Buspirone and Imipramine for the Treatment of Major Depression in the Elderly

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Background: The current study was designed to assess the safety and efficacy of imipramine and buspirone in the treatment of major depression in elderly depressed attendees of primary care practices.

Method: 177 patients aged 65 and over (mean age = 72 years; range, 65–89) who met DSM-III-R criteria of unipolar major depression with a minimum Hamilton Rating Scale for Depression score of 18 were randomly assigned to 8 weeks of double-blind, placebo-controlled treatment with flexible doses of either imipramine or buspirone.

Results: Moderate to marked global improvement after 8 weeks of treatment (LOCF analysis) occurred in 70% of patients treated with imipramine, 61% of patients treated with buspirone, and 42% of patients treated with placebo ($\chi^2 = 9.1$, df = 2, $p < .02$). Drug treatment was well tolerated, with 77% of imipramine- and 61% of buspirone-treated patients completing 8 weeks of therapy. Imipramine/placebo differences were present from week 2 on, but buspirone/placebo differences occurred only at week 8. The presence of comorbid medical illness or concomitant use of nonpsychiatric prescription medications was not associated with poorer antidepressant response, increased adverse effects, or study attrition.

Conclusion: Imipramine and to a lesser extent buspirone were found to be effective and well tolerated in the treatment of elderly depressed outpatients.

(J Clin Psychiatry 1998;59:175–183)

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Supported by a grant-in-aid from Bristol-Myers Squibb Pharmaceuticals Research Division. Data were analyzed by the Statistics Departments of Bristol-Myers Squibb and of the Psychopharmacology Research Unit with the guidance of Karl Rickels, M.D.

Presented at the New Clinical Drug Evaluation Unit 34th annual meeting, Marco Island, Fla., June 2, 1994.

The authors thank Cathryn M. Clary, M.D.; Ira L. Fox, M.D.; Joseph M. Hassman, D.O.; Charles C. Weise, M.D.; and Sallie Hildenbrandt, Ph.D., for their participation in the data collection phase of the study and Rajesh Shrotriya, M.D., and staff at Bristol-Myers Squibb for their contribution to the conduct of the study.

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In elderly patients under medical care in either outpatient or institutional settings, the prevalence of late-life depression is relatively high, ranging from 5% to 12%.[1–4] The impact of late-life depression appears to be significant, in terms of impairment in quality of life and limitation of functioning and disability and increased cost of medical services.[5] The severity of its impact has been reported to be comparable with that for other common chronic medical conditions.[6]

In the past 30 years, hundreds of double-blind, placebo-controlled trials have been conducted investigating the efficacy of antidepressive agents for the treatment of major depression in adults under the age of 65. By contrast, Salzman (1994),[7] in a comprehensive review of drug-treatment studies of late-life depression, could identify fewer than a dozen studies that utilized both a double-blind design and had sample sizes greater than 25; none of these utilized a placebo control. Salzman found only half a dozen relatively small, placebo-controlled antidepressant trials[8–12]; all but 1 had less than 15 patients per treatment group. The relative neglect of the study of late-life depression has led to a recent National Institute of Mental Health (NIMH)-sponsored consensus conference whose strong recommendation[13] was for more well-designed research on pharmacologic treatments.

We report here a double-blind, placebo-controlled trial of buspirone compared with imipramine in the treatment of major depression in a group of elderly patients who are living in the community. Buspirone was chosen, not only because of its absence of anticholinergic side effects, but also because of its effectiveness in the treatment of younger adults who have major depression complicated by significant levels of anxiety.[14–16] Furthermore, preclinical research has found that chronic treatment with azapirones down-regulates the 5-HT_2 receptor in the same manner as other established antidepressants.[17,18] Imipramine was chosen as the standard because it is the tricyclic antidepressant that has been the most widely studied in antidepressant clinical trials in younger adults over the past 3 decades. In the elderly, however, only a few small placebo-controlled pilot studies have been published,[8–10] all demonstrating antidepressant efficacy, yet there remain serious concerns about its safety in older patients.

METHOD

Study Subjects

The study was conducted in several satellite sites of the Private Practice Research Group, which consists of community-based primary care practices affiliated with the University of Pennsylvania Psychopharmacology Unit.[19] Most patients either came from the private practices of participating family physicians or responded to outreach programs. Signs and screening questionnaires were placed in waiting rooms, and office staff encouraged patients to complete them. Patients also were recruited through outreach programs such as talks given at senior centers and life care facilities. No financial incentive was provided to patients for participation.

Inclusion criteria required that study participants be at least 65 years of age, live in a community setting (and not in a nursing home), and meet DSM-III-R criteria for major depressive episode, unipolar type, with a minimum duration of illness of 3 months, and a minimum severity score of 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[20] To ensure consistency across sites, the diagnosis of major depression was facilitated by using a semistructured interview based on a DSM-III-R diagnostic checklist.

Exclusion criteria consisted of Alzheimer's disease or other dementia; a current or past history of psychosis, schizophrenia, schizoaffective disorder, or bipolar disorder; a current or past history of seizures or glaucoma; or any acute or unstable medical condition, including Parkinson's disease, unstable endocrine dysfunctions, or cancer in the past 5 years. Concomitant psychotropic medication was not permitted, and the use of alcohol during the study was discouraged. A history in the past year of alcoholism or drug dependence, including daily use of benzodiazepines for more than 6 continuous weeks, was also reason for exclusion.

