

Escitalopram in the Treatment of Depressed Elderly Patients

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Objective: Management of depression in elderly patients presents a significant medical challenge, and there is a need for further clinical trials. The authors examined the efficacy and tolerability of escitalopram and fluoxetine versus placebo in the treatment of elderly patients with major depressive disorder (MDD). **Methods:** This was an 8-week, randomized, double-blind comparison of the efficacy and tolerability of escitalopram (10 mg/day) and fluoxetine (20 mg/day), to placebo in elderly patients with MDD. The prospectively defined primary efficacy parameter was the change from baseline in mean Montgomery-Åsberg Depression Rating Scale (MADRS) total score at endpoint, using last observation carried forward. **Results:** The intent-to-treat set comprised 517 patients; the escitalopram group included 173 patients; fluoxetine, 164 patients; and placebo, 180 patients. Mean age was 75 years, with a range of 65 to 93. Formally, this was a “failed study” (i.e., neither active treatment was superior to placebo), and the efficacy results should, therefore, be interpreted with caution. On the basis of the primary efficacy parameter, fluoxetine showed significantly lower efficacy than both escitalopram and placebo, which were not significantly different from each other. Rates of withdrawal because of adverse events/lack of efficacy were: placebo (2.8%/4.4%, respectively), escitalopram (9.8%/1.7%, respectively), and fluoxetine (12.2%/1.8%, respectively). No single adverse event occurred at an incidence $\geq 10\%$ in escitalopram-treated patients. **Conclusions:** Both escitalopram and fluoxetine were well tolerated by elderly patients with MDD. Neither demonstrated superior efficacy on primary endpoint versus placebo. (Am J Geriatr Psychiatry 2005; 13:884-891)

Depression in elderly persons is widespread and is a serious public health concern.¹ The prevalence of clinically significant depression in elderly patients is as high as 14%.² Several studies have demonstrated that depression is not only underdiagnosed, particularly among geriatric patients, but also

undertreated.³ Not only are older people more likely than younger people to suffer from physical illnesses and disabilities, but they often also suffer, as a consequence or simultaneously, from anxiety and depression, which increases the medical and social costs of their care.⁴

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In a recent study in the United States, only 35.7% of elderly patients diagnosed as suffering from depression were treated.⁵ There are difficulties in diagnosing depression in late life, and it is not uncommon to encounter depressive episodes that do not fulfil DSM criteria for a major depressive episode. Other psychiatric disorders are sometimes present and can mask the underlying depression: anxiety symptoms, somatic complaints, sleep disorders, and varying degrees of cognitive impairment. These symptoms may lead the primary-care physician to prescribe hypnotics and sedatives, mostly benzodiazepines, further complicating the clinical presentation.

The effective treatment of depression in elderly patients has an immense impact, not only on symptoms of depression, as might be expected, but also on well-being and physical symptoms, and that treatment can also significantly reduce rates of suicide, more than in any other age-group.⁶ Clinical trials in elderly patients are often more difficult to conduct because of high comorbidity, high adverse-event and withdrawal rates, and fears of non-compliance. Also, there have been ethical concerns in conducting research in what may be regarded as a particularly vulnerable group.⁷

Escitalopram is the most selective of the selective serotonin reuptake inhibitors (SSRIs).⁸ It is well tolerated, as shown in clinical studies in adult patient populations.⁹⁻¹¹ Escitalopram has pharmacokinetic as well as pharmacodynamic features that make it attractive for the treatment of elderly patients: it is metabolized by three CYP450 isozymes in parallel;¹² it is neither an inducer nor an important inhibitor of CYP450; it has low protein-binding, and therefore presents a low risk of clinically relevant pharmacokinetic drug-drug interactions.

The aim of this study was to compare the efficacy and tolerability of escitalopram in a fixed dose of 10 mg with that of placebo in elderly patients with major depressive disorder (MDD), in both general practice and psychiatric-specialist settings, using fluoxetine at a fixed dose of 20 mg as a reference drug.

