Drug Intolerance Due to Nonspecific Adverse Effects Related to Psychiatric Morbidity in Hypertensive Patients

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Background: Poor adherence to antihypertensive drug regimens is common and may increase the risk for cardiovascular morbidity and mortality. Adverse effects of the drugs can contribute to poor adherence, but some patients who discontinue several different antihypertensive drugs may misinterpret nonspecific symptoms as adverse effects of the drug because of psychiatric morbidity. We examined the relationship between intolerance to antihypertensive drugs and the presence of panic disorder, panic attacks, anxiety, and depression.

Methods: We included all patients with hypertension who attended a hospital hypertension clinic during 1 year with at least 2 episodes of intolerance (resulting in reduction of the dosage or stopping an antihypertensive drug) recorded on standardized problem lists and a similar number of patients with no recorded episodes of intolerance. Psychiatric morbidity, assessed by self-administered questionnaires, was analyzed against the number of episodes of nonspecific and drug-specific intolerance, verified by means of individual case-note scrutiny, and scored independently by 2 assessors masked to patient identity.

Results: Analyzable questionnaires were returned by 233 (84%) of 276 patients who had experienced 576 (85%) of 679 episodes of intolerance assessed. Five hundred thirty-two episodes (92%) were subjective (patient was symptomatic); of these, 284 were judged to be drug specific; 248, nonspecific. Having more episodes of nonspecific intolerance was associated with significantly higher diastolic blood pressure ($P=.003$). Episodes of nonspecific intolerance were associated with panic attacks ($P=.008$), anxiety (Hospital Anxiety and Depression Scale score, $P=.04$), and depression (Hospital Anxiety and Depression Scale score, $P=.005$). Drug-specific intolerance was not associated with psychiatric morbidity.

Conclusions: Intolerance to multiple antihypertensive drugs, particularly non–drug-specific intolerance, is strongly associated with psychiatric morbidity. Physicians treating hypertensive patients need to recognize and manage the psychiatric aspects of intolerance to multiple antihypertensive drugs.

Arch Intern Med. 2003;163:592-600

ANTIHYPERTENSIVE drugs prevent cardiovascular complications in patients with hypertension (hereafter referred to as hypertensive patients), but control of blood pressure is often suboptimal. One reason for this may be discontinuation of drugs because of adverse effects. Newly prescribed antihypertensive drugs were stopped within 6 months by about 55% of patients in the United Kingdom and within 1 year by about 49% of patients in the United States. This finding was ascribed at least in part to adverse effects of the drug. Adverse effects were cited as the most common reason for changing medication by hypertensive patients. Some hypertensive patients discontinue or change antihypertensive drugs repeatedly owing to apparent adverse effects, a phenomenon termed multiple-drug intolerance. Several authors have questioned whether the adverse effects experienced by patients with multiple-drug intolerance are always genuinely related to the pharmacological action of the drugs involved. Some patients seem to complain of similar nonspecific symptoms, eg, weakness, dizziness, fatigue, or vague ill health, with several different drugs, irrespective of their pharmacological action. These patients may be very difficult to treat, and medication intolerance was held responsible in 25% of patients with treatment resistance. In many of these cases, the intolerance to treatment was ascribed to misinterpretation of psychological symptoms as adverse effects of drugs, and it was suggested that anxiety and depression may cause recurrent adverse effects that are not drug specific. In ordinary clinical practice, multiple-drug intolerance is strongly suspected of...
being related to psychiatric factors, but very little evidence of this exists. Psychiatric disorders are even more common in hypertensive patients than in the general population. As many as 37% of hypertensive patients have experienced panic attacks, and hypertension has been significantly associated with panic disorder, anxiety, and depression. The aim of this study was to examine the hypothesis that intolerance to multiple antihypertensive drugs is associated with psychiatric morbidity such as panic attacks, panic disorder, anxiety, and depression, and that any association is particular to non-specific intolerance, meaning apparent adverse effects that are not typical of the drug implicated.