The study was approved by the Institutional Review Board of the University of Pennsylvania, and written informed consent was obtained from all patients prior to study entry.

Study Design

This was an 8-week, randomized, double-blind, flexible-dose, placebo-controlled, parallel-group comparison of imipramine and buspirone for the treatment of major depression in the elderly. Patients underwent a screening evaluation that consisted of both a psychiatric evaluation and history, as well as a comprehensive medical evaluation including electrocardiogram (ECG) and clinical laboratory tests (CBC with differential, urinalysis, SMA-6 and SMA-12, thyroid function tests). Patients' medical charts were reviewed to document the presence of medical illness. After completion of a 1-week screening period (that could be extended up to 4 weeks) to ensure that patients met all psychiatric and medical criteria, patients were randomly assigned to double-blind therapy beginning with imipramine 25 mg b.i.d. or buspirone 10 mg b.i.d. After 1 week, imipramine daily dose was increased to 25 mg t.i.d. and buspirone to 10 mg t.i.d. After the second week, if tolerated, imipramine could be increased to 100 mg/day and buspirone to 40 mg/day in divided doses. Thereafter, study treatment could be increased, based on clinical response up to a daily maximum of 150 mg of imipramine and 60 mg of buspirone. Minimal daily medication intake was 2 capsules per day (50 mg of imipramine, 20 mg of buspirone). At the end of 8 weeks of double-blind treatment, the acute phase of the study was complete, at which point patients reporting moderate-to-marked improvement were offered continuation treatment (still double-blind) for an additional 44 weeks.

Assessment of Outcome

An assessment of the clinical status of the patient, including the safety and efficacy of study treatment, was made weekly by either a physician or Ph.D.-level clinical psychologist trained in antidepressant drug treatment research. Interrater reliability was maintained at a kappa > 0.85 for the HAM-D by videotape ratings conducted before and once during the study. Whenever possible, one rater provided all assessments for a given patient throughout the study period. Overall, 6 experienced raters participated in the study. During frequent visits to the participating sites by 1 of the authors (K.R.), patients were jointly seen in the private practice of the participating physician, and joint ratings of the HAM-D and Clinical Global Improvement scale, as well as diagnostic assessments, were made for quality assurance purposes.

Primary efficacy measures consisted of the following: (1) the 17-item HAM-D,[20] (2) the Clinical Global Impression (CGI)-Severity of Illness scale (CGI-S),[21] and (3) the CGI-Global Improvement scale (CGI-I) (range of scores, 1–7).[21] Secondary efficacy measures consisted of the following: (1) a core depression factor derived from the HAM-D,[22] which consisted of depressed mood, guilt, suicide, work activity, retardation, agitation, weight loss, and diurnal variation items; (2) 4 individual factors of the HAM-D,[20] namely, cognitive disturbance, anxiety, depressed mood, and retardation; (3) the Hamilton Rating Scale for Anxiety (HAM-A)[23]; and (4) the anxiety and depression factors of the Hopkins Symptom Checklist (SCL).[24]

Safety assessments included weekly measurements of vital signs and a review of adverse effects and concomitant medications. Laboratory assessment was done at baseline and end of treatment. Compliance with study treatment was evaluated by pill counts and encouraged by a medication diary that patients completed on a daily basis.

Statistical Analyses

All efficacy analyses utilized the intent-to-treat sample defined as any patient receiving double-blind study medication with at least 1 assessment on treatment. Categorical data were analyzed by chi square or Fisher's exact test, and noncategorical or continuous data by analysis of variance (ANOVA) or covariance (ANCOVA). Analyses were carried out both for the sample of patients with assessment scores available at each study visit (available patient analysis), as well as on a sample that included patients who had dropped out of the study, but whose assessment scores were carried forward from their last available evaluation visit to week 8, i.e., endpoint (LOCF data set). A repeated measures analysis, using the PROC Mixed Procedure of the SAS package,[25] was used to compare the mean HAM-D slopes over the 8 weeks of study treatment for the 3 study conditions. All significance levels were conservatively set as 2-tailed. Results are presented in this report conservatively for the LOCF data set. However, the 8-week completer set provided similar results. Finally, a set of factorial analyses of variance was performed with the LOCF data set, using HAM-D change and CGI-I scores as dependent variables. Daily dose of study medication (≤ 3 pills/day vs. > 3 pills/day), level of initial anxiety (above vs. below the median on HAM-A), level of initial depression (above and below the median of the HAM-D), sex, age, age at onset of first depressive episode (before and after the age of 60), number of prior depressive episodes, extent of current medical conditions (none or 1 vs. 2 or more), and extent of regular concomitant nonpsychiatric medication treatment (none or 1 vs. 2 or more drugs) were used as possible predictors of treatment outcome.

RESULTS

Study Patients

Elderly depressed patients who completed the screen evaluation and met study entry criteria were randomly assigned to double-blind treatment (N = 177). There were no significant between-group differences on any baseline demographic or depression-related clinical variables, so they are summarized in aggregate form in Table 1.

