Effects of Antihypertensive Medications on Vitality and Well-Being

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The effects of captopril, methyldopa, and propranolol were assessed for sense of well-being and vitality among 626 men with mild to moderate hypertension in a multicenter, randomized, double-blind clinical trial. After a 24-week treatment period, patients taking captopril, compared with patients taking methyldopa and propranolol, scored significantly higher on measures of well-being and vitality. In addition, patients on captopril had more favorable results in being able to keep up with their work and in not feeling tired or sleepy at work. The effects of each of the drugs manifested themselves at different periods. For example, the negative effects of methyldopa on vitality were evident by week 8, whereas the negative effects did not become manifest for propranolol until week 24. On the other hand, a steady progressive improvement in vitality scores was evident at week 8 and at week 24 for patients on captopril.

The findings of the study also suggest that the effects of the treatment drugs were most marked in patients who had had previous antihypertensive medications and who were on single-drug therapy during the course of the clinical trial. Further, the differences between patients taking captopril and those on methyldopa and propranolol appear to be obscured by the addition of a diuretic. The findings of the study may guide the physician in orienting his or her patient and in planning and implementing a therapeutic regimen.

This paper reports the effects of three differing antihypertensive medications on feeling of vitality and sense of well-being of patients with mild to moderate hypertension. This report is based on a secondary analysis of data from a large multicenter, randomized, double-blind clinical trial that assessed and compared the effects of captopril, methyldopa, and propranolol on the quality of life in patients.[1]

The objectives of this study were (1) to report changes in measures of general well-being and vitality as well as changes in perceived energy in the work situation among patients in the three treatment groups after 24 weeks, (2) to document changes in the vitality measures and selected items for patients in the three treatment groups at specific time intervals over a 24-week period, and (3) to explore the separate and combined effects of diuretics and previous medications on the vitality and other subscale scores of the General Well-Being Adjustment Scale[2,3] on the three treatment groups after 24 weeks.

Previous studies have shown that antihypertensive medications that take differing physiologic pathways can have very different effects on the patient's sense of well-being and feelings of energy and vitality.[4–6] In fact, feelings of lethargy and malaise are among the more common complaints of hypertensive patients on medications. Although increasingly able to control the patient's hypertension, physicians are often unaware of the unpleasant side effects of antihypertensive medications and their impact on the patient's feelings of vitality, energy, and well-being. Some patients may feel that antihypertensive medicines entail so much discomfort that they fail to adhere to the therapeutic regimens prescribed by their physicians.[7]

A previous report compared captopril, methyldopa, and propranolol in regard to their impact on various areas of quality of life of hypertensive patients over 24 weeks.[1] This paper is a follow-up report centering on issues of

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vitality and general well-being in greater detail by comparing the effects of these drugs, which differ in the antihypertensive mechanism of action.

METHODS

Patient Population and Research Design

The design and methods employed in the clinical trial from which these data are drawn are described in detail elsewhere.[1] Briefly, the clinical trial was a multicenter, randomized, double-blind study that was designed to compare the effects of captopril, methyldopa, and propranolol on the quality of life of patients with mild to moderate hypertension.

To study a relatively homogeneous population, 761 patients fulfilling the following criteria were recruited from 30 clinical centers throughout the United States: white men aged between 21 and 65 years, employed full time, and having a primary diagnosis of uncomplicated hypertension (median seated diastolic blood pressure between 92 and 109 mmHg).

A lead-in placebo period of one month was followed by a six-month active treatment period during which the patients received either captopril (50 mg, twice a day), methyldopa (500 mg, twice a day), or propranolol (80 mg, twice a day). Patients were unaware of when the placebo period occurred. Standard step-2 level doses were chosen to maximize therapeutic efficacy with a single-drug program. To maintain the double-blinding during active treatment, each patient received his assigned drug plus two placebos. Patients were medically evaluated at two-week intervals during the placebo period and on a monthly basis during the active period. The goal of therapy was a diastolic pressure of less than 90 mmHg. Patients whose diastolic pressure was 95 mmHg or greater at eight weeks into the active treatment period or at any subsequent visit received additionally hydrochlorothiazide, 25 mg, twice a day, unblinded. This dose could be varied or the drug discontinued by the physician at subsequent visits.