### METHODS

#### PATIENTS

Problem lists are maintained in the standardized medical records of the Sheffield Hypertension Clinic, Sheffield, England. The lists are updated after each visit and include a summary of medical and psychiatric diagnoses and other features, including episodes of drug intolerance, alcohol or other drug misuse, and relevant family history. From these lists, we identified all patients who attended the clinic during a single year and were documented as having previously experienced intolerance to 2 or more antihypertensive drugs. A demographic reference sample of patients with no episodes of drug intolerance documented in their problem list was drawn from the clinic records for the same year by searching forward alphabetically from each index patient with multiple-drug intolerance to identify the first patient receiving antihypertensive treatment who was matched for age (same decade) and sex and had no episodes of treatment intolerance documented in the problem list. Patients who had been invited to participate in more than 1 study before were excluded as required by the ethics committee. For those patients included, blood pressure, the number of antihypertensive drugs currently prescribed, and psychiatric diagnoses in the problem list were taken from the record for the last clinic visit of the index year.

#### CLASSIFICATION OF DRUG INTOLERANCE

The original clinic records were scrutinized to confirm the episodes of drug intolerance and to identify additional episodes that had not been recorded in the problem lists. Drug intolerance was defined as stopping an antihypertensive drug or reducing the dosage because of adverse effects, but not lack of efficacy. All episodes of intolerance were evaluated independently for subjectivity and specificity by 2 assessors (P.R.J. and L.E.R.) who were masked to the identity of patients and the questionnaire findings for psychiatric morbidity. For subjectivity, episodes of intolerance were categorized as symptomatic (ie, reduction or cessation of drug due to an adverse effect experienced subjectively by the patient) or asymptomatic (eg, discontinuation by a physician due to disturbed electrolyte levels). Symptomatic intolerance was categorized further for specificity on the following scale of 3 to 0: 3 indicates symptom(s) probably due to drug (eg, persistent cough with atenolol); 2, symptom(s) possibly due to drug (eg, fatigue with atenolol); 1, symptom(s) probably not due to drug (eg, lethargy with nifedipine); and 0, symptom(s) almost certainly not due to drug (eg, edema with a loop diuretic). Where information was insufficient, specificity was rated as indeterminate. Differences between the assessors were reconciled by discussion, with masking maintained, when they disagreed on subjectivity or when their scores for specificity differed by 2 or more points. Scores for specificity by the 2 assessors were then averaged. Symptomatic episodes of intolerance were classified as nonspecific when the average score ranged from 0 to 1.5 or was indeterminate, or as drug specific when the average score ranged from 2 to 3. The final classification of patients was according to the number of episodes of intolerance that were nonspecific (which was the primary end point of the study), specific episodes, and all episodes of intolerance, including symptomatic and asymptomatic episodes.

CLINIC REFERENCE GROUP FOR ASSOCIATION OF AGE AND SEX WITH DRUG INTOLERANCE

The method of recruiting the patients for the study tended to abolish or weaken any possible relation between sex or age and drug intolerance. To examine this relation, the age and sex of patients with drug intolerance were compared with those of the separate clinic reference sample of the same number of patients drawn from the clinic by searching the records for the index year forward alphabetically and taking sequential hypertensive patients documented in the problem list irrespective of drug intolerance.

ASSESSMENT OF PSYCHIATRIC MORBIDITY

All patients were mailed an introductory letter, questionnaires for panic attacks and panic disorder, the Hospital Anxiety and Depression Scale (HAD), the trait anxiety section of the Spielberger State-Trait Anxiety Inventory for Adults, and supplementary questions on alcohol consumption, medication, and age at diagnosis of hypertension. The introductory letter was approved by the ethics committee and mentioned panic, anxiety, and depression but made no mention of treatment intolerance to avoid introducing bias. Patients who did not respond by 2 months were sent a second questionnaire and were deemed nonresponders if they did not reply within an additional 2 months. The questionnaire for panic attacks and panic disorder is based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition diagnostic system, which is described in Table 1, and derived from [Panic Attack](#)

