Hypertension and Pheochromocytoma Testing

The Association With Anxiety Disorders

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Objective: To test the hypothesis that patients with hypertension who were screened for pheochromocytoma would have a higher prevalence of panic disorder, an increased prevalence of other anxiety and affective disorders, more psychological distress, a greater tendency to amplify somatic complaints, and increased functional disability compared with a control group. Our study also describes the clinical reasons for pheochromocytoma workups and the number of such workups with positive results in two large hospitals over a 1-year period based on a review of laboratory and chart data.

Design: Forty patients with hypertension who were screened for pheochromocytoma were compared with 30 group-matched controls with hypertension who were screened for cholesterol levels on a structured psychiatric interview as well as self-rating questionnaires measuring psychological distress, functional disability, and the tendency to amplify symptoms.

Main Results: The prevalence of current and lifetime panic disorder, agoraphobia, and multiple phobias was significantly higher in patients screened for pheochromocytoma compared with those screened for cholesterol levels. Moreover, the patients with hypertension who were screened for pheochromocytoma reported significantly higher levels of psychological distress, significantly lower levels of vocational and social role functioning and vitality, and a more adverse view of their physical and mental health. Current anxiety disorders in this group were especially associated with the primary care presentation of episodic physical symptoms (ie, palpitations and headache) and labile hypertension but not with severe or treatment-resistant hypertension.

Conclusion: Patients presenting with episodic somatic symptoms such as tachycardia, flushing, headache, and/or labile hypertension, who may normally be screened for pheochromocytoma, should be screened for anxiety disorders, especially panic disorder, by their primary care physicians.

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PANIC DISORDER is an anxiety disorder characterized by discrete episodes of dyspnea, palpitations, chest pain, tachycardia, sweating, dizziness, nausea, or abdominal discomfort, fears of dying or "going crazy," and feelings of derealization.[1] Individuals with panic disorder usually selectively focus on the frightening physical symptoms, and their disease is often misdiagnosed.[2] Moreover, panic attacks heighten the level of symptom awareness, leading to increased somatization, medical utilization, and worry about illness.[3-5] Thus, patients with panic attacks often have numerous visits to the emergency department, consultations with specialists, and diagnostic examinations.[6,7] In fact, panic disorder has been shown to be one of the strongest predictors of mental health and medical utilization.[5]

Many researchers have suggested that the sympathetic arm of the autonomic nervous system is dysregulated or hyperfunctional in some patients with panic disorder.[8,9] Studies of patients with panic disorder during spontaneous or situational-induced panic have reported increases in heart rate and elevated systolic and diastolic blood pressure recordings,[8-11] although other studies have not always confirmed these findings.[12,13] Anecdotal reports have also suggested that panic

See Patients and Methods on next page

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PATIENTS AND METHODS

All study subjects were patients from the University of Washington Medical Center or the Group Health Cooperative of Puget Sound (a large health maintenance organization), Seattle. Computer-automated pharmacy and laboratory data were obtained and detailed chart reviews and brief telephone interviews were performed to ensure subjects met the inclusion criteria. When tested, patients in the PS group did not have abnormal levels of urinary catecholamines, vanillylmandelic acid (VMA), or metanephrines within the year prior to the study. Both the University of Washington and the Group Health Cooperative clinical laboratories used high-performance liquid chromatography for detection of urinary catecholamine and metabolite levels. The university laboratory also used spectrophotometric analysis for detection of VMA levels. Both assay methods are highly sensitive and specific.[18] Both chart reviews and telephone calls ensured that the patients resided in the Seattle metropolitan area (within a 30-mile radius of Seattle) and met the following criteria: (1) a history of diagnosable hypertension with a diastolic blood pressure greater than 90 mm Hg; (2) age greater than 18 years; (3) no known personal or family history of pheochromocytoma; (4) no known history of problems frequently associated with pheochromocytoma such as adrenal tumors, multiple endocrine neoplasia, or neurofibromatosis; and (5) no known cause of hypertension such as renal or endocrine abnormalities. Patients in the CS group were identified by matching a list of patients who had undergone cholesterol screening over the last year with automated pharmacy data suggesting that the patient was taking antihypertensives. Patients in the CS group were required to not have been screened for urinary catecholamine, VMA, or metanephrine levels in the past and to meet the above five inclusion criteria. The patients in the CS group were group-matched to those in the PS group by age and gender.

