Effect of Bupropion SR on the Quality of Life of Elderly Depressed Patients With Comorbid Medical Disorders

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Background: There is a need for additional studies of the quality of life (QOL) of elderly depressed subjects with medical comorbidity.

Method: We conducted an 8-week, open trial of bupropion sustained release (SR) in 18 elderly (60–81 years) subjects with DSM-IV major depressive disorder and one or more serious medical illnesses (e.g., congestive heart failure, type 1 diabetes mellitus, irritable bowel syndrome) with a week-12 follow-up interview. The intent-to-treat method with the last observation carried forward was used to analyze depression and QOL measures. Dosing was initiated at 100 mg once daily and increased at weekly intervals to a maximum of 150 mg twice daily as clinically indicated.

Results: Bupropion SR treatment was associated with reductions in Clinical Global Impressions-Severity of Illness scale ($p < .0001$) score and in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score ($p < .0001$). QOL as measured by the Medical Outcomes Study Short Form-36 (SF-36) also tended to improve with treatment. The SF-36 "mental health" ($p < .01$) and "social functioning" ($p < .0006$) domains improved significantly by week 4. "Vitality" ($p < .03$) improved significantly by week 12. On the HAM-D, statistically significant improvement was noted on "depressed mood" ($p < .0001$), "feelings of guilt" ($p < .01$), "work and activities" ($p < .001$), "hypochondriasis" ($p < .02$), and "insomnia" ($p < .01$) at week 8. The mean dose of bupropion SR at endpoint was 222 mg/day, and the drug was relatively well tolerated. Two subjects dropped out owing to adverse events and 2 owing to other reasons. No drug-drug interactions occurred.

Conclusion: These data suggest that bupropion SR is well tolerated and may improve depression, insomnia, somatic symptoms, work functioning, and certain quality-of-life measures in elderly depressed subjects with medical disorders. A randomized, placebo-controlled study is warranted to confirm these promising findings.

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There is a high prevalence of depression in elderly subjects with serious medical illnesses. Studies have established that untreated depression in the elderly is associated with lower quality of life (QOL) and increased disability.[1,2] Subjects with both physical illnesses and depression may be at greater risk for developing impaired functional health and well-being than those with either condition alone.[1–3]

Some evidence suggests that acute antidepressant therapy may improve the QOL in elderly subjects with depression.[4] However, broadly speaking, previous studies on this topic were not designed to study depressed subjects with serious medical illnesses, did not systematically quantify medical comorbidity, and generally tended to exclude a variety of concomitant medications. In addition, most prior studies of geriatric depression rarely used QOL measurements (i.e., sense of well-being) to assess treatment outcome. Together, QOL assessments and symptom rating scales can provide a more comprehensive assessment of change and improvement in depressed subjects.

Bupropion sustained release (SR) is frequently used to treat geriatric depression in practice, as it has relatively few gastrointestinal and sexual adverse effects.[5,6] Bupropion SR is also increasingly being prescribed for the management of smoking cessation in subjects with medical illnesses. The precise mechanism of action of bupropion is unknown, although it is postulated that bupropion exerts its effects through noradrenergic and/or dopaminergic systems.[7] We report here the results of an open trial evaluating the efficacy of bupropion SR on depression ratings and QOL in elderly depressed subjects with medical comorbidities.

METHOD

The protocol was approved by the Duke University Medical Center institutional review board, and written informed consent was obtained from each subject prior to enrollment. The study was conducted at a single site and was designed to include subjects who were representative of the elderly population and had a broad range of serious medical conditions and concomitant medications. Inclusion criteria were as follows: age 60 years and older, DSM-IV criteria for current major depressive disorder, one or more serious medical illnesses requiring first-line therapy, and a score of ≥ 5 on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (a validated instrument designed specifically to quantify medical comorbidity).[8,9] A major depressive episode (according to DSM-IV) was diagnosed on the presence of either one of the following in the 2 weeks preceding the diagnosis: depressed mood or loss of interest or pleasure. In addition, subjects had at least 5 of the following symptoms in the 2 weeks preceding the diagnosis: significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slow thinking or impaired concentration, and suicide attempt or suicidal ideation.