Data concerning well-being, vitality, work performance, and other components of quality of life were collected through interviews and psychological tests at the beginning and end of the placebo period and at 8 and 24 weeks into the active treatment period. In the case of patients who withdrew from the study during active therapy, an attempt was made to obtain exit interview assessments. Additional data have been derived from monthly physician reports on the patients.

Data Collection and Management

The interviewer staff consisted of registered nurses and medical administrative and technical health personnel who were not directly associated with the care of the patients. They were given standardized training to carry out the survey-type interviews and to administer psychological tests. Interviewers were blinded to the specific drug that each patient had been assigned. Completed quality-of-life interviews were sent for editing, quality control, and coding to the project office at the University of Connecticut Health Center. Data were analyzed on the IBM 3081 using the SAS statistical package[8] and on the Univac 1100/70 using the SPSS statistical package.[9] An "intention to treat" analysis was followed, whereby all originally randomized patients were analyzed according to their assigned treatment.

Assessment of Well-Being

The General Well-Being Adjustment Scale[2,3] was employed to assess the effects of the three antihypertensive medications on the patient's sense of well-being. The scale is based on the work of Dupuy[10] and has been used in a variety of studies, including the Rand Health Insurance Study.[2,3]

The scale consists of 22 questions and encompasses six states or components, each of which constitutes a subscale. The subscales assess vitality, positive well-being, anxiety, depression, self-control, and general health. The subscales consist of three to five items. For each item there are six response options that may be scored from 1 to 6. For example, for one item on the anxiety subscale, "Have you been bothered by nervousness or your nerves during the past month?" the respondent checks one of the six responses ranging from "extremely so" to "not at all." For an item on the depression subscale, "Have you felt downhearted and blue during the past month?" the possible responses range from "all of the time" to "none of the time."

In addition to its wide usage in the field of health care, the General Well-Being Adjustment Scale has several positive features. It is easy to understand and can be self-administered in a short period of time ranging from eight to 15 minutes. Moreover, the validity of this measure of general well-being has been subjected to a number of statistical tests of association with other established psychological tests. Reliability scores (Cronbach's alpha) for the total General Well-Being Adjustment Scale and the vitality subscale are .94 and .81, respectively.

The General Well-Being Adjustment Scale is relatively comprehensive and reflects the range of dimensions that are customarily associated with the concept of well-being. Obviously people who are anxious, depressed, exhausted, and jittery, or who do not feel they have self-control, cannot be viewed as possessing a high sense of well-being. These feelings are reflected, then, in their scores on the General Well-Being Adjustment Scale. The scale, thus, not only meets various established methodological criteria

but tends also to be in accord with lay conceptions of well-being.

Work Performance

Additional data relating to vitality and well-being were obtained through questions on work performance. These were part of a Work Performance Scale described elsewhere, based in part on questions developed by House.[1,11,12] Questions employed for this report requested the patient to rate on a seven-point scale the degree to which he felt "able to keep up with the work" and "tired and sleepy at work."

Diuretics and Previous Antihypertensive Medications

The intervening effects of diuretics and of previous antihypertensive medications on well-being and vitality measures were also examined. Previous studies have shown that diuretics have side effects of their own and that they may cloud or mask the effects of the specific drugs used in this clinical trial. Hence patients are classified by whether they were on single-agent therapy for the full treatment period or whether they had a diuretic added to the primary drug assigned as of week 8. By the 16th week, 36, 31, and 22 percent of patients in the captopril, methyldopa, and propranolol groups, respectively, were taking a diuretic. At week 24 the corresponding values were 33, 28, and 22 percent.

Patients who entered the study without having had previous antihypertensive medications constituted 23 percent of the group taking captopril, 27 percent of patients taking methyldopa, and 29 percent of the patients taking propranolol. Of the remaining patients who had had previous therapy, most were on either a diuretic alone, a beta blocker, or a diuretic in combination with a beta blocker.

Statistical Analysis

All major analyses were based on the degree of change from baseline over time, with each patient serving as his own control. If significant overall multivariate test statistics were obtained for a set of orthogonal effects, pairwise comparisons were made with use of simple linear contrasts.[13,14] When assumptions of normality were not justified, the quality-of-life data, adjusted for baseline levels, also were analyzed with the nonparametric Kruskal-Wallis and Friedman techniques.[15] The reported statistical significance of paired differences took into account the multiple-comparisons nature of the data by means of multiple-range test statistics.[16] The chi-square test statistic was used in the analysis of proportions in associations among categorical variables. P values were based on two-tailed tests of significance when applicable.

