Key Words: paroxetine, selective serotonin reuptake inhibitors, depression, elderly

Paroxetine Treatment of Depression in Late Life

By Charles F. Reynolds III, MD

ABSTRACT *~ The elderly population is growing at a rapid rate and currently constitutes more than 12% of the United States' population. Within the next 30 years, the number of elderly persons is expected to more than double, creating a concerning situation regarding provision of healthcare services. Depression is a prevalent and underrecognized disorder in older adults and is associated with both increased healthcare utilization and suicide. Treatment of depression improves quality of life and reduces functional decline and suicidal ideation. Maintenance therapy for depression is commonly overlooked and must be emphasized for management of depression in elderly patients. First-line treatment options include selective serotonin reuptake inhibitors (SSRIs), one of which, paroxetine, has been studied extensively in older adults. The findings of studies that have evaluated the efficacy of paroxetine demonstrate successful treatment of depression and long-term relapse prevention in this population. With the significant personal and societal burden that is associated with major depression in the elderly, appropriate treatment is important and must be incorporated into standard practices by healthcare professionals.* Psychopharmacology Bulletin. *2003;37(Suppl 1):123-134.*

INTRODUCTION

The elderly, defined as persons 65 years of age or older, are the fastest-growing segment of the United States' population.[1] In 2000, the elderly population consisted of 35 million people, which reflects a 12% increase over the previous decade. During the next 30 years, it is predicted that the number of elderly persons in the United States will more than double. Current life expectancy of individuals reaching the age of 65 ranges from 16 to 18 years for males and females, respectively. With the increasing number of aging individuals who are expected to live longer than ever before, the utilization of healthcare resources is expected to rise significantly.

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DEPRESSION IN THE ELDERLY

Aside from the numerous functional and medical problems that commonly afflict elderly individuals, many elderly persons also experience clinically significant symptoms of depression. In one sample population of more than 4500 elderly persons between the ages of 65 and 100 years, the overall lifetime prevalence of depression was 15.8%, ranging from 9.6% in men to 20.4% in women.[2] The World Health Organization predicts that by the year 2020, depression will be the second most common cause of disability and premature death in countries with established economies.[3] Many factors may complicate the identification and treatment of depression in older persons, including comorbid medical or neurologic illness, ageism, cognitive decline, and bereavement.[4] As a result, mood and anxiety disorders in older adults frequently are treated inadequately, resulting in continued disability, functional decline, diminished quality of life, caregiver burden, and increased risk of hospitalization.[5-7] Furthermore, older adults with depression are high utilizers of healthcare resources. In one study of more than 3400 elderly primary care patients, those with depression visited their physicians more often ($P<.0001$), and required more laboratory screenings ($P=.008$), radiologic procedures ($P<.0001$), and consultations ($P<.0001$) than elderly patients without depression.[8]

Another area of concern for the elderly population is the correlation between depression and mortality. In a study of 5201 persons, higher baseline depressive symptoms were associated with a higher mortality rate (relative risk, 1.43; 95% C.I. 1.23, 1.66; $P<.001$) when controlled for various sociodemographic factors, clinical disease, subclinical disease indicators, and health risk factors.[9] Depression in nursing home residents can be a particularly lethal development. In one study of 454 new admissions to a nursing home, 47.4% of persons with major depressive disorder did not survive at the 1-year follow-up compared with death rates of 24.4% of persons with depressive symptoms (ie, subsyndromal depression) and 29.8% of those without depression ($P<.05$).[10]

Suicide is another important factor to consider in elders with depression. Depression is a key predictor of suicide in older adults,[11] and common precipitants of suicide are physical illness and loss.[12] Individuals aged 65 years and older account for approximately 19% of yearly suicide deaths,[13] and the rate of completed suicide is highest in Caucasian men older than the age of 85 years (>60%).[14] There is a great unfulfilled need for adequate mental health treatment and services for the elderly.[15]

