Background: The use of placebo in clinical trials has been vigorously debated. Placebo control may be useful in disease states, such as stage 1 and stage 2 hypertension as defined by the Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI), in which response rates for placebo are high or close to response rates for effective therapies, or when established interventions have significant adverse effects.

Objective: To compare rates for the control of blood pressure and adverse effects of placebo vs active treatment in patients with stage 1 and stage 2 hypertension.

Methods: This study is a randomized controlled trial evaluating the blood pressure response and adverse effects of placebo vs 6 active treatments administered in 15 Veterans Affairs hypertension centers. The 1292 subjects of the Veterans Affairs Cooperative Study receiving single-drug therapy for hypertension were randomly allocated to receive treatment with 1 of 6 active drugs (n=1105) or placebo (n=187). Treatment success was defined as maintaining a diastolic blood pressure of less than 95 mm Hg for at least 1 year. We compared treatment success rates for the control of blood pressure and adverse effects of placebo vs active treatment. Using the Kaplan-Meier method, we also compared rates of discontinuation from placebo vs active drug treatment over time as a result of adverse drug effects and blood pressure exceeding safety limits.

Results: At the end of the titration phase, 58 patients who were treated with placebo (31%) achieved a goal diastolic blood pressure lower than 90 mm Hg and 57 (30%) achieved success at 1 year. Older white patients who received placebo had a success rate of 38% vs 23% to 27% for the other age-race subgroups. The rates of discontinuation as a result of adverse drug effects were 13% for patients receiving placebo vs 12% for patients receiving active treatment (P=.40). The rates of discontinuation for blood pressure being too high were 14% for patients receiving placebo vs 7% for patients receiving active treatment (P=.01).

Conclusions: Placebo control provides an important benchmark for both efficacy and adverse effects. It continues to have an appropriate place in certain therapeutic trials, particularly those involving the treatment of stage 1 and stage 2 hypertension.

Arch Intern Med. 2000;160:1449-1454
PATIENTS AND METHODS

STUDY DESIGN

We screened 1635 ambulatory men with primary hypertension for entry into a randomized double-blind study at 15 VA hypertension clinics.\textsuperscript{10-30} All patients were screened for secondary causes of hypertension by clinical history, physical examination, routine laboratory tests, and urinalysis. Patients entered a washout phase lasting from 4 to 8 weeks before randomization, during which they received 1 placebo tablet twice daily that was administered in a single-blind fashion. The criteria for inclusion were age 21 years or older, written informed consent, and a reasonable expectation that the patient’s diastolic blood pressure would be between 95 and 109 mm Hg with placebo.

The baseline blood pressure was calculated as the average of the readings obtained at the last 2 clinic visits in the placebo run-in period. Compliance was determined on the basis of the patient’s clinic attendance and a count of pills. Patients were randomized if their mean diastolic blood pressure from 2 consecutive visits was between 95 and 109 mm Hg and if the values did not differ by more than 6 mm Hg between visits.

At the time of randomization, the patients were assigned in a double-blind manner to receive placebo or 1 of the 6 active study drugs and then entered a titration phase of 4 to 8 weeks. The active study drugs and their doses (listed from initial to maximum dose) were hydrochlorothiazide (12.5, 25, and 50 mg daily), atenolol (25, 50, and 100 mg daily), clonidine (0.2, 0.4, and 0.6 mg in divided doses given twice daily), captopril (25, 50, and 100 mg in divided doses given twice daily), prazosin hydrochloride (4, 10, and 20 mg in divided doses given twice daily), and a sustained-release preparation of diltiazem hydrochloride (120, 240, and 360 mg in divided doses given twice daily). The blind was maintained throughout the study using a double-dummy scheme. A matched placebo for each of the 6 active study drugs was available. Each patient received 2 medication bottles; one bottle contained 1 of the 6 active study drugs and the other contained placebo. For the placebo group, both bottles contained placebo. The treatment blood pressure was the mean of the blood pressure measurements recorded during the last 2 visits of the titration phase. Treatment response was defined as the attainment of goal diastolic blood pressure lower than 90 mm Hg during the titration phase and lower than 95 mm Hg sustained for 1 year of maintenance treatment.

Patients could be removed from the study for a defined set of reasons, including exceeding blood pressure safety limits. The study chairman (B.J.M.) reviewed all 514 withdrawals from the study while blinded to the drug regimen. Any cause that could possibly be the result of an adverse drug reaction was so labeled. Withdrawals as a result of a violation of the blood pressure safety limits were so labeled.

