

# Managing Mood Disorders in Older Patients:

## A Focus on Depression and Anxiety

J. Craig Nelson, MD, Helen Lavretsky, MD,  
and William J. Burke, MD (Program Chair)



*A symposium entitled,  
"Managing Mood  
Disorders in Older*

*Patients: A Focus on Depression  
and Anxiety," was presented on  
March 4, 2003, at the 16th  
Annual Meeting of the American  
Association for Geriatric  
Psychiatry in Honolulu, HI. The  
presentations focused on the effi-  
cacy and safety benefits of current  
treatments for depression and anx-  
iety, the role of gender differences  
in treating late-life depression, and  
the emerging new treatment strate-  
gies for geriatric depression and  
anxiety.*

### CME Certified

#### EDUCATIONAL OBJECTIVES

- Identify evidence-based efficacy and safety benefits of selective serotonin reuptake inhibitors (SSRIs) in the treatment of geriatric depression and anxiety.
- Describe the role gender differences play in treating depression and anxiety in older adults.
- Evaluate the advantage of improved tolerability in single isomer SSRI treatment for elderly patients with depression.
- Recognize the potential value of improved efficacy, faster onset, and increased tolerability emerging in new therapies to treat late-life depression and anxiety.

Supplement to *Annals of Long-Term Care*  
and *Clinical Geriatrics*

A Freedom Magazines Publication

## Depression and Anxiety in the Old-Old

*J. Craig Nelson, MD, Professor of Psychiatry, Leon J. Epstein, MD, Chair in Geriatric Psychiatry, and Director of Geriatric Psychiatry, University of California at San Francisco, presented a review of available data for antidepressant treatment in older patients. He also examined the significance of older age, late-onset compared to recurrent depression, and nonspecific interventions as factors implicated in the degree of selective serotonin reuptake inhibitor (SSRI) treatment response observed in the elderly.*

### Evidence-Based Review of Antidepressant Efficacy in the Elderly

The number of older patients age 85 and over is increasing rapidly. People live much longer lives today, and yet few studies have been conducted that examine the pharmacologic treatment of depression and anxiety in the *elderly*, described as patients age 75 and older, or age 80 and older.<sup>1</sup>

#### Nortriptyline

Katz and colleagues<sup>2</sup> conducted the first placebo-controlled study of elderly patients over 80 years of age with major depression in a nursing home setting. Of the 79 patients who were determined to need treatment, 35 (44%) entered the study with a mean age of 84. They received 65 mg/day of nortriptyline, a dose similar to that used to treat younger patients, and achieved a mean plasma level of 76 ng/mL. A dropout rate of 34% (12 patients) was observed. Using Clinical Global Impressions (CGI) or Hamilton Depression (HAM-D) rating scales, nortriptyline was significantly more effective than placebo. This is the only study to date that shows an advantage for drug treatment in this group of patients.

#### Desipramine

Dr. Nelson et al<sup>3</sup> conducted a fixed desipramine dose (2.5 mg/kg) plasma level study on 34 nursing home residents with a mean age of 79 (range 75-89). The primary outcome measurement was the CGI scale, which showed 42% of patients to be much improved with an adverse event rate of 21%. Overall, older patients had

less of a response than younger participants during a similar duration of treatment. The relationship of response and plasma levels appeared to be similar across different age groups.<sup>3-5</sup>

#### Fluoxetine

In 1996, Finkel<sup>6</sup> analyzed the subset of 70 patients aged 75 and older who participated in a fluoxetine-placebo study of 671 patients aged 60 and older. All patients were treated with a 20-mg dose of fluoxetine for a 6-week period. Although response to fluoxetine was greater than that to placebo in the entire sample, in patients 75 years and older placebo was just as effective as fluoxetine.<sup>6,7</sup>

#### Paroxetine

Burrows and associates<sup>8</sup> conducted a placebo-controlled study of paroxetine in 24 nursing home residents aged 80 and older (mean age = 88; range 80-94) with non-major depression, but “with symptoms that warranted treatment.” The 8-week, double-blind, random-assignment trial involved paroxetine up to 30 mg/day (mean dose = 23 mg). Patient- and nurse-rated assessment instruments found a mean Mini-Mental State Examination (MMSE) score of 24 (range 16-30) and a mean HAM-D score of 14 (range 4-23). Twenty of 24 patients completed the trial. Using the CGI response as the primary outcome measure, the paroxetine response rate was slightly higher (56% vs 36%), but in this small sample the difference was not significant. Anticholinergic assays did not find evidence that paroxetine was having an anticholinergic effect. The mean change in the MMSE (2.0 vs -0.1) on paroxetine and placebo, respectively, was near significant ( $P = .07$ ).

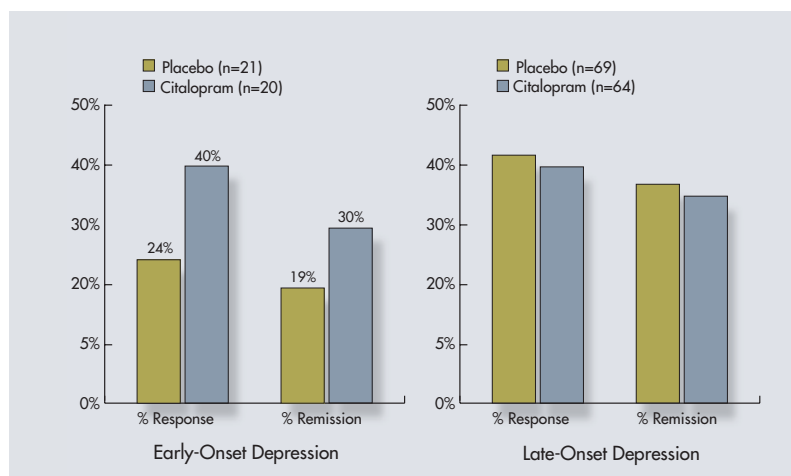
#### Citalopram

Roose and colleagues<sup>9</sup> conducted the first large multicenter, randomized, placebo-controlled, double-blind outpatient study in patients aged 75 and older with nonpsychotic unipolar major depressive disorders (MDD). In this study of 170 patients with MDD over age 74 years, response to citalopram was compared with response to placebo over an 8-week period. Mean patient age was 79.8 years in the citalopram group, and 79.3 years for patients in the placebo-control group. Citalopram dosage began with 20 mg/day for 4 weeks followed by an option