<table>
<thead>
<tr>
<th>Table 1. Criteria for Panic Attacks and Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panic attack</strong> is a discrete period of intense fear or discomfort involving ≥4 of the following symptoms:</td>
</tr>
<tr>
<td>• Shortness of breath (dyspnea) or smothering sensations</td>
</tr>
<tr>
<td>• Dizziness, unsteady feelings, or faintness</td>
</tr>
<tr>
<td>• Palpitations or accelerated heart rate (tachycardia)</td>
</tr>
<tr>
<td>• Trembling or shaking</td>
</tr>
<tr>
<td>• Sweating</td>
</tr>
<tr>
<td>• Choking</td>
</tr>
<tr>
<td>• Nausea or abdominal distress</td>
</tr>
<tr>
<td>• Depersonalization or derealization</td>
</tr>
<tr>
<td>• Numbness or tingling sensations (paresthesias)</td>
</tr>
<tr>
<td>• Hot flushes or chills</td>
</tr>
<tr>
<td>• Chest pain or discomfort</td>
</tr>
<tr>
<td>• Fear of dying</td>
</tr>
<tr>
<td>• Fear of going crazy or doing something uncontrolled</td>
</tr>
</tbody>
</table>

A diagnosis of panic disorder requires 4 attacks within a 4-week period or ≥1 attacks followed by ≥1 month of persistent fear of having another attack. Some attacks must be spontaneous, must have developed suddenly, and must have increased in intensity within 10 minutes of the onset of the first symptom. There must be no organic cause.
the relevant section of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. It provides information on the severity and frequency of attacks, individual panic symptoms experienced, whether the attacks were ever spontaneous, whether an attack had occurred in the past 6 months, and age at the first attack. The HAD scale is a self-rating instrument that provides separate scores for anxiety and depression. Scores greater than 7 on the subscales indicate possible anxiety or depression. The Spielberger State-Trait Anxiety Inventory provides separate scores for anxiety (a measure of anxiety level at time of completing the questionnaire) and trait anxiety (a more stable measure of predisposition to symptoms of anxiety). We used only the trait anxiety section in this study. Excessive alcohol consumption was defined as an intake of greater than 21 U/wk for men and 14 U/wk for women. One unit of alcohol was defined as 10 mL by volume of pure alcohol (8 g); therefore, 1 U equals 1 “measure” (25 mL) of spirits, 1 glass of wine, or 1 half-pint of beer or alcoholic cider.

STATISTICAL ANALYSIS

We examined the relations between the number of episodes of drug intolerance and measures of psychiatric morbidity by the χ² (exact) test for linear trend in proportions (for discrete variables), and by the Spearman rank correlation (ρ) or analysis of variance (for continuous variables).

RESULTS

After detailed review of the original records for all 276 patients who were sent questionnaires (138 of whom had ≥2 episodes of drug intolerance documented in the problem list and 138 of similar age and sex who had no episodes of drug intolerance recorded), 679 episodes of intolerance to antihypertensive drugs were identified. Of these episodes, 574 (85%) were among patients who had intolerance recorded in the problem list, and 105 (15%) were among patients who had no intolerance recorded in the problem list.

RESPONSE TO QUESTIONNAIRES

Of the 276 patients, 233 (84%) returned analyzable questionnaires that yielded information pertinent to 576 (85%) of the 679 episodes of drug intolerance (Figure 1).

PATTERN OF DRUG INTOLERANCE

Of these 576 episodes of intolerance, 532 (92%) were symptomatic and 44 (8%) were asymptomatic. Two hundred forty-eight symptomatic episodes (47%) were classified as nonspecific, and 284 (53%) as drug specific. The total number of episodes of intolerance ranged from 0 to 11 per person; nonspecific intolerance, 0 to 8 episodes per person; and drug-specific intolerance, 0 to 6 episodes per person.

To illustrate the classification of episodes and patients, 1 patient with multiple-drug intolerance was a 49-year-old woman with hypertension and type 2 diabetes mellitus who had attended the clinic for 9 years. Intolerance to 8 antihypertensive drugs had been documented. Five of these episodes were judged to be nonspecific, ie, nifedipine made her sluggish; atenolol caused migraine, dizziness, and sickness; propranolol hydrochloride caused migraine; furosemide caused nausea; and losartan potassium caused nausea, vomiting, and bad dreams. Another 3 episodes of intolerance were rated as drug specific, ie, verapamil hydrochloride caused constipation; hydralazine hydrochloride caused constipation; and methylodopa caused abdominal pain and pyrexia. Certain symptoms such as nausea and migraine were experienced repeatedly and attributed to different classes of antihypertensive agents. She had had bouts of depression, but did not tolerate antidepressant medication. Blood pressure levels often exceeded 200/120 mm Hg and recently averaged 176/96 mm Hg while she was receiving spironolactone, valsartan, and verapamil. She now has severe angina, diabetic retinopathy, and diabetic neuropathy.