METHODS

Study Design

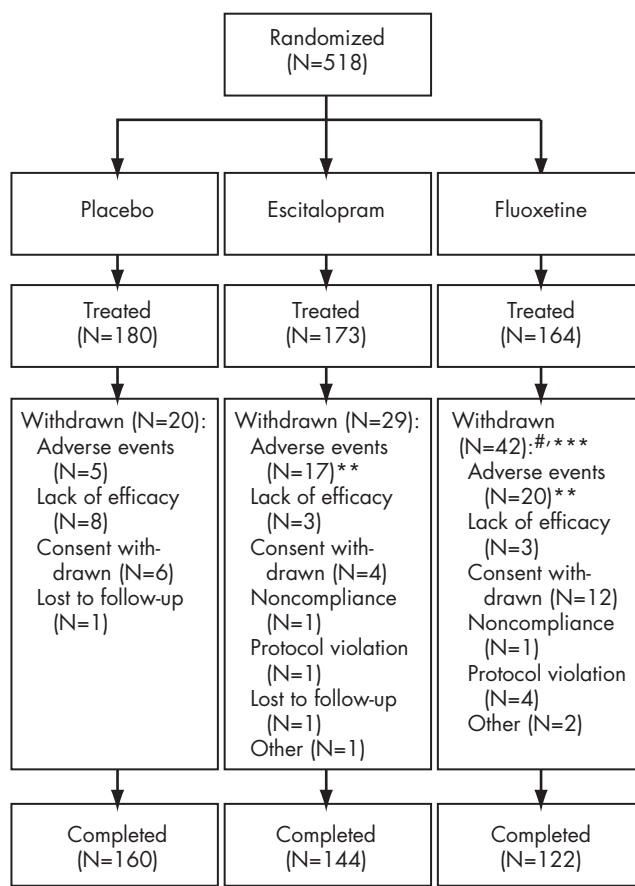
This was a randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study con-

ducted in 11 countries, in both general practice and specialist settings. Fluoxetine was used as the reference antidepressant.

After screening and a 1-week, single-blind, placebo period, patients were randomized to 8 weeks of double-blind treatment with escitalopram (10mg), fluoxetine (20mg), or placebo (see Figure 1). The patients were included if they were 65 years of age or over and fulfilled DSM-IV criteria for MDD. They were required to have a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥ 22 and ≤ 40 at both the screening and baseline visit and a minimum score of 22 on the Mini-Mental State Exam (MMSE) at the screening visit. The latter criterion was to ensure good patient compliance and reliable assessment of tolerability and efficacy.

The following exclusion criteria were applied: subjects met DSM-IV criteria for mania or any bipolar disorder, schizophrenia, or any psychotic disorder,

FIGURE 1. Patient Disposition for the Study



Note: *p < 0.05 versus escitalopram; **p < 0.01; ***p < 0.001.

obsessive-compulsive disorder, eating disorders, or mental retardation or any pervasive developmental or cognitive disorder; had an MADRS score ≥ 5 on Item 10 (suicidal thoughts); were receiving treatment with antipsychotics, antidepressants, hypnotics, anxiolytics (except oxazepam [maximum 30 mg/day], temazepam [maximum 10 mg/day], zopiclone [maximum 3.75 mg/day], or zolpidem [maximum 5 mg/day]), antiepileptics, barbiturates, chloral hydrate, antiparkinsonian drugs, diuretics, 5-HT receptor agonists; ongoing prophylactic treatment with lithium, sodium valproate, or carbamazepine; were receiving electroconvulsive treatment; were receiving treatment with behavior therapy or psychotherapy; had received treatment with any investigational drug within 30 days before entry; had a history of schizophrenia, psychotic disorder, or drug abuse (as defined by DSM-IV); had a history of severe drug allergy or hypersensitivity (including to citalopram); or had a lack of response to more than one antidepressant treatment (including citalopram) during the present depressive episode.

Efficacy Parameters

The efficacy parameters were assessed at all visits during the double-blind period. The prospectively-defined primary efficacy analysis was based on the change from baseline in MADRS total score at final assessment, using the last observation carried forward (LOCF). Prospectively-defined secondary efficacy parameters were change from baseline to each visit on the Clinical Global Impression of Severity (CGI-S) score; response, at last assessment, defined as at least a 50% reduction on the MADRS total score from baseline; and remission, defined as a MADRS total score ≤ 12 .