TREATMENT OF DEPRESSION IN THE ELDERLY

Depression is a significant problem in the elderly population and presents wide-ranging repercussions influencing physical and mental health. It is scandalous that late-life depression remains both underrecognized

and undertreated. In a survey of 4,559 elderly individuals, only 59.3% of patients with lifetime major depression reported their depression to a physician, and approximately one fourth received treatment, in the form of psychosocial counseling.[2] Less than half of elderly depressed patients in the survey were receiving or had received any pharmacologic treatment, which is tragic because late-life depression is very responsive to medication.[2,16]

The selective serotonin reuptake inhibitors (SSRIs) are considered first-line options in the treatment of depression in older patients.[17,18] The SSRIs have been shown to be superior to placebo[23-25] and as effective as the tricyclic antidepressants (TCAs) for the treatment of major depressive disorder in older adults, but generally better tolerated.[19-22]

PAROXETINE TREATMENT OF LATE-LIFE DEPRESSION

In keeping with the objective of this supplement, the pertinent clinical studies of paroxetine and paroxetine controlled-release (CR) treatment of depression in elderly patients are reviewed herein.

ACUTE TREATMENT WITH PAROXETINE

There are a number of well-controlled, short-term studies of paroxetine in the treatment of depression in the elderly. Methods and findings of double-blind comparator trials are summarized in Table 1. The findings from these studies, which included nearly 1,000 patients in total, demonstrate that paroxetine is as effective as the TCAs and fluoxetine in treating elderly patients with depression and depressive symptoms.

TREATMENT WITH PAROXETINE CR

A controlled-release formulation of paroxetine has been developed and studied in older adults.[31] Patients included in this randomized, controlled trial were at least 60 years of age and had a diagnosis of major depressive disorder and mean baseline Hamilton Rating Scale for Depression (HAM-D) total scores of approximately 22. In addition, patients in this study generally had chronic depression, with a mean duration of depression of at least 3 years. A total of 323 patients were randomized to receive paroxetine CR 12.5 mg daily, paroxetine immediate-release (IR) 10 mg daily, or placebo. After 1 week, doses were increased to a maximum of 50 mg paroxetine CR or 40 mg paroxetine IR in 12.5-mg/day (CR) or 10-mg/day (IR) increments no more frequently than once a week, as required and as tolerated.

In the last observation carried forward (LOCF) population, mean HAM-D total scores at end point were 10 for paroxetine CR (P=.007 for change from baseline to endpoint vs placebo) and paroxetine IR (P=.003 for change from baseline to endpoint vs placebo). Response, which was

defined as a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impressions improvement scale, was achieved by 72% of paroxetine CR patients (*P*<.002 vs placebo), 65% of paroxetine IR patients (*P*=.06), and 52% of placebo patients. Remission, defined as HAM-D total score of 7 or lower, was achieved by 43% of the paroxetine CR group (*P*=.009 vs placebo), 44% of the paroxetine IR group (*P*=.01 vs placebo), and 26% of the placebo group at LOCF end point. Remission rates in the observed cases population were somewhat higher (Figure 1). Adverse events were reported to be generally mild, and included somnolence, dry mouth, headache, diarrhea, nausea, constipation, and dyspepsia. Withdrawal rates because of adverse events were low (12.5% for paroxetine CR, 16% for paroxetine IR, 8.3% for placebo). Notably, incidences of hypotension and insomnia, which are of concern in older patients, were similar between the paroxetine CR group and the placebo group. Overall, paroxetine CR was well tolerated and resulted in high remission rates in elderly patients with major depressive disorder.