The mean ± SD total score on the 17-item HAM-D scale at pretreatment baseline was 23.9 ± 4.0 for imipramine, 24.1 ± 3.9 for buspirone, and 24.1 ± 4.2 for placebo. Similarly close were the CGI-S mean scores for the 3 treatments (4.6, 4.7, and 4.7, respectively). On the DSM-III-R diagnostic checklist utilized as part of the initial evaluation, 100% of patients reported either persistent depressed mood or diminished interest or anhedonia of moderate or greater severity as required to make the diagnosis of major depression. A majority complained of notable fatigue or loss of energy (96%), 92% complained of persistent disturbance of sleep, 85% reported diminished ability to concentrate, 78% reported psychomotor agitation, and 72% reported feelings of guilt or worthlessness. Sixteen percent of patients met 5 of the 8 DSM-III-R diagnostic criteria, 32% met 6, 38% met 7, and 15% met all 8 criteria. These results clearly define the population as being moderately to markedly depressed. In fact 27% of the study population met DSM-III-R criteria for melancholia.

Table 1. Demographic and Clinical Characteristics of the Patient Sample (N = 177)

Variable	Value
Age, mean ± SE y	72 ± 0.5
Range, y	65–89
Women, %	53
Married, %	42
Weight, mean ± SE lb (kg)	165 ± 2.7 (75 ± 1.2)
Range, lb (kg)	91–316 (41–143)
Type of major depression	
Single episode, %	59
Recurrent episode, %	41
No. of prior episodes, mean ± SE	1.6 ± 0.4
Duration of current episode, % ≥ 6 mo	70
Age at onset of first episode, mean ± SE	60 ± 1.4
Use of psychotropic medication in past 3 years, %	47

The mean baseline HAM-A score was 20.6 for imipramine, 20.8 for buspirone, and 20.6 for placebo. These scores are consistent with much of the existing literature, which suggests that anxiety is commonly comorbid with depression, not only in the elderly but in patients of all ages.[26] In fact presence of anxiety in depressed patients is associated with increased impairment and poorer response to drug treatment.

An important feature of this study was that the sample were elderly patients residing in the community, 87% of whom were currently receiving outpatient medical treatment for a variety of conditions: arthritis or related musculoskeletal problems, 31%; coronary artery disease or arrhythmia, 21%; hypertension, 20%; endocrine or metabolic disorders, 16%; gastrointestinal disorders (e.g., ulcer), 15%; chronic obstructive pulmonary disorders, 8%; and miscellaneous other disorders, 5%. Many patients were being treated for more than one medical disorder. In fact, 32% of patients were currently being treated for 3 or more medical conditions. The percentage of patients who were being treated with a regular, daily regimen or who utilized p.r.n. (primarily over-the-counter medication), were respectively for imipramine, buspirone, and placebo as follows: imipramine: 92% regular, 58% p.r.n.; buspirone: 84% regular, 47% p.r.n.; and placebo: 68% regular, 48% p.r.n. (for use of daily medication regimen: $\chi^2 = 11.2$, df = 2, $p < .01$). There were no notable changes in the frequency of concomitant medication used between baseline and week 8, since patients per protocol had to be stabilized for 3 months on their medication regimen.

Table 2. Sample Size and Mean Daily Dose of Study Drug for 177 Patients

	Imipramine		Buspirone		Placebo	
Week	Patient N	Mean Dose (mg/d) (Range, 25–150)	Patient N	Mean Dose (mg/d) (Range, 10–60)	Patient N	Mean Capsules (Range, 1–6)
Baseline	60	…	57	…	60	…
Week 1[a]	56	49	51	19	56	2.3
Week 2	52	64	51	27	51	3.0
Week 4	46	80	39	36	45	3.9
Week 8[b]	46[c]	89	35	38	47	4.2
Endpoint	60		54		58	

[a]Four imipramine, 6 buspirone, 4 placebo patients dropped out owing to adverse events during the first treatment week.
[b]Completers in each group: 77% imipramine, 61% buspirone, and 78% placebo.
[c]Four imipramine completers had no week 8 efficacy data.

Table 3. Frequency of Treatment-Emergent Adverse Events (≥ 10% in Any Group) in 177 Patients

Adverse Effect	Imipramine (N = 60)	Buspirone (N = 57)	Placebo (N = 60)
Anticholinergic			
Dry mouth	58[a,b]	15	15
Constipation	25[a,b]	9	3
Urinary retention	22[a,b]	7	2
GI			
Gastric distress	7[c]	22	18
Nausea	17	17	10
Diarrhea	0[c]	15	10
Vomiting	2	10	5
CNS			
Light-headedness	8	10	10
Dizziness	20[a]	22[a]	7
Nervousness	15	7	8
Drowsiness	20[b]	5	12
Insomnia	15	15	10
Miscellaneous			
Headaches	20	20	18
Fatigue	20	12	13
Sweating	12	15	3
Musculoskeletal pain	10	12	25

[a]$p < .01$ for active drug/placebo comparisons.
[b]More events than with buspirone ($p < .05$).
[c]Fewer events than with placebo or buspirone ($p < .05$).

