Bupropion Sustained Release Versus Paroxetine for the Treatment of Depression in the Elderly

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Background: Depression is a serious and widespread emotional disorder among the elderly. This study compared the efficacy and safety of bupropion sustained release (SR) with the selective serotonin reuptake inhibitor paroxetine in the treatment of major depression in elderly outpatients.

Method: Elderly (≥ 60 years) outpatients with major depressive disorder (DSM-IV criteria) were evaluated in this 6-week multicenter, randomized, double-blind study comparing bupropion SR, 100–300 mg/day, and paroxetine, 10–40 mg/day. Efficacy was assessed by changes in scores on the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A) and the Clinical Global Impressions-Severity of Illness and -Improvement scales. Safety was assessed by monitoring adverse events, vital signs, and body weight.

Results: A total of 100 patients ranging in age from 60 to 88 years were randomly assigned to treatment with bupropion SR (N = 48) or paroxetine (N = 52). Measurements of efficacy were similar between the 2 treatment groups, with both groups showing improved scores on all depression rating scales. Headache, insomnia, dry mouth, agitation, dizziness, and nausea occurred in > 10% of patients in both groups; somnolence, diarrhea, constipation, and anorexia occurred in > 10% of patients in the paroxetine group. No statistically significant differences between groups in vital signs or weight were found.

Conclusion: Both bupropion SR and paroxetine were safe and effective for the treatment of depression in the elderly. Because of its favorable side effect profile, bupropion SR may provide a safe and effective nonserotonergic treatment alternative that is well suited as an antidepressant for the elderly.

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Major depression is a common and potentially life-threatening disorder in the elderly that poses a major public health problem.[1] Depression has been associated with more social disability than coronary artery disease, pulmonary disease, hypertension, diabetes, arthritis, back problems, or gastrointestinal disorders and is the third leading cause of physical disability, behind only coronary artery disease and pulmonary disease.[2] Depressive symptoms have been estimated to occur in approximately 15% of community residents over the age of 65 years, and as the population ages, the number of elderly persons with depressive disorders can be expected to increase.[3]

Although advanced age in itself is not a risk factor for depression,[4,5] depressive symptoms in the elderly may be inappropriately viewed as a natural consequence of aging,[5] resulting in the underdiagnosis and undertreatment of depression compared with younger patients.[6] The symptoms and presentation of depression in the elderly may be the same as in younger patients or may differ.[7] For example, older patients may display more vegetative signs, cognitive disturbances, social withdrawal and isolation and may complain less of subjective dysphoria than younger patients.[8,9] Depression in the elderly may also be characterized by preoccupation with somatic symptoms, higher degrees of fatigue, lack of interest in usual activities, or lack of drive.[10,11] Thus, the recognition and diagnosis of depression in the elderly is different from, and potentially more difficult than, that in younger patients owing to its sometimes differing presentation and the possibility that symptoms may be viewed as a consequence of getting older.

The failure to diagnose and treat depression in the elderly may increase the risk of social dysfunction[12] and may also result in increased use of medical services, polypharmacy, inappropriate institutionalization, or suicide.[4,10,13,14] The suicide rate in the elderly is higher than in any other age group,[15] and major depression is the primary contributing cause of suicide in this population.[16–18] Effective treatment of depression in the elderly may decrease depression-related mortality and improve patients' overall quality of life.[12]

Bupropion hydrochloride sustained release (SR) and selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, offer treatment alternatives to older-generation antidepressants, such as tricyclic antidepressants (TCAs)

and monoamine oxidase inhibitors (MAOIs). Although both bupropion and SSRIs have been studied extensively and shown to be effective in the general population of depressed outpatients, the comorbidity of psychiatric and physical disorders and differences in the presentation of the illness in the elderly prevent the automatic extrapolation of the results of studies in young patients to elderly patients.[19]

Bupropion is a unique aminoketone antidepressant that has been shown to be effective and well tolerated in the treatment of depressed outpatients.[20–25] Bupropion affects noradrenergic and/or dopaminergic, but not serotonergic, function and has no known affinity for postsynaptic receptors.[26,27] Bupropion has not been reported to possess anticholinergic, antihistaminic, antiserotonergic, cardiotoxic, or sedating properties.[28–30] It is chemically unrelated to other available antidepressant agents, including TCAs, MAOIs, and SSRIs.

Bupropion has been marketed in the United States in an immediate-release formulation since 1989 and in an SR formulation since 1996. The SR formulation was developed with the goal of improving tolerability and allowing for more convenient dosing (data on file, Glaxo Wellcome Inc.)