Exclusion criteria were as follows: (1) currently taking theophylline; (2) had received an investigational drug during the 30 days prior to enrollment in the study; (3) had taken monoamine oxidase inhibitors (MAOIs) within the 3 weeks prior to the first administration of study medication; (4) had history of seizures, loss of consciousness, or head injury; or (5) current diagnosis of psychotic disorders, active suicidality, mania, substance abuse, or eating disorder. Subjects were not allowed to take concurrent antidepressant medications. All other concomitant medications were allowed to be continued as appropriate. Subjects with a previous history of treatment resistance or failure were not excluded. Subjects were instructed not to take an MAOI for 2 weeks after completing the study.

Subjects meeting entry criteria were treated with bupropion SR. Dosing was initiated at 100 mg daily for 1 week and titrated to a maximum of 150 mg twice a day at intervals of not less than 1 week, based on tolerability and response. The Medical Outcomes Study 36-Item Short Form Health Status Survey (SF-36),[1,10] a self-reported questionnaire, was used to measure QOL components of physical and mental health. The SF-36 has 9 domains, of which 4 assess mental health QOL and 4 physical health QOL. The SF-36, the 17-item Hamilton Rating Scale for Depression (HAM-D),[11] the Patient Global Impression of Change scale (PGI),[12] the Clinical Global Impressions-Severity of Illness scale (CGI-S),[12] and the Clinical Global Impressions-Improvement scale (CGI-I)[12] were administered at baseline and at weeks 2, 4, and 8. In addition, we administered the SF-36 during a follow-up assessment at week 12. Safety assessments (for adverse events, pulse, and blood pressure) were collected at all clinic visits and, as necessary, by telephone calls to follow up on adverse events.

We hypothesized that bupropion SR would be associated with improvements in depression and QOL ratings. Efficacy analyses were performed on data sets for last observation carried forward (LOCF; subjects randomly assigned to treatment with at least one evaluation while on study treatment; last evaluation is carried forward) and observed cases (subjects randomly assigned treatment with at least one evaluation while on study treatment at designated assessment time). We used the Statistical Analysis System (JMP 1999 ed., SAS Institute, Cary, N.C.) for all of our statistical analyses. A t test was used to compare the mean change from baseline to subsequent study time points in CGI-S, HAM-D, SF-36, and global ratings. Safety measures were compared from week 8 (or last observation) to baseline. Where appropriate, unequal variances were accounted for by using a test for unequal variances. Two-sided p values less than .05 were considered significant, and many p values shown as $< .05$ were significant at $p < .01$ or $p < .0001$ levels. Actual p values that did not reach significance are shown for comparisons. All data are expressed as mean ± standard error of mean (SEM).

RESULTS

Eighteen subjects were enrolled; their baseline and endpoint characteristics are listed in Table 1. Figures 1–4 depict the effects of treatment on change from baseline.

Forty-four percent of subjects had been treated previously with an SSRI, and 56% were believed to have a history of relative treatment resistance. The mean ± SEM dose of bupropion SR at endpoint was 222 ± 18 mg daily, and the most frequent (mode) dose was 150 mg twice daily (N = 8).