TABLE 1. GENERAL WELL-BEING MEASURE AND PERCENTAGE OF CHANGE IN PATIENTS FROM BASELINE TO 24 WEEKS

General Well-Being	Improvement	Stable	Worsening
Captopril (n = 181)	51.3	17.7	30.9
Methyldopa (n =143)	39.2	9.8	51.1
Propranolol (n = 161)	39.1	15.5	45.4

Chi-square (3 × 3) for independence with 4 df significant at P < .01

RESULTS

From Baseline to 24 Weeks: Changes in Well-Being

The effects of the three antihypertensive drugs on the global sense of well-being from baseline to 24 weeks are seen in part in differential rates of withdrawal from the study. Of the 761 patients who were enrolled and randomized, 626 participated in a baseline quality-of-life interview. Among 134 patients who withdrew from the study during the period of active therapy, 83 discontinued because of adverse drug reactions. The main complaint of these patients was having feelings of fatigue and lethargy. Next in order of frequency were complaints of sexual disorders, sleep disorders, and headaches. The percentage of withdrawals because of adverse reactions was significantly lower in the captopril group (8 percent) when compared with the methyldopa group (20 percent; P = .001) and marginally lower in the propranolol group (13 percent) when compared with the methyldopa group (P = .058). The difference between the captopril and propranolol groups was not statistically significant.

In the 486 patients for whom baseline and 24-week follow-up data were available, comparisons were made in general well-being measures by treatment group between baseline and 24 weeks. Patients were categorized on general well-being scores by their degree of worsening (mild vs moderate vs substantial), improvement (mild vs moderate vs substantial), or stability (little or no change) at 24 weeks relative to their baseline measurements.

Patients on captopril exhibited significantly more positive changes in their overall general well-being than did patients on methyldopa or propranolol (P < .01) (Table 1). The changes are shown in greater detail within subscales of the General Well-Being Adjustment Scale Index. Patients on captopril exhibited more favorable changes in subscale scores from baseline to 24 weeks than did patients on methyldopa and propranolol (Figure 1). Specifically, in comparison with patients on methyldopa, those on captopril manifested more favorable changes in scores (P < .05 to <.01) on the subscales of anxiety, positive well-being, general health, and vitality. When com-

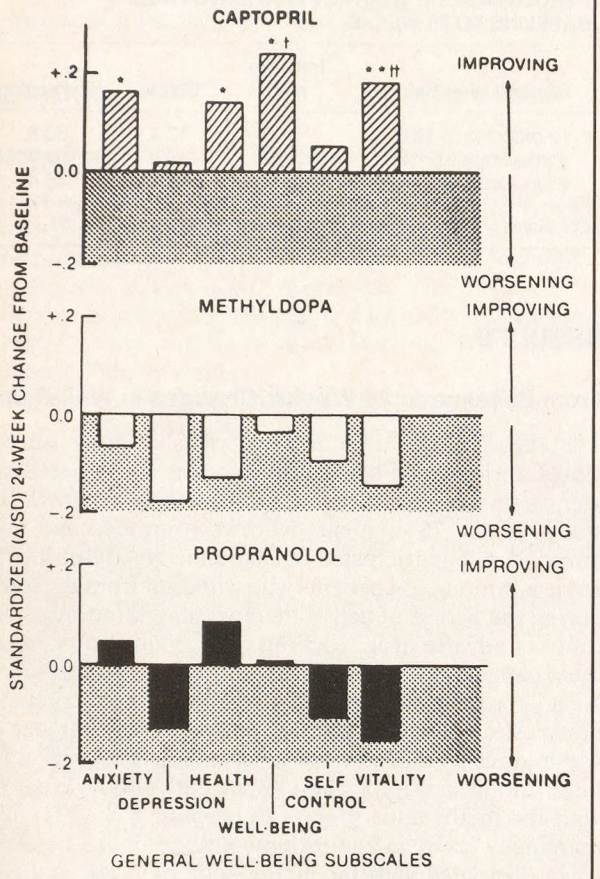

Figure 1. Comparisons of standard mean rates of change (24 weeks) in general well-being subscales. P values for pairwise comparison of mean change from baseline: captopril vs methyldopa: **P < .01; *P < .05; captopril vs propranolol: ††P < .01; †P < .05