Study Treatment and Attrition

Table 2 indicates that mean daily medication intake during the last 2 weeks of the study was 89 mg/day for imipramine and 38 mg/day for buspirone.

Of the 177 patients who enrolled in the study, 172 were available for at least 1 post-randomization efficacy assessment (intent-to-treat sample). Table 2 summarizes the sample sizes during the course of the study, which shows a nonsignificant trend for a higher completion rate among patients taking imipramine (77%) or placebo (78%) than patients treated with buspirone (61%) ($\chi^2 = 5.04$, df = 2, $p < .10$). Treatment groups did not differ significantly in such reasons given for attrition as adverse events, lack of efficacy, withdrawn consent, lost to follow-up, or a non–study-related medical condition. Yet, adverse events were given as reason for dropout by a slightly higher number of patients on buspirone (8 [36%] of 22) than on imipramine (2 [14%] of 14) or placebo therapy (3 [23%] of 13) ($\chi^2 = 2.25$, df = 2, NS).

Adverse Events

Table 3 summarizes the emergent adverse events observed during study treatment in more than 10% of patients in any treatment group. Ninety-three percent of imipramine, 89% of buspirone, but only 75% of placebo patients reported at least 1 adverse event during the study ($\chi^2 = 9.21$, df = 2, $p < .01$). Adverse events most frequently reported with imipramine were anticholinergic effects (dry mouth, constipation, and urinary retention), CNS effects (drowsiness and dizziness), fatigue, and headaches. Side effects most frequently reported with buspirone were gastric distress, nausea, headaches, and dizziness. However, only dizziness was reported significantly more frequently with buspirone than with placebo treatment. Interestingly, imipramine's anticholinergic adverse events also had certain beneficial effects, namely, less gastric distress and less diarrhea. Study treatment resulted in no clinically important effects on blood pressure, heart rate, ECG, or clinical laboratory tests. No patients discontinued study treatment owing to laboratory abnormalities.

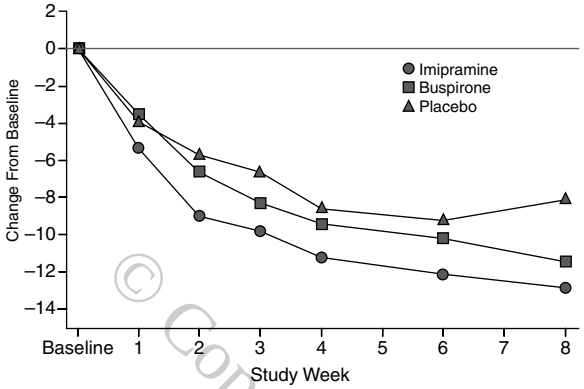
Clinical Response

Figure 1 shows the results of the last-observation-carried-forward (LOCF) analyses for the HAM-D total score. Both study drugs demonstrated significantly greater efficacy than placebo, with the imipramine effect occurring earlier in therapy and being more robust. Results of a repeated measures analysis of the HAM-D total score (PROC Mixed Procedure) provided similar significant results (week by treatment interaction: $F = 7.65$; df = 2,1009; $p < .001$), and imipramine was significantly ($p < .01$) different from placebo from week 2 on and buspirone only at week 8 ($p < .01$).

A more detailed summary of clinical outcome is given in Table 4 using the LOCF or endpoint approach. Consistently, efficacy results were slightly more marked for imipramine than for buspirone when compared with placebo and occurred by week 2 or 3 for imipramine but by week 6 or 8 for buspirone.

Global improvement as indicated by a score of 1 (very much improved) or 2 (much improved) on the 7-point

Figure 1. Results of Repeated Measures Analyses of HAM-D Total Score for Visitwise Data Set*



*PROC mixed procedure: week-by-treatment interaction: F = 7.65, df = 2,1009; p < .001. Individual slope comparison: Imipramine vs. placebo: F = 12.12, df = 1,1009; p < .001, with imipramine significantly different from placebo from week 2 on (p < .01); buspirone vs. placebo: F = 10.22, df = 1,1009; p < .001, with buspirone significantly different from placebo only at week 8 (p < .01).

Table 4. Clinical Improvement: Change From Baseline to Week 8 Endpoint (ANOVA) for 172 Patients*

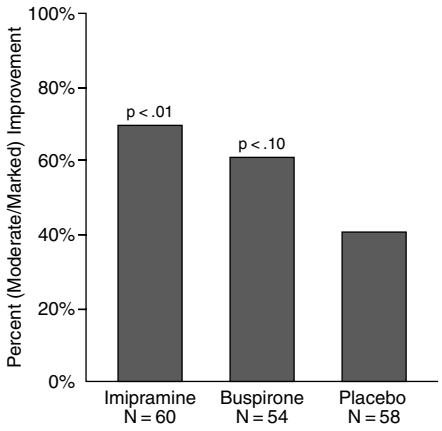
Outcome Measure	Imipramine (N = 60)	Buspirone (N = 54)	Placebo (N = 58)
HAM-D total score	–12.8[a]	–11.4[b]	–8.1
HAM-D factors:			
Retardation	–4.0[a]	–3.8[b]	–2.0
Cognitive disturbance	–3.3[a]	–3.2[b]	–1.9
Depressed mood	–1.9[a]	–1.6[b]	–1.1
Anxiety	–3.8[a]	–3.5	–2.3
Core depression	–6.8[a]	–6.4[a]	–4.1
Sleep disturbance	–2.5[a]	–1.9	–1.5
HAM-A	–9.5[a]	–9.3[b]	–5.5
CGI-Severity	–1.9[b]	–1.8	–1.3
SCL			
Anxiety	–4.4	–3.7	–3.4
Depressive	–9.2[a]	–6.9	–4.7