STATISTICAL METHODS

The comparison between placebo and the 6 active treatment groups and the age-race subgroup analysis were defined prior to the start of data collection. Response rates for the combined 6 active treatment groups and the placebo group were calculated by age-race subgroups and overall. The age-race subgroups were as follows: younger (<60 years) African Americans, younger whites, older (≥60 years) African Americans, and older whites. Baseline differences for those who responded to placebo and those who did not respond to placebo were statistically compared using the 2-sample t test for continuous data and the Fisher exact test for categorical data. The placebo and active treatment rates of specific types of reported adverse effects during the dose titration phase were compared using the Fisher exact test.

The distribution of times from randomization to withdrawal from the study as a result of an adverse event was estimated using Kaplan-Meier survival curve estimation methods. Patients were “censored” at the time of withdrawal if they withdrew for any reason other than an adverse event or if they were classified as a nonresponder at the end of the dose titration phase. The log-rank test was used to determine whether the placebo and active treatment distributions differed.

The same analyses were done to estimate and statistically compare the distribution of times from randomization to withdrawal from the study as a result of blood pressure safety limits being exceeded. Patients were “censored” at the time of withdrawal if they withdrew for any reason other than blood pressure safety limits being exceeded or if they were classified as a nonresponder at the end of the dose titration phase.

All statistical tests were 2-sided and \( P \leq .05 \) was the criterion for statistical significance. However, because of the large number of types of adverse effects analyzed, \( P \leq .001 \) was used for that component of the analysis. All statistical analyses were done using SAS, version 6 (SAS Institute Inc, Cary, NC).
placebo control to validate both treatment effect and adverse effects. Although the placebo, per se, was never the focus of these studies, the purpose of this article is to review the most recent VA experience with placebo in a randomized controlled clinical trial of 6 antihypertensive agents and placebo in 1292 patients with diastolic blood pressure ranging from 95 to 109 mm Hg.

Our original hypothesis was that antihypertensive agents would have different effectiveness depending on age-race subgroups. This article examines the blood pressure response to placebo and whether there are differences in response to placebo based on age-race subgroups. We also seek to characterize the adverse effect profile attributed to placebo compared with active drug treatment among our population of patients with stage 1 and stage 2 hypertension.

Table 1. Response Rates to Placebo and Active Drug by Subgroup

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo*</th>
<th>Active Treatment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire group</td>
<td>57 (30) [n = 187]</td>
<td>643 (58) [n = 1105]</td>
</tr>
<tr>
<td>Younger African Americans</td>
<td>9 (20) [n = 44]</td>
<td>122 (49) [n = 247]</td>
</tr>
<tr>
<td>Younger whites</td>
<td>8 (26) [n = 31]</td>
<td>121 (56) [n = 215]</td>
</tr>
<tr>
<td>Older African Americans</td>
<td>12 (27) [n = 44]</td>
<td>158 (55) [n = 286]</td>
</tr>
<tr>
<td>Older whites</td>
<td>24 (38) [n = 64]</td>
<td>237 (69) [n = 344]</td>
</tr>
</tbody>
</table>

* n = 183 for age-race analysis subgroups because of the random allocation of 4 patients who were coded as neither white nor African American to the placebo group.
† n = 1092 for age-race analysis subgroups because of the random allocation of 13 patients who were coded as neither white nor African American to the active treatment group.

At the end of the titration phase, there were 1105 patients who were treated with active drugs and 187 patients who received placebo.

RESPONSE RATES

Of the 187 patients randomized to receive placebo during the drug titration phase, 58 (31%) achieved a goal diastolic blood pressure lower than 90 mm Hg and 62 (33%) achieved a systolic blood pressure lower than 140 mm Hg. Of the 187 patients receiving placebo, there were 57 (30%) who achieved treatment success by reaching the goal blood pressure at the end of the titration phase and maintaining a diastolic blood pressure lower than 95 mm Hg for 1 year (Table 1). The age-race subgroup breakdown for those in the placebo group who reached the goal blood pressure at the end of the titration phase and maintained a diastolic blood pressure lower than 95 mm Hg for 1 year was as follows: younger African Americans, 9/44 (20%); younger whites, 8/31 (26%); older African Americans, 12/44 (27%); and older whites, 24/64 (38%). There were no differences between those who responded to treatment and those who did not respond to treatment with respect to resting pulse rate, age, or baseline laboratory values, including hematocrit, serum electrolyte levels, creatinine levels, cholesterol levels, triglyceride levels, or 24-hour urine sodium or potassium excretion (n = 183 for age-race analysis because of the random allocation of 4 patients who were coded as neither white nor African American to the placebo group).

Of the patients who responded to placebo, 24/58 (41%) responded to the lowest “dose,” 11/58 (19%) to the middle “dose,” and 23/58 (40%) to the highest “dose.” This was either a function of additional time (because there was no drug “dose”), regression toward the mean, or an additional placebo effect related to the expectations of the patient that the “dose” was increasing.