Paroxetine is a potent and specific SSRI that causes down-regulation of serotonin-2 (5-HT_2) receptors, but not β-receptors.[31] It has little or no activity on monoamines other than serotonin, has no monoamine oxidase–inhibiting activity, and is weakly anticholinergic.[31] Its antidepressant activity is believed to be related to its selective inhibition of serotonin uptake into presynaptic neurons. Compared with other SSRIs and tricyclic antidepressants, paroxetine is the most potent inhibitor of serotonin reuptake.[32]

No well-controlled study has been conducted to date comparing the efficacy and safety of bupropion SR with that of an SSRI in elderly depressed outpatients. We conducted this study to compare the efficacy and safety of bupropion SR, 100–300 mg/day, with paroxetine, 10–40 mg/day, in elderly outpatients with moderate-to-severe recurrent major depression to determine if bupropion SR may be an appropriate treatment alternative to paroxetine in this population.

METHOD

Patients

Men and women 60 years of age and older with a minimum baseline score of 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[33,34] who presented with a recurrent episode of nonpsychotic major depressive disorder (DSM-IV)[35] with a duration of at least 8 weeks, but not more than 24 months, and who were considered clinically appropriate for treatment with either bupropion SR or paroxetine were eligible for the study. Patients who had a known predisposition to seizures were excluded from the study. Patients taking medications or treatments that lower the seizure threshold were also excluded. Patients were excluded if they were actively suicidal, had a history or current diagnosis of anorexia nervosa or bulimia nervosa, had an unstable medical disorder, or had a history of nonresponsiveness to pharmacotherapy for depression. Patients were also excluded if they had a history of alcohol or substance abuse within 1 year prior to the study or myocardial infarction, uncontrolled hypertension, or unstable heart disease within 6 months prior to the study. Patients could not have received any psychoactive drug within 1 week of the treatment phase of the study (2 weeks for MAOIs and 4 weeks for fluoxetine or investigational drugs) or have had previous treatment with bupropion or paroxetine. The study protocol was approved by the Institutional Review Board for each study site, and written informed consent was obtained from each patient after the study procedures and possible adverse effects were fully explained.

Study Procedures

This multicenter study consisted of a 1-week screening phase followed by a 6-week randomized, double-blind, double-dummy, parallel-group, active-treatment phase. The screening phase permitted the identification and exclusion of patients whose total score on the HAM-D decreased by more than 20% or fell below 18 between screening and study entry.

During the screening phase, medical and psychiatric histories and concomitant medication use were recorded; physical examinations, clinical laboratory tests (blood chemistry, hematology, and thyroid battery), psychiatric evaluations, and a standard 12-lead electrocardiogram (ECG) were performed; and vital signs and weight were measured.

Patients who successfully completed the screening phase were eligible for entry into the treatment phase in which they received either active bupropion SR, 100–300 mg/day, and placebo paroxetine, or active paroxetine, 10–40 mg/day, and placebo bupropion SR. Patients initially took bupropion SR at a dosage of 100 mg/day or paroxetine at 10 mg/day. If clinically indicated, the dosage of bupropion SR was increased to 200 mg/day and that of paroxetine increased to 20 mg/day on day 8 or later; similarly, the dosage of bupropion SR was increased to 300 mg/day and that of paroxetine to 30 mg/day on day 15 or later. The paroxetine dosage was further increased to 40 mg/day on day 22 or later if clinically indicated. Treatment dosage was not to exceed 300 mg/day of bupropion SR or 40 mg/day of paroxetine. The bupropion SR 100-mg/day dosage and all dosages of paroxetine were taken in the morning; all other bupropion SR dosages were equally divided between morning and evening.

The doses of both bupropion SR and paroxetine were adjusted simultaneously, taking into account the maxi-

mum dose for each medication. All dose increases were maintained for a minimum of 7 days before any further dose increases were made. Patients unable to tolerate the minimum doses of study drugs were discontinued from the study.

At each clinic visit after baseline, patients were to return the medication blister cards dispensed at the previous visit. Study site personnel resolved any discrepancies in medication counts on dosing records and issued new blister cards with written and verbal dosing instructions.