*Abbreviations: CGI = Clinical Global Impressions scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, SCL = Symptom Checklist. Drug/placebo differences: [a]p < .01; [b]p < .05.

CGI-Improvement scale is given for the treatment endpoint (LOCF) data set in Figure 2. Statistically significant improvement occurred in patients taking imipramine when compared with placebo (p < .01) but only at a statistical trend level for buspirone (p < .10). Using percentage of patients who experience at least a 50% reduction in the HAM-D total score for the LOCF data set, we found results similar to global improvement (62% respondents for imipramine, 52% for buspirone, and 36% for placebo; $\chi^2 = 7.75$, df = 2, p < .05).

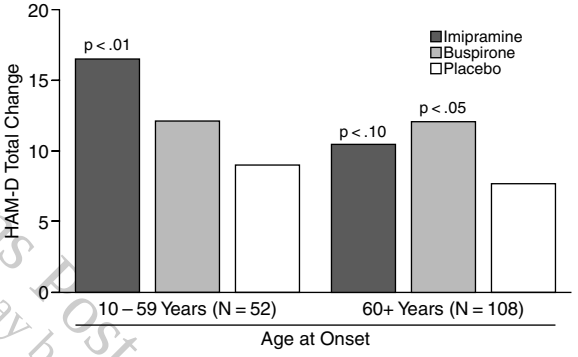
A set of factorial analyses (see Method) was undertaken to assess the possible differential effects of several clinically relevant variables on treatment outcome, using LOCF endpoint in the total HAM-D score and CGI global

Figure 2. Percentage of Patients Reporting Moderate/Marked Global Improvement for the Treatment Endpoint Data Sets*



*$\chi^2 = 9.1$, df = 2, p < .02; N = 172.

Figure 3. Effect of Age at Onset of First Depressive Episode on Drug Response*



*Significant comparisons are drug vs. placebo.

improvement as outcome measures. None of these variables was found to have a statistically significant association with treatment outcome. (Treatment-by-predictor variable interactions were statistically not significant.) The main statistically significant treatment effect (p < .01), described earlier, was, however, again present in all analyses.

Nevertheless, at least at a statistical trend level (p < .17), age at onset of first depressive episode affected treatment outcome differentially (Figure 3). Patients with an earlier onset of depression reported significantly larger treatment differences between imipramine and placebo (p < .01), while buspirone differed significantly from placebo only in patients with a late onset of depression (60 years or older) (p < .05). Thus, patients with an earlier onset of first episode of depression gave the response expected from younger patients. In contrast, the group with a late onset of depression (60 years or older) had a slightly higher placebo response and a lower imipramine response than patients with an earlier onset of depression; the buspirone response was not affected by the onset of depression variable.

When the 3 treatment groups were combined, results showed that more patients with 2 or more medical disorders achieved a favorable clinical response (65%) than patients with fewer medical disorders (46%) ($\chi^2 = 4.6$, df = 1, $p < .05$) (HAM-D ≥ 50% reduction from baseline). The same holds true when the study population was divided into patients with (N = 59) and without (N = 65) cardiovascular disease ($\chi^2 = 6.04$, df = 1, $p < .02$). Also, patients taking 2 or more nonpsychiatric medications improved more (65%) than patients taking 1 or no medication (45%) ($\chi^2 = 4.45$, df = 1, $p < .05$). Thus, presence of medical illness, including cardiovascular illness, and nonpsychiatric drug use did not adversely affect overall treatment outcome with either buspirone or imipramine. More recently, Small et al.[27] reported that elderly depressed patients with severe chronic medical conditions responded as well to fluoxetine treatment as patients without such conditions.

Extension Phase

Seventy-five patients (23 buspirone, 29 imipramine, and 23 placebo) elected to continue double-blind study medication, some patients for up to 12 months. Only 23 of these patients (31%) continued treatment for 1 year. There were no significant between-drug differences either in attrition rates or in reasons for attrition during the extension phase. Fifteen patients were still in continuation treatment when the pharmaceutical sponsor closed out the study, and so they were discontinued for this reason. Twenty-two patients chose to stop owing to sustained improvement in depression which, they felt, obviated the need for further treatment. Eight patients discontinued for non–study-related intercurrent illness and 7 patients for persisting and bothersome adverse effects. Of these 7 patients, 5 were taking imipramine, 1 was taking buspirone, and 1 was taking placebo. One imipramine patient experienced an acute bowel obstruction, 1 had elevated liver enzymes, 1 patient had significant ECG changes, 1 patient experienced orthostatic hypotension and arrhythmia, and 1 patient experienced excessive sweating. The patient taking buspirone experienced syncopes, and the placebo patient experienced decreased sexual performance.