to systematically increase it to 40 mg/day for the remainder of the trial unless a patient was much improved. Magnetic resonance imaging (MRI) and neuropsychological testing were performed by the study coordinator. Participants were assessed with a 24-item HAM-D scale (score  $\geq 20$ ) with mean baseline HAM-D scores of 24.4 in the citalopram-treated group, and 24.3 in the placebo-control group. Patients presenting symptoms of early dementia (MMSE scores  $> 18$ ) or stable medical illnesses were included as typical characteristics for this type of patient group. Other axis 1 disorders, unstable medical illness, or patients who had already failed to respond to one

first episode occurring after age 59 years. In late-onset depression, response rates with citalopram and placebo were similar. Patients with *early-onset depression* by definition were also those with recurrent depression. In this group, citalopram was numerically superior to placebo (40% vs 24%), but again, in this smaller group of 41 patients, the difference was not significant (Figure 1).

Effects of nonspecific interventions—such as the amount of time the study coordinator spent with patients, which was appreciable—appeared to have meaningful effects in patients with less severe or late-onset depression. These supportive interventions may have been quite helpful for older patients who were demoralized about declining health or other age-related stressors. There was considerable site-to-site variation in drug-vs-placebo response, possibly due to the small numbers of patients at each site or other unaccounted interventions that patients received.



**Figure 1.** Response to treatment with citalopram and age of onset (late-onset  $\geq 60$  years old). Response =  $\geq 50\%$  improvement; remission = HAM-D  $\leq 7$ .

SSRI were excluded. Completion rate for the study was 87% (placebo) and 76% (citalopram). Using the HAM-D and Hamilton Anxiety (HAM-A) scales as the primary outcome measures, no observed differences in the drug-vs-placebo groups or the responders-vs-nonresponders were observed. Both treatments were effective, with response rates of about 40% in these older patients.

Severity and age of onset appeared related to response. In patients with severe depression (HAM-D score of  $> 24$ ), citalopram remained effective with 43% of patients responding, but placebo response dropped to 18%. In this smaller group of 45 patients, this difference was not statistically significant. In less severe patients, the nonspecific effects in the placebo group appeared to be just as effective as citalopram. *Late-onset depression* was defined as the

## Augmenting SSRI Treatment in Primary Care

One example of an “unaccounted-for” intervention was telephone calls to check on the patients’ status. At one of the sites, this was required by the Internal Review Board. Hunkeler and associates<sup>10</sup> have reported on the value of this intervention. They looked at 302 patients with MDD who received SSRI treatment with fluoxetine or paroxetine for 6

months. In addition to SSRI treatment, patients were randomly assigned to receive brief telephone calls from the nurse or peer support, or the SSRI alone. The study demonstrated that peer support added no benefit, but nurse telehealth care did. Keeping in touch with the patient, providing reassurance and education, and answering questions made a difference and enhanced response to SSRI treatment.

Other forms of intervention may also prove useful in older patients with depression. Alexopoulos et al<sup>11</sup> are researching a type of behavioral treatment called Problem Solving Therapy (PST) for patients with MDD and executive dysfunction. Investigators recently reported on an initial sample of 25 patients over age 65 years with depression (HAM-D  $\geq 18$ ) who had evidence of

executive dysfunction. Results of this 12-week random-assignment study indicated that PST was more effective than supportive therapy (70% vs 20%).

## Benefits of SSRI Treatment of Geriatric Depression

Supported by a review of evidence on the efficacy and safety of SSRIs in older patients, SSRIs may merit primary consideration in the pharmacologic approach to treating geriatric depression. SSRIs may be particularly useful in patients with recurrent depression or those with more severe depression for whom nonspecific supportive interventions may be less effective. However, these nonspecific supportive treatments may prove to be quite important in elderly patients with late-onset or less severe depression. In general, these recent findings challenge our assumptions about late-onset depression and indicate the need to further explore a variety of treatments.

### References

1. NIH Consensus Conference: Diagnosis and treatment of depression in late life. *JAMA* 1992;268(8):1018-1024.
2. Katz IR, Simpson GM, Curlik SM, et al. Pharmacologic treatment of major depression for elderly patients in residential care settings. *J Clin Psychiatry* 1990;51(suppl):41-47.
3. Nelson JC, Mazure CM, Jatlow PI. Desipramine treatment of major depression in patients over 75 years of age. *J Clin Psychopharmacol* 1995;15(2):99-105.
4. Nelson JC, Jatlow PI, Quinlan DM, Bowers MB Jr. Desipramine plasma concentration and antidepressant response. *Arch Gen Psychiatry* 1982;39(12):1419-1422.
5. Nelson JC, Jatlow PI, Mazure C. Desipramine plasma levels and response in elderly melancholic patients. *J Clin Psychopharmacol* 1985;5(4):217-220.
6. Finkel SI. Efficacy and tolerability of antidepressant therapy in the old-old. *J Clin Psychiatry* 1996;57(suppl 5):23-28.
7. Tollefson GD, Holman SL. Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. *Int Clin Psychopharmacol* 1993;8(4):253-259.
8. Burrows AB, Salzman C, Satlin A, et al. A randomized, placebo-controlled trial of paroxetine in nursing home residents with non-major depression. *Depress Anxiety* 2002;15(3):102-110.
9. Roose S, et al. Treatment of depression in patients over 75. Presented at: 15th Annual Meeting of the American Association for Geriatric Psychiatry; May 24-27, 2002; Orlando, FL.
10. Hunkeler EM, Meresman JE, Hargreaves WA, et al. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Arch Fam Med* 2000;9(8):700-708.
11. Alexopoulos GS, Raue P, Arean P. Problem-solving therapy versus supportive therapy in geriatric major depression with executive dysfunction. *Am J Geriatr Psychiatry* 2003;11(1):46-52.