Table 2 shows the number of episodes of intolerance and their classification for the major classes of antihypertensive drugs. Dihydropyridine calcium channel blockers were associated with 133 episodes of intolerance; ACE inhibitors, 113 episodes; β-blockers, 104 episodes; diuretics, 90 episodes; and other drug classes combined, 96 episodes. Asymptomatic intolerance was uncommon with all the major drug classes, ranging from 6% of episodes with β-blockers to 14% with diuretics. For episodes of symptomatic intolerance, the proportion of specific to nonspecific episodes differed among the drug classes used most commonly in the clinic. For dihydropyridine calcium channel blockers, most episodes (64%) were judged to be drug specific, and only 30%, to be nonspecific. Conversely, only 30% of episodes involving diuretics were judged to be specific, whereas 56% were judged to be nonspecific.

Table 3 shows the symptoms reported for episodes of drug intolerance that were classified as drug specific. Edema (49%), headache (39%), and flushing (28%) were notable symptoms for dihydropyridine calcium channel blockers; cough (76%), for ACE inhibitors; tiredness (46%) and wheeze (27%), for β-blockers; urinary frequency (37%) and gout (30%), for diuretics; gastrointestinal tract disturbance (41%), edema (36%), and headache (27%), for nondihydropyridine calcium channel blockers; and dizziness (44%), tiredness (33%), and headache (22%), for α-blockers. The symptoms...
reported in nonspecific episodes were too diverse to tabulate.

**DRUG INTOLERANCE IN RELATION TO SEX AND AGE**

Within the study, we found no association between the number of episodes of nonspecific intolerance, the principal end point of the study, and sex or age, a negative finding attributable to the method of selecting the study population. Compared with the clinic reference group, the 66 patients with 2 or more episodes of nonspecific symptomatic intolerance were more likely to be women (44/66 [67%] vs 117/233 [50%]; \( \chi^2 = 5.6; P = .02 \)) and were older (mean age, 64 vs 59 years; \( P < .01 \)). We found similar results when we compared the clinic reference group with the 135 patients who had experienced 2 or more episodes of any intolerance (91/135 [67%] vs 117/233 [50%] women \( P < .01 \); mean age, 63 vs 59 years \( P < .01 \)) and the 82 patients who had 2 or more episodes of drug-specific intolerance (66/82 [67%] vs 117/233 [50%] women \( P < .01 \); mean age, 64 vs 59 years \( P < .01 \)).

**DRUG INTOLERANCE AND CLINICAL VARIABLES**

We found no significant association between the number of episodes of nonspecific intolerance and the number of antihypertensive drugs taken (Table 4). We found significant associations between the number of episodes of nonspecific intolerance and systolic and diastolic blood pressure (analysis of variance for trend, \( P = .05 \) for systolic; \( P = .003 \) for diastolic). Thus, blood pressure averaged 168/93 mm Hg in the 66 patients who had 2 or more episodes of intolerance, compared
with 160/89 mm Hg in the 167 patients who had 0 or 1 episodes. The higher blood pressure, by an average of 8/4 mm Hg, in patients with nonspecific intolerance to 2 or more drugs, occurred despite treatment with a similar number of antihypertensive drugs. Patients with nonspecific intolerance to 5 or more drugs had higher blood pressure by an average of 15/16 mm Hg, again despite treatment with a similar number of antihypertensive drugs. We found no significant relations between the number of episodes of drug-specific intolerance or any drug intolerance and blood pressure (data not shown).