Tolerability

Safety and tolerability were evaluated on the basis of spontaneously reported adverse events (AEs), clinical laboratory tests, ECGs, and physical examinations (including vital signs and weight). All ECGs were resting 12-lead, and ECG parameters (PR, RR, and QTcB [Bazett's correction]) were retrospectively measured from printouts by a cardiologist who was blinded to the randomization code. Pulse rate and systolic and diastolic blood pressures were measured after the patient had rested for 5 minutes while in a

supine position, and again after 1 minute in a standing position.

Statistical Methods

The efficacy data for the modified intent-to-treat population (ITT), which included all randomized patients who took at least one dose of double-blind study medication and who had at least one post-baseline assessment of the MADRS total score, were analyzed by the LOCF approach. Analyses of efficacy parameters (MADRS and CGI-S) were based on analysis of covariance (ANCOVA), with factors for treatment group and center, and with baseline score as a covariate. Safety analyses were performed on all patients treated.

RESULTS

The patient demographics were similar across the three groups (Table 1). There was an approximately 3-to-1 ratio of women to men. Mean age was 75 years (standard deviation [SD]: 7 years). Mean baseline MADRS total score was 28.6 (SD: 4.2), indicating a population with moderate-to-severe depression. There were no significant imbalances noted between the various treatment groups regarding age, gender, race, or severity of depression.

A total of 518 patients were randomized to the three treatment groups (Figure 1). The overall completion rate for the study was 82.4%. One patient assigned to treatment with escitalopram withdrew before taking study medication, and three patients took medication, but were withdrawn without a valid efficacy assessment. The ITT population thus comprised 514 patients.

Efficacy

The primary efficacy endpoint was the adjusted mean change from baseline in MADRS total scores by visit (observed cases) and at last assessment (LOCF) for the ITT population (Figure 2). The primary analysis did not detect a statistically significant difference between escitalopram and placebo. Placebo treatment was statistically significantly superior to fluoxetine, at Weeks 1, 2, and 3, as well as at Week 8 (LOCF; $p < 0.01$). There was a statistically significant treat-

TABLE 1. Disposition, Demographics, and Mean Baseline Scores

	Placebo	Escitalopram	Fluoxetine
Disposition			
Patients randomized: N	180	174	164
Patients treated (APTS): N	180	173	164
Patients withdrawn: N (%)	20 (11%)	29 (17%)	42 (26%)*
Patients completed: N (%)	160 (89%)	144 (83%)	122 (74%)
Intent-to-treat (ITT): N	180	170	164
Demographics			
Female patients: N (%)	137 (76%)	130 (75%)	126 (77%)
Male patients: N (%)	43 (24%)	44 (25%)	38 (23%)
Mean age (SD), years	75 (7)	75 (7)	75 (7)
Range, years	65-93	65-93	65-92
Mean weight (SD), kg	69 (14)	68 (13)	68 (13)
Caucasian: N (%)	180 (100%)	172 (99%)	164 (100%)
Baseline scores			
Mean MADRS Total score (SD)	28.6 (4.2)	28.2 (3.8)	28.5 (3.8)
Mean CGI-S Total score (SD)	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)

Note: SD: standard deviation; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-S: Clinical Global Impression of Severity; APTS: All Patients Treated Set.

*p < 0.05 versus placebo.

ment × center interaction ($p < 0.05$), indicating that the response by treatment differed between centers.

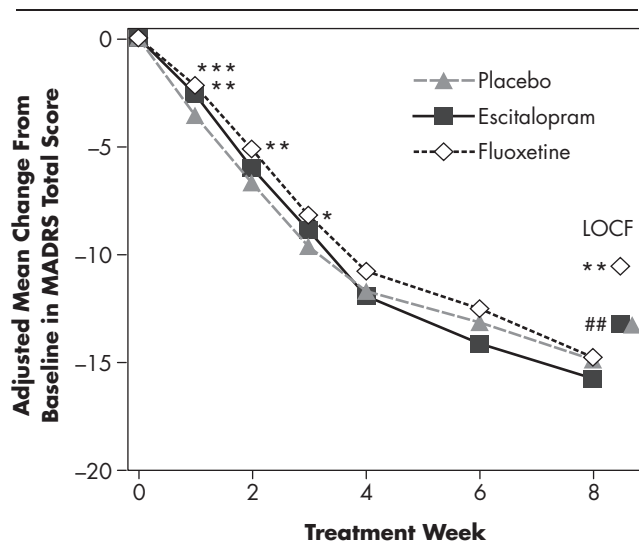
Response on the MADRS scale was defined as a $\geq 50\%$ decrease from baseline in the MADRS total

score. At last assessment (LOCF), 46% of the patients in the escitalopram group had responded to treatment, as compared with 47% in the placebo group (NS) and 37% in the fluoxetine group (NS).