## Sex Differences in Late-Life Depression

*Helen Lavretsky, MD, Assistant Professor of Psychiatry, Division of Geriatric Psychiatry, UCLA-Neuropsychiatric Institute, Los Angeles, discussed the existing evidence of sex differences in depression by describing epidemiology, phenomenology, neurobiology, and antidepressant response in geriatric depression. Dr. Lavretsky also reviewed the relationship of depression to sex by age or age of onset, and evaluated the sex differences in risk factors and brain structure in geriatric depression.*

## Epidemiology of Sex Differences in Major Depression

The most consistent finding in psychiatric research is that of gender differences in the prevalence of depression: a 2:1 ratio in women versus men, and a lifetime prevalence of 4% in women versus 1.7% in men.<sup>1</sup> A fact that is frequently overlooked is that this prevalence rate only exists from puberty through menopause. Boys have higher depression rates during childhood, and the ratio becomes nearly 1:1 by age 80. Multiple explanations are used to explain these differences, including disparities in seeking help or reporting symptoms. Men tend to underreport episodes of depression, and women tend to report occurrences more frequently. Prior history of depression would place women at greater risk for recurrent or future episodes.

Another explanation of gender differences in the prevalence of depression may be social risk factors. Adverse childhood experiences such as sexual abuse, which accounts for 35% of the variance in sex differences, show women to be at greater risk. Limitations, lack of choice, and competing societal roles affect women more often. More than 50% of women compared to 25% of men live alone as older adults. This can mean that women face greater financial strain and loss of independence due to declining health. In addition, women are even more likely to be placed in a nursing home.

Stress and coping styles are also offered as an explanation of sex differences. Childhood trauma and life stresses affect men and women differently because men may cope with stress differently. Women are three times more likely than men to develop depression in response to any stressful life event, according to research observations.

Biological theories have been proposed to explain gender differences in depression. Inheriting major depression is about 30% more likely in women because there is a 60% overlap in the genes responsible for depression that are found in men and women. Since no increased depression rates are seen in postmenopausal women and hormone replacement therapy (HRT) has a minimal to modest effect on treatment response, hormonal influences are thought to have less effect on depression rate differences than environmental factors. Hormones of the adrenal and thyroid axes, long considered the missing link, have a contrasting or lim-

ited role. The differences in the neurotransmitter systems are unclear, as is brain laterality or lack of it in women.

Two paradoxes exist in gender differences of depression rates among men versus women. The first is that rates of completed suicide in men, particularly white men, are greater even though women have higher rates of depression. Access to guns and gun control laws only partially explain this paradox, because women also have access to guns but choose less lethal methods such as drug overdose, and overall rates of suicide are comparable among men in countries with gun control laws (eg, Canada).

A second paradox is that men live an average of 8 years less than women, even though women reportedly suffer more chronic illnesses and disabilities. This may be because older men, who have a higher prevalence of vascular diseases, may be more prone to developing comorbid, late-onset depression, which increases mortality and disability secondary to vascular conditions.

## Sex Differences in Antidepressant Response

Kornstein and associates<sup>2</sup> reported on a randomized trial of 635 patients, of which 400 were female, showing that women have a preferential response to SSRIs (sertraline) and men to tricyclic antidepressants (TCAs; imipramine). In a meta-analysis conducted by Quitkin and colleagues,<sup>3</sup> a

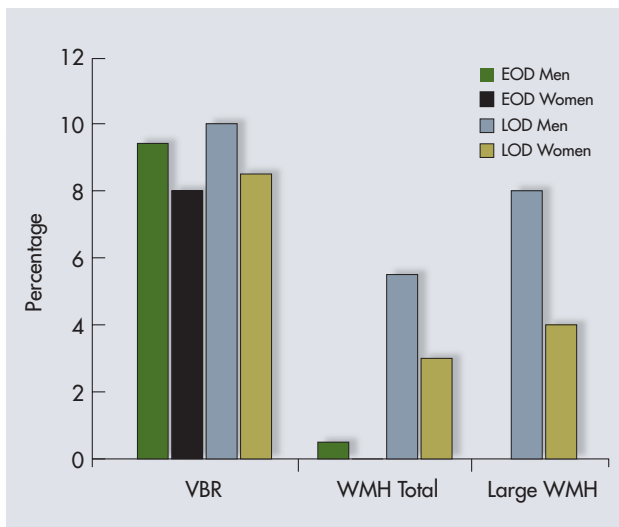
number of studies including over 1700 patients ages 18-65 were analyzed. Patients were then divided into two groups, age 50 and over and under 50, and then divided into men versus women. Researchers found no differences in the response rate to TCAs and SSRIs, but a greater rate of response to monoamine oxidase inhibitors (MAOIs) in women overall with a preferential response from women under 50. Frank et al<sup>4</sup> reported that men had a greater overall speed of response compared to women, and relapses were seen more often in women.

