confronted by the mundane trials of daily living. Therefore, to better approximate what happens in response to minor stress, Komesaroff et al used a psychological challenge, performing difficult arithmetic tasks in a distracting milieu.

Komesaroff et al found that estrogen administration reduced cardiovascular and endocrine reactivity. They suggested a direct link between reduced adrenal secretion and reduced blood pressure during challenge. While their dis-

cussion focused on the implications of reduced endocrine reactivity for cardiovascular risk, reduced cortisol and catecholamine secretion in response to mundane challenges could have other benefits as well. Another likely benefit of reduced endocrine reactivity is a lower risk of depression and dementia. Bone health is reduced by chronic glucocorticoid elevations, even when the glucocorticoid exposure is from an endogenous source. Chronic adrenal activation leads to reproductive compromise and hypothalamic hypothyroidism. Animal tests suggest that sustained increases in endocrine reactivity accelerate the aging process in general, possibly by increasing programmed cell death (apoptosis). Obviously, it is impossible to rid ones life of stress, so the prudent course is to take measures to reduce ones endocrine and cardiovascular reactivity to such pressures. While many of the ways to reduce mental stress involve psychological mechanisms such as "attitude readjustment" (in hypogonadal women at least), one should ensure that estrogen levels are adequate.

This study nicely demonstrates the profound effect of estrogen administration upon cardiovascular and endocrine reactivity, but, like all good studies, it raises certain questions. As Komesaroff et al point out, the effect of progestins in this model have not been determined. Perhaps more important, the effect of phytoestrogens, tamoxifen, or raloxifene upon these parameters should be studied. Many women have chosen these and other estrogen alternatives in the belief that their use would confer the benefits of estrogen while reducing the risk of breast cancer. Given that we are still engaged in specifying the multiple mechanisms underlying the benefits (and risks) of postmenopausal estrogen use, it is impossible to know what to expect from the long-term use of estrogen alternatives. However, the development of investigative paradigms, such as the one in this study, may well allow for informative comparisons that are less labor- and time-intensive than long-term, large-scale epidemiological trials. ❖

DHEA for Depression

ABSTRACT & COMMENTARY

Source: Wolkowitz OM, et al. Double-blind treatment of major depression with dehydroepiandrosterone. *Amer J Psychiatry* 1999;156:646-649.

This study was designed to assess possible antidepressant effects of dehydroepiandrosterone (DHEA), an abundant adrenocortical hormone in humans. Twenty-two patients with major depression, either medication-free or on stabilized antidepressant regimens, re-ceived either DHEA (maximum dose = 90 mg/d) or placebo for six weeks in a double-blind manner. Assessment was repeated at baseline and at the end of the six weeks with the Hamilton Depression Rating Scale. Patients previously stabilized with antidepressants had the study medication added to that regimen; others received DHEA or placebo alone. DHEA was associated with a significantly greater decrease in Hamilton Depression Scale ratings than was placebo. Five of the 11 patients treated with DHEA, compared with none of the 11 given placebo, showed a 50% decrease or greater in depressive symptoms. These results suggest that DHEA treatment may have significant antidepressant effects in some patients with major depression. Further, larger-scale trials are warranted.

★ COMMENT BY JOHN LAPUMA

The authors of this thoughtful, well-referenced pilot studyhnote that despite the epidemiological evidence for a direct relationship between DHEA and DHEA-S levels and positive mood, reports of levels in patients with major depression are inconsistent. Potential mechanisms include DHEA metabolism to testosterone and estrogen, modulation of testosterone bioavailability, and cortisol antagonism. These actions may also, of course, exacerbate hormone-mediated tumors, including breast, prostrate, uterus, and cervix.

Supported by a grant from the National Alliance for Research in Schizophrenia and Affective Disorders, these UCSF and City of Hope investigators randomized 20 unipolar and two bipolar type II patients (12 males, 10 female, mean age 44 years) to DHEA or placebo. Seven subjects (three in the DHEA group and four in the placebo group) were medication free; the others were on stable doses of antidepressants for at least two months. DHEA was given 30 mg once daily for the first two weeks, then twice daily for two weeks and then three times daily for two weeks. The dosage was chosen to give the high end of the physiological range of healthy young adults. All subjects began with a Hamilton Depression Scale score of 16 or greater.

No one dropped out because of side effects; the drug was equally effective in medication-free subjects and those continuing treatment with antidepressants. The authors note that oily skin, acne, hirsutism, and voice-deepening are reported side effects, together with anecdotal reports of significant negative mood changes.

Recommendation

DHEA for depression has real therapeutic possibili-

ties, though its endo-crinologic effects are worrisome and not all known. Patients who want to try it should be closely monitored and should be enrolled by a research protocol. DHEA should not be recommended without better long-term data.

(Editor's note: As with all putative antidepressants, DHEA has been associated with treatment-emergent mania and should not be used as a monotherapy for patients with bipolar disorder.

-- Lauren Marangell, MD)

Clinical Brief

Is There Gulf War Syndrome?

MILITARY VETERANS FROM THE UNITED KINGDOM WHO were STAtioned in the Persian Gulf during the Gulf War from Sept. 1, 1990, until June 30, 1991 (n = 53,462) have reported impaired physical functioning, psychological morbidity, and perception of poor physician health more frequently than individuals not deployed in this area. A similar picture has been reported for U.S. servicepersons. Using a population-based cross-sectional design, Ismail and colleagues sent a standardized survey about 50 physician symptoms to 12,592 men who had served in either the Gulf War or Bosnia, or servicemen who had not been deployed overseas.

The most commonly reported symptoms were headaches, irritability, sleeping difficulties, feeling jumpy, feeling unrefreshed after sleep, fatigue, feeling cut off from others, forgetfulness, loss of concentration, avoidance behaviors, distressing dreams, difficulty breathing deeply, tachypnea, dyspnea, wheezing, and numbness or tingling in extremities. The structure of correlations between symptoms was similar among Gulf War veterans to Bosnia veterans, or servicemen not deployed abroad.

Ismail et al conclude that, although results from complex modeling procedures must be interpreted with caution, the data do not support a unique Gulf War syndrome.

Ismail, K, et al. Lancet 1999;353:179-182.

CME Questions

32. Which of the following statements are true regarding SAMe?
a. It may be an effective antidepressant
b. It is particularly advantageous in patients with bipolar disorder (manic-depression)
c. Safety and efficacy studies are comparable to standard antidepressant medication
d. It is an effective hypnotic

33. Depression is associated with:
a. Increase platelet reactivity
b. Decreased platelet reactivity

34. The 'atypical' antipsychotic medication most likely to produce hyperprolactinemia is:
a. Clozapine (Clozaril)
b. Risperidone (Risperdal)
c. Olanzapine (Zyprexa)
d. Quetiapine (Seroquel)

35. Potential benefits of estrogen-induced reductions in cortisol and catecholamine reactivity in response to psychological challenge include all of the following except:
a. reduced cardiovascular risk
b. increased risk of breast cancer
c. reduced risk of dementia
d. reduced risk of depression
e. increased risk of osteoporosis

In Future Issues:

Valerian Root for Insomnia