Efficacy Measures

Efficacy was measured by psychiatric evaluations consisting of investigator ratings using the HAM-D,[33,34] the Clinical Global Impressions-Severity of Illness scale (CGI-S),[36] the CGI-Improvement scale (CGI-I),[36] and the Hamilton Rating Scale for Anxiety (HAM-A).[37] The HAM-D measures the severity of symptoms in patients with a diagnosis of depression. The CGI-S is a clinical evaluation of the overall severity of illness that compares each patient with the total population of patients with the illness on the basis of a 7-point scale ranging from 1 (normal) to 7 (among the most extremely ill patients). The CGI-I is an overall rating of improvement compared with baseline using a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The HAM-A measures symptoms of anxiety.

Safety Measures

At each weekly study visit, vital signs (pulse and blood pressure) and weight were monitored, and reports of adverse events (defined as any untoward medical occurrence, potentially drug related or not) were elicited using a standard verbal probe procedure ("Have you had any problems since the last visit?"). If patients reported a partial response, investigators were instructed to probe further for a fuller response to elucidate details such as onset, severity, and treatment of the adverse event, if any.

Statistical Analyses

Two-sided tests with a .05 alpha level of significance were used for treatment comparisons. A sufficient number of patients were screened to provide 100 patients who were randomly assigned to 1 of the 2 treatment groups. Stratified randomization was used to ensure that comparable numbers of patients aged 60 to 69 years and patients 70 years and older were assigned to each treatment group.

Background and demographic characteristics were summarized using descriptive statistics or frequency counts. Mean compliance rates were derived by calculating individual compliance rates during the treatment period (expressed as a percentage) and averaging across each treatment group. Reasons for premature discontinuation from the study were also tabulated for both treatment groups.

All patients who received at least one dose of study medication and completed one or more treatment-phase efficacy assessments beyond baseline were included in the efficacy analyses (intent-to-treat population). Both observed and last-observation-carried-forward (LOCF) scores were analyzed.

Change scores between baseline and each treatment-week assessment were computed for each efficacy measure except the CGI-I. Analysis of variance comparing the 2 treatments was performed on change scores (observed and LOCF) for each treatment-week assessment. Chi-square tests were also performed to compare the percentages of responders in the 2 treatment groups. For the HAM-D, treatment responders were defined as patients whose HAM-D total scores decreased by at least 50% between baseline and discontinuation of treatment. For the CGI-I, patients were considered to be responders if their final CGI-I rating was "much improved" (2) or "very much improved" (1). Chi-square analyses were also performed on these 2 efficacy scales to compare the frequency of responders in the 2 treatment groups.

The safety population consisted of all patients who received at least 1 dose of study medication. The frequency and percentage of patients reporting treatment-emergent adverse events (adverse events that developed or worsened during treatment) were tabulated; the Fisher exact test was used to determine statistical differences in the occurrence of adverse events. Change scores were computed between baseline and each treatment week assessment for blood pressure, pulse, and weight, and summary statistics were compiled.

RESULTS

Patient Characteristics, Dosing, and Disposition

Of the 100 patients enrolled in the study, 48 were randomly assigned to treatment with bupropion SR and 52 were randomly assigned to treatment with paroxetine. Treatment groups were comparable at baseline with respect to age, gender, race, and psychiatric history (Table 1). Treatment groups were also similar at baseline with respect to concomitant medical illnesses (Table 2).

The overall mean ± SD daily doses were 197 ± 53 mg/day of bupropion SR (range, 100–300 mg/day) and 22 ± 7 mg/day of paroxetine (range, 10–40 mg/day). Overall mean medication compliance rates (number of milligrams taken divided by the number of milligrams prescribed) were high in both treatment groups (95% with bupropion SR and 98% with paroxetine).

Efficacy Evaluations

LOCF and observed scores were similar for each measure of efficacy, and no statistically significant differences were found between treatment groups in any of these measures. Only LOCF scores are presented.

Table 1. Patient Characteristics and Dosing[a]

Variable	Bupropion SR (N = 48)	Paroxetine (N = 52)
Age, y, mean (range)	69.2 (60–85)	71.0 (60–88)
Women, N (%)	26 (54)	31 (60)
Ethnic origin, N (%)		
White	47 (98)	47 (90)
Black	1 (2)	4 (8)
Other	0 (0)	1 (2)
Severity[b] of current episode, N (%)		
Moderate	42 (88)	46 (88)
Severe	6 (13)	6 (12)
No. of previous episodes, N (%)		
1–2 episodes	26 (54)	26 (50)
3–4 episodes	16 (33)	17 (33)
≥ 5 episodes	6 (13)	9 (17)
Duration of current episode, N (%)		
2–6 mo	16 (33)	17 (33)
7–12 mo	15 (31)	19 (37)
13–24 mo	17 (35)	16 (31)
Prior antidepressant used for current episode, N (%)	8 (17)	6 (12)
Reason for premature discontinuation, N (%)[c]		
Adverse experience	4 (50)	3 (38)
Consent withdrawn	2 (25)	5 (62)
Protocol violation	2 (25)	0 (0)
Daily dose over treatment phase, mg/d		
Mean ± SD	197 ± 53	22 ± 7
Range	100–300	10–40
Compliance, mean % of prescribed dose	95	98