Postmenopausal women have an increased volume of distribution and decreased absorption and bioavailability. The effect of estrogen tends to increase certain neurotransmissions (5-HT). Drugs are metabolized via hydroxylation in women and by demethylation in CYP2D6 in men. Hydroxymetabolites are more toxic; therefore, women are more prone to developing drug toxicity, a fact supported by greater dropout rates of women versus men in clinical trials due to adverse reactions.

## Relationship of Age, Age at Onset, and Sex to Depression in Elderly Patients

Dr. Lavretsky and colleagues<sup>5</sup> performed a cross-sectional comparison of 96 outpatients with moderate MDD (HAM-D > 15; MMSE > 24) by dividing patients into an early-onset depression (EOD) group (33 patients; onset before age 50; 64% women) and a late-onset depression (LOD) group (63 patients; onset after age 50; 43% women). Investigators conducted on each participant a neuropsychiatric assessment and evaluation of medical burden, as well as history of medical illness, such as hypertension and smoking. MRI was conducted to calculate ventricular brain ratio, a measure of atrophy, and total white-matter hyperintensities (WMH) lesion size. Comparison of the two groups, LOD versus EOD, by clinical variables differed only in the lower number of episodes in the LOD group.

Sex differences were found in rates of LOD, EOD, degree of severity, hypothyroidism, neurovegetative factors, suicidal ideations, and history of smoking. Comparing the effect of sex versus age of onset on phenomenology, rates of depression in the four groups (LOD men, LOD women, EOD men, EOD women) showed the presence of suicidal ideations, and vegetative and cognitive signs, which resulted in more severe depression based



**Figure 2.** Brain structural changes: Sex vs age of onset. EOD = early-onset depression; LOD = late-onset depression; VBR = ventricle-to-brain ratio; WMH = white-matter hyperintensities.

on HAM-D ratings. Men also had more severe vegetative signs and suicidal ideations compared to women. Comparing brain structural changes by sex versus age of onset showed that men had greater ventricle-to-brain ratio and areas of WMHs (Figure 2). The LOD group had greater percentages of WMHs (defined as greater than 10 ccs). Results showed that men were more severely depressed with neurovegetative signs present and a history

ropsychiatric symptoms. All patients received a three-dimensional MRI segmentation into gray matter, white matter, and cerebrospinal fluid (CSF) volumes. Regional volumes were calculated automatically and total frontal lobe volume was examined. Depression and quality of life were assessed using a 21-item HAM-D scale (short form [SF]-36) and questionnaire. Medical burden was assessed using the Cumulative Illness Rating Scale (CIRS), geriatric version, and a cere-

**Table I: Multivariate Analysis: Diagnosis by Sex (Clinical Measures)**

	Men With Depression (n = 9)	Women With Depression (n = 13)	Controls Men (n = 4)	Controls Women (n = 11)	Dx P (F)	Sex P (F)	Age P (F)
Apathy	25.0 (6.3)	28.7 (10.1)	49.5 (9.1)	46.3 (2.8)	0.001	0.9	0.9
CIRS	6.3 (4.6)	4.0 (2.2)	2.5 (0.7)	3.0 (2.4)	0.07	0.3	0.02
CVRF	13.2 (8.8)	10.3 (4.5)	10.5 (6.4)	10.9 (3.6)	0.6	0.1	0.001
MMSE	28.3 (1.5)	28.5 (1.8)	29.5 (0.7)	29.7 (0.5)	0.1	0.6	0.3
UPDRS	3.8 (5.8)	0.8 (1.8)	0	0.8 (1.5)	0.2	0.3	0.03
SF-36 (physical)	70.8 (32.6)	71.4 (19.9)	97.5 (3.5)	90.0 (13.8)	0.04	0.9	0.2
SF-36 (mental)	36.0 (30.4)	85.1 (5.5)	94.0 (2.8)	85.1 (5.5)	0.001	0.6	0.5

*CIRS = Cumulative Illness Rating Scale; CVRF = cerebrovascular risk factor [scale]; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; SF-36 = 36-item short form of the MMSE.*

of smoking. The LOD group had increased WMH, larger ventricle-to-brain ratio (VBR) and a history of hypertension. Age also influenced WMH, atrophy, hypertension, and a lack of social support. Researchers concluded that the relationship of sex to the age of onset may be an influence in the phenomenology and neurobiology of late-life depression. Older men may be at greater risk for LOD associated with brain structural changes and cerebrovascular disease.

## Pathophysiology of Geriatric Depression

In another study using a similar approach, Dr. Lavretsky and associates<sup>6</sup> recruited 22 patients age 60 and older (9 men, 13 women; mean age, 71.4) with major depression, and 15 control patients (4 men, 11 women; mean age, 72), whose age, education, and sex ratio matched normal controls, in order to compare total brain, frontal gray and white matter volumes, and measures of medical burden and neu-

brovascular risk factor (CVRF) scale to determine stroke factors. Unified Parkinson's Disease Rating Scale (UPDRS) was used to evaluate psychomotor retardation. The Apathy Evaluation Scale (AES) was used to look at the severity of apathy due to its prevalence in the population.

Observations based on clinical variables compared to the control group showed no differences by age. Patients with depression had lower MMSE scores that were consistent across all samples. CIRS score was higher in these patients (ie, they were much more ill than other patients with only depression). Groups did not differ in stroke risk factors. Compared to controls, apathy, retardation, and lower quality of life were more prevalent in the patients with depression.

Corrected volumes of the intracranial volume (ICV) were used because patients vary widely based on their circumference and brain volumes, and men tend to have larger brain ICVs. Patients with depression had smaller corrected volumes in frontal, left frontal, and right frontal areas, and smaller frontal white matter volumes.

Age accounted for a greater medical burden, vascular and nonvascular factors, and psychomotor retardation. No sex differences were found; however, differences between diagnostic groups remained. Patients with depression were still more apathetic, more medically ill, and had poorer quality of life.