### Table 4. Clinical Features of Hypertensive Patients Related to the Number of Episodes of Nonspecific Intolerance

<table>
<thead>
<tr>
<th>No. of Episodes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>115</td>
<td>52</td>
<td>35</td>
<td>13</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>233</td>
</tr>
<tr>
<td>Mean age, y*</td>
<td>63</td>
<td>63</td>
<td>64</td>
<td>65</td>
<td>63</td>
<td>57</td>
<td>75</td>
<td>...</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>Women, %*</td>
<td>66</td>
<td>69</td>
<td>63</td>
<td>54</td>
<td>87</td>
<td>71</td>
<td>100</td>
<td>...</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>Mean No. of antihypertensive drugs</td>
<td>2.5</td>
<td>2.4</td>
<td>2.6</td>
<td>2.5</td>
<td>2.6</td>
<td>1.9</td>
<td>3.0</td>
<td>...</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg†</td>
<td>160</td>
<td>160</td>
<td>168</td>
<td>164</td>
<td>169</td>
<td>177</td>
<td>164</td>
<td>...</td>
<td>184</td>
<td>163</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg‡</td>
<td>89</td>
<td>87</td>
<td>91</td>
<td>91</td>
<td>92</td>
<td>105</td>
<td>104</td>
<td>...</td>
<td>102</td>
<td>90</td>
</tr>
<tr>
<td>Taking psychotropic drugs, %§</td>
<td>13</td>
<td>27</td>
<td>20</td>
<td>15</td>
<td>25</td>
<td>57</td>
<td>50</td>
<td>...</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Any psychiatric diagnosis, %¶</td>
<td>13</td>
<td>19</td>
<td>20</td>
<td>15</td>
<td>25</td>
<td>57</td>
<td>50</td>
<td>...</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Excess alcohol consumption, %§</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>...</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

**Abbreviations:** ANOVA, analysis of variance; BP, blood pressure.

*The method of sampling tends to abolish or weaken any relation of drug intolerance with age or sex.

†P = .05 for trend by means of ANOVA.

‡P = .003 for trend by means of ANOVA.

§Determined by means of questionnaire.

¶Recorded in the problem lists. P = .02 for trend by exact χ² test for linear trend in proportions (χ² = 5.88).

### Table 5. Relations of the Number of Episodes of Drug Intolerance With the Prevalence of Psychiatric Morbidity

<table>
<thead>
<tr>
<th>No. of Episodes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>≥4</th>
<th>Total No. (%)*</th>
<th>χ²†</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Non-specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>233 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of episodes</td>
<td>115</td>
<td>52</td>
<td>35</td>
<td>13</td>
<td>18</td>
<td>85/232 (37)</td>
<td>7.03</td>
<td>.008</td>
</tr>
<tr>
<td>Panic attacks, %</td>
<td>32</td>
<td>31</td>
<td>43</td>
<td>31</td>
<td>72</td>
<td>32/232 (14)</td>
<td>0.67</td>
<td>.43</td>
</tr>
<tr>
<td>Panic disorder, %</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>6</td>
<td>100/222 (43)</td>
<td>2.82</td>
<td>.1</td>
</tr>
<tr>
<td>Anxiety, %‡</td>
<td>40</td>
<td>46</td>
<td>36</td>
<td>38</td>
<td>72</td>
<td>96/222 (43)</td>
<td>5.07</td>
<td>.02</td>
</tr>
<tr>
<td>Depression, %§</td>
<td>21</td>
<td>27</td>
<td>26</td>
<td>31</td>
<td>56</td>
<td>59/223 (26)</td>
<td>7.10</td>
<td>.008</td>
</tr>
<tr>
<td>Drug specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>233 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of episodes</td>
<td>100</td>
<td>51</td>
<td>40</td>
<td>25</td>
<td>17</td>
<td>85/232 (37)</td>
<td>1.21</td>
<td>.29</td>
</tr>
<tr>
<td>Panic attacks, %</td>
<td>25</td>
<td>60</td>
<td>45</td>
<td>16</td>
<td>47</td>
<td>32/232 (14)</td>
<td>0.30</td>
<td>.59</td>
</tr>
<tr>
<td>Panic disorder, %</td>
<td>10</td>
<td>26</td>
<td>15</td>
<td>8</td>
<td>6</td>
<td>96/222 (43)</td>
<td>1.50</td>
<td>.22</td>
</tr>
<tr>
<td>Anxiety, %‡</td>
<td>35</td>
<td>61</td>
<td>34</td>
<td>48</td>
<td>50</td>
<td>96/222 (43)</td>
<td>5.68</td>
<td>.02</td>
</tr>
<tr>
<td>Depression, %§</td>
<td>22</td>
<td>39</td>
<td>21</td>
<td>29</td>
<td>24</td>
<td>59/223 (26)</td>
<td>0.01</td>
<td>.96</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>233 (100)</td>
<td></td>
<td></td>
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<tr>
<td>No. of episodes</td>
<td>66</td>
<td>32</td>
<td>31</td>
<td>29</td>
<td>75</td>
<td>85/232 (37)</td>
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<td>.008</td>
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<tr>
<td>Panic attacks, %</td>
<td>21</td>
<td>34</td>
<td>65</td>
<td>34</td>
<td>41</td>
<td>32/232 (14)</td>
<td>0.76</td>
<td>.39</td>
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<tr>
<td>Panic disorder, %</td>
<td>11</td>
<td>11</td>
<td>29</td>
<td>28</td>
<td>7</td>
<td>96/222 (43)</td>
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<td>Anxiety, %‡</td>
<td>32</td>
<td>52</td>
<td>53</td>
<td>41</td>
<td>46</td>
<td>96/222 (43)</td>
<td>5.68</td>
<td>.02</td>
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<tr>
<td>Depression, %§</td>
<td>17</td>
<td>34</td>
<td>21</td>
<td>28</td>
<td>33</td>
<td>59/223 (26)</td>
<td>5.68</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Abbreviation:** HAD, Hospital Anxiety and Depression Scale.