[a]Abbreviation: SR = sustained release.
[b]Severity based on Clinical Global Impressions-Improvement scale (CGI-I) ratings.
[c]Percentages based on a total N of 8 patients in each group who prematurely discontinued medication.

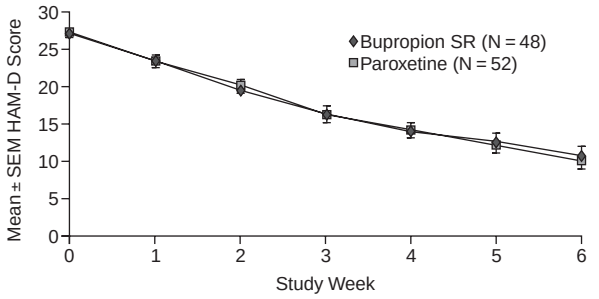
Table 2. Concomitant Medical Illnesses Present at Baseline

	Bupropion SR (N = 48)		Paroxetine (N = 52)	
Body System	N	%	N	%
Cardiovascular	17	35	15	29
Endocrine/metabolic	7	15	4	8
Hepatobiliary/pancreatic	0	0	1	2
Musculoskeletal	12	25	9	17
Respiratory	4	8	6	12
Skin	5	10	7	13
Urinary tract	8	17	9	17

HAM-D. Mean LOCF HAM-D scores for all patients were similar between treatment groups at baseline and decreased by approximately 60% by week 6 in both groups (59% reduction with bupropion SR and 63% reduction with paroxetine; Figure 1). No statistically significant differences in mean HAM-D scores were found between treatment groups at any week in LOCF analyses (see Figure 1).

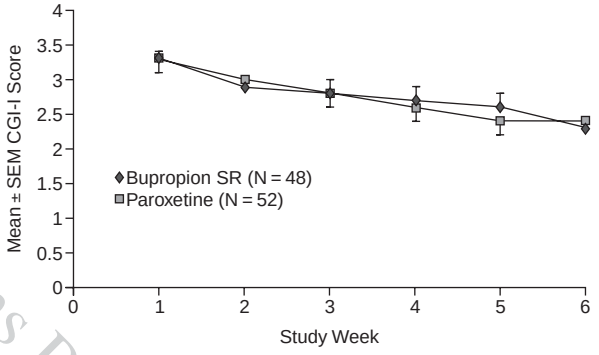
On the basis of a 50% or greater reduction in HAM-D scores at the end of treatment, 71% of patients treated with bupropion SR and 77% of patients treated with paroxetine were defined as responders to treatment. The difference in response rates between treatment groups was not statistically significant.

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores for All Patients (LOCF)[a]



[a]Abbreviation: LOCF = last observation carried forward.

Figure 2. Clinical Global Impressions-Improvement Scale (CGI-I) Scores for All Patients (LOCF)

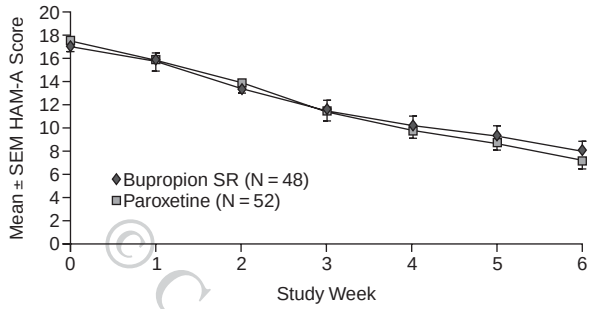


CGI-S. Mean LOCF CGI-S scores for all patients were similar between treatment groups at baseline and decreased by nearly 50% by week 6 in both groups (47% reduction with bupropion SR and 48% reduction with paroxetine). No statistically significant differences in mean CGI-S scores were found between treatment groups at any week in LOCF analyses.