Diagnosis by sex revealed that age accounted greatly for atrophy in frontal lobe volumes (Table I). Men had smaller corrected volumes throughout frontal, left frontal, right frontal, and frontal white matter volumes. Differences between diagnostic groups were observed. Logistic regression showed that frontal total volume and frontal white matter volume predicted sex assignment after controlling for age in the group with depression, but not in the control group.

Another study of brain structure conducted by Gur and colleagues<sup>7</sup> reported that age correlates with reduced gray matter volume and increased sulcal CSF. Therefore, atrophy is increased in men because of age, and the association is prominent in frontal, temporal, and basal ganglia structures, but less in subcortical regions. Men experience a greater volume decrement across ages, particularly in dorsolateral prefrontal cortex regions, which may place them at greater risk for late-onset depression.

Geriatric depression is associated with greater severity of medical comorbidity and brain structural changes. Sex differences in neuroanatomy may be important in the pathophysiology of geriatric depression.

## Gender-Sensitive Approach

The ultimate goal in treating geriatric depression in men and women should be the optimization of pharmacotherapy and other forms of treatment by maximizing therapeutic benefits and minimizing negative effects. However, before that can be achieved, underlying sex differences and other neurobiological variables of this illness must be understood.

### References

1. Blazer D, Williams CD. Epidemiology of dysphoria and depression in an elderly population. *Am J Psychiatry* 1980;137(4):439-444.
2. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry* 2000;157(9):1445-1452.
3. Quitkin FM, Stewart JW, McGrath PJ, et al. Are there differences between women's and men's antidepressant responses? *Am J Psychiatry* 2002;159(11):1848-1854.
4. Frank E, Thase ME, Spanier CA, et al. Gender-specific response to depression treatment. *J Genet Specif Med* 1999;2(4):40-44.
5. Lavretsky H, Lesser IM, Wohl M, Mill BL. Relationship of age, age at onset, and sex to depression in older adults. *Am J Geriatr Psychiatry* 1998;6(3):248-256.

6. Lavretsky H, Kumar A, Pham D, et al. Sex differences in brain structure in geriatric depression [abstract]. Presented at: 2002 Annual Meeting of the Society of Biological Psychiatry; May 2003; Philadelphia, PA.
7. Gur RC, Gunning-Dixon FM, Turetsky BI, et al. Brain region and sex differences in age association with brain volume: a quantitative MRI study of healthy young adults. *Am J Geriatr Psychiatry* 2002;10(1):72-80.

## New Treatments for Depression and Anxiety

*William J. Burke, MD, Professor and Vice-Chair for Research, Department of Psychiatry, and Director of Geriatric Psychiatry, University of Nebraska Medical Center, Omaha, discussed the benefits of increased efficacy and safety in new SSRI therapies for the treatment of mood and anxiety disorders. Dr. Burke also evaluated new and developing pharmacotherapeutic strategies for depression and anxiety.*

Very little age-specific data are available for the newer antidepressants and anxiolytics. Although it is important to treat older adults, they are less likely to participate in clinical trials, and often get excluded. Therefore, current data tend to be of very healthy individuals, making the applicability uncertain.

## New SSRI Strategies

### Escitalopram

Escitalopram, the most recently approved antidepressant, is the pure S-enantiomer (single isomer) of citalopram, and was developed specifically to see if the tolerability of citalopram could be improved by eliminating the R-enantiomer. Gorman and colleagues<sup>1</sup> conducted a pooled analysis of three randomized, double-blind, placebo-controlled, 8-week trials comparing escitalopram and citalopram in the treatment of MDD. One trial used a fixed dose and the other two trials used flexible doses. The primary outcome measure of efficacy was the Montgomery-Asberg Depression Rating Scale (MADRS; Figure 3).<sup>1</sup> In this analysis, escitalopram was statistically superior to placebo from week 1 through week 8, and to citalopram at week 1 and week 8. However, at the time of Food and Drug Administration (FDA) approval of escitalopram, no specific depression studies had been done in the elderly. Analysis of covariance (ANCOVA) was performed on the available data on MADRS scores, using age as a covariate to look at the effect of age on response.<sup>2</sup>

No significant age effect or age-by-treatment interaction was observed. Improvement in MADRS scores produced by escitalopram was not related to patient age.

Escitalopram was well tolerated in patients age 60 and over (Table II).<sup>6</sup> No side effect was present in more than 10% of patients, and nausea and abdominal pain were the only side effects that occurred in more than 5% of patients and more frequently than placebo.<sup>6</sup> Three percent of patients taking placebo discontinued for adverse events compared to 9% of the escitalopram-treated patients.

There are no specific data available on efficacy of escitalopram for anxiety in older patients, although a number of positive trials have been completed in younger adults with generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder.<sup>1,3-5</sup>