TABLE 1

PAROXETINE TRIALS IN ELDERLY DEPRESSED PATIENTS

Reference	Study Design	Duration (wk)	No. of Patients	Age (y) (mean ± SD; range)
Dunner et al, 1992[26]	db, ac	6	271	68; >60
Geretsegger et al, 1995[27]	db, ac	6	91	71 ± 5.9; >65
Guilibert et al, 1989[28]	db, ac	6	79	69; >60
Hutchison et al, 1992[29]	db, ac	6	101	72
Katona et al, 1998[30]	db, ac	8	198	77; 59-98
Mulsant et al, 1999[21]	db, ab	6	80	75 ± 7.4; >60
Schone & Ludwig, 1993[22]	db, ac	6	106	74; 61-85

Adapted from Solai et al, 2001 with permission.
* Modest improvement observed for intent-to-treat patients of both treatment groups.
ac=active-controlled; AMI=amitriptyline; CLO=clomipramine; db=double-blind; DOX=doxepin; FLU=fluoxetine; HAM-D=Hamilton Depression Rating Scale; IMI=imipramine; MADRS=Montgomery-Asberg Depression Rating Scale; NOR=nortriptyline; PAR=paroxetine;=indicates as effective as.

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SUICIDE PREVENTION

The relationship between paroxetine or nortriptyline treatment and suicide risk has been studied. A post hoc analysis of 3 studies evaluated the rates of response and improvement in suicidal ideation during treatment with nortriptyline or paroxetine in 395 elderly patients with major depressive disorder.[32] The HAM-D total score was used as the primary outcome measure of efficacy, and response was defined as a HAM-D total score of less than 10. Patients were stratified according to suicide risk using the HAM-D suicide item. Overall, suicidal ideation and recurrent thoughts of death declined markedly during treatment, regardless of baseline suicide risk. At pretreatment baseline, 77% of all patients endorsed suicidal ideation, but by week 12, thoughts about death or suicide and feelings of emptiness improved significantly in both the paroxetine and nortriptyline groups ($P<.0001$). Only 18% of patients in this analysis endorsed continued suicidal thoughts.

Of those patients considered at low risk for suicide, 85% were responders to nortriptyline or paroxetine after 12 weeks of treatment, 77% of

Dosage (mg/day)	Result	Comment
PAR 10-40, DOX 75-200	PAR = DOX	
PAR 20-30, AMI 100-150	PAR = AMI	Severely depressed inpatients (HAM-D score >25). PAR higher incidence of anxiety, agitation; AMI higher rates of anticholinergic adverse events.
PAR 30, CLO 75	PAR = CLO	
PAR 30, AMI 100	PAR = AMI	Significantly fewer adverse effects and anticholinergicity seen with PAR
PAR 20-40, IMI 50-100	PAR = IMI	75% of patients had ≥1 concurrent illness
PAR 20, NOR 50	PAR = NOR	55% of patients met criteria for major depression with melancholic features
PAR 20-40, FLU 20	PAR = FLU*	Higher response rate in PAR group according to HAM-D and MADRS criteria

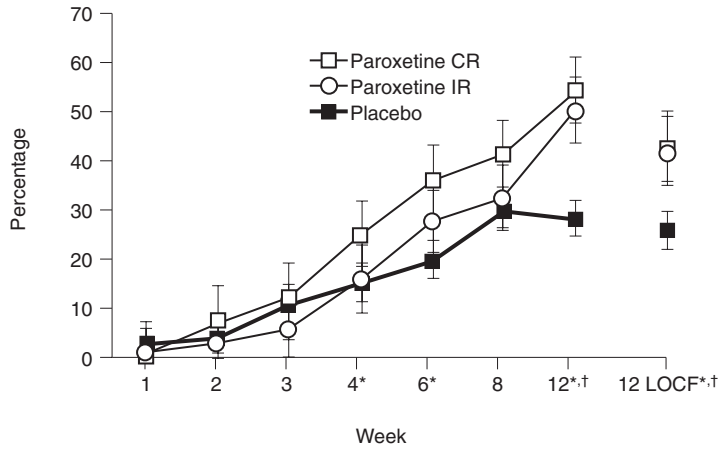
moderate-risk patients responded, and 67% of high-risk patients responded. Time to therapeutic response was shorter for patients at low suicide risk, and low-risk patients were more likely to be full responders at weeks 6 and 12 compared with moderate- or high-risk patients.[32] These findings suggest that patients with suicidal thoughts or behaviors may need longer courses of acute treatment to achieve full therapeutic response. In addition, this analysis underscores the need for vigilance toward suicidality and the importance of treating elderly patients with depression to full remission.

