Depression Associated with Antihypertensive Drugs

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Background. Depression is a potential side effect of antihypertensive drug therapy. Consideration of this side effect is a reason often cited by physicians for not choosing certain drugs.

Methods. In this prospective study the relative rates of depression were measured by the Zung Self-Rating Depression Scale (SDS) in patients from four hypertension treatment groups. Treatment groups consisted of 466 patients receiving: (1) no drug therapy, (2) diuretics only, (3) diuretics plus reserpine, and (4) diuretics plus β-blockers. Demographic data including age, sex, and race were collected. Analysis of variance was used to compare the rate of depression among the treatment groups, as well as among age, sex, and racial groups.

Results. Using a Zung SDS index of ≥50, 35.4% of the hypertensive population was depressed. Age and sex were not significant factors in the frequency of depression. Blacks scored higher than whites in all drug treatment groups except those treated with high lipophilic β-blockers, but the rate of depression was not higher. Whites on the lowest dose of reserpine had the lowest rate of depression. The rate of depression among those taking reserpine or β-blockers was no different than that among those receiving either no treatment or diuretics.

Conclusions. Reserpine or β-blocker therapy did not cause any more depression than any other antihypertensive treatment.

Key Words. Depression; hypertension; drugs.

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Depression is a potential side effect of antihypertensive drug therapy.[1–8] Depression is often mentioned as a particular concern with reserpine[5–7] and β-blockers.[8,9] Quality of life is diminished with certain antihypertensive drugs used in clinical research studies[10]; however, the role of antihypertensive medication in drug-associated depression (thereby diminishing quality of life) is controversial.[11] This prospective study was conducted to examine the rates of depression among hypertensive patients as measured by the Zung Self-Rating Depression Scale (SDS).

Methods

Study Population

The charts of all patients enrolled in each of several ambulatory hypertension clinics were prospectively reviewed over a 1-year period to identify patients in one of four treatment groups. These treatment groups included patients receiving no drug therapy, diuretics alone, diuretics plus reserpine, and diuretics plus β-blockers. All patients had been on their treatment regimen for at least 3 months. The patients receiving no medications and those receiving diuretics alone served as control groups. Patients with a history of depression, who were receiving other medications known to produce depression (except for antihypertensives) or who were receiving antidepressant medications were excluded from the study.

Qualified candidates were requested at their next scheduled visit to complete the Zung SDS. In addition to the Zung SDS raw score and SDS score index (see below), additional information collected included demographic data, hypertension history, and concomitant nonantihypertensive drug therapy. Institutional approval of this protocol was obtained from the Human Assurance Committee.

Study Instrument

The Zung Self-Rating Depression Scale provides an objective measurement of depression as a clinical disorder.[12–14] It consists of 20 statements that are based on the

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diagnostic criteria most commonly used to characterize depressive disorders. The statements for all of the items are worded symptomatically, half of them in positive and half in negative terms.[13] The subject rates each item as it applies to him or her at the time of testing by selecting one of four quantitative phrases ("a little of the time," "some of the time," "a good part of the time," "most of the time"). This self-rating depression scale is easy to administer and does not obstruct or detract from physician practice habits. The Zung SDS *score* is the sum of all responses, each of which is assigned a value of 1, 2, 3, or 4. The Zung SDS *index* is derived by dividing the Zung SDS score by the maximum possible score of 80 and multiplying the result by 100.

The Zung SDS is constructed such that less depressed patients will have a low score while more depressed patients will have a higher score.[13,14] The Zung SDS index is interpreted as follows: normal = 25 to 43; borderline depression = 44 to 49; mild-to-moderate depression = 50 to 59; moderate-to-severe depression = 60 to 69; and severe depression ≥70.[13]

The validity of any rating instrument can be determined by two criteria. First, expert opinion must confirm that the symptoms and signs described by the scale represent a recognizable clinical condition. Second, the instrument must demonstrate that the results obtained by the scale can detect those patients with the disorder. Therefore, one would predict that the instrument would correlate with other scales that are considered to be valid. The Zung SDS has been shown to be effective in discriminating patients with depressive disorders from patients with other diagnostic disorders.[13–15] Studies have been conducted that demonstrated significant correlation of the Zung SDS with other depression instruments (including Hamilton, Beck Depression Inventory, the D Scale of the Minnesota Multiphasic Personality Inventory-Depression Scale, and the Depression Adjective Check List).[15–19]

Statistics

A two-way analysis of variance was used to determine the rate of depression among the treatment groups, as well as between sex and race within the groups. Means are reported as ±1 standard deviation. Confidence intervals were calculated. Chi-square analysis was used to determine the differences in the prevalence of depression between patients taking β-blockers (based on lipophilicity) and between high- and low-dose (≤0.125 mg) reserpine therapy. A P value of less than .05 was selected as the a priori level of significance. All data were analyzed using the Statistical Analysis System (SAS Institute, Cary, NC).

Results

Four hundred sixty-six patients met the entry criteria. Age ranged from 17 to 89 years with a mean age of 55.9 ± 13.0 years. Approximately 75% of the patients were younger than 65 years of age; 44% were male, and 59% were black.