*Denominators differ owing to incomplete responses.

†Indicates the χ² exact test for linear trend in population.

‡Indicates HAD anxiety score of greater than 7.

§Indicates HAD depression score of greater than 7.

### DRUG INTOLERANCE AND PSYCHIATRIC MORBIDITY

According to the questionnaire results, 85 patients (37%) had experienced panic attacks; 32 (14%) met the criteria for panic disorder; 96 (43%) had possible or definite anxiety as determined by means of the HAD score; and 59 (26%) had possible or definite depression by HAD score. We cross-tabulated the number of episodes of drug intolerance in each category against these findings for psychiatric morbidity in Table 5. We found significant associations between the number of episodes of nonspe-
specific intolerance and panic attacks (P = .008) and depression (P = .008) (Table 5 and Figure 2), but not with anxiety or panic disorder. Thus, 13 (72%) of 18 patients with 4 or more nonspecific episodes of intolerance had had panic attacks, compared with 53 (32%) of 166 patients with nonspecific intolerance to at most 1 drug. Of those with 4 or more episodes of nonspecific intolerance, 10 (56%) of 18 patients had possible depression compared with 36 (23%) of 158 with 0 or 1 episode. Of 18 patients with 4 or more episodes of nonspecific intolerance, 13 (72%) had possible anxiety, compared with 66 (42%) or 158 with 0 or 1 episode, although this difference was not significant. However, panic disorder was actually less common in those with 4 or more episodes of nonspecific intolerance (1/18 [6%]) than in those with 0 or 1 episode (24/166 [14%]), although not significantly so. For total episodes of intolerance, the results were broadly similar to those for nonspecific intolerance. We found significant associations with panic attacks (P = .008) and with depression (P = .02) (Table 5) and a significant relationship with anxiety (P = .02). The number of episodes of drug-specific intolerance (Table 5 and Figure 2) showed no significant relations with panic attacks (8 [47%] of 17 patients with ≥4 episodes of drug-specific intolerance compared with 55 [37%] of 150 with 0 or 1 episode), panic disorder (1/18 [6%] vs 23/150 [15%]), anxiety (8/16 [50%] vs 64/145 [44%]), or depression (5/17 [24%] vs 40/143 [28%]).

Correlations between the number of episodes of nonspecific intolerance and measures of psychiatric morbidity are shown in Figure 3. The number of episodes of nonspecific intolerance was significantly associated with the HAD scores for anxiety (p = .14; P = .04) and depression (p = .01; P = .005) but not with trait anxiety (p = .12; P = .07). Any intolerance was associated significantly with the HAD anxiety score (p = .17; P = .01), HAD depression score (p = .14; P = .04). We found no significant associations between drug-specific intolerance and any measure of anxiety or depression (p = .09 for the HAD anxiety score; p = .04 for the HAD depression score; and p = .09 for trait anxiety).