A total of 63 patients who had been screened for pheochromocytoma with one or more of the three laboratory tests were contacted by telephone. A total of 16 were found to meet one of the contraindications: eight did not have hypertension, two had a history of a pheochromocytoma, and six had other miscellaneous causes of hypertension such as multiple endocrine neoplasia or renal vascular disease. Forty (85%) of the remaining 47 patients agreed to participate in the study. A total of 61 subjects screened for cholesterol levels were contacted by telephone. Thirteen were excluded because they did not have hypertension, one had been previously tested for pheochromocytoma, and one had secondary hypertension. Of the remaining 46 subjects, 30 (65%) of these patients with hypertension agreed to participate. There were no significant differences in age or gender between patients in the PS group who chose to participate and those eligible patients who refused to participate or between patients in the CS group and those eligible patients who refused to participate.

STUDY MEASURES

After subjects underwent an initial brief telephone interview, the study risks and benefits were described to the eligible subjects, and preliminary verbal consent to participate was obtained. At the time of the 1- to 2-hour, in-person interview, subjects reviewed and signed a University of Washington Human Subjects informed consent. The following five study measures were then administered.

1. The Diagnostic Interview Schedule (DIS) is a structured psychiatric interview designed by the National Institute of Mental Health for administration by lay interviewers.[19] It assesses current and lifetime psychiatric diagnoses using the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*)[1] and has been used extensively in epidemiological field work and clinical trials. For each positive identification of a psychiatric diagnosis, the DIS follows a highly structured question sequence to determine whether the symptom meets

disorder is associated with labile hypertension that returned to normal after effective treatment of the anxiety disorder.[11]

Prospective follow-up studies are another mechanism to study the link between panic disorder and the autonomic nervous system. One such study linked panic disorder to the development of chronic hypertension; Noyes and colleagues[4,14] examined patients 6 years after a diagnosis of panic disorder was made and found a significantly higher prevalence of hypertension than in controls. They also found that the diagnosis of hypertension followed that of anxiety neurosis by more than 2 years in 19 of 22 patients. In a 35-year follow-up study of patients with panic disorder, Coryell and colleagues[15,16] found an increased incidence of cardiovascular disease. Hypertension could explain the higher incidence of cardiovascular illness in these patients.

To further understand the potential link between panic disorder and hypertension, we elected to study a population of patients with hypertension identified on the basis of a recent evaluation for pheochromocytoma. Patients with hypertension are often screened for the presence of this rare catecholamine-secreting tumor if they present complaining of episodes of heart palpitations, shortness of breath, sweating, flushing, headache, and anxiety.[17] Significant blood pressure elevation, treatment resistance, and lability are hallmarks of pheochromocytoma.[17] Therefore, we used the pheochromocytoma workup as a marker for severe and/or labile hypertension associated with episodic symptoms such as palpitations, headache, flushing, and anxiety (which are also likely to be associated with panic disorder). Labile hypertension is marked by fluctuations in blood pressure that suggest autonomic dysregulation. In addition, diagnostic evaluations of both severe and labile hypertension are frequently extended, expensive, and unrevealing.

Our article presents a case-control study compar-

severity criteria and whether the symptom is due to use of alcohol or other drugs or medications or to physical or psychiatric illness. The DIS also asks the patient to chronologically date psychiatric symptoms as occurring in the last 1 month, in the last 3 to 6 months, in the last 6 to 12 months, or more than 1 year ago.

An abridged version of the DIS with sections on demographics, somatization disorder, panic disorder, agoraphobia, major depression, generalized anxiety disorder, dysthymic disorder, and alcohol use and/or dependence was administered. The sections on panic disorder and generalized anxiety disorder were modified to meet *DSM-III-R* criteria, and the section on major depression was amended to include current depressive symptoms.[20] Patients were classified as having a current *DSM-III-R* diagnosis when they met criteria within 1 month. Lifetime diagnoses were also recorded. The DIS interviewers (J.F. and C.C.E.) were trained by the senior investigator (W.K.), who had used the DIS in numerous studies. Study interviewers watched experienced interviewers and role-played interviews. Five percent of the interviews were completed with both interviewers present to ensure uniformity in use of instruments.