The mean SDS index for the population was 46.3. Using a Zung SDS index ≥50 as indicative of depression, 35.4% of all patients were depressed. Depression was present in 37.7% of men vs 33.6% of women (χ^2 = 0.67, P = .41), 37.2% of blacks vs 32.8% of whites (χ^2 = 0.76, P = .38), and 32.8% of patients under 65 years of age vs 36.3% of patients 65 years of age or older (χ^2 = 0.33, P = .41). These differences were not statistically significant.

Of 466 patients, 111 (23.8%) received reserpine, with 21 patients (18.9%) receiving ≤0.125 mg per day (low dose) and 90 patients (81.1%) receiving >0.125 mg per day (high dose). Five of 21 (23.8%) patients receiving low-dose reserpine were depressed compared with 31 of 90 (34.4%) patients receiving high-dose reserpine (χ^2 = 0.91, P = .34). The mean SDS index for low-dose reserpine was 44.0, and for high-dose, 46.2. There was no significant difference between the groups.

Eighty-six (18.5%) of 466 patients were treated with a β-blocker. Sixty-six (76.7%) patients received high lipophilic β-blockers, and their mean SDS index was 47.9. Twenty (23.3%) patients received low lipophilic β-blockers and the mean SDS index was 44.5. There was no significant difference between the groups. Twenty-eight (42.4%) of 66 patients receiving β-blockers of high lipophilicity and 6 (30%) of 20 patients receiving β-blockers of low lipophilicity had scores on the Zung index ≥50 (χ^2 = 0.54, P = .46).

Two-way analyses of variance of SDS index by age and drug group and by sex and drug group were not significant. A two-way analysis of variance of SDS index by race and drug group found that blacks had a higher Zung SDS index than whites (P = .047). This was not related to drug group. Table 1 shows the mean SDS index for each of the five treatment groups, by race. The β-blocker group is subdivided according to the lipophilicity of the drug. The SDS index for blacks was higher in all drug groups except the β-blocker group. It should be recalled that there was no difference in the rate of depression between blacks and whites; however, this analysis suggests a subtle difference in SDS index.

A second analysis of variance was performed, by race and sex, after the β-blocker group was subdivided into two groups to compare the highly lipophilic β-blockers with other less lipid soluble β-blockers (Table 1). Statis-

Table 1. Zung Self-Rating Depression Scale Index (mean) and Confidence Interval, by Race and Drug Group (N = 466)

	No Drug	Diuretics	Reserpine ≤0.125 mg/d	Reserpine >0.125 mg/d	β-Blocker Total	β-Blocker High Lipophilicity	β-Blocker Low Lipophilicity
White	42.6 (39.8–45.3)	46.0 (43.2–48.9)	42.3 (33.2–51.5)	44.6 (39.8–49.4)	47.4 (44.0–50.7)	50.2 (46.6–53.8)	40.8 (33.9–47.7)
Black	48.7 (44.5–52.7)	47.5 (45.3–49.8)	44.7 (40.5–48.8)	46.6 (43.6–49.7)	46.9 (43.4–50.3)	46.0 (42.6–49.5)	51.4 (37.7–65.2)
Total	44.7 (42.4–47.1)	47.0 (45.3–48.8)	44.0 (40.5–47.5)	46.2 (43.6–48.9)	47.1 (44.8–49.5)	47.9 (45.4–50.4)	44.5 (38.2–50.8)

tical significance due to race but not due to the drug for the SDS index was very close ($P = .053$). Again blacks were consistently higher in all treatment groups except for the high lipophilic β-blocker group.

Discussion

Prevalence

Depression rating scales have been used to detect depression in outpatients.[12,20,21] This study demonstrated that 35.4% of this hypertensive population was depressed as measured by the Zung SDS index. This seems to be a surprisingly high rate. The relationship between depression and hypertension has been previously evaluated in two studies, both using Zung SDS. Friedman and Bennett[21] tested 1101 subjects (28% were hypertensive) and found no statistically significant correlation between the Zung index and diastolic pressure. Wood et al[20] tested 61 subjects (44% hypertensive) and found statistically significant higher Zung scores in hypertensive patients compared with normotensive patients. These differences, however, were not considered clinically important. The mean values of the SDS index for both groups were below the cutoff point of 50 for classification as depression. The prevalence of depression in hypertensive patients is not clear from these studies nor is the effect of medications. The prevalence of 35.4%, however, is higher than the prevalence of 21% to 23% observed in other primary care settings.[22] A recent report of 690 elderly (older than 60 years of age) hypertensive veterans found a 22.0% to 22.8% prevalence of clinical depression (Zung SDS index >50).[23] Maintenance therapy over 6 months in 351 patients treated with hydrochlorothiazide did not significantly alter this rate of depression.[23]