### Duloxetine

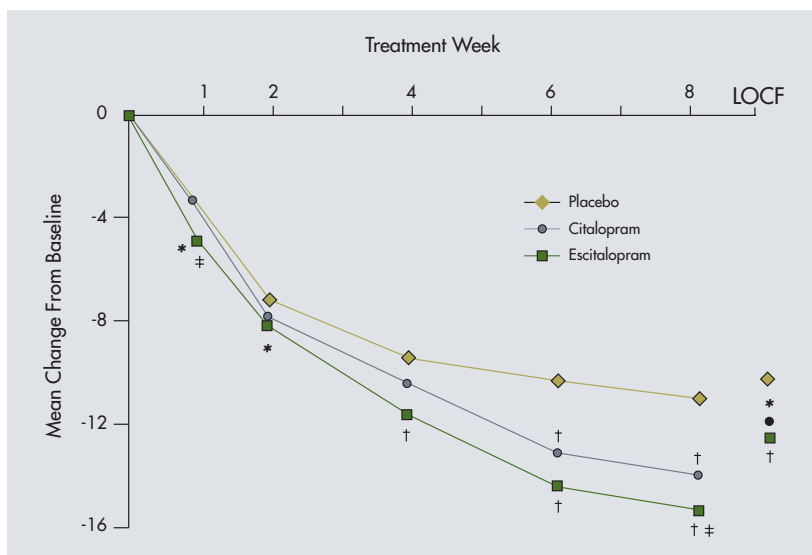
Dr. Burke believes the next available drug may be duloxetine, which has shown results in balanced uptake inhibition of both serotonin and norepinephrine (NE) at starting doses. Evidence suggests NE is an important neurotransmitter with concentrations that are reduced in CSF of patients with depression.<sup>7-9</sup> Duloxetine has some similarities to venlafaxine, except that venlafaxine affects serotonin at lower doses and only begins to have norenergic effects once the dosage passes 150 mg/day. Imipramine, a tricyclic antidepressant, also has a similar balanced effect on serotonin and NE uptake inhibition.

Nelson and colleagues<sup>10</sup> performed a pooled analysis on outpatients age 55 and older with *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV)-defined major depression. Data were extracted from two identical randomized, multicenter, placebo-controlled, double-blind trials. Patients received 60 mg/day of duloxetine over a 9-week study period. The primary efficacy measure was the HAM-D. Duloxetine was significantly superior to placebo at week 9 on the HAM-D.

Tran and associates<sup>11</sup> conducted a pooled analysis of 753 patients evaluating the efficacy of duloxetine using three studies in which the drug was statistically superior to placebo in patients under age 55 versus patients age 55 and older.

Only 61 patients receiving duloxetine and 50 patients receiving placebo, respectively, were age 55 and older. Researchers found no significant differences across subgroups; older patients appeared to do as well as younger patients.

Tran et al<sup>11</sup> conducted a second pooled analysis study of duloxetine safety by looking at data from 1755 patients in seven double-blind, placebo-controlled trials. Only 34 patients receiving duloxetine and 31 patients receiving placebo, respectively, were age 65 and older in these trials. No significant differences were observed across subgroups. In patients aged 65 and older who received duloxetine, discon-



**Figure 3.** Pooled analysis: Efficacy comparison of escitalopram and citalopram using the Montgomery-Asberg Depression Rating Scale.<sup>1</sup> LOCF = last observation carried forward. \*  $P < .05$  vs placebo; †  $P < .001$  vs placebo; ‡  $P < .05$  vs citalopram.

tinuation rates due to adverse events were 26%, compared to 12% in the placebo group. For patients taking duloxetine, the mean change in systolic blood pressure (BP) was 2 mm Hg; in diastolic BP, 4 mm Hg; and in pulse rate, -1 bpm. Adverse events occurring  $\geq 5\%$  for duloxetine-treated patients and  $\geq 2$  times the placebo rate included nausea, dry mouth, decreased appetite, insomnia, and decreased libido.<sup>12</sup>

### Substance P Antagonists (SPAs)

Kramer and colleagues<sup>13</sup> reported evidence, which suggests that substance P or its receptor (NK<sub>1</sub>) is abnormally expressed in depression. Drugs that work as substance P receptor antagonists, if found to have antidepressant

effects, would be important since their mechanism of action would not be via direct effects on monoamine transmission (ie, SPAs would not work by having an effect on serotonin, NE, or dopamine).

Kramer et al<sup>13</sup> conducted a 6-week, randomized, double-blind, placebo-controlled Phase IIA proof-of-concept study of 210 patients with MDD and moderately high anxiety enrolled at four sites using a substance P antagonist called MK-869. Patients were divided into three groups of 70 and received either 300 mg/day MK-869, 20 mg/day paroxetine, or placebo. All medications were taken orally every evening for the duration of the trial preceded by a 7-day washout period.

The antidepressant effect of MK-869 was nearly identical to paroxetine, and the anxiolytic response was significantly better than placebo at endpoint, according to HAM-A assessment. MK-869 was very well tolerated with no clear mechanism-based side effects. MK-869-treated patients experienced adverse events significantly less frequently than the placebo- or paroxetine-treated patients. Additionally, MK-869-treated patients experienced significantly less sexual dysfunction than the paroxetine group.

## Corticotropin-Releasing Hormone Antagonists

Chalmers et al<sup>14</sup> reported that corticotropin-releasing hormone (CRH) hypersecretion is observed in patients with MDD and is considered to have a depressogenic effect. Researchers speculate that this may occur via stimulation of cytokines, an interaction between the HPA axis and the immune system. CRH administration in laboratory animals was observed to produce depression-like symptoms and anxiogenic effects. In other laboratory tests with animals, CRH peptide antagonists produced anxiolytic effects.

Schatzberg et al<sup>7</sup> reported that mifepristone produced significant improvement in some patients with psychotic depression. Zobel and colleagues<sup>15</sup> studied a corticotropin-releasing factor (CRF-R) antagonist called R121919 in 20 patients with MDD. They noted dose-dependent improvements in anxiety and depression in 80% of patients. Another CRF-R antagonist known as NBI34041 is currently in Phase I trials for anxiety and depression.<sup>16</sup>

## 5-HT<sub>1A</sub> Agonists

Leslie<sup>17</sup> reported that compared to buspirone, gepirone has much greater selectivity for 5-HT<sub>1A</sub> receptors over dopamine (D2) receptors due to a differential action at presynaptic (agonist) and postsynaptic (partial agonist) 5-HT<sub>1A</sub> receptors. Efficacy studies of all ages show improvement with gepirone ER versus placebo using the HAM-D scale to measure outcome.<sup>18</sup> Remission data