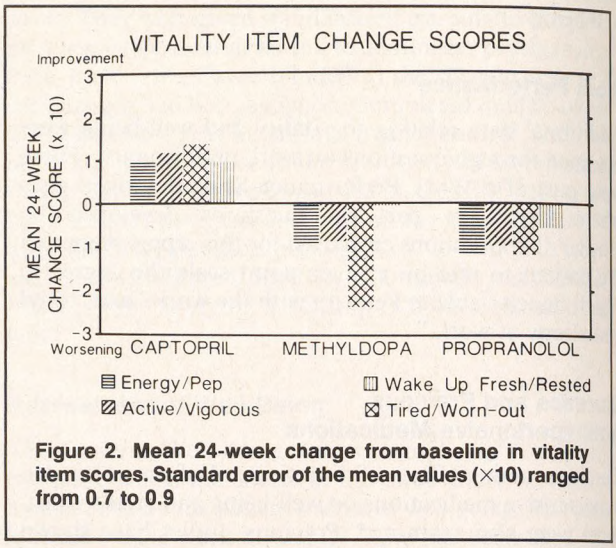

Figure 2. Mean 24-week change from baseline in vitality item scores. Standard error of the mean values (×10) ranged from 0.7 to 0.9

pared with patients on propranolol, patients on captopril showed significantly more favorable changes on the subscales of positive well-being and vitality (P < .05 to <.01).

Over a 24-week period of treatment, marked differences emerged among the three drugs with regard to the four vitality items and total scores. At week 24, patients on captopril differed significantly (P < .01) from those taking methyldopa and propranolol in their total vitality score.

Changes from baseline to week 24 in the scores of four specific items that make up the vitality subscale are shown in Figure 2. While patients taking captopril scored higher than patients on methyldopa or propranolol on all four items of the vitality subscale, they were significantly less likely to feel tired and worn out when compared with patients in the other two treatment groups (P < .05). Patients taking captopril were also significantly more likely to feel active and vigorous than those taking propranolol (P < .05).

Some additional support for these results may be found in the responses to another item in the questionnaire in which patients were asked to indicate their degree of satisfaction with their level of energy. After 24 weeks of treatment, patients taking captopril expressed more satisfaction on this item than those taking methyldopa (P < .05).

Work Performance and Vitality

Further analysis centered on detecting changes in two items in the work performance scale that tapped aspects similar to those in the vitality subscale: "am able to keep up with the work" and "feel tired or sleepy at work." Patients receiving captopril tended to score more favorably than patients in the other two groups on both items. Captopril patients were significantly less likely than those taking methyldopa to respond "feeling tired or sleepy at work" (P < .05). These findings on work performance are also in the same direction with results in the overall vitality scores.

As noted, changes were observed in vitality and related items over a 24-week period of treatment. The clinician and the patient also have an interest in knowing whether these changes take place evenly or progressively over time. Do these changes become manifest early or later in the treatment program? In Figure 3 the mean values for the vitality scale are presented for each of the three treatment groups before treatment, eight weeks later, and 24 weeks later.

There are markedly different effects not only in magnitude and direction of change but also in its timing, ie, when changes become manifest. Patients on captopril showed progressive increase in vitality level at eight weeks and at 24 weeks. Those on methyldopa experienced a dramatic decrease in vitality level after the first eight weeks of treatment, with partial improvement at 24 weeks. Patients on propranolol did not manifest a substantial decline at week 8 but did so at week 24. These trends are also apparent but less conspicuous when changes in individual items are examined. In Figure 4 mean scores are depicted at specific times among patients as to "feeling active and vigorous" or, conversely, "feeling tired."

Patients also were asked how they felt in the work setting. Though not as marked as the vitality data, the findings with regard to feeling tired at work (Figure 4) are in the same general direction. Differences in the mean values recorded for the patient's perception of his ability to keep up with the work also depict the same treatment differential trend.

Again, the negative effects on those taking methyldopa are most evident at the eight-week follow-up and persist with little change by week 24. Patients on propranolol indicated they were doing better at eight weeks than at 24 weeks. Patients on captopril improved by week 8 and maintained that improvement at week 24.