2. The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36) is a comprehensive survey of health-related quality of life derived from questionnaires developed and validated in the Health Insurance Experiment and the Medical Outcomes Study.[21] This 36-item scale measures nine concepts, including the extent that health limits physical activities (physical functioning); the extent that physical health interferes with work or other daily activities (role functioning–physical); the extent that mental health interferes with daily activities (role functioning–emotional); social functioning; the effect of pain on work (bodily pain); mental health; vitality; general health perceptions; and change in health evaluation compared with the previous 1 year. Subscales are scored from zero to 100, with higher scores associated with more optimal health status.

3. Hopkin's Symptom Checklist–90 Revised (SCL-90-R) is a self-reported symptom inventory that includes 90 current symptoms (scored on a severity scale of zero to four) of anxiety, phobic anxiety, somatization, depression, and other subscales.[22] It has been used in numerous studies of medical patients and has been found to have high reliability and validity.[22]

4. Medical comorbidity was measured on a standard checklist of 10 chronic physical illnesses.[23]

5. The Somatosensory Amplification Scale is a 10-item self-report scale that measures the tendency to amplify physiologic sensations on an ordinal scale from 1 to 5.[24]

To categorize the medical reason for pheochromocytoma testing and the number of antihypertensives prescribed, a chart review of all cases and controls was also performed. To investigate the diagnostic yield of the urinary tests for catecholamine, VMA, and metanephrine levels, we audited the laboratory records for this test during 1991 at both the Group Health Cooperative of Puget Sound and the University of Washington Medical Center and then reviewed the charts of patients who had elevated levels to determine the incidence of documented pheochromocytoma.

STATISTICAL ANALYSES

χ^2 Tests with corrections for continuity were used to examine group differences on the dichotomous demographic variables and the psychiatric diagnoses, and *t* tests were used to determine group differences on the continuous variables (eg, age and SCL-90-R and MOS-SF-36 scores). A discriminant analysis was used to determine which study variables best discriminated the two groups of patients while accounting for the intercorrelation among the study variables. To reduce type I error (erroneously concluding that a variable is significant, or false-positive results), only variables that were significantly different between the groups ($P<.05$) were included in this analysis. Data are presented as percentages or as mean±SD.

ing psychiatric diagnoses, psychological distress, functional disability, symptom amplification, and health status in a group of 40 patients with hypertension who were tested for pheochromocytoma (PS group) and in 30 controls of comparable age and sex with essential hypertension who were not tested. The PS group consisted of patients receiving antihypertensives who were selected from a laboratory list of patients undergoing diagnostic evaluation for pheochromocytoma. Patients with essential hypertension were those receiving antihypertensives and who had undergone recent screening of serum cholesterol levels (CS group).

Our principal hypothesis was that, compared with the CS group, patients in the PS group would manifest (1) a higher prevalence of panic disorder, (2) an increased prevalence of other anxiety disorders, and (3) more psychological distress, a greater tendency to amplify somatic complaints, and increased functional disability.

RESULTS

There were no significant differences between the two groups with regard to age, gender, and level of education. The PS group consisted of 27 women (67.5%) and 13 men (32.5%), with a mean age of 48.7±15.3 years and a mean of 14.9±3.2 years of education. The CS group consisted of 19 women (63.3%) and 11 men (36.7%), with a mean age of 49.5±11.3 years and a mean of 14.7±2.5 years of education (age, $t[68]=0.25$; education, $t[68]=0.33$; and gender, $\chi^2[1]=0.01$). The PS group had a mean of 1.97±1.4 medical illnesses vs 1.63±0.9 medical illnesses in the CS group ($t[68]=1.25$). Patients in the PS group were prescribed a mean of 1.42±.96 antihypertensives and a mean of 2.85±1.88 medications overall vs a mean of 1.41±.63 antihypertensives and a mean of 2.48±1.8 medications overall in the CS group ($t[68]=.96$ and $t[68]=.42$, respectively).