DISCUSSION

The central finding of this study is that antidepressant therapy utilizing relatively low doses of imipramine was clearly effective in treating elderly patients suffering from major depression who were living in the community. Although buspirone differed from placebo at week 8 of treatment, imipramine showed significantly more improvement than placebo already at week 2, and its effect was more robust. Imipramine appeared to be most effective in patients with an early onset of depression, while buspirone response was not affected by this variable.

The relatively late onset of the buspirone response as compared with onset of the imipramine response has to be taken into consideration when making a treatment plan for elderly depressed patients. In addition, late-life depression might be a better indicator for buspirone therapy and a poorer indicator for imipramine therapy when compared with early-onset depression (< 60 years of age).

When both active drugs were compared with placebo, significant improvement in the clinical features of depression was consistently observed across most measures at treatment endpoint, including depressed mood, core depressive symptoms (such as loss of appetite, low interest and energy, hopelessness, guilt, and retardation) and cognitive disturbance. The improvement in subjectively rated cognitive function is especially notable for imipramine in light of its central anticholinergic effect, which might be expected to adversely affect cognition in this age group.[28]

Anxiety, frequently noted[7] to be a prominent feature of late-life depression, also improved significantly with both treatments, however, only according to the HAM-A scale but not according to the patient-completed SCL anxiety factor. This finding lets one wonder how much of the change observed in the HAM-A scale may represent a change in depression and not necessarily anxiety, as both scales correlate very highly with each other.

Previous studies in younger adults have shown buspirone[15,16] to possess moderate therapeutic efficacy in depressed patients with concomitant symptoms of anxiety, and the antidepressant, imipramine, has recently been shown[29] to have anxiolytic properties, even in a nondepressed population.

It is of clinical interest that onset of first depressive episode has some predictive value for treatment outcome at least in the early-onset depressed patients. Early-onset elderly depressed patients, as mentioned earlier, are probably more similar to adult depressed patients, while later-onset depressed patients (over 60 years) more probably represent late-life depression. Clearly, in this study, patients with an early onset of their depressive episodes improved the most with imipramine and the least with placebo.

Safety

Both buspirone and imipramine were generally well tolerated in the doses employed in this study. In fact, fewer patients on imipramine dropped out for adverse effects than patients on buspirone treatment (NS). Anticholinergic and sedative adverse events occurred more frequently with imipramine treatment, and both active treatments produced dizziness in some patients. Although central anticholinergic effects were a concern with imipramine, and in fact, 1 patient in the extension phase was hospitalized for acute bowel obstruction, patients actually reported subjective improvement in cognitive disturbance for both drugs. Another safety concern was the effect of

permitting patients who had significant medical comorbidity to enter the study. Consistent with previous research suggesting a high prevalence of such medical comorbidity in the depressed elderly,[30–32] 87% of the study sample reported a comorbid medical condition that was currently being treated. Yet, neither medical comorbidity nor concomitant medication was associated with poor tolerance to treatment, higher attrition, or poor therapeutic response. In fact, the presence of medical comorbidity, while not a prescriptive predictor of response, was actually a prognostic predictor of favorable treatment response—even to placebo. This is in contrast to reported lower treatment response rates in younger patients whose affective illness is complicated by medical illness. The reason for this relatively more favorable response in the elderly is uncertain.

The apparent safety and efficacy of imipramine in this study makes us revisit our clinical biases that nortriptyline and desipramine are safer tricyclic antidepressants for the elderly than imipramine and that the tricyclics in general should not be used in the elderly.[33,34] The relatively low mean dose (89 mg/day) may help explain why imipramine was so well tolerated in this study, but caution in prescribing tricyclic antidepressants in the elderly is nevertheless justified.

Finally, 10 mg b.i.d. of buspirone may be an excessive starting dose in an elderly population, as suggested by the fact that 6 buspirone patients dropped out during the first week of therapy, primarily because of dizziness, and that the overall dropout rate was slightly higher for buspirone than for imipramine. In contrast, the dose of imipramine was a more conservative one; thus, it was better tolerated.

The current study differed from most other placebo-controlled, geriatric depression studies in several important ways. First, a larger sample size was available. Second, medical comorbidity was more extensive, whereas previously reported studies involved healthier (and more selective) populations of elderly outpatients. Third, the mean age of patients in the current study (72 years) was somewhat older (all but 2 of the previous studies allowed patients under the age of 65). Fourth, the imipramine dose (mean = 89 mg/day) for the current study was relatively low, yet similar to the daily dose (87 mg/day) used by Möller and Volz.[35]

Study Limitations

Several limitations of the current study should be mentioned. First, the study would have been strengthened considerably had we obtained plasma imipramine levels. This would have allowed us to examine the extent to which modest doses of imipramine yielded therapeutic plasma levels, and whether nonresponse was due to inadequate plasma drug levels. Much of the normative data on plasma imipramine levels was obtained on younger adult populations, and it is uncertain if it can be generalized to the elderly.