**Table II: Escitalopram: Efficacy in Persons Over 60 Years<sup>6</sup>**

Adverse Event	Placebo (n = 214)	Escitalopram (10-20 mg/d) (n = 216)
Nausea	3.7%	9.3%
Headache	9.8%	6.5%
Abdominal pain	3.3%	5.6%
Back pain	4.2%	4.6%
Insomnia	2.3%	3.7%
Somnolence	1.4%	3.2%
Diarrhea	5.1%	2.8%
Hypertension	5.6%	1.9%
Dry mouth	1.9%	1.4%
Fatigue	1.4%	0.9%
Upper respiratory tract infection	2.3%	0.5%
Ejaculation disorder	0	0

presented by Gilbertini<sup>20</sup> also supported a significant drug-placebo difference. Although some patients had difficulties with nausea and dizziness on the extended-release formulation, gepirone was well tolerated in general, with no sedation, weight gain, or sexual dysfunction that is associated with this drug. Comparisons so far using age as a covariant show no differences.

## Summary

New therapies are emerging with new mechanisms of action, as well as improvements on old mechanisms of action. Escitalopram appears to be efficacious for depression and anxiety, and safe for elderly patients with improved tolerability. Duloxetine is nearing approval and substance P inhibitors are demonstrating evidence of being effective with minimal side effects. CRF-R antagonists are proceeding in early clinical trials, and the 5-HT<sub>1A</sub> agonist

gepirone looks promising in terms of efficacy and tolerability. Some very well done trials have demonstrated that if older patients are treated properly, they do well. Providing quality depression care to older patients is crucial, and additional age-specific data is greatly needed.

#### References

1. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: Pooled analysis of placebo-controlled trials. *CNS Spectr* 2002;7(suppl 1):40-44.
2. Forest Pharmaceuticals, Inc. Data on file.
3. Davidson J, Bose A, Su G. Escitalopram in the treatment of generalized anxiety disorder [abstract]. Poster presented at: 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); June 23-27, 2002; Montreal, Canada.
4. Stahl S, Gergel I, Li D. Escitalopram in the treatment of panic disorder [abstract]. Poster presented at: 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); June 23-27, 2002; Montreal, Canada.
5. Kasper S, Loft H, Smith JR. Escitalopram is efficacious and well-tolerated in the treatment of SAD [abstract]. Poster presented at: 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); June 23-27, 2002; Montreal, Canada.
6. Burke WJ, Rothschild T, de Swart H, Ruby J. Safety of escitalopram in the treatment of elderly patients [abstract]. Poster presented at: Annual Meeting of the International College of Geriatric Psychoneuropharmacology; October 10-12, 2002; Barcelona, Spain.
7. Schatzberg AF. Noradrenergic versus serotonergic antidepressants: Predictors of treatment response. *J Clin Psychiatry* 1998;59(suppl 14):15-18.
8. Nutt DJ. Noradrenaline in depression: Half a century of progress. *J Psychopharmacol* 1997;11(4 suppl):S3.
9. Montgomery SA. Is there a role for a pure noradrenergic drug in the treatment of depression? *Eur Neuropsychopharmacol* 1997;7(suppl 1):S3-S9.
10. Nelson JC, Clary C, Leon A, Schneider L. Symptoms of late life depression [abstract]. Poster presented at: Annual Meeting of the International College of Geriatric Psychoneuropharmacology; October 10-12, 2002; Barcelona, Spain.
11. Tran P, Mallinckrodt C, Detke M, et al. Safety and tolerability of the antidepressant duloxetine [abstract]. Poster presented at: 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); June 23-27, 2002; Montreal, Canada.
12. Mallinckrodt CH, et al. Poster presented at: Annual Meeting of the International College of Geriatric Psychoneuropharmacology; October 10-12, 2002; Barcelona, Spain.
13. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 1998;281(5383):1640-1645.
14. Chalmers DJ, Lovenberg TW, Grigoriadis DE, et al. Corticotropin-releasing factor receptors: From molecular biology to drug design. *Trends Pharmacol Sci* 1996;17(4):166-172.
15. Zobel AV, Nickel T, Kunzel HE, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: The first 20 patients treated. *J Psychiatr Res* 2000;34(3):171-181.
16. CRF Receptor Antagonist: Anxiety/Depression. Neurocrine Biosciences. Available at: [http://www.neurocrine.com/html/clin\\_anxietyDepression.html](http://www.neurocrine.com/html/clin_anxietyDepression.html). Accessed April 15, 2003.
17. Leslie RA. Gepirone: Organon. *Curr Opin Investig Drugs* 2001;2(8):1120-1127.
18. Organon, Inc. Data on file.
19. Gilbertini M. Presented at: Annual Meeting of the American College of Neuropsychopharmacology; 2001; Waikaloa, HI.

## CME Accreditation & Instructions

### Managing Mood Disorders in Older Patients: A Focus on Depression and Anxiety

This activity was developed for primary care physicians and geriatric psychiatrists.

#### Accreditation

- The American Association for Geriatric Psychiatry (AAGP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.
- AAGP designates this continuing medical education activity for one credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit he/she actually spent on the educational activity.
- This CME activity was planned and produced in accordance with the ACCME Essentials.
- Based upon trials, the estimated time to complete this program is 1 hour.

#### Instructions

A certificate of completion will be awarded to physicians completing the post-test and evaluation form.

Please complete the post-test and program evaluation on the following page and mail to:

American Association for Geriatric Psychiatry  
7910 Woodmont Ave  
Suite 1050  
Bethesda, MD 20814-3004

Please allow three weeks for processing. Program expiration date is June 2004. Please phone (301) 654-7850 or fax (301) 654-4137 with any questions.