The relations between the episodes of drug intolerance and clinical diagnoses of psychiatric disorders recorded in the clinic problem lists and the use of psychotropic drugs elicited by means of questionnaire are shown in Table 4. We found a significant association between psychiatric diagnoses recorded in problem lists and the number of episodes of nonspecific drug intolerance (Table 4) (χ² for trend, P = .02). Thus, psychiatric diagnoses were recorded for 7 (39%) of 18 patients with 4 or more episodes of nonspecific intolerance, 9 (19%) of 48 patients with 2 to 3 episodes; and 25 (15%) of 167 patients with 0 or 1 episode. We found a nonsignificant trend for the use of psychotropic drugs to increase with increasing episodes of nonspecific intolerance (4 [22%] in 18 patients with ≥4 episodes, 10 [21%] in 48 patients with 2 or 3 episodes, and 29 [17%] in 167 patients with 0 or 1 episode). We found no association between excess alcohol consumption and the number of episodes of intolerance of any category (Table 4).

**COMMENT**

We were able to identify and study 135 patients who had been intolerant of 2 or more antihypertensive drugs among the patients who attended our hospital hypertension clinic during 1 year. Two patients had as many as 11 episodes of drug intolerance, and 43 had more than 4 episodes. The phenomenon of intolerance to multiple antihypertensive drugs is therefore relatively common, at least in hospital practice. More than two thirds of these patients were women, a significant excess compared with the 50% of all patients attending the clinic who were women. We also found a significant relationship of multiple-drug intolerance with older age. Asymptomatic adverse reactions causing withdrawal of drug were uncommon. Most episodes of drug intolerance were symptomatic, and of these, 53% were categorized as drug specific (eg, persistent cough with an ACE inhibitor) and 47% as nonspecific (eg, edema with a loop diuretic). In a previous study,24 adverse effects causing withdrawal of antihypertensive drugs were considered drug specific in only 28% of cases, implying that as many as 72% of episodes of drug intolerance may be nonspecific.

The phenomenon of nonspecific adverse effects is illustrated well by the apparent adverse effects reported by patients taking only placebo treatment, termed adverse nondrug reactions by Reidenberg and Lowenthal.23 These symptoms are commonly ascribed to treatment by patients and physicians alike, although they occur frequently in perfectly healthy individuals who are tak-
In our patients, we found no relation between the number of episodes of intolerance in the past and the number of antihypertensive drugs prescribed currently, so that previously intolerant patients were recorded as supposedly receiving treatment with 2 or 3 drugs on average. Despite this, the blood pressure was higher by an average of 8/4 mm Hg in patients who had previously experienced 2 or more episodes of nonspecific drug intolerance, and 15/16 mm Hg in patients who had experienced 5 or more nonspecific episodes. Thus, multiple-drug intolerance was associated with inadequate blood pressure control and apparent treatment resistance, which could well cause higher morbidity and mortality due to hypertension. This suggests that multiple-drug intolerance is important and common. The inadequate blood pressure control, despite the similar intensity of drug therapy, also raises the question whether patients with a history of nonspecific drug intolerance may be incompletely compliant with the drug regimen that they are supposedly following.

Psychiatric morbidity is particularly common in hypertensive patients,12-18 as shown by significant associations of hypertension with panic disorder,12,13 panic attacks,12,14 anxiety,12,15-17 and depression.15,18 Psychiatric problems have been suggested as a cause of multiple-drug intolerance,9,11 and most physicians probably believe that this is so. However, very little evidence exists for this. Our findings indicate that multiple-drug intolerance is indeed related to psychiatric morbidity, with the total number of episodes of drug intolerance of all types strongly and significantly related to panic attacks, anxiety, and depression. Moreover, this was explained entirely by a relation between nonspecific intolerance and psychiatric problems. Episodes of nonspecific intolerance were significantly associated with panic attacks (dichotomous variable), with depression (dichotomous variable), and with anxiety (measured as a continuous variable). We found no significant association with panic disorder, perhaps because this diagnosis rests on the application of an arbitrary diagnostic threshold, which is not the case for panic attacks. In contrast, we found no significant association between episodes of intolerance that were specific to the drug implicated and any measure of psychiatric morbidity.