Second, although patients with medical comorbidity were permitted into the study and comorbidity was documented by chart review, no systematic method of rating the severity of medical illness was utilized, thus limiting the usefulness of any analysis relating to this variable.

Third, the lack of a serotonin selective antidepressant (e.g., fluoxetine) as a comparator will strike some as a study limitation. It should be noted, however, that this study was initiated in 1990 when serotonin selective antidepressant treatment was far from being as well established as it is currently. Furthermore, longer experience with this class of compounds suggests that they, too, have side effects that are difficult to tolerate (e.g., akathisia, agitation, insomnia, nausea, sexual dysfunction, and weight loss), as well as the potential for significant drug interaction and slow or modest response rates, especially in the elderly. In fact, few placebo-controlled prospective large-scale clinical trials have been conducted with the elderly in recent years.[36] Perhaps the most well-controlled prospective study comparing a serotonin selective reuptake inhibitor with placebo was reported by Tollefson and Bosomworth.[37] The authors conducted a large, multicenter study in depressed geriatric patients (N = 671) comparing 20 mg of fluoxetine with placebo. They reported a 6-week overall response rate (≥ 50% HAM-D on the reduction) of 36% for fluoxetine and 27% for placebo, which was statistically significant ($p < .02$) because of the large sample size employed, but hardly impressive. In contrast, in the present study, imipramine, buspirone, and placebo produced response rates of 62%, 52%, and 36% respectively, using the LOCF data set.

Fourth, even though the study permitted 10 months of continuation treatment for responders, it was not designed to assess either the appropriate duration of acute antidepressant therapy or the efficacy of continuation therapy. The appropriate duration of antidepressant therapy in the elderly is an important treatment parameter that deserves further research. It should not be assumed, though, that depression in the elderly warrants a lengthy period of continuation therapy, as indicated for many young adults suffering from depression, especially those suffering from recurrent depressions. It is interesting that nearly 60% of study patients reported the current episode as being their first depression, and the mean age at onset of depression was 60 years. This suggests that many elderly patients presenting with depression, at least in outpatient medical settings, do not suffer early-onset affective illness (for which the current episode is but 1 in a series of lifelong recurrences) so that major depressive disorders in this age group may have a much different treatment course. Therefore, recommendations concerning optimal duration of treatment for elderly patients who develop depression cannot be confidently extrapolated from existing research, which is predominantly based on younger depressive cohorts. We should note, however, the potential

unreliability of retrospective assessment of age at onset of affective illness.

Clinical Implications

The community-dwelling elderly who are cared for in outpatient primary care settings constitute the largest single subgroup of persons over age 65.[38] The 1-year prevalence rate of depression in this subgroup appears to approximate 10% to 15%.[1–3] Previous research has suggested that depression complicated by medical illness may be more persistent and less responsive to antidepressant medication than is depression in the absence of medical comorbidity.[39] At least in our study, this does not appear to be the case. Unrecognized depression has also been shown to be associated with significant increases in medical health care utilization and disability, while improvement in depression results in improvement in disability.[40]

Previously, the value of antidepressant intervention in the elderly who have medical problems was uncertain. The only published antidepressant drug trial specifically targeting elderly depressed patients with comorbid medical illness[5] was limited to hospitalized patients, and failed to be completed because of concerns over adverse drug interactions with medications used by the subjects to treat medical conditions. In contrast, the current study finds that antidepressant therapy with imipramine, and to a lesser extent with buspirone, is well tolerated and efficacious for elderly outpatients, even those with significant comorbid medical illness requiring medication.

Caution should be exercised in generalizing from the results of this one study. This caution is especially warranted since, as noted previously, imipramine is a tricyclic antidepressant whose benefit-risk ratio is less favorable than that of most newer serotonin selective reuptake inhibitor antidepressants. Similarly, buspirone is not approved by the FDA for the treatment of depression, and its antidepressant efficacy (even for younger adults) rests on a rather small evidentiary base. What is clearly needed are further placebo-controlled studies in elderly patients. These studies should not only compare the safety and efficacy of various classes of antidepressants on primary outcome measures, but should also include careful assessment of changes in cognitive function, functional status, and quality of life—all of which are especially crucial indicators of response in this elderly population.

Drug names: buspirone (BuSpar), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others) nortriptyline (Pamelor and others).

