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EFFICACY OF VENLAFAXINE IN GERIATRIC DEPRESSION

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Geriatric patients with major depression present clinical challenges not encountered in younger individuals, including a greater incidence of medical comorbidity, higher rates of multiple medication use, changes in drug metabolism due to age or physical illness, and increased sensitivity to antidepressant side effects. Nevertheless, successful treatment of depressive disorders in the elderly improves mental and physical functioning, decreases morbidity and perhaps mortality, and enhances quality of life. Recent research indicates that newer antidepressants are effective for late life depression and safer for older individuals. Among newer antidepressants, venlafaxine has a pharmacological profile that makes it an attractive choice for geriatric patients. It has limited potential to interact with other medications because it only weakly inhibits the cytochrome P450 system and binds to plasma proteins at a low level. Dosing may have to be adjusted for patients with renal failure, but typically not for those with liver disease or other medical conditions. Data from three double-blind and four open clinical trials support the safety and efficacy of venlafaxine for geriatric depression. Patients may experience transient, generally tolerable side effects such as insomnia, nausea, agitation, or dry mouth early in treatment, but more serious problems such as falls or cardiac rhythm disturbances seem to be rare. Treatment emergent hypertension occurs in a small percentage of older patients, generally at doses above 150 mg/day. Finally, emerging data suggest that venlafaxine may be effective for conditions such as stroke, anxiety, and neuropathic pain that frequently accompany depressive disorders in the elderly. Depression and Anxiety, Volume 12, Supplement 1:63–68, 2000. *© 2000 Wiley-Liss, Inc.*

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INTRODUCTION

The detection, diagnosis, and treatment of depressive disorders in the elderly involve a number of clinical challenges that are not encountered in younger individuals; yet, there clearly are clinical benefits to mastering these challenges for older patients living independently as well as for those in institutional settings [Salzman, 1999]. Research over the last two decades has differentiated the morbidity and mortality of major mood disorders from non-pathological periods of grief, demoralization, and dysphoria that may accompany the physical and psychosocial changes of advancing years [Blazer and Konig, 1996]. Rates of major depression vary from as low as 5% in medically healthy, community-dwelling elderly to approximately 25% in nursing home residents [NIH Consensus Development Panel, 1992], and even higher for patients in acute medical care settings [Katon and Sullivan, 1990; Cassem, 1995]. Depressive disorders are associated with poorer quality of life and increased morbidity and mortality from co-existing medical illnesses [Evans et al., 1999]. The elderly, particularly white males, have the highest rates of suicide of any demographic group in the United States [Blazer and Konig, 1996].

Fortunately, the growing recognition of the burden that depressive disorders place on the elderly has coincided with the introduction of new generations of antidepressant medications over the last decade. Each of these new drugs offers advantages over tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) for older individuals, particularly those with active medical problems [DeBattista and Schatzberg,

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1996; DeVane and Pollock, 1999; Evans et al., 1999; Salzman, 1999]. Effective use of these medications requires an understanding of their unique characteristics and the benefits that each agent brings to depressed geriatric patients. Specific considerations include: (1) age-related alterations in pharmacokinetics and pharmacodynamics due to reduced renal and hepatic clearance as well as changes in volumes of distribution for fat soluble compounds, (2) increased potential for drug-drug interactions because of the high likelihood that older individuals will be taking multiple medications, (3) lower tolerance for medication side effects because of normal physiological changes with age as well as concomitant medical illnesses, and (4) simplicity of dosing regimens for individuals who require several medications [DeBattista and Schatzberg, 1996; Rothschild, 1996; DeVane and Pollock, 1999; Salzman, 1999]. The benefits of mastering these challenges for older patients include enhanced physical and psychological functioning and better quality of life [Salzman, 1999]. In addition, aggressive treatment of depression may reduce the negative impact that depression can have on the course of co-existing medical illnesses [Evans et al., 1999]. This review will focus on venlafaxine, examining its pharmacological properties and effectiveness for treating geriatric depression. Specific attention will be paid to emerging data on its safety, efficacy, and dosing patterns in older individuals.