Remission was defined as a MADRS total score ≤ 12 . At last assessment (LOCF), 40% of the patients in the escitalopram group had achieved remission, compared with 42% in the placebo group and 30% in the fluoxetine group. There was no significant difference between the placebo group and the escitalopram group, whereas there were significantly fewer remitters in the fluoxetine group versus placebo ($p < 0.05$).

For the adjusted change in mean CGI-S scores from baseline for each treatment group, there was a statistically significant difference between placebo (mean score 2.70) and fluoxetine (mean score 3.02) at last assessment (LOCF), in favor of placebo ($p < 0.05$), and no significant difference between placebo and escitalopram (mean score 2.64; NS).

FIGURE 2. Adjusted Mean Change From Baseline in MADRS Total Scores by Visit (Observed Cases) and at Last Assessment (LOCF) for the Intent-to-Treat Population



Note: MADRS: Montgomery-Åsberg Depression Rating Scale; LOCF: last observation carried forward.

*p < 0.05; **p < 0.01; ***p < 0.001 for active treatment (escitalopram or fluoxetine) versus placebo; ##p < 0.01 escitalopram versus fluoxetine.

Tolerability

Both escitalopram and fluoxetine were safe and well-tolerated. Withdrawals were significantly higher in the fluoxetine group (25.6% patients withdrawn) than in both the escitalopram (16.8% patients withdrawn; $p < 0.05$) and the placebo group (11.1% patients withdrawn; $p < 0.001$). There was no significant difference between withdrawal rates in the escitalopram group and the placebo group. The frequency of

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patients who withdrew because of adverse events was significantly higher in both the fluoxetine (12.2%) and escitalopram (9.8%) groups, compared to the placebo group (2.8%; $p < 0.01$ for escitalopram and $p < 0.001$ for fluoxetine; Figure 1). The majority of adverse events were mild or moderate, and unrelated to treatment. Approximately half of all patients had at least one treatment-emergent adverse event (TEAE), the incidence of which was similar in the treatment groups.

Nausea was the only TEAE with an incidence $\geq 2\%$ that occurred significantly more frequently in both the escitalopram and the fluoxetine groups than in the placebo group (escitalopram versus placebo, $p < 0.01$; fluoxetine versus placebo, $p < 0.01$). Only nausea, headache, and abdominal pain had an incidence $> 5\%$ for elderly patients treated with escitalopram (Table 2), and headache was reported with a higher incidence in the placebo group. Dizziness, orthostatic hypotension, accidental injury, insomnia, and somnolence during active treatment were at placebo levels in this study. There was only one sexual adverse event reported in this study, which was by one patient in the placebo-treatment group.

In total, 42 patients withdrew because of adverse events: 5 in the placebo group, 17 in the escitalopram group, and 20 in the fluoxetine group. The most fre-

quent adverse event contributing to withdrawal in the escitalopram group was nausea (7 patients). The majority of the adverse events that led to withdrawal in the escitalopram group were considered to be moderate and probably related to study product by the investigator. In the fluoxetine group, nausea, abdominal pain, and anxiety were the most frequent adverse events leading to withdrawal, and the majority were judged to be moderate and probably or possibly related to the study product by the investigator.

Safety

There were no clinically relevant differences in changes in mean clinical laboratory values, weight, ECG values, and blood pressure and pulse rate within or between the treatment groups. No patients were withdrawn because of potentially clinically significant clinical laboratory values, including glycemia and hyponatremia.

Three patients died during the study period. One patient died during the screening period from heart failure, before initiation of active drug treatment. One escitalopram-treated patient, a 77-year-old man, who showed no signs of suicidality at study entry or during the study but had twice attempted suicide in the 3 months before enrollment, committed suicide 1 week after completing treatment. A third patient, on placebo treatment, was found dead during the treatment period and had probably drowned.