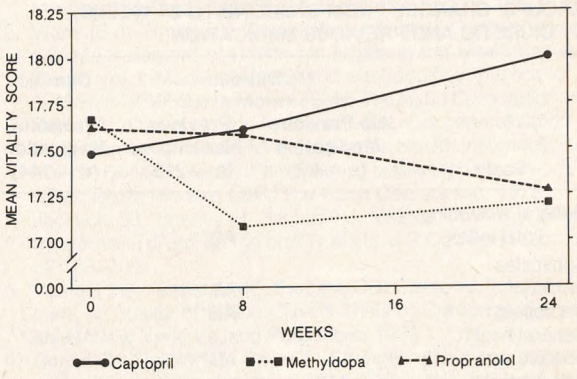

Figure 3. Mean values for vitality scale at entry, eight weeks, and 24 weeks. Standard errors for all means are not statistically different and are equal approximately to 0.25. Scale range is from 4 (lowest vitality) to 24 (highest vitality)

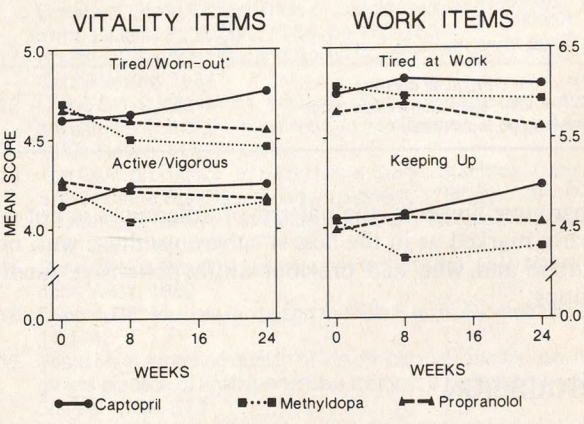

Figure 4. Vitality and work performance item mean scores at entry, eight weeks, and 24 weeks. Scale range is from 1 to 6 for vitality items and 1 to 7 for work items. Higher scores indicate a more favorable response

Well-Being, Diuretics, and Previous Medications

To examine the differential effects of diuretics and previous medications on measures of well-being and vitality, the patients were stratified according to previous medication history and by whether a diuretic was assigned during the active clinical trial. Changes in the three patient groups on general well-being, its subscales, and other measures from baseline to week 24 are compared in Table 2.

In examining the data in Table 2, it must be noted that about one fourth of the patients in the study had not received medications for hypertension prior to their enrollment into this clinical trial. In this study, previous use of antihypertensive medications or type of previous antihypertensive medication was not used as a criterion for selection of patients, nor were patients randomly assigned to diuretic or nondiuretic treatment groups. Accordingly, observations must be made with caution and regarded only as exploratory and descriptive.

The differences in outcome among the three drug groups are mostly evident among the largest category of patients (n = 219): those who were not receiving diuretics and who had taken previous medications. In particular, captopril patients differed from those on methyldopa in measures of the General Well-Being Adjustment Scale and its component subscales for positive well-being, depression, and vitality. Captopril patients differed from those on propranolol in changes in the vitality subscale. The differences in the vitality subscale between captopril and the other two drug groups were on items "feel active" and "feel tired." In all comparisons involving captopril, the captopril patients had the more favorable scores.

Other significant differences were also found within the groups designated as "no diuretic, no previous medication" and "diuretic, some previous medication." In these

TABLE 2. COMPARISON BETWEEN CAPTOPRIL (A), METHYLDOPA (B) AND PROPRANOLOL (C) TREATMENT GROUPS: CHANGES FROM BASELINE TO 24 WEEKS, BY DIURETIC AND PREVIOUS MEDICATION

Scale	No Diuretic		Diuretic
	No Previous Medication (n = 89)	Previous Medication (n = 219)	Previous Medication (n = 144)
General well-being: Total index		AB**	
Subscales			
Anxiety		AB*	
Depression		AB***	
General health			AB, AC*
Positive well-being		AB***	
Self-control	AB*		
Vitality		AB, AC***	AC*
Vitality subscale items			
Feel active		AB, AC***	
Feel tired	AB*	AB, AC***	
Work performance subscale items			
Keeping up		AC*	
Tired at work		AB*	

* $P < .05$, orthogonal contrast
** $P < .05$, Tukey Studentized range
*** $P < .05$, both tests

subgroups, however, the pattern of differences is not so clearly marked as in the largest subgroup: those with no diuretic and who had previous antihypertensive medications.

DISCUSSION

This report has noted the importance of feelings of vitality and well-being in the quality of life of the hypertensive patients as perceived through reasons for withdrawal from the clinical trial. As reported by patients, the main adverse effects that led to withdrawal involved feelings of fatigue and lethargy, perceived as induced by their drug regimen.