CGI-I. Both treatment groups showed similar improvement in CGI-I scores (30% reduction in scores with bupropion SR and 27% reduction with paroxetine by week 6; Figure 2). No statistically significant differences were found between treatment groups in LOCF ratings of improvement during treatment. On the basis of being rated as "much improved" or "very much improved" on the CGI-I at the end of treatment, 62% of patients treated with bupropion SR and 57% of patients treated with paroxetine were defined as responders to treatment. The difference in response rates between treatment groups was not statistically significant.

HAM-A. Mean LOCF HAM-A scores for all patients were similar between treatment groups at baseline and decreased by approximately 55% by week 6 in both groups (53% reduction with bupropion SR and 59% reduction

Figure 3. Hamilton Rating Scale for Anxiety (HAM-A) Scores for All Patients (LOCF)



with paroxetine; Figure 3). No statistically significant differences in mean HAM-A scores were found between treatment groups at any week.

Safety Evaluations

Adverse events reported by more than 10% of patients in both treatment groups included headache, insomnia, dry mouth, agitation, dizziness, and nausea. Somnolence, diarrhea, constipation, and anorexia were also reported in more than 10% of patients treated with paroxetine (Figure 4).

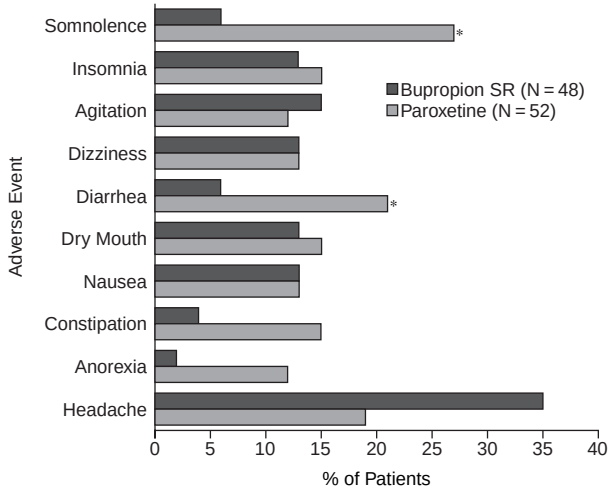
Investigators were allowed to decrease the dose of study medication as needed to manage adverse events. Reductions or temporary discontinuations of the dose of study medication were prescribed for 24 patients. Paroxetine was discontinued for 3 patients owing to adverse events including agitation, tachycardia, and anxiety; none of these events were considered to be serious. Bupropion SR was discontinued for 4 patients owing to adverse events including dehydration, vertigo, trembling, and weakness; only the episode of dehydration was classified as serious, but was not considered by the investigator to be drug related.

Assessments of vital signs and body weight were similar between treatment groups. At the end of treatment, the mean changes from baseline for the bupropion SR and paroxetine groups, respectively, were –0.7 and –2.0 mm Hg in systolic blood pressure, –0.7 and –1.0 mm Hg in diastolic blood pressure, –0.1 and +0.5 beats per minute in pulse rate, and –0.7 and –0.4 kg in weight. None of these differences were clinically significant, and no patients were removed from the study owing to changes in vital signs or weight loss.

DISCUSSION

This was the first well-controlled study to compare bupropion SR with paroxetine for the treatment of depression in elderly outpatients. After 6 weeks of treatment with either bupropion SR or paroxetine, patients had improved

Figure 4. Frequently Reported Adverse Events[a]



[a]Adverse events reported by > 10% of patients in either treatment group.
*p < .05 vs. paroxetine.

scores on all depression rating scales (HAM-D, CGI-S, and CGI-I); both treatments were similarly effective.

Selection of an Antidepressant

Safety and tolerability often determine the selection of an appropriate antidepressant for elderly patients, provided that efficacy is comparable.[38] Antidepressants that are effective; have few adverse effects (especially lethargy and effects on cardiac function, blood pressure, and mental alertness), low potential for drug interactions, and low dosing frequency; and are safe in overdose are ideal for the treatment of the elderly.[39,40] Safety in overdose is an especially important consideration in treating depression in the elderly given the relatively high rate of suicide in this population.[15]

Common Adverse Events

Consistent with other reports,[31,41,42] adverse events associated with both paroxetine and bupropion SR in the present study were dry mouth (15% and 13%, respectively), nausea (13% each), and agitation (12% and 15%, respectively). With the exception of headache, which occurred in 35% of patients treated with bupropion SR and 19% of patients treated with paroxetine (p = .076), the occurrence of other adverse events in the present study was generally higher with paroxetine compared with bupropion SR. The majority of headaches in both treatment groups were of short duration (< 5 days) and mild in intensity; none were severe and none led to premature discontinuation from the study. Fewer than half of the patients in either treatment group used over-the-counter medications for headache relief. No difference in the

occurrence of headache was found in either group on the basis of gender or age (60–69 years vs. ≥ 70 years).