#### Educational Objectives

- Identify evidence-based efficacy and safety benefits of selective serotonin reuptake inhibitors (SSRIs) in the treatment of geriatric depression and anxiety.
- Describe the role gender differences play in treating depression and anxiety in older adults.
- Evaluate the advantage of improved tolerability in single isomer SSRI treatment for elderly patients with depression.
- Recognize the potential value of improved efficacy, faster onset, and increased tolerability emerging in new therapies to treat late-life depression and anxiety.

# CME Examination & Evaluation

## Managing Mood Disorders in Older Patients: A Focus on Depression and Anxiety

1. SSRI treatment for depression and anxiety in geriatric patients shows greater advantage when:
  - a. Age of onset is  $\geq 60$  years
  - b. There is a history of depression
  - c. Early-onset dementia is present
  - d. All of the above
2. Patients age 75 and older were shown to have SSRI response rates similar to samples of patients of all ages.
  - a. True
  - b. False
3. According to data presented on SSRI efficacy in treating geriatric patients with less severe depression:
  - a. SSRI treatment was less effective than placebo
  - b. Peer support enhances SSRI response rates
  - c. Nonspecific interventions are as important as drug treatment
4. Keeping in touch with patients is more effective than SSRI treatment
5. In elderly patients with recurrent or early-onset depression receiving SSRI treatment, data showed:
  - a. Placebo response rate declined
  - b. Effect of nonspecific interventions increased
  - c. Drug-placebo separation increased
  - d. Both a and b
  - e. Both a and c
6. Women are more likely than men to drop out of clinical trials due to adverse events because:
  - a. Estrogen increases neurotransmission
  - b. Women are 30% more likely to have inherited depression
  - c. Women metabolize drugs via hydroxylation
  - d. Women live 8 years longer than men
  - e. Women suffer from more chronic illnesses and disabilities than men
7. Older men may be at greater risk for late-onset depression associated with:
  - a. Chronic illnesses
  - b. Brain structural changes
  - c. Cerebrovascular diseases
  - d. All of the above
  - e. b and c only
8. The SSRI S-enantiomer escitalopram has better tolerability than citalopram.
  - a. True
  - b. False
9. The differential action seen in new 5-HT<sub>1A</sub> agonists at pre- and postsynaptic 5-HT<sub>1A</sub> receptors increases their:
  - a. Selectivity
  - b. Toxicity
  - c. Speed of response
  - d. Side effects
  - e. Both b and d
10. SSRIs that have combination effects will work on both:
  - a. Serotonin and dopamine
  - b. Serotonin and norepinephrine
  - c. Serotonin and corticotropin-releasing hormone
  - d. Serotonin and 5-HT<sub>1A</sub> receptors

## CME EVALUATION

Please circle the number that best reflects your opinions on the following statements, using the following rating scale:  
1 = Strongly Agree; 2 = Agree; 3 = Disagree; 4 = Strongly Disagree.

- |                                      |   |   |   |   |
|--------------------------------------|---|---|---|---|
| 1. The program objectives were met.  | 1 | 2 | 3 | 4 |
| 2. The program content was useful.   | 1 | 2 | 3 | 4 |
| 3. The program content was relevant. | 1 | 2 | 3 | 4 |
| 4. The program was educational.      | 1 | 2 | 3 | 4 |
| 5. The program was not promotional.  | 1 | 2 | 3 | 4 |

Additional Comments: \_\_\_\_\_

\_\_\_\_\_

Certificates will be mailed to the address listed below. Please allow three weeks for processing.

Participant Information (Please Print):

Name: \_\_\_\_\_ Degree: \_\_\_\_\_

Title: \_\_\_\_\_

Specialty: \_\_\_\_\_

Institution: \_\_\_\_\_

Street: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip code: \_\_\_\_\_

Telephone: \_\_\_\_\_

Signature: \_\_\_\_\_

I certify that I have completed this activity as designed.

The American Association for Geriatric Psychiatry requires that the authors participating in a continuing medical education activity disclose to participants any significant financial interest or other relationship (1) with the manufacturers of any commercial service discussed in an educational presentation, and (2) with any commercial supporters of the activity.

Dr. Nelson reported that he has received research support or lecture honoraria from and/or has served as a consultant or advisory board member for Bristol-Myers Squibb Company, Organon, Inc., Pfizer, Inc., Abbott Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, and Eli Lilly and Company. He has also received support from Pharmacia, Wyeth-Ayerst Pharmaceuticals, and Forest Pharmaceuticals, Inc.

Dr. Lavretsky reported that she has received grants/research support from Forest Pharmaceuticals, Inc. She has served as a consultant for Forest Pharmaceuticals, Inc., and Eli Lilly and Company. She has also served on an advisory board and on the speaker's bureau for Forest Pharmaceuticals, Inc.

Dr. Burke reported that he has received research support from Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Eli Lilly and Company, Merck & Co., Pfizer, Inc., Cyberonics, and Novartis. He has also served as on the advisory board and/or received lecture honoraria from Abbott Laboratories, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica, Eli Lilly and Company, Pfizer, Inc., Cyberonics, and Novartis.

This special report was sponsored by the American Association for Geriatric Psychiatry and produced by MultiMedia HealthCare/Freedom, LLC, under an unrestricted educational grant from Forest Pharmaceuticals, Inc. The views expressed in this publication are not necessarily those of Forest Pharmaceuticals or the publishers. This publication may not be reproduced in whole or in part without the express written permission of MultiMedia HealthCare/Freedom, LLC.

Copyright © 2003 MultiMedia HealthCare/Freedom, LLC.  
All rights reserved. Office Center at Princeton Meadows, Building 400,  
Plainsboro, NJ 08536. Telephone: (609) 275-3800.  
Printed in USA.

SRTD-03027