Table 1. Comparison of Psychiatric Diagnoses in 40 Patients With Hypertension Screened for Pheochromocytoma (PS Group) and 30 Patients With Hypertension Screened for Cholesterol Levels (CS Group)

Diagnostic Interview Schedule	PS Group, No. (%) of Patients	CS Group, No. (%) of Patients	Significance, χ^2
Panic disorder			
Current	11 (28)	1 (3)	5.4*
Lifetime	14 (35)	3 (10)	4.5*
Generalized anxiety			
Current	4 (10)	1 (3)	0.4
Lifetime	11 (28)	4 (13)	1.3
Agoraphobia	8 (20)	0	4.9*
Multiple phobias (≥2)	7 (18)	0	4.0*
Depression			
Current	4 (10)	0	1.6
Lifetime	21 (53)	12 (40)	0.6
Alcohol abuse			
Current	0 (0)	0	
Lifetime	3 (8)	5 (17)	0.66
Somatization disorder	4 (10)	2 (7)	0.01

*P<.05.

Table 2. Hopkin's Symptom Checklist–90 Revised Findings in Patients With Hypertension Screened for Pheochromocytoma (PS Group) and for Cholesterol Levels (CS Group)*

	PS Group (N=38), Mean±SD	CS Group (N=28), Mean±SD	t (64)
Scale			
Somatization	1.05±1.04	0.64±0.65	2.00†
Depression	0.98±0.90	0.73±0.76	1.20
Phobic Anxiety	0.53±0.82	0.11±0.22	3.00‡
Obsessive-Compulsive	0.78±0.85	0.63±0.63	0.78
Anxiety	0.98±1.05	0.51±0.62	2.27†
Paranoid Ideation	0.42±0.57	0.38±0.44	0.26
Interpersonal Sensitivity	0.68±0.73	0.60±0.67	0.48
Hostility	0.50±0.65	0.51±0.58	0.07
Psychoticism	0.32±0.42	0.29±0.45	0.28
Additional items	1.01±0.86	0.71±0.69	1.57
General Symptom total	68.63±63.98	43.74±43.56	1.75
General Symptom index	0.76±0.71	0.49±0.48	1.87
Positive Symptom total	35.05±23.74	30.03±23.63	0.86
Positive Symptom index	1.72±.58	1.43±.37	2.48†

*Mean indicates raw scores. Data are incomplete for two patients in each group.
†P<.05.
‡P<.01.

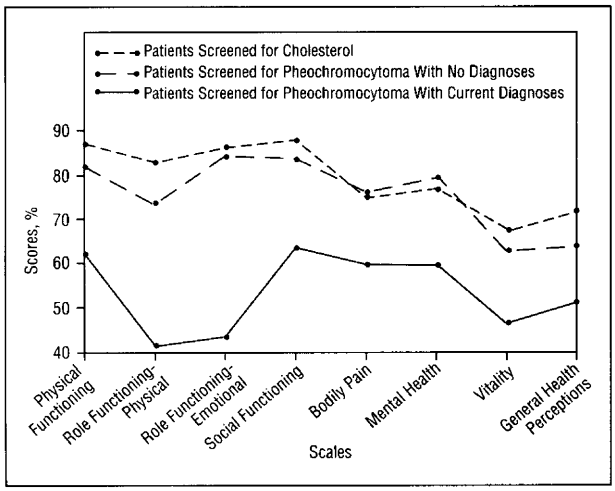
Data on psychiatric diagnoses are summarized in **Table 1**. Compared with the CS group, the PS group had a significantly higher prevalence of current and lifetime diagnoses of panic disorder, agoraphobia, and multiple phobias (two or more simple phobias). In addition, there was a significantly greater prevalence in the PS group of at least one current anxiety disorder (45% vs 6.7%; $\chi^2[1]=10.5$; $P<.001$) and at least one lifetime anxiety disorder (60% vs 20%; $\chi^2[1]=9.6$; $P<.001$). The PS group also had a significantly higher mean number of current psychiatric diagnoses (1.02±1.54 vs 0.17±0.46; $t[68]=3.32$; $P<.002$) and lifetime psychiatric diagnoses (1.82±1.83 vs 0.83±1.23; $t[68]=2.70$; $P<.009$). There were no statistical differences between the two groups for diagnoses of depression, dysthymia, alcoholism, or somatization disorder.