PROFILE OF VENLAFAXINE

Venlafaxine was introduced into the United States in 1994, and now is marketed in two preparations, immediate- and extended-release tablets. Venlafaxine inhibits the reuptake of serotonin, norepinephrine, and, more weakly, dopamine [Muth et al., 1986]. Inhibition of serotonin reuptake occurs at low doses whereas norepinephrine reuptake inhibition does not come into play until doses reach approximately 150 mg/day or higher [Harvey et al., 2000]. Venlafaxine is metabolized in the liver to the active metabolite *O*-desmethylvenlafaxine, largely through cytochrome P450 2C9, 2C19, and 2D6 isoenzymes. It also is metabolized to *N*-desmethylvenlafaxine by cytochrome P450 2C9, 2C19, and 3A4 pathways. Both of these metabolites are excreted by the kidneys [Kahn et al., 1995; Fogelman et al., 1999]. Venlafaxine is approximately 28% bound to plasma proteins [Kahn et al., 1995]. Furthermore, it is a very weak inhibitor of the cytochrome P450 isoenzyme system [Kahn et al., 1995; von Moltke et al., 1997; Owens and Nemeroff, 1998; Alfaro et al., 2000]. These properties mean that venlafaxine has a low potential to interact with other medications through either hepatic metabolism or competition for plasma protein binding sites. Dosing does not have to be adjusted for hepatic disease, but should be reduced for renal insufficiency (creatinine clearance <30 ml/min) [Troy et al., 1994; Goldberg, 1997].

The most common side effects of venlafaxine are headache, gastrointestinal upset, sleep changes (most often insomnia), restlessness or agitation, sweating, dry mouth, and sexual dysfunction [Anderson et al., 2000]. A similar side effect profile has been found in the elderly [Khan et al., 1995; Dierick, 1996; Amore et al., 1997; Mahapatra and Hackett, 1997; Smeraldi et al., 1998]. Most often these side effects are transient and can be managed by gradually titrating the medication. Venlafaxine also can cause dose-related increases in blood pressure. In data pooled from pre-marketing trials in adults of all ages, approximately 5% of patients taking 200 mg or more per day experienced a significant increase in blood pressure defined as a diastolic blood pressure ≥105 mm Hg or elevations ≥15 mm Hg above baseline [Feighner, 1995]. Using a different definition of sustained hypertension (diastolic blood pressure ≥90 mm Hg and elevation ≥10 mm Hg above baseline for three consecutive visits), 13% of patients developed treatment emergent hypertension at doses above 300 mg/day [Wyeth Laboratories, 1999]. There is some evidence that venlafaxine-related blood pressure elevations may normalize with time [Thase, 1998]. No systematic cardiac conduction changes were attributed to venlafaxine in the early clinical trials of adults across the age spectrum [Feighner, 1995].

Over the last few years, a greater emphasis has been placed on attaining full remission of depressive episodes (e.g., HAM-D <8), rather than a simple reduction in depressive symptoms during medication trials (e.g., decline in HAM-D by 50%, regardless of final symptom score). With full remission as a goal, there is emerging evidence that venlafaxine may be superior to selective serotonin reuptake inhibitors (SSRIs) in treatment resistant depression [Poirier and Boyer, 1999; Rudolph and Feiger, 1999; Mehtonen et al., 2000], possibly due to its dual action on serotonin and norepinephrine. For this reason, some expert panels [e.g., Anderson et al., 2000] have recommended starting with a TCA or venlafaxine instead of an SSRI or MAOI for severe depression, though other consensus conferences have not determined that any newer antidepressants are superior in efficacy [e.g., Parker et al., 1999].

VENLAFAXINE IN DEPRESSION WITH CO-EXISTING ILLNESSES

Co-existing anxiety may be an important part of the total morbidity of major depression, particularly in the elderly. A meta-analysis of data from the early depression trials of venlafaxine in adults of all ages showed significant reductions in anxiety accompanying the antidepressant effect [Rudolph et al., 1998]. In a large study of depressed outpatient adults, extended-release venlafaxine was as effective as fluoxetine for depressive

symptoms, but was superior in reducing anxiety [Silverstone and Ravidran, 1999]. Venlafaxine also is effective for generalized anxiety disorder (GAD) [Sheehan, 1999], an illness with physical symptoms that may overlap with those of chronic depression in the elderly. An analysis of pooled data from five placebo-controlled trials of venlafaxine for GAD showed that its positive effect on anxiety applied equally well to subjects older and younger than age 60 [Mahe et al., 1999].

The neurobiology of depression beginning in late life may differ from that of depressive disorders with onset in younger years. Recent data have raised the possibility that late life depression may be associated with cerebrovascular disease, particularly small, subcortical cerebral infarctions [Steffens et al., 1999]. Treatment studies in patients with recent strokes suggest that antidepressants with noradrenergic activity (e.g., nortriptyline [Robinson et al., 2000] and venlafaxine [Dahmen et al., 1999]) may have a specific role in post-stroke therapy, improving both physical functioning and psychiatric outcomes. Additional studies are needed to confirm the possible link between small vessel cerebrovascular disease and depression, and to follow up on the initial trials of noradrenergic antidepressants.

Patients with depression and active medical illnesses present a challenge regardless of age, though co-existing illnesses are much more likely to be encountered in older patients. Aggressive treatment of depression in medically ill individuals is warranted, as depression carries not only its own morbidity and mortality, but increases the likelihood of unfavorable outcomes from co-existing medical illnesses [Evans et al., 1999]. The best studied example of this is the adverse effect that depression has on the course of atherosclerotic coronary artery disease [for review, Musselman et al., 1998]. Untreated depression after a myocardial infarction is as great a risk factor for sudden cardiac death as is the presence of ventricular arrhythmias. Furthermore, depression and arrhythmias have a multiplicative, negative effect on mortality when they are present simultaneously [Frasure-Smith et al., 1993, 1995].

Researchers are conducting an increasing number of open-label and double-blind trials of newer antidepressants in depressed, medically ill patients, providing evidence that these medications are effective and safer than TCAs or MAOIs for this patient population. To date, data of varying levels of sophistication exist to support the use of the SSRIs, venlafaxine, bupropion, nefazodone, and mirtazepine in the medically ill [for reviews see Evans et al., 1996–97, 1999; Beliles and Stoudemire, 1998; Sutor et al., 1998]. There are, however, no head-to-head comparisons of newer medications in the medically ill. Clinical experience suggests that the side effects of the newer agents often present trade-offs depending on the clinical situation. In addition, some of the newer antidepressants have a greater potential for certain drug-drug interactions than the others because of their profiles of cytochrome P450 isoenzyme inhibition [for reviews, see Ereshevsky et al., 1996; Nemeroff et al., 1996].

Some antidepressants have direct positive benefits for specific medical conditions. Tricyclic antidepressants, for example, have been used for years to treat migraine, chronic neuropathic pain, and fibromyalgia. Recent open trials suggest that venlafaxine also may be helpful for patients with these conditions [Davis and Smith, 1999; Dwight et al., 1998; Nascimento, 1998].

EVIDENCE SUPPORTING VENLAFAXINE FOR GERIATRIC DEPRESSION

Three double-blind comparisons and four open-label trials have investigated the efficacy of venlafaxine in geriatric patients with major depression. In the first double-blind study [Mahapatra and Hackett, 1997], venlafaxine proved to be as efficacious as dothiepin (a TCA marketed in Europe, considered to have a more favorable side effect profile than other TCAs) for a group of medically healthy geriatric outpatients aged 64–87 years. Both drugs produced remission rates of about 60% after six weeks of treatment as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Scale (HAM-D). Venlafaxine yielded significantly lower suicidal ideation scores on the MADRS. The dose ranges of both medications were 50–150 mg per day. Treatment emergent side effects occurred in 32 of 44 (73%) patients treated with venlafaxine and 32 of 48 (67%) of those treated with dothiepin, yet the majority of patients in both groups (≥80%) tolerated their medications and successfully completed the study. Most of the side effects were typical of the two medications (e.g., dry mouth, constipation, headache, and urinary retention). Venlafaxine, however, produced significantly lower rates of more serious side effects. The authors reported 7 cases of prolonged PR or QTc intervals on the electrocardiogram in the dothiepin group, but only one instance of QTc prolongation in a venlafaxine patient. They also noted significantly fewer cases of treatment emergent, standing systolic hypertension with venlafaxine (2%) vs. dothiepin (17%), though they did not publish their blood pressure parameters. Eight patients in the dothiepin group reported vertigo or postural hypotension and three sustained falls. Four patients treated with venlafaxine reported dizziness, but there were no instances of hypotension or falls.

The second double-blind investigation of venlafaxine in late life depression was a six-week, randomized comparison of venlafaxine (n = 55), clomipramine (n = 58), and trazodone (n = 57) for inpatients and outpatients, 65 years and older, meeting the DSM-III-R criteria for major depression [Smeraldi et al., 1998]. The dose range of venlafaxine was 75–150 mg per day, compared to 50–100 mg/day for clomipramine and

150–300 mg/day for trazodone. Significantly more patients treated with venlafaxine (74%) and clomipramine (69%) were much or very much improved on the Clinical Global Improvement (CGI) scale compared to trazodone (57%). Venlafaxine and clomipramine also produced significantly greater decreases on the MADRS and HAM-D ($P < 0.05$ for the comparisons on all three scales). Venlafaxine was tolerated significantly better than the other two medications with 20% of venlafaxine treated patients reporting any adverse effects vs. 28% for clomipramine and 37% for trazodone ($P < 0.02$). Venlafaxine and clomipramine did not cause any ECG changes, whereas trazodone produced alterations in 3 patients. Treatment emergent hypertension occurred in 2 patients in the venlafaxine group and 3 each for clomipramine and trazodone. Postural hypotension was not reported in any venlafaxine patient vs. 1 for clomipramine and 4 for trazodone.

The initial results of the largest controlled trial of venlafaxine in geriatric depression were reported recently [Schatzberg and Cantillon, 2000]. This investigation was an 8-week, randomized study of venlafaxine (n = 104) vs. fluoxetine (n = 100) and placebo (n = 96) in medically healthy outpatients, aged 65 years and older with major depression by DSM-IV criteria. The dose range for venlafaxine was 75–225 mg/day and for fluoxetine 20–60 mg/day. Approximately 50–60% of patients in all three groups had a positive treatment response (≥50% reduction from baseline on the HAM-D or MADRS, much or very much improved on CGI), and 29–42% achieved complete remission (HAM-D <8). Given the large placebo response rate, there were no statistically significant differences in treatment outcome among the three groups at the 8-week endpoint. Scores on the HAM-D and MADRS during the third and fourth weeks of treatment, however, showed that venlafaxine produced a significantly faster therapeutic response. Nearly all patients reported at least one treatment emergent side effect (venlafaxine 92%, fluoxetine 94%, placebo 86%). Nausea and headache were most frequent in both medication groups, whereas headache and dry mouth were most common in the placebo group. Only 2 patients in the venlafaxine group developed sustained, diastolic hypertension compared to 1 each for fluoxetine and placebo.

Four open label studies [Khan et al., 1995; Dierick, 1996; Amore et al., 1997; Zimmer et al., 1997] also support the safety and efficacy of venlafaxine in geriatric patients with major depression. These studies ranged in size from 18 to 116 patients. Venlafaxine doses averaged 104–130 mg/day for 6 to 24 months. Patients who remained in the studies had significantly reduced depressive symptoms and improved global functioning and quality of life. Typical venlafaxine-related side effects occurred in one-quarter to two-thirds of patients. More serious side effects occurred at low rates. In three of the four studies [Khan et al., 1995; Dierick, 1996; Zimmer et al., 1997], approximately 1 in 10 patients reportedly developed elevated blood pressures, though none of the authors specified the criteria by which they made this judgment. Dierick (1996) reported three falls that he considered drug related and seven cases of unspecified EKG changes among 116 patients studied. Zimmer et al. [1997] reported no cardiac conduction effects in their 18 medically ill, older subjects.

One of the open label studies [Amore et al., 1997] examined maintenance treatment for geriatric depression with venlafaxine. Twenty-one of 28 patients with recurrent major depression who responded positively to acute treatment at a mean dose of 112.5 mg/day (range 75–225 mg daily) were followed for 24 months. Eighty percent remained in remission. All of those who relapsed responded well to a dose increase.

MANAGEMENT CONSIDERATIONS IN THE ELDERLY

Collectively, the seven studies cited above support the safety and efficacy of venlafaxine for the treatment of depression in older adults. Very few of the subjects in these studies, however, were in the old old age range (>85 years) and all of the studies, except the small trial by Zimmer et al. [1997], excluded patients with significant cardiac, neurological, hepatic, or renal disease. A retrospective analysis of data pooled from 3082 patients in the pre-marketing clinical trials of venlafaxine showed similar safety and tolerability between older and younger patients [Rudolph and Derivan, 1996]. The double-blind studies reviewed here reported a wide range (20–92%) of side effects from venlafaxine and other antidepressants. Venlafaxine was tolerated better than clomipramine and trazodone [Smeraldi et al., 1998], and produced fewer serious side effects than dothiepin [Mahapatra and Hackett, 1997]. In the large, placebo-controlled trial of Schatzberg and Cantillon [2000], both venlafaxine and fluoxetine were well tolerated. The most common venlafaxine side effects in the seven geriatric trials were headache, gastrointestinal upset, sleep disturbances, restlessness or agitation, and dry mouth. This side effect profile is typical for younger adults as well, and most patients in the geriatric trials elected to continue their medication. These results demonstrate that side effects are likely to occur early in the course of treatment with venlafaxine, but that, in most cases, they will be tolerable or resolve over a short period of time.

More serious venlafaxine side effects occurred at very low rates in the geriatric depression trials. The open studies suggested a potential problem with treatment emergent hypertension in as many as 1 of 10 older patients, but this finding was not replicated in the larger and more rigorously controlled, double-blind investigations where elevated blood pressures occurred in only 2–4% of patients taking venlafaxine. Lower rates of cardiac conduction problems, postural hypotension, and falls were reported.

The basic pharmacologic data for venlafaxine suggest that dose reductions are not needed for older patients [Kahn et al., 1995; Klamerus et al., 1996], except for those with renal failure [Troy et al., 1994]. The average daily doses of venlafaxine used in the geriatric depression trials (104-130 mg), however, were lower than the doses employed in comparable studies of younger patients 140–175 mg [e.g., Rudolph and Feiger, 1999; Silverstone and Ravindran, 1999]. Overall, the geriatric treatment outcomes were positive and rates of serious side effects were low. None of the geriatric investigations used total daily doses in excess of 225 mg. This suggests that a reasonable initial target dose of venlafaxine for geriatric depression may be just over 100 mg/day (three 37.5 mg extended release tablets), with a range of 50–150 mg daily. Doses above this range may be necessary for patients who have not attained a full remission of their depressive symptoms, provided that they are tolerating the medication well. Extended release venlafaxine can be prescribed in single or divided doses [Rudolph and Feiger, 1999; Silverstone and Ravindran, 1999], simplifying administration for patients with complex schedules of other medications.

CONCLUSIONS

Depressive disorders can be diagnosed and treated effectively in geriatric patients, improving their quality of life and reducing medical and psychiatric morbidity and possibly mortality. The pharmacokinetic and pharmacodynamic profiles of venlafaxine make it an attractive medication for use in the elderly. Three double-blind studies and four open trials support its safety and efficacy in older adults with major depression. In addition, venlafaxine may exert positive benefits on conditions such as anxiety, neuropathic pain, and stroke that often are encountered in the geriatric population. Side effects such as nausea, sleep disturbances, and dry mouth were relatively common in the geriatric depression trials, but they usually were tolerable and manageable with gradual dose adjustments. Treatment emergent hypertension occurred in only a small percentage of patients. Safety and efficacy data remain sparse for individuals over age 85 and for those with serious medical conditions, so future studies should also focus on these populations of geriatric patients. Overall, the available data are encouraging for the use of venlafaxine for the treatment of geriatric depression.

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