PREVENTION OF RECURRENT DEPRESSION

Depression in late life often can be chronic and recurrent. An important treatment goal, therefore, is to achieve and maintain full recovery and prevent recurrent depressive episodes. Simply put, "It's not getting well that counts, it's staying well." Long-term antidepressant maintenance therapy may be necessary, and psychotherapeutic interventions can assist in sustaining remission. For example, maintenance therapy with nortriptyline in older patients with major depression significantly reduced recurrence of depressive episodes compared with placebo during a period of 3 years (Figure 2).[33] The combination of antidepressant

FIGURE 1

WEEKLY REMISSION RATES ACROSS 12 WEEKS OF TREATMENT WITH PAROXETINE CR, PAROXETINE IR, OR PLACEBO



Weekly remission rates (Hamilton Rating Scale for Depression [HAM-D] total score ≤7) across 12 weeks of treatment with paroxetine controlled-release (CR), paroxetine immediate-release (IR), or placebo.

* Paroxetine CR vs placebo=P<.05; † paroxetine IR vs placebo=P<.01.

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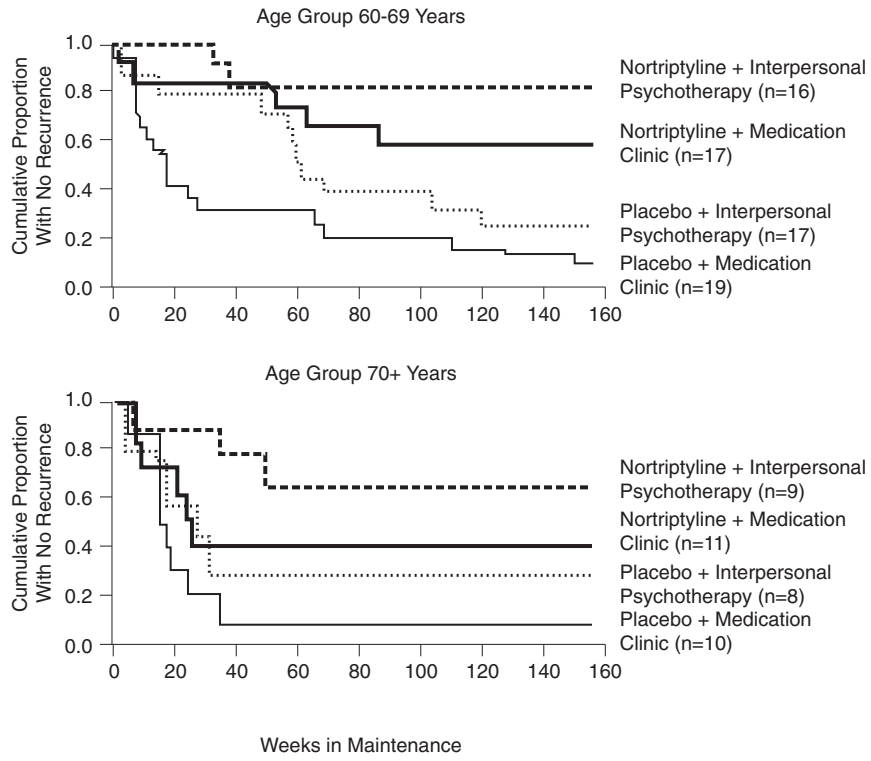
therapy with interpersonal psychotherapy further reduced recurrence rates and was significantly more effective than interpersonal psychotherapy combined with placebo (P=.003), allowing approximately 80% of patients to maintain recovery.