Table 2 shows that compared with the CS group, the PS group had significantly higher mean self-rated scores on the Anxiety, Phobic Anxiety, Somatization, and Positive Symptom subscales of the SCL-90-R. There was no significant difference between the groups' somatosensory questionnaire scores (mean score in the PS group, 15.8±8.4; in the CS group, 13.1±6.8; $t[66]=2.1$). When compared with the CS group, the PS group had significantly greater decrements in their role functioning due to physical illness (57.1±46.9 vs 82.7±34.1; $t[64]=2.5$; $P<.05$), in role functioning due to emotional illness (63.3±45.1 vs 85.1±30.3; $t[64]=2.4$; $P<.05$), in social functioning (73.1±24.9 vs 87.5±19.2; $t[64]=2.6$; $P<.01$), and in vitality (54.4±21.0 vs 64.7±15.6; $t[64]=2.2$; $P<.05$). Patients in the PS group also had a significantly more adverse perception of their physical health (57.1±21.8 vs 71.3±21.0; $t[64]=2.7$; $P<.01$) and mental health (68.9±19.2 vs 76.8±13.9; $t[64]=2.0$; $P<.05$) when compared with the CS group, but no significant differences in physical functioning or pain. The **Figure** demonstrates that when the PS group is divided into patients with and without one or more current psychiatric diagnoses and compared with the CS group, the functional disability is accounted for by the members of the PS group with one or more current psychiatric diagnoses.

A discriminant function analysis was performed to determine which of the study variables best discriminated the groups. This analysis accounts for the interrelationships among the study variables. Only variables that were significantly different between the groups ($P<.05$) were used for the analysis. The stepwise discriminant analysis revealed that at least one current anxiety diagnosis was the best and only significant predictor of group status ($F[1,68]=14.56$; $P<.001$). Classification of the subjects based on this analysis resulted in correct classification in 93.3% (28/30) of the CS group and 45% (18/40) of the PS group.

At the Group Health Cooperative, 151 tests for either urinary catecholamine, VMA, or metanephrine levels were performed over a 1-year period. Thirteen test results were elevated (often leading to more than one repetition of the same test). Only one of the patients among the 13 with elevated results was found to have a pheochromocytoma. At the University of Washington Medical Center, there were 153 urinary tests performed over a 1-year period and results were elevated in 12 patients. Three of the 12 patients with elevated test results were found to have pheochromocytoma: one with a previous diagnosis, one with a multiple-endocrine neoplasia (a rare endocrine problem known as a potent risk factor for pheochromocytoma), and one with newly diagnosed pheochromocytoma.

The chart review of the 40 patients in the PS group de-



Scales of the Medical Outcomes Study 36-Item Short-Form Health Survey for patients with hypertension stratified by current phychiatric diagnoses. Physical Functioning indicates the extent that health limits physical activities; Role Functioning-Physical, the extent that physical health interferes with work or other daily activities; Role Functioning-Emotional, the extent that mental health interferes with daily activities; and Bodily Pain, the effect of pain on work. Higher scores indicate more optimal health status.

termined that 14 patients (35%) were tested as a result of severe, malignant, or treatment-resistant hypertension; 11 (28%), labile hypertension; and 24 (60%), episodic symptoms (many patients had at least two of these factors noted in their charts). Patients tested because of severe, malignant, or treatment-resistant hypertension were significantly less likely to suffer from one or more current anxiety disorders (6.7% vs 64%; $\chi^2[1]=10.4; P<.001$). Patients tested because of labile hypertension were significantly more likely to have one or more current anxiety disorders (66.7% vs 32.1%; $\chi^2[1]=4.1; P<.05$), as were patients tested owing to episodic symptoms such as palpitations or headaches (60% vs 13%; $\chi^2[1]=6.6; P<.01$).

COMMENT

The study findings support the hypothesis that patients in the PC group more frequently suffer from panic disorder and other anxiety disorders, are generally more distressed, and are more functionally impaired than the patients in the CS group. The PS group in our study had significantly higher prevalences of current and lifetime panic disorder, agoraphobia, multiple phobias, and total current and lifetime DIS psychiatric diagnoses than did the CS group. Moreover, patients in the PS group reported significantly higher levels of SCL-90-R anxiety, phobic anxiety, and somatization; significantly lower levels of MOS-SF-36 physical and emotional role functioning, social functioning, mental health, and vitality; and a more adverse view of their general health. These findings have implications for clinical diagnosis and illness recognition as well as the potential biologic relationship between panic disorder and hypertension.