Why might apparent intolerance to antihypertensive drugs, characterized by symptoms that are not typical of the offending drug, be linked to psychiatric morbidity? This study was designed to determine whether such an association exists, although not to explain it. Nevertheless, several possibilities deserve consideration. Repeated episodes of intolerance to antihypertensive drugs could possibly cause psychiatric morbidity. Perhaps repetitive experience of adverse effects that are unpleasant or frightening could precipitate depression, anxiety, or panic attacks. Multiple-drug intolerance was associated with inadequate blood pressure control, and depression, anxiety, or panic could conceivably develop if the patients were concerned about this. Inadequate blood pressure control also predisposes to cardiovascular complications, which could cause psychiatric morbidity. Panic attacks are indeed associated with cardiovascular complications, and particularly with ischemic heart disease, in hypertension.26 These possibilities all imply that repeated episodes of drug intolerance cause psychiatric morbidity directly or indirectly. If this were so, one might anticipate that psychiatric morbidity would be associated similarly with episodes of drug-specific and nonspecific intolerance. This was not the case. Nonspecific intolerance was strongly related to psychiatric morbidity, whereas drug-specific intolerance was not, although such episodes were actually slightly more common. This suggests that psychiatric problems were, on
balance, more likely to be the cause rather than the consequence of repeated episodes of drug intolerance, and particularly of episodes characterized by nonspecific symptoms that could not be attributed readily to the drug implicated.

How might psychiatric morbidity cause nonspecific drug intolerance? Patients with psychiatric problems might tend to ascribe any unfamiliar symptoms to their medication. Hypertensive patients who have depression may tend to focus on and amplify negative aspects of treatment. Patients with anxiety or panic attacks may actually be frightened of taking tablets. A further possibility is that patients with psychiatric problems actually misinterpret symptoms of their psychiatric illness as the adverse effects of drugs. Many of the symptoms described in episodes of nonspecific intolerance are common symptoms of psychiatric conditions. Low mood, lethargy, tiredness, mental slowness, poor concentration, blunted feelings, and loss of libido were often attributed to drug treatment but are common symptoms of depression. Sweating, dizziness, breathlessness, and a sense of impending collapse all featured in episodes of intolerance that were rated as nonspecific and are characteristic symptoms of generalized anxiety or panic attacks. Many symptoms of the adverse nonspecific reactions described by Reidenberg and Lowenthal are also common in depression, anxiety, and panic attacks. A third possibility is that biochemical changes associated with psychiatric morbidity might modulate thresholds for the onset of symptoms, and so increase the chance that antihypertensive drugs provoke adverse effects. However, psychiatric morbidity would then be associated with drug-specific intolerance as well as nonspecific intolerance, and that was not the case. A final consideration is that some common factor or characteristic may be associated with both psychiatric morbidity and intolerance to multiple drugs. For example, patients with an obsessional personality trait may be prone to development of depression and could also have a tendency to experience apparent adverse effects of drugs.

Whatever the explanation, the association of multiple-drug intolerance with psychiatric morbidity is undoubtedly important. In ordinary practice, newly prescribed antihypertensive drugs are commonly stopped within a relatively short time, and adverse effects are often blamed. However, observations in these open and uncontrolled surveys contrast starkly with the findings in large, long-term, double-blind placebo-controlled trials comparing the major classes of commonly prescribed antihypertensive drugs. In these properly controlled studies, the withdrawal rates because of intolerance to thiazide diuretics, β-blockers, ACE inhibitors, and calcium channel blockers are no different or little different from the withdrawal rates from placebo treatment. This finding suggests that drug-specific adverse effects contribute very little to withdrawals with these drug classes, and that nonspecific symptoms similar to those experienced with placebo treatment are a major factor in apparent drug intolerance. This is also likely to be true in uncontrolled studies and in ordinary medical practice. Nonspecific adverse effects that cause repeated stopping or changing of antihypertensive drugs may be associated with suboptimal blood pressure control and an increased risk for cardiovascular complications and death. In the present study, patients who were intolerant to multiple antihypertensive drugs had suboptimal blood pressure control compared with those without drug intolerance, confirming that patients with nonspecific adverse effects are particularly difficult to treat.

Psychiatric morbidity is much more common among hypertensive patients than normotensive people and is