Follow-up analysis of a double-blind comparative trial of paroxetine and nortriptyline demonstrated low rates of recurrence of symptoms of major depression for both agents in older patients.[34] Five of 25 patients receiving paroxetine and 1 of 15 patients receiving nortriptyline relapsed within 12 months. In another comparison of paroxetine and nortriptyline maintenance therapy in the elderly, both agents again demonstrated similar efficacy in relapse prevention over 18 months. Of 38 patients receiving paroxetine treatment, 6 suffered a depressive episode compared with 2 of 21 patients receiving nortriptyline. Time to relapse for both groups also was comparable (60.3 weeks for paroxetine, 58.8 weeks for nortriptyline).[35]

FIGURE 2

RECURRENCE RATES OF DEPRESSIVE EPISODES DURING MAINTENANCE THERAPY IN ELDERLY PATIENTS WITH LATE-LIFE DEPRESSION



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IMPROVEMENT IN COGNITIVE IMPAIRMENT

In addition to potential relapses of depressive episodes, late-life depression is associated with reduced quality of life and is an independent predictor of cognitive and functional decline.[36] Although treatment with SSRIs is not expected to entirely alleviate symptoms of cognitive decline, it may reduce the severity of impairment.[15] Improvement in symptoms of depression correlates with improvement in quality of life, and elderly patients who have recovered from depression experience greater perceived physical and social functioning compared with partial responders and nonresponders.[37]

Paroxetine improved symptoms of depression and measures of cognitive and behavioral function as measured by the Sandoz Clinical Assessment Geriatric Scale and Mini-Mental State Examination in a 6-week, randomized, double-blind trial evaluating 106 elderly depressed patients.[38] The findings of a 1-year, double-blind study of patients randomized to either paroxetine (123 patients) or fluoxetine (119 patients) demonstrated significant improvement from baseline in the Blessed Information and Memory Test ($P<.004$ for paroxetine, $P<.0001$ for fluoxetine), Clifton Assessment Schedule ($P<.01$ for paroxetine at week 6, $P<.05$ for fluoxetine at week 6), and Wechsler Paired Word Test ($P<.0008$ for paroxetine, $P<.003$ for fluoxetine).[20] In another study of 29 elderly patients with depression, treatment with 20 to 40 mg of paroxetine daily for 6 weeks resulted in significant improvement over baseline in both parts of the Trail Making Test ($P<.002$ for part A, $P<.006$ for part B), Digit Symbol Substitution Test ($P<.0001$), and Copy Task ($P<.0001$).[39] Such findings demonstrate marked improvement in measures of attention and cognitive speed with paroxetine therapy.

ADVERSE EVENTS OF CONCERN IN THE ELDERLY

Falls

Antidepressant treatment has been associated with dizziness, orthostatic hypotension, extrapyramidal effects, and other adverse events that may be associated with falls, which is an enduring worry for older patients and their caregivers. For example, SSRI treatment has been reported to transiently increase postural sway in older depressed patients after a 1-week course of therapy.[40] A 6-week, randomized, double-blind study comparing paroxetine and nortriptyline found no evidence of postural sway for either medication.[41] The lack of postural sway observed in this study is clinically important because of the high incidence of falls and fractures in elderly individuals. The SSRIs and TCAs also have been reported to cause extrapyramidal side effects. Thirty-nine patients enrolled in a 6-week, randomized, double-blind trial comparing

extrapyramidal signs and symptoms with paroxetine and nortriptyline reported baseline symptoms as mild for both groups. At study completion, no significant between-group differences were observed, and baseline symptom scores did not increase (Figure 3).[42]

Weight Gain

Although the SSRIs have been reported to be associated with weight gain during treatment,[43] this issue has not been studied in elderly patients. In the first analysis of weight change associated with antidepressant treatment in late life, 62 elderly patients with major depression were randomized to either paroxetine or nortriptyline for a 12-week course of therapy.[44] This study is unique in the literature because premorbid weight and body mass index (BMI) were documented and compared with both pretreatment and posttreatment weight and BMI. Among the patients who completed therapy, depression severity was positively correlated with weight loss (mean 9.7-pound loss in nortriptyline group; 1.9-pound loss in paroxetine group; P=.01), and pretreatment weight loss also was significantly correlated with weight gain during treatment (8.1-pound gain in nortriptyline group; 4.7-pound gain in paroxetine group; P=.08 for between-group differences). In both the paroxetine and nortriptyline groups, weight that was lost during the depressive episode was regained following treatment. Posttreatment body weight and BMI values were not significantly different from premorbid values. Further studies are warranted to assess the relationship between weight change and response status. These findings are an important contribution to the literature because they demonstrate that major depression in the elderly can be associated with weight loss and that successful treatment normalizes depression-related body weight.