Our findings are consistent with the known frequency and distribution of both panic disorder and pheochromocytoma. Pheochromocytoma is very rare compared with anxiety disorders. Several large epidemiological studies have placed the incidence of pheochromocytoma between 1.6 and 8.0 new cases per million person-years at risk[25] and involving less than 0.1% of patients with hypertension.[18,26] Since it is most often definitively treated following diagnosis, its prevalence is likely to be exceedingly low as well. In comparison, approximately 1.6% to 3.9% of women and 0.4% to 1.7% of men in the general population have panic disorder,[3,27] and approximately 6.5% of primary care patients suffer from panic disorder.[28]

One major medical text recommends that for patients with hypertension, "a history of headaches, palpitations, anxiety attacks, unusual sweating, hyperglycemia and weight loss should lead to tests to exclude pheochromocytoma."[17] These symptoms are quite similar to those associated with panic and other anxiety disorders. Panic disorder also tends to be associated with discrete episodes of common medically unexplained symptoms such as headache, chest pain, and sweating, as well as labile hypertension.[2,3,11] The results of chart reviews suggested that physicians screened patients with hypertension for pheochromocytoma based on episodic physical symptoms and severe or labile hypertension. One would predict from the differences in prevalence of the two disorders that the fraction of patients complaining of these somatic symptoms who have panic and other anxiety disorders would be much higher than the fraction of patients complaining of symptoms who have pheochromocytoma. Our findings that 45% of our PS group suffered from a current anxiety disorder and that the presence of anxiety disorder correctly classified nearly two thirds of study participants as in either the PS or CS group are consistent with this view.

Review of the medical records of the patients in the PS group demonstrated that they were screened because of suggestive symptoms (ie, episodic headache, flushing, and palpitations), refractory or severe hypertension, and labile hypertension. These results are quite similar to those in the study by Stein and Black.[18] They reviewed 28 pheochromocytoma workups with negative results and found that eight patients were referred because of severe and/or resistant or labile hypertension and 20 because of paroxysmal or suggestive symptoms.[18] They also found a high rate of psychiatric illness in these 28 patients, with five having anxiety or panic disorder; five, alcohol abuse and withdrawal; and five, mitral valve prolapse (30% to 40% of patients with panic disorder have mitral valve prolapse).[3] On the other hand, a study of 17 patients with documented pheochromocytoma found that none of these patients exhibited psychological symptoms consistent with panic disorder.[29] Moreover, none of these patients exhibited anticipatory anxiety, phobic anxiety, or agoraphobia.

These data suggest that patients with hypertension who are screened for pheochromocytoma often suffer from disabling but unrecognized psychiatric problems. On the MOS-SF-36, subjects in the PS group who also had comorbid current psychiatric disorders were significantly more impaired in their role and social functioning and vitality than patients in the PS group without psychiatric disorders and controls

in the CS group. These patients also had a more adverse perception of their physical and mental health. Recent research has shown that patients with anxiety and depressive disorders are often high utilizers of medical care[30] and frequently have multiple, medically unexplained somatic symptoms.[31] These disorders can be as debilitating as many important chronic medical conditions.[8,32] Excess mortality due to suicide and/or comorbid medical conditions has also been noted in patients with anxiety and depressive disorders.[7,33,34] Thus, relegating panic disorder to the position of an exclusionary diagnosis in patients with labile hypertension with episodic physical symptoms may leave patients significantly disabled by serious, unrecognized, and untreated psychiatric conditions.

Several studies have linked panic disorder to either labile hypertension or prospectively to the development of hypertension.[4,9,11,14] Hypertension affects approximately 25% of the adult population,[35] and there may be a subgroup of patients with hypertension manifesting sympathetic nervous system hyperreactivity secondary to panic disorder. Also, in individuals genetically prone to hypertension, panic disorder may lead to either an expression of that genetic potential or a worsening of preexisting hypertension. Finally, patients with established hypertension, in whom panic disorder develops, may become refractory or treatment resistant to antihypertensives. This situation is analogous to the problems of controlling hypertension in patients with alcohol abuse in whom the autonomic hyperactivity secondary to alcohol withdrawal often leads to blood pressure lability, making control of hypertension difficult.[36] Defining these groups of patients with hypertension with comorbid panic disorder and providing effective treatment may lead to the return to either a nonhypertensive state or to a hypertensive state that is less refractory to treatment, much as is occasionally seen in the successful treatment of alcohol abuse in patients with hypertension.

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