Significantly more patients treated with paroxetine (27% [14/52]; $p < .05$) reported somnolence compared with patients treated with bupropion SR (6% [3/48]), but no discontinuations were due to this side effect. Elderly patients may be more sensitive to sedative side effects than younger patients, and bupropion is well suited for the elderly because it is among the least sedating antidepressants.[8]

The elderly may also be especially interested in avoiding drugs that cause gastrointestinal disturbances. The incidence of diarrhea in this study was significantly higher with paroxetine (21% [11/52]; $p < .05$) compared with bupropion SR (6% [3/48]; $p < .05$). Constipation was also more common with paroxetine compared with bupropion SR (15% [8/52] with paroxetine vs. 4% [2/48] with bupropion SR). The greater affinity of paroxetine for muscarinic receptors compared with other SSRIs[43] may explain the higher incidence of sedative effects[44] and constipation[45] observed with paroxetine compared with other SSRIs and bupropion.

Cardiovascular Effects

Cardiovascular side effects are an important consideration in selecting an appropriate antidepressant for the elderly, who tend to be particularly susceptible to the orthostatic effects of some antidepressants.[8,46] Orthostatic hypotension is a common and potentially serious adverse effect associated with TCAs and MAOIs and may be particularly dangerous in patients with impaired cardiac function.[8,47]

Bupropion has been shown to be safe for patients with preexisting cardiac disease,[47,48] and neither bupropion nor paroxetine has been commonly associated with orthostatic hypotension.[8,31,47] No reports of orthostatic hypotension were found with either bupropion SR or paroxetine in the present study. Furthermore, unlike TCAs, bupropion and paroxetine are not associated with cardiac conduction abnormalities[31,49–51] and do not cause significant changes in heart rate or blood pressure.[41,44,49]

Dosing Considerations

Successful pharmacotherapy for depression in the elderly requires careful consideration of the pharmacokinetics and pharmacodynamics of available antidepressants to identify a favorable balance of therapeutic effects and safety.[12] Physiologic changes in gastrointestinal, liver, and kidney function associated with aging, as well as age-related changes in body composition, may produce clinically significant differences in drug metabolism and pharmacokinetics in elderly patients compared with younger patients. These changes may complicate treatment of the elderly.[1,52–54] Because doses of psychotropic drugs generally produce higher plasma concentrations in the elderly compared with younger patients,[55] lower starting doses of antidepressants are generally used in the elderly,[49] and dosage increases need to be made gradually on the basis of response and tolerability.[56,57]

Risk of Seizures

The incidence of seizures increases substantially with age, mostly because of the increase in stroke and brain tumors. Dementia, infection, trauma, and alcoholism are also associated with late-onset seizures.[58] For each 100,000-person population, the incidence of seizure is 76 for individuals in their 60s, 147 for individuals in their 70s, and 159 for individuals in their 80s. This compares with an incidence of 69 in the general population.[59] For this reason, it is especially important to screen for factors predisposing elderly patients to seizures prior to choosing a medication for depression.

Seizure risk is known to increase in a dose-related way with all antidepressants.[51] SSRIs are associated with an incidence of 1 to 2 seizures per 1000 individuals treated; seizures occurred in 0.1% of paroxetine-treated patients in premarketing studies.[60] In adults screened for predisposition to seizure and taking 300 mg/day or less of bupropion SR, there is an associated incidence of 1 seizure in every 1000 individuals,[61] a rate comparable to that of SSRIs.

CONCLUSION

Bupropion SR and paroxetine appear to be generally as effective in the treatment of depression in the elderly as in younger patients and may have advantages over some other antidepressants owing to their relatively low risk of life-threatening cardiac toxicity in overdose.[31] The tolerability of an antidepressant may enhance compliance in the elderly and may prevent the premature discontinuation of treatment, even if treatment is likely to be prolonged. Both bupropion SR and paroxetine were well tolerated in this sample of medically stable elderly adults, and lower incidence of side effects with bupropion SR recommend it as a nonserotonergic treatment alternative for adults over age 60.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), paroxetine (Paxil).

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