Among patients who were followed throughout the clinical trial, men on captopril consistently had more favorable scores at 24 weeks than those on methyldopa and propranolol in regard to General Well-Being Adjustment Scale scores and measures on the vitality subscale. Similarly, in regard to items dealing with energy and activities at work, captopril patients were more likely to score better than those on methyldopa in regard to not feeling tired or sleepy at work and better than those on propranolol in regard to being able to keep up with the work.

Differences between drug groups favoring captopril on vitality and well-being measures were most marked among men who had been on previous medications before enrolling in the clinical trial. These differences were particularly evident among men on single-drug therapy regimens during the trial. This finding, previously reported,[1] that diuretics had the effect of obscuring differences between the drugs was seen here as well as in the more detailed analyses on individual well-being, vitality, and work performance measures.

Aside from the important differences between the three drug groups in the measures, differing patterns of change were evident over the time span of the study. In future research it would be useful to examine the effects of the drugs at differing intervening times to obtain more precise information on when changes occur. This finding may be useful in orienting patients to when they may expect to note changes in the effects of pharmacologic therapy on their vitality, well-being, and alertness at work tasks.

The clinical impact of these quality-of-life differentials cannot be directly quantified. How to interpret the results of a study such as this for use in clinical practice is a question that often arises among practicing clinicians. It is important for the practicing clinician to view the magnitude of the observed treatment differences from the perspective of group differences and not individual differences. Because treatment group differences are based upon sample differences between means, the sampling distributions of group effects are much more sensitive to small changes. Therefore, a single unit difference in the vitality score from 17.0 to 18.0, while minor for an individual, would be a relatively large distance between group means. In fact, the average standard error of the mean for the overall vitality score was 0.25 in this study. Thus, a distance of four standard errors would span a single unit.

As indicated by Testa[17] in addressing interpretation of quality-of-life data, "what might appear at first to be a rather small treatment differential can actually have a profound effect on the lives of many patients." Since the incidence of side effects and quality-of-life changes are not uniform among all patients, a shift in a sample of 100 patients in a quality-of-life mean scale actually represents a distribution of changes among patients. For example, a treatment differential of 0.3 standard deviations for a sample size of 100 can result in an increase of patients demonstrating substantial worsening or improvement in a quality-of-life scale to a degree almost double that of the comparison group. According to Testa, this potential implies that if the clinician has a clinic of 500 patients, an additional 25 patients would experience a severe decrease in their level of vitality if treated by a medication that scored worse by no more than 0.3 standard deviations when compared with another medication.

Why and how these three drugs differ in the ways shown deserves further examination, tracking the pharmacologic

effects on perceived vitality and energy. Although there is mixed evidence on the degree to which captopril crosses the blood-brain barrier, there is suggestive evidence that captopril affects metabolism of enkephalins and angiotensin II in the brain.[18,19] Its effect on brain peptidases may thus link to feelings of vitality and well-being. In the case of methyldopa, the drug may act in lowering blood pressure by means of a central α-agonist effect, which may depress feelings of well-being and alertness.[20,21] In addition to blockade of β-adrenergic receptors, the mechanism of action of β-blocking drugs may involve stimulation of central α-adrenergic receptors. Thus interference with adrenergic nervous system function may underlie the adverse effects of both methyldopa and propranolol on the well-being and vitality measures examined for this study.

Does captopril improve feelings of well-being and vitality in the sense of enhancing them or are other mechanisms and explanations involved? Some reports and clinical impressions have provided tentative suggestions that captopril may have elation or mood-enhancing effects.[18,22] Although this line of inquiry certainly should be pursued, change in the measures reported occurred primarily in men on previous medications, leading to the suggestion that the removal of previous side effects may be a factor in their feelings of well-being during the trial. In other words, such patients no longer may feel as listless and lethargic as they did before. Such differential perceptions were not seen among those men who were not on previous medications for hypertension before the trial and thus had no similar point of comparison.

These findings may underline for physicians the importance of feelings of well-being and vitality as indicators of quality of life of their patients, with their absence leading to negative psychologic response to a drug and possible withdrawal or noncompliance with a drug regimen. By taking such factors into account, physicians can better weigh the relative merits and efficacy of the drugs to be prescribed to the hypertensive patient, leading to a program based both on considerations of blood pressure reduction and the patient's potential for high compliance with the therapeutic regimen if feelings of vitality, energy, and subjective well-being at home and at work are preserved.

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