There were instances in which the response rate for those receiving placebo approached that for those receiving active treatment. Among older African American patients, the response rate to placebo was 27% and to captopril 33%. In younger white patients, the response rate to placebo was 26% and to hydrochlorothiazide 32%. Among older white patients, there was a high response rate to placebo (38%) that corresponded to a high response rate to active drug treatment.

ADVERSE EFFECTS

The commonly reported adverse effects of active treatment vs placebo during the drug titration phase are shown in Table 2. Of the 23 adverse effects, headache (7.9% vs 15.5%; P = .002) was significantly more common among those receiving placebo than among those receiving active drug treatment. Joint pain was prevalent and more commonly reported among patients receiving placebo than among those receiving active drug treatment. Fatigue was a commonly reported adverse effect (9.2% of the active treatment group vs 7.5% of the placebo group), but the difference between groups was not significant (P = .49). Dry mouth was also commonly reported (9.9% of the active treatment group vs 16.6% of the placebo group; P = .04). Nightmares (P = .09), vivid dreams (P = .09), and cold extremities (P = .07) tended to be reported more among patients receiving placebo but did not reach statistical significance. There were substantial rates of other adverse effects reported by both groups, but the differences between groups were not statistically significant. Fatigue was a commonly reported adverse effect (9.2% of the active treatment group vs 7.5% of the placebo group), but the difference between groups was not significant (P = .49). Dry mouth was also commonly reported (9.9% of the active treatment group vs 6.4% of the placebo group), but the difference between groups was not significant (P = .17). The same was true for impotence (7.4% of the active treatment group vs 5.4% of the placebo group; P = .36).

DISCONTINUATIONS AS A RESULT OF ADVERSE REACTIONS

A variety of adverse reactions were reported by patients receiving placebo and occurred at various points in the study (Table 3). There were 15 discontinuations for presumed adverse drug reactions among patients who received placebo vs 117 among patients receiving active treatment. In Figure 1, the rate of these discontinua-
tions was estimated to be 13% for patients receiving placebo vs 12% for patients receiving active treatment (P = .40).

**DISCONTINUATIONS AS A RESULT OF BLOOD PRESSURE SAFETY LIMITS BEING EXCEEDED**

**Figure 2** is a cumulative plot of the time from randomization to withdrawal as a result of blood pressure safety limits being exceeded. There were 39 discontinuations related to uncontrolled blood pressure in the placebo group vs 85 in the active treatment group. By Kaplan-Meier estimation, the percentage of patients who withdrew because blood pressure safety limits were exceeded was estimated to be 14% for the placebo group vs 7% for the active treatment group (P = .01).

**SERIOUS ADVERSE EVENTS**

The rates of serious adverse events did not significantly differ between the placebo and active drug groups. Serious adverse events included cerebral hemorrhage, cerebrovascular accident, acute myocardial infarction, new onset of symptomatic ischemic heart disease, atrial fibrillation, congestive heart failure, symptomatic bradycardia, and death (any cause). There were 7 serious adverse events in the placebo group and 43 in the active drug group (P = .92).

**COMMENT**

The placebo-associated response is not well understood and may actually consist of several complex components17,18,20,21: the natural history of the disease, the regression to the mean, and nonspecific effects of

---

**Table 2. Adverse Effects Reported During Titration of Active Drug and Placebo**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Active Treatment Group (n = 1105)</th>
<th>Placebo Group (n = 187)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>9.2</td>
<td>7.5</td>
<td>.49</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>11.8</td>
<td>6.6</td>
<td>.03</td>
</tr>
<tr>
<td>Weakness</td>
<td>3.3</td>
<td>2.1</td>
<td>.50</td>
</tr>
<tr>
<td>Nightmares</td>
<td>1.1</td>
<td>2.7</td>
<td>.09</td>
</tr>
<tr>
<td>Vivid dreams</td>
<td>2.4</td>
<td>4.8</td>
<td>.09</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>4.6</td>
<td>3.7</td>
<td>.70</td>
</tr>
<tr>
<td>Stomach cramps</td>
<td>1.5</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4</td>
<td>2.7</td>
<td>.80</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.4</td>
<td>2.7</td>
<td>.82</td>
</tr>
<tr>
<td>Headache</td>
<td>7.9</td>
<td>15.5</td>
<td>.002</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1.1</td>
<td>0.5</td>
<td>.71</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.5</td>
<td>5.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5</td>
<td>2.7</td>
<td>.21</td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>3.3</td>
<td>1.1</td>
<td>.16</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>3.3</td>
<td>4.3</td>
<td>.51</td>
</tr>
<tr>
<td>Impotence</td>
<td>7.4</td>
<td>5.4</td>
<td>.36</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>4.1</td>
<td>2.7</td>
<td>.54</td>
</tr>
<tr>
<td>Cold extremities</td>
<td>1.0</td>
<td>2.7</td>
<td>.07</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2.4</td>
<td>4.3</td>
<td>.14</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2.5</td>
<td>2.7</td>
<td>.80</td>
</tr>
<tr>
<td>Change in taste</td>
<td>1.3</td>
<td>2.1</td>
<td>.32</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9.9</td>
<td>6.4</td>
<td>.17</td>
</tr>
<tr>
<td>Joint pain</td>
<td>10.9</td>
<td>16.6</td>
<td>.04</td>
</tr>
</tbody>
</table>