Medical Comorbidity

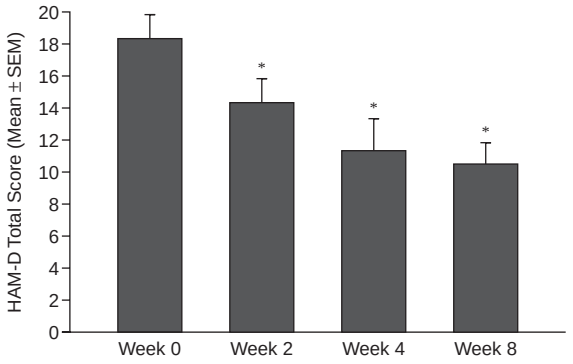
Ten subjects received doses of less than 300 mg daily. The number of concomitant medications used ranged from 1 to 19 (mean ± SEM = 8.7 ± 0.9), reflecting the medically ill elderly population. Examples of major medical illnesses in each of these patients are as follows: coronary artery disease, congestive heart failure, ovarian cancer, breast cancer, non–small cell lung cancer, hypertension, severe thrombophlebitis, chronic obstructive pulmonary disease/emphysema, chronic irritable bowel syndrome, type 1 and type 2 diabetes mellitus, hypothyroidism, cardiac valvular or conduction abnormalities, gastroesophageal reflux disease, sigmoid diverticulitis, osteoporosis, severe osteoarthritis, Wolff-Parkinson-White syndrome, and aortic aneurysm. Most patients had multiple comorbid medical disorders and were receiving multiple medications. The

Table 1. Baseline and Endpoint Characteristics of Study Sample[a]

Characteristic	Baseline	Endpoint (Week 8)
N	18	…
Age, y, mean ± SEM	69.9 ± 1	…
Male/Female	7/11	…
Age at onset of depression, y, mean ± SEM	58.2 ± 4	…
Mean duration of depression, y, mean ± SEM	2.3 ± 0.6	…
History of treatment resistance (%)	56	…
Previously treated with SSRIs (%)	44	…
HAM-D total score (mean ± SEM)	18.3 ± 1.0	10.5 ± 1.0[b]
CGI-Severity scores (mean ± SEM)	3.8 ± 0.1	2.6 ± 0.2[b]
Severity: Borderline (%)	0	56
Mild (%)	28	33
Moderate (%)	61	11
Marked (%)	11	0
CIRS-G total score, mean ± SEM	12.2 ± 1	…
SF-36 item scores, mean ± SEM		
Physical functioning	50.0 ± 7.1 (69.4)	60.3 ± 6.5
Role-physical	31.9 ± 8.5 (64.5)	54.2 ± 9.7
Bodily pain	59.1 ± 6.8 (68.5)	73.3 ± 5.9
General health	51.3 ± 5.8 (62.6)	60.3 ± 5.6
Vitality	31.9 ± 5.7 (59.9)	47.8 ± 6.3
Social functioning	43.8 ± 6.5 (80.6)	61.8 ± 7.3
Role-emotional	31.5 ± 9.1 (81.4)	50.0 ± 9.8
Mental health	46.7 ± 4.2 (76.4)	63.8 ± 6.0[b]
Reported health transition	44.4 ± 5.6	50.0 ± 6.1

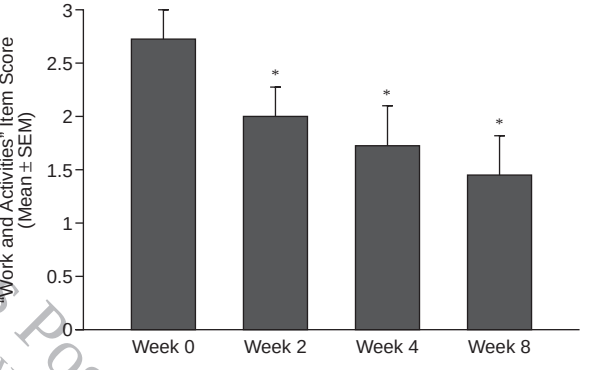
[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness subscale, CIRS-G = Cumulative Illness Rating Scale for Geriatrics, HAM-D = Hamilton Rating Scale for Depression, SF-36 = Medical Outcome Study 36-item Short Form Health Status Survey, SSRIs = selective serotonin reuptake inhibitors. Higher SF-36 numbers indicate improved quality of life. SF-36 numbers shown in parentheses are the published population norms for healthy community-dwelling elderly subjects (from reference 10) shown here for schematic comparison; all SF-36 items improved from baseline to endpoint, but only the changes on the mental health domain reached statistical significance.
[b]$p < .05$ for comparison of baseline and endpoint values.