TABLE 2. Treatment-Emergent Adverse Events (TEAEs) With an Incidence of $\geq 2\%$ in One of the Active Treatment Groups, N (%)

Preferred Term	Placebo	Escitalopram	Fluoxetine
Patients with TEAEs	96 (53.3%)	88 (50.9%)	93 (56.7%)
Nausea	3 (1.7%)	12 (6.9%)*	12 (7.3%)*
Abdominal pain	7 (3.9%)	11 (6.4%)	10 (6.1%)
Headache	15 (8.3%)	9 (5.2%)	7 (4.3%)
Hypertension	11 (6.1%)	4 (2.3%)	4 (2.4%)
Diarrhea	9 (5.0%)	3 (1.7%)	8 (4.9%)
Back pain	7 (3.9%)	8 (4.6%)	4 (2.4%)
Anxiety	5 (2.8%)	5 (2.9%)	6 (3.7%)
Dizziness	1 (0.6%)	5 (2.9%)	6 (3.7%)
Dyspepsia	8 (4.4%)	4 (2.3%)	7 (4.3%)
Hypertension	11 (6.1%)	4 (2.3%)	4 (2.4%)
Insomnia	4 (2.2%)	4 (2.3%)	3 (1.8%)
Somnolence	1 (0.6%)	4 (2.3%)	0 (0%)
Accidental injury	4 (2.2%)	3 (1.7%)	7 (4.3%)
Vertigo	3 (1.7%)	3 (1.7%)	7 (4.3%)
Anorexia	2 (1.1%)	2 (1.2%)	4 (2.4%)
Constipation	8 (4.4%)	2 (1.2%)	7 (4.3%)
Depression aggravated	1 (0.6%)	2 (1.2%)	4 (2.4%)
Dry mouth	1 (0.6%)	1 (0.6%)	4 (2.4%)
Orthostatic hypotension	1 (0.6%)	2 (1.2%)	1 (0.6%)

Note: * $p < 0.01$.

DISCUSSION

In the current study, the primary analysis did not detect a statistically significant difference between escitalopram and placebo. Both response ($\geq 50\%$ improvement in MADRS scores) and remission (MADRS ≤ 12) were not statistically significantly different for escitalopram versus fluoxetine or placebo, although depressive symptoms improved during the study. The placebo response rate of 47% is high compared with placebo responses of 32%,¹³ 36%,¹⁴ and 36%¹⁵ in other studies in elderly patients with MDD. The increase in placebo response from 1981 to 2000 in adult patients with MDD found in 75 published trials, has been previously noted.¹⁶ This may partly explain the outcome of the study. Furthermore, the

high withdrawal rate in the first weeks of the study is a potential reason for lower response and remission rates in the fluoxetine group. More patients in the fluoxetine group withdrew their consent during the trial, and, given their relatively high MADRS scores at the time of withdrawal, lack of efficacy may have been a secondary reason for withdrawal of consent.

In previous placebo-controlled trials in adults between age 18 and 65, 10 mg/day of escitalopram has been shown to be an effective dose, comparable in efficacy to citalopram 40 mg/day, with a rate of discontinuation due to adverse events not different from placebo.⁹⁻¹¹ When this study was planned, fluoxetine was the only SSRI with proven efficacy in elderly patients.¹⁷

Open-label trials with SSRIs with elderly patients have presented some encouraging results, even in a trial where all patients were hospitalized in an internal-medicine unit for other ailments.¹⁸ In this trial, response was particularly robust among those over 75 years of age. There is a relative paucity of placebo-controlled trials of SSRIs in elderly depressed patients. One such study, with a flexible (50 mg–100 mg) dose of sertraline, in patients over age 60, showed that sertraline was superior to placebo, although the absolute difference on the Hamilton Rating Scale for Depression (Ham-D) was small.¹⁹ In another investigation, physically ill geriatric patients with depression (N = 82) were treated in a double-blind, placebo-controlled study with fluoxetine, 20 mg, fixed dose, for 8 weeks. In the primary analysis, no significant difference was found between the active treatment and placebo, although, numerically, fluoxetine-treated patients fared better.¹⁴ It is possible that elderly patients may require a longer time to respond to treatment, and a 12-week trial might allow a sufficient time for clinical response in most of this patient population.²⁰