- *A total of 1121 adverse effects were reported among 1105 patients receiving active drug (1.01 adverse effects per patient), and 198 adverse effects were reported among 187 patients receiving placebo (1.06 adverse effects per patient).
- †Fisher exact test.
treatment. The natural history of a disease may appear to affect the response to treatment. Many chronic illnesses undergo spontaneous exacerbations and remissions during their course. Given a lengthy follow-up period, a patient may have spontaneous improvement in his or her condition that could be interpreted as a positive result in the context of a clinical trial.

Many acute and some chronic problems tend to resolve on their own whether or not treatment is provided. Subjects tend to enroll in hypertension trials when their blood pressure is the highest, and their blood pressure may spontaneously return to normal over time. This tendency to return to the individual’s baseline state is termed regression to the mean. Apparent improvement may also reflect measurement error or random variation in patient findings over time. Regardless of the mechanisms involved, it is important that there are responses in the placebo group, and if there is no placebo group, non–drug-related events will be counted as drug effects.

Data from the VA Cooperative Study on single-drug therapy for hypertension suggest that responses in the placebo group that led to sustained control of hypertension for as long as 1 year may have occurred, depending upon age-race subgroup, in 23% to 38% of patients receiving placebo, even though all patients went through a placebo run-in period prior to randomization and dose titration. There seems to be a difference in the response to placebo among age-race subgroups, with a higher rate of response to placebo in the older white subgroup. In addition, placebo is associated with a significant rate of adverse effects, which is similar in magnitude to that for active drug treatment in many cases and, in some cases, greater. In addition, several other adverse effects tended toward a higher rate among patients receiving placebo. Apparent drug-related adverse effects that the patient was unable to tolerate, resulting in discontinuations from the trial, occurred in 13% of patients receiving placebo, a figure similar in magnitude to that for patients receiving active treatment (12%). In one study, 2 patients withdrew from the study because their proteinuria levels were higher than 1 g/d while receiving placebo.35

Veterans Affairs Cooperative Studies on hypertension, from the studies chaired by Edward D. Freis, MD, to those undertaken currently, have included a placebo control. The studies were approved by a central institutional review committee as well as the institutional review boards of each of the participating medical centers. All studies were closely monitored by data review boards. However, the study of severe hypertension was terminated prematurely because the patients receiving treatment clearly had a better outcome than those not receiving treatment. The prevailing wisdom of the day was that there was no need to treat severe hypertension because treatment was thought to do more harm than good.39

Researchers study the effectiveness and adverse effects of antihypertensive drugs, but all treatments are confounded by a placebo effect that is difficult to measure and may vary depending upon the population under study. Although the true causes of improvement in hypertension while receiving placebo remain unknown, nonspecific effects, a disease’s natural history, and regression to the mean can cause high rates of good outcomes, which may be mistakenly attributed to specific treatment. Conversely, placebo control aids in properly assigning adverse-effect profiles to medications. Several examples in our data of high rates of adverse effects would have been incorrectly assigned to active drug treatment had we not included placebo control. Assessing how much benefit is owing to placebo remains extremely difficult and is particularly problematic for the large multicenter collaborative trials that include many physicians, whose personal therapeutic impact and contribution to placebo benefit vary considerably and are impossible to identify and measure.

We conclude that placebo control continues to have an appropriate place in certain therapeutic trials, particularly those involving the treatment of stage 1 and 2 hypertension. We believe that the approach to the use of placebo in clinical trials should be a balanced one, based upon the natural course of a particular disease and the risks of withholding active treatment.

Accepted for publication October 4, 1999.

Corresponding author: Richard A. Preston, MD, Division of Clinical Pharmacology and Pharmacokinetics and Clinical Research Center, Department of Medicine, University of Miami School of Medicine, 1500 NW 12th Ave, 15th Floor, West Tower, Miami, FL 33136.

REFERENCES

23. Georgiou A. Placebo mania: high quality placebos should be used. BMJ. 1996;313:1009.