Figure 1. Change From Baseline (LOCF) in HAM-D Scores[a]



[a]Abbreviation: LOCF = last observation carried forward.
*$p < .05$.

Figure 2. Change From Baseline (LOCF) in HAM-D "Work and Activities" Scores



*$p < .05$.

mean CIRS-G scores and SF-36 QOL scores of this population are listed in Table 1 and contrasted with SF-36 population norms (since norms are not given for CIRS-G).

CGI and PGI Ratings

There was a statistically significant improvement in CGI-I ($p < .0001$) and CGI-S scores ($p < .0001$). The CGI-I ($p < .0001$) and CGI-S ($p < .0006$) mean scores also improved from baseline to week 4. The mean PGI score improved significantly from baseline to week 2 ($p < .0001$) and continued to improve significantly at week 4 ($p < .0001$) and week 8 ($p < .0001$).

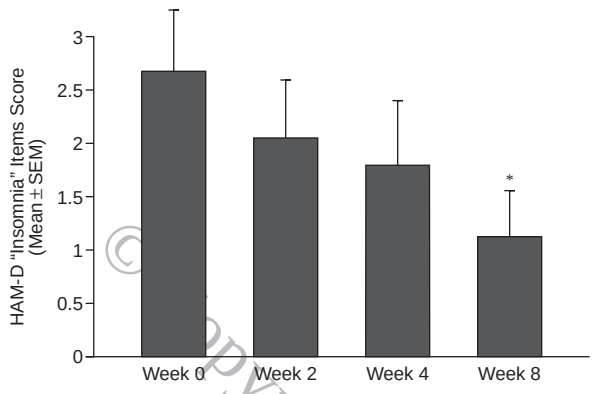
HAM-D Ratings

Improvements in HAM-D total score were noted at week 2 ($p < .02$) and continued to week 4 ($p < .0004$) and week 8 ($p < .0001$). In post hoc analyses of the individual HAM-D items, "depressed mood" ($p < .0001$), "feelings of guilt" ($p < .01$), "work and activities" ($p < .001$), "insomnia" factor (the total of all 3 insomnia items, "early," "middle," and "late" insomnia) ($p < .01$), and "hypochondriasis" were improved from baseline to week 8 ($p < .02$). The "work and activities" item showed significant improvements by week 2 ($p < .02$). The HAM-D item "general somatic symptoms" approached significance at week 8 ($p < .06$).

Quality of Life

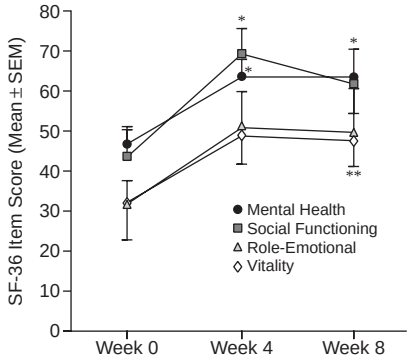
The SF-36 item "mental health" improved significantly from baseline to week 4 ($p < .01$), to week 8 ($p < .0004$), and to week 12 ($p < .01$). The item "social functioning" improved from baseline to week 4 ($p < .0006$), approached significance at week 8 ($p < .06$), and became significant at week 12 ($p < .02$). The item "vitality" was significant at week 12 ($p < .03$) compared with baseline, and, in the observed case analyses, at week 8 ($p < .05$). The physical health measures "physical functioning" ($p < .06$), "role-physical" ($p < .1$), "bodily pain" ($p < .4$) and "general health" ($p < .09$) tended to improve but did not reach statistical significance. On observed case analyses, the SF-36 item "physical functioning" reached significance from baseline to week 12 ($p < .0007$).

Figure 3. Change From Baseline (LOCF) in HAM-D "Insomnia" Scores[a]



[a]Mean of the HAM-D items "early insomnia," "middle insomnia," and "late insomnia."
*p < .05.

Figure 4. SF-36 Mental Health Scores (LOCF)



*p < .05.
**p < .05 in the observed case analysis.