Age and sex were not significant factors in the frequency of depression. A subtle difference is suggested, however, by the significant race-related difference on mean SDS index. Blacks scored consistently higher than whites in all drug treatment groups except for the β-blocker treatment group. Blacks receiving no antihypertensive medications had the highest SDS index; however, when β-blockers were subdivided, the blacks taking the low lipophilic β-blockers had the highest Zung SDS index. Whites on low-dose reserpine had the lowest SDS index. Nevertheless, these differences may not be clinically important. A similar finding had been reported from a study in a family practice setting. The prevalence for depression was 23% in blacks and 21% in whites.[22]

Reserpine

A 1982 Veterans Administration Cooperative Study proved reserpine to be an effective and inexpensive antihypertensive agent. Blood pressure in about two thirds of 329 patients with mild to moderate hypertension was adequately controlled by varying dosages of chlorthalidone and reserpine (≤0.25 mg per day).[24] Reports of reserpine's depression-inducing side effect are often cited, however, as a reason for not prescribing the drug.[5–7]

Reserpine acts by gradually depleting catecholamines from the sympathetic nerve endings, both centrally and peripherally.[25] It is thought that reserpine's depression-inducing actions are related to central depletion of serotonin, which is involved in mood regulation.[2] Depression may be more related, however, to a psychologic reaction from reserpine's physiologic effects than from a direct neurochemical effect.[26] Physiologic weakening may result in a poor body image and a decrease in ability to deal with conflicts and stress.[27]

Interestingly, reserpine did not cause more depression than any other treatment group in the present study. Previous studies on reserpine-induced depression report a prevalence from 0% to 26%.[5,28] These investigations, performed between 1950 and 1960, generally used doses greater than 0.25 mg per day, and often used 5 mg or more per day. In the Hypertension Detection and Follow-Up Program, 5.0% of reserpine-treated stepped-care hypertensive patients had treatment terminated because clinically relevant depression was a suspected side effect.[29] However, the 39 elderly hypertensive patients in the VA Cooperative Study treated with varying doses of reserpine (0.05 to 0.25 mg per day) had no significant

change in their mean Zung index over 6 months.[23] Indeed, there was a nonsignificant decline in the rate of depression from 35.4% to 28.2%. Furthermore, the rate of change was not significantly different from other treatment groups (diuretic in combination with hydralazine, methyldopa, or metoprolol).[23] Our study documented depression (based on a Zung SDS index ≥50) in 35.1% of reserpine-treated patients, with no difference in low-dose therapy vs high-dose therapy vs no medication, supporting the view that at these doses reserpine is no more likely to produce depression.[30]

β-Blockers

The degree of β-blocker lipophilicity did not significantly alter the mean Zung index in this study, although the sample size was small. β-Blockers can cause a variety of central nervous-system–related side effects.[31] Bad dreams, sleep disturbances, fatigue, hallucinations, and mood changes have all been reported. The exact mechanisms of these adverse effects are still unclear.[1,9,32] It has been postulated that β-blockers cross the blood-brain barrier and act on β-receptors located in the brain to cause these various neurobiochemical effects.[33–36] There is further thought that the lipophilicity of β-blockers correlates with this ability to cause central nervous system side effects,[37] although not all studies support this.[38]

Several case reports have been published describing β-blocker–induced depression.[39,40] In 77 patients undergoing elective cardiac catheterization, however, the prevalence of depression (using American Psychiatric Association criteria for major depressive disorder) in the 39 patients receiving β-blockers was 21%, compared with 33% in the 36 patients receiving other medications.[41] This rate was not statistically different.

In a retrospective analysis of 143,253 Medicaid prescription profiles, Avorn et al[8] reported that the prevalence of tricylic antidepressant use in patients treated with β-blockers over 2 years was 23%, compared with 10% in patients taking either reserpine or methyldopa, 17% in hydrochlorothiazide-treated patients, and 15% in hydralzine-treated patients. This study suggested that β-blockers may be an important cause of iatrogenic depression.[8] However, concerns of study design biases have been documented.[42]

Recently, 43 elderly male hypertensive veterans treated with metoprolol over 6 months had no change in mean Zung index, although there was a nonsignificant increase in the prevalence of depression from 29.2% at baseline to 37.2% at the end of maintenance therapy.[23]

Quality of life is an issue in selecting the most appropriate antihypertensive drug therapy.[10] One particular determinant, depression, is a frequently mentioned side effect of reserpine and β-blockers. The study reported here provides corroborating data demonstrating that reserpine at a dose of 0.25 mg or less per day and β-blockers as compared with no drug treatment or diuretics are not associated with higher Zung index. Our study has implications for the choice of antihypertensive drugs in patients where cost of therapy is a barrier to high blood pressure control.[43] Real or perceived high cost of medical care and antihypertensive drugs may be a barrier to access and may be a cause of depression.

Conclusions

In the study reported here the Zung SDS index was used to define depression, and the analysis relates to *groups* rather than to *individuals*. Also, none of the patients were believed to have clinically treatable depression. This group data analysis does support the view that reserpine at the doses used in this study population was no more likely to cause depression than diuretics, β-blockers, or no medication. This study is relevant because a considerable number of people with hypertension in the United States have limited access to medical care and drug therapy. Reserpine offers a low-cost alternative for these hypertensive patients.

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