In a randomized 8-week trial in MDD comparing citalopram with placebo in the treatment of 174 patients age 75 and older, medication was not more effective than placebo for treatment of depression. There are, however, many aspects of the treatment protocol in a placebo-controlled trial that may have therapeutic effect, such as the frequency and duration of visits, free medical evaluation, and free medication. Furthermore, those patients willing to enter a placebo-controlled trial when there are many antidepressants available may be a non-representative

sample. It is clear that placebo-controlled trials in late-life depression need to be done, but can they be designed so that the results are more clinically relevant?²¹ Finally, the results from 121 older patients in a recurrence-prevention trial with citalopram versus placebo showed that treatment with citalopram conferred a clear and significant effect on time-to-recurrence.²²

Peripheral and central anticholinergic effects, such as constipation, urinary retention, delirium, and cognitive dysfunction; antihistaminergic effects, such as sedation; and anti-adrenergic effects, such as postural hypotension are particularly troublesome among older persons. In addition to interfering with basic activities, pronounced sedation and orthostatic hypotension pose a significant risk to them, since they can lead to falls and fractures.¹⁷ Barak et al.²³ concluded that there is a higher incidence of bradycardia in elderly patients, but fewer gastrointestinal side effects and less sweating, diarrhea, and headache. Nausea was the only symptom reported significantly more frequently among those treated with escitalopram or fluoxetine, as compared with the placebo group. When the present study was designed, it was not considered necessary, for safety and tolerability reasons, to titrate escitalopram or fluoxetine in elderly patients. Although initiating treatment in elderly patients with escitalopram 5 mg is recommended, the withdrawal rate with escitalopram 10 mg was significantly lower than that for fluoxetine, indicating that escitalopram may have been better-tolerated. The suicide rate observed in the present study (1:174) is consistent with that reported in other clinical trials in depression in elderly patients, which ranged from 1:320 (citalopram²⁴) to 1:119 (fluoxetine²⁵).

The study has several limitations that may have affected the results. Patients with comorbid psychiatric disorders were excluded, as were those with an increased risk of suicide, so this patient population is not entirely representative of elderly patients with depression. Also, there was a significant center interaction that may have resulted from recruitment of both in- and outpatients from both general-practice and specialist centers. The treatment length of 8 weeks may have been too short to see a difference in efficacy between placebo and escitalopram treatment. In an analysis of patients responding to fluoxetine treatment, it was suggested that partial responders at

Week 8 could benefit from a further 2–4 weeks of treatment.²⁶ In an open-label study of elderly patients in primary practice, the median time to response was 7 weeks, indicating that half of the patients benefited from further treatment.²⁷

An additional limitation is that the dosages of both active drugs were relatively low. In other, non-placebo-controlled studies in geriatric depression, fluoxetine dosages up to 40 mg/day²⁸ or 60 mg/day²⁹ achieved high remission rates and were well-tolerated. On the other hand, the results of this study indicate that lower starting doses and gentle up-titration of active treatment during the first 1–2 weeks might have reduced early patient withdrawal. Patients who were treatment-resistant (i.e., had failed to respond to more than one antidepressant treatment) were excluded from this study. Such patients have been included in some studies,^{13,14,22} but excluded from others.^{19,28–30}

The lack of a placebo group in trials reporting the efficacy of antidepressant treatment in open-label or comparator trials has been criticized. An alternative trial design that might be more suitable for elderly patients suffering from major depression is a relapse-prevention trial, in which patients who respond to open-label treatment are randomized in a continuation period to placebo or the active drug. This design has shown efficacy for citalopram,²² but not sertraline.³¹ Other possible methodological solutions for conducting future antidepressant trials in elderly patients might be to recruit more severely depressed inpatients from specialist settings, with greater acceptance of some adverse events at the beginning of treatment achieved through improved patient education.

In summary, escitalopram did not demonstrate greater efficacy than placebo on the primary efficacy parameter. Both escitalopram and fluoxetine were well tolerated and safe in this elderly population.

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