Adverse Events

Of the 4 subjects that dropped out of the study, 2 left owing to adverse events, 1 owing to severe constipation and the other to nausea and vomiting. Four other events that met the definition for "serious adverse event" were noted during the study. Serious adverse events included ovarian carcinoma relapse, recurrent hidradenitis suppurative, pneumonia, and lung cancer. All 4 of these were considered to be unrelated to the study medication by the investigator.

There were no significant differences in heart rate ($p < .8$), systolic blood pressure ($p < .7$), and diastolic blood pressure ($p < .5$) between baseline and endpoint values. The most common adverse events at endpoint included dry mouth (N = 6), constipation (N = 4), belching (N = 3), decrease in appetite (N = 3), headaches (N = 2), insomnia (N = 2), nausea (N = 2), sweating (N = 2), nervousness (N = 1), and diarrhea (N = 1). Some patients had more than one adverse event.

CASE REPORT

A female patient, aged 66 years, presented with a history of recurrent depression and was diagnosed by the investigator at baseline to have moderate depression (CGI-S = 4). A prior trial with sertraline was unsuccessful in improving her low mood. She had a history of ovarian cancer, breast cancer, hypothyroidism, irritable bowel syndrome, spastic colon, hepatic cysts, and osteoarthritis. Her medications included thyroid replacement, antacids, calcium, vitamins, and hyoscyamine sulfate. Bupropion SR was initiated at 100 mg daily for the first week and then titrated up to 150 mg twice daily. With the higher dose, the patient complained of dry mouth and late insomnia. The dose was decreased to 150 mg daily (administered in the morning), which helped to minimize the insomnia and dry mouth. During the trial, the patient was diagnosed with a recurrence of ovarian cancer, which was treated with topotecan chemotherapy. She reported being able to cope with her diagnosis of cancer and attributed her optimistic attitude to bupropion SR. Her mood, energy, optimism, and general sense of well-being improved substantially. At the end of 8 weeks, she rated herself as "very much better" on the self-rated PGI-Improvement (PGI-I) scale, and the investigator also rated her as "very much improved" on the CGI-I scale. She showed sustained improvement at the end of 12 weeks. This case demonstrates not only the value of bupropion SR in a depressed medical patient, but also the potential for lower doses (e.g., 150 mg daily) to be effective.

DISCUSSION

This pilot study was designed to measure the effect of antidepressant therapy on QOL in a representative sample of elderly depressed subjects with serious medical illnesses. Several findings emerged from this trial. Bupropion SR treatment decreased symptoms of depression throughout the 8-week trial, with improvements noted as early as week 2. These improvements were noted by the clinician, by subject, and on objective ratings. On the HAM-D, significant improvement was noted in the "work and activities" item 2 weeks after therapy was initiated, and this item continued to show significant improvement until endpoint at week 8. Insomnia and hypochondriasis were also improved at endpoint compared with baseline. These data are particularly encouraging, since geriatric depression in medical practice may often present with lethargy, fatigue, somatic symptoms, or insomnia.

Bupropion SR was relatively well tolerated, and there were few serious adverse events. There were no drug-drug interactions noted. The relatively broad range of

concomitant medications being taken also supports the relative tolerability and safety of bupropion SR. However, readers must bear in mind that we excluded subjects receiving theophylline and did not specifically examine plasma concentrations for drug interactions. Many of the adverse events seen were relatively minor, and therapy could be continued in the majority with clinical monitoring and dose adjustments. There was no significant change in blood pressure or pulse. The 5 most common treatment-emergent adverse events in placebo-controlled trials[7] of bupropion SR (300 mg/day; N = 376) were headaches, dry mouth, nausea, constipation, and insomnia. The placebo-adjusted treatment-emergent rates for these 5 adverse events in controlled trials of bupropion SR (300 mg/day) were headaches (3%), dry mouth (10%), nausea (5%), constipation (3%), and insomnia (5%). Side effects seen in our elderly medical sample appeared to be generally similar to those listed in the package insert for healthy adults, with dry mouth and constipation being common complaints. As with many other medications, clinicians must routinely query for constipation or dry mouth when using bupropion SR in medically ill elderly patients receiving multiple medications. Our experience suggests that most side effects are generally mild or transient and can be managed using simple measures such as increasing intake of fruits or fiber, lower initial dose, or dose reduction.

The mean bupropion SR dose at endpoint was 222 mg daily, suggesting that doses lower than the 300 mg daily dose recommended for adult depression may be effective in the elderly. These findings are consistent with anecdotal evidence from clinical practice and with recent data demonstrating antidepressant equivalence of 150 mg daily with 150 mg b.i.d. in younger subjects.[13] As always, in the elderly and medically ill, the use of a lower initial dose (e.g., 100 mg or 150 mg daily) and slower titration may be prudent, given the frequency of polypharmacy in the elderly and the effects of aging on pharmacokinetics.[14] A controlled trial of a relatively low dose of bupropion SR, 150 mg/day, thus may be worthwhile in geriatric depression.

The relatively low baseline QOL ratings in this sample are consistent with the synergistic impact of depression and medical illness. The SF-36 measures QOL for the past 4 weeks and is a validated instrument for which published norms are available. Several QOL domains improved significantly with acute bupropion SR therapy, and some others did not improve. None of the QOL domains worsened. The most consistent improvement was in the "mental health" item and it was seen as early as weeks 4, as well as at endpoint. The QOL domains "vitality" and "social functioning" also improved significantly. While the physical health measures of the SF-36, "role-physical," "bodily pain," and "general health," did not reach significance in the LOCF analysis, they all tended to improve with treatment. The item "physical functioning" did reach significance at week 12 in the observed cases analysis. These data are also encouraging and suggest that antidepressant therapy may be linked to meaningful improvements in general well-being in the medically ill. Improvements in the "vitality" and "social functioning" domains are consistent with the improvements in the "work and activities" item on the HAM-D and could speculatively reflect the noradrenergic activity of bupropion.

Nearly half of the subjects in this trial had been previously treated with an SSRI. Our findings also lend some support to the benefit of bupropion SR in subjects who inadequately respond to such prior therapy. In practice, bupropion SR is frequently used as an augmentation or switch strategy, and a prospective study addressing this issue would also be worthwhile.

In this study, pharmacotherapy was the treatment modality, and patients were not offered any formal psychotherapy. This was done in order to study only the effects of bupropion SR on depression and QOL. However, in practice it is important to provide education (on diagnosis, treatment options, side effects, and compliance, for example) and to select appropriate therapy after discussing treatment options. Such options may include formal psychotherapy (e.g., interpersonal therapy or cognitive therapy) and/or medication treatment. The choice of therapy lies in a variety of factors such as prior treatment response, safety, side effects (e.g., propensity for sexual side effects), efficacy, convenience, and cost. A combination of psychotherapy and medication may increase compliance and/or efficacy in the elderly. In addition, some data suggest that regular aerobic exercise and lifestyle changes may improve depression in the elderly. Thus, it is important, especially in the medically ill, to tailor treatment for optimal mind/body wellness.

The main strength of the study is the inclusive nature of the sample, careful quantification of medical comorbidity, and use of QOL outcomes. Our findings add to the relatively sparse literature on clinical trials for depression in elderly medically ill subjects. However, this was a pilot study and, as such, was limited by the relatively small sample size and the lack of a control group. The contribution of nonspecific improvement ("placebo effects") cannot be separated fully from medication effects in an open naturalistic study. Hence, our findings must be generalized and interpreted within this context. A randomized, placebo-controlled study with a larger sample is warranted to confirm and expand upon these findings. Given the accumulating data linking depression to increased morbidity and mortality in the elderly, additional studies examining the impact of antidepressant therapy on medical outcomes are urgently needed.

Drug names: bupropion (Wellbutrin, Zyban), hyoscyamine sulfate (Levsinex and others), sertraline (Zoloft), theophylline (Quibron and others), topotecan (Hycamtin).

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