REFERENCES

1. Koenig HG, Meador KG, Cohen HJ, et al. Depression in elderly hospitalized patients with medical illness. Arch Intern Med 1988;148:1929–1936
2. Barrett JE, Barrett JA, Oxman TE, et al. The prevalence of psychiatric disorders in a primary care practice. Arch Gen Psychiatry 1988;45: 1100–1106
3. O'Riordan TG, Hayes JP, Shelley R, et al. The prevalence of depression in an acute geriatric medical assessment unit. Int J Geriatr Psychiatry 1989;4: 17–21
4. Parmelee PA, Katz IR, Lawton MP. Depression among institutionalized aged: assessment and prevalence estimation. J Gerontol A Biol Sci Med Sci 1989;44:M22–M29
5. Koenig HG, Goli V, Shelp F, et al. Antidepressant use in elderly medical inpatients: lessons from an attempted clinical trial. J Gen Intern Med 1989; 4:498–505
6. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1994;262:914–919
7. Salzman C. Pharmacological treatment of depression in elderly patients. In: Schneider LS, ed. Diagnosis and Treatment of Depression in Late Life: Results of the NIH Consensus Development Conference; Washington, DC: American Psychiatric Press; 1994:181–245
8. Cohn JB, Varga L, Lyford A. A two-center double-blind study of nomifensine, imipramine, and placebo in depressed geriatric outpatients. J Clin Psychiatry 1984;45(4, sec 2):68–72
9. Merideth CH, Feighner JP, Hendrickson G. A double-blind comparative evaluation of the efficacy and safety of nomifensine, imipramine, and placebo in depressed geriatric outpatients. J Clin Psychiatry 1984;45(4, sec 2):73–77
10. Gerner R, Estabrook W, Steuer J, et al. Treatment of geriatric depression with trazodone, imipramine, and placebo: a double-blind study. J Clin Psychiatry 1980;41:216–220
11. Georgotas A, Stokes P, McCue RE, et al. The usefulness of DST in predicting response to antidepressants: a placebo-controlled study. J Affect Disord 1986;11:21–28
12. Georgotas A, McCue RE, Friedman E, et al. Response of depressive symptoms to nortriptyline, phenelzine and placebo. Br J Psychiatry 1987;151: 102–106
13. NIH consensus conference: diagnosis and treatment of depression in late life [editorial]. JAMA 1992;268:1018–1024
14. Fabre LF. Buspirone in the management of major depression: a placebo-controlled comparison. J Clin Psychiatry 1990;51(9, suppl):55–61
15. Rickels K, Amsterdam JD, Clary C, et al. Buspirone in major depression: a controlled study. J Clin Psychiatry 1991;52:34–38
16. Robinson DS, Alms DR, Shrotriya RC, et al. Serotonergic anxiolytics and treatment of depression. Psychopathology 1989;22(suppl 1):27–36
17. Eison AS, Yocca FC. Reduction in cortical 5-HT_2 receptor sensitivity after continuous gepirone treatment. Eur J Pharmacol 1985;111:389–392
18. Schecter LE, Bolanos FJ, Gozlan H. Modulations of central serotonergic neurotransmission by chronic ipsapirone in the rat. In: Briley M, File SE, eds. New Concepts in Anxiety. London, England: MacMillan Press; 1991
19. Rickels K, Hesbacher PT, Fisher S, et al. The private practice research group (PPRG): a working model from psychopharmacology for clinical research in family practice. J Clin Pharmacology 1977;17:541–554
20. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
21. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
22. Rickels K, Chung HR, Csanalosi I, et al. Alprazolam, diazepam, imipramine and placebo in outpatients with major depression. Arch Gen Psychiatry 1987;44:862–866
23. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
24. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974;19: 1–15
25. SAS Institute Inc. SAS User's Guide: Statistics. 6th ed. Cary, NC: SAS Institute; 1990
26. Angst J. Introduction. Depression and anxiety: implications for nosology, course, and treatment. J Clin Psychiatry 1997;58(suppl 8):3–5
27. Small GW, Birkett M, Myers BS, et al. and the Fluoxetine Collaborative Study Group. Impact of physical illness on quality of life and antidepressant response in geriatric major depression. J Am Geriatr Soc 1996;44: 1220–1225
28. Plotkin DA, Gerson SG, Jarvik LF. Antidepressant drug treatment in the elderly. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987
29. Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treat-

ment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone and diazepam. Arch Gen Psychiatry 1993;50: 884–895
30. Kovar M. Health of the elderly and use of health services. Public Health Rep 1977;92:9–19
31. Lacro JP, Jeste DV. Physical comorbidity and polypharmacy in older psychiatric patients. Biol Psychiatry 1994;36:146–152
32. Fried LP, Bush TL. Morbidity as a focus of preventive health care in the elderly. Epidemiol Rev 1988;10:48–64
33. Schneider LS. Pharmacologic considerations in the treatment of late-life depression. Am J Geriatr Psychiatry 1996;4(suppl 1):S51–S65
34. Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. JAMA 1994;272:292–296
35. Möller HJ, Volz HP. Brofaromine in elderly major depressed patients: a comparative trial versus imipramine. Eur Neuropsychopharmacol 1993;3: 501–510
36. Volz HP, Möller HJ. Antidepressant drug therapy in the elderly: a critical review of the controlled clinical trials conducted since 1980. Pharmacopsychiatry 1994;27:93–100
37. Tollefson GD, Bosomworth JC. A double-blind placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. Int Psychogeriatr 1995;7:89–104
38. Gurland BJ, Wilder DE, Berkman C. Depression and disability in the elderly: reciprocal relations and changes with age. Int J Geriatr Psychiatry 1988,3:163–179
39. Popkin MK, Callies AL, MacKenzie TB. The outcome of antidepressant use in the medically ill. Arch Gen Psychiatry 1985;42:1160–1163
40. Von Korff M, Ormel J, Katon W, et al. Disability and depression among high utilizers of health care: a longitudinal analysis. Arch Gen Psychiatry 1992;49:91–100