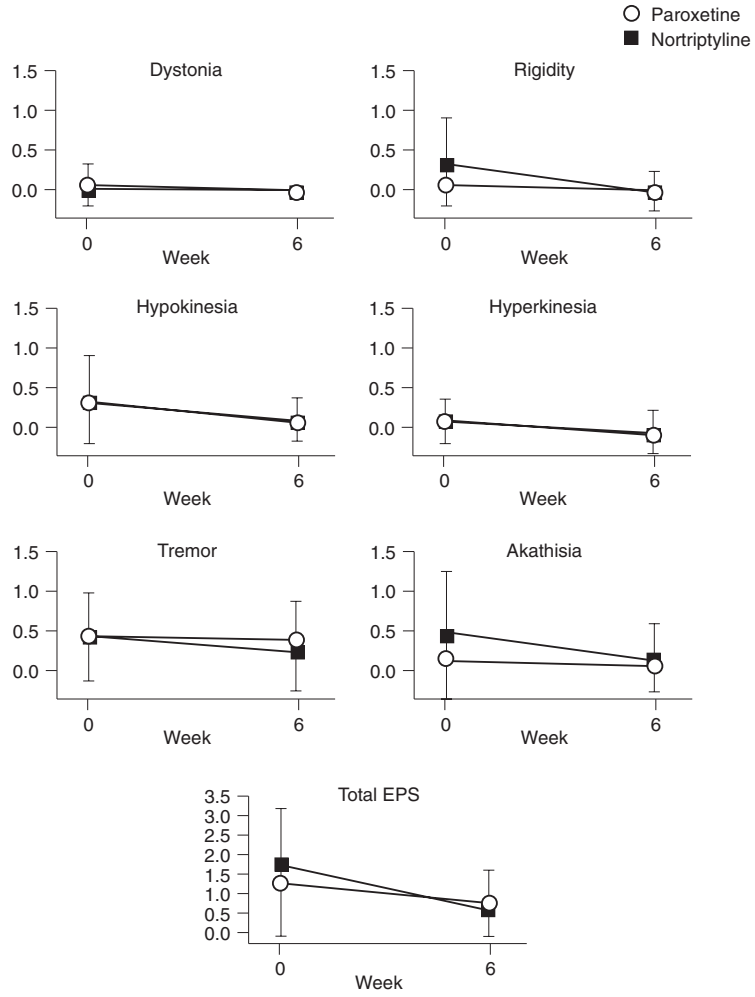
CONCLUSION

Depression in late life remains of concern for the growing elderly population because of the significant burden of disability, impaired quality of life, healthcare resource utilization, and increased risk of death associated with this disorder. Successful treatment is important to maintain quality of life and functional capacity during the later years of life. A combination of SSRIs and psychotherapy appears to be an effective treatment for major depression in older adults. The SSRI paroxetine is particularly well studied in older patients in studies of relapse prevention and studies of special populations, including patients at risk for suicide or with cognitive impairment. In addition, studies of paroxetine have contributed to our understanding of adverse events associated with falls and with weight change during antidepressant therapy in this population.

The results from paroxetine trials strongly support first-line use of SSRIs in elderly patients with major depression. Reinforcement of medication adherence must be emphasized to provide adequate long-term therapy for prevention of relapse and maintenance of recovery. Such practice policies need to be disseminated to primary care providers, rehabilitation and long-term care facilities, and other areas with many underserved elderly. ✤

FIGURE 3

CHANGE IN EXTRAPYRAMIDAL SIGNS ON AN OBJECTIVE RATING SCALE AFTER 6 WEEKS OF TREATMENT WITH PAROXETINE OR NORTRIPTYLINE



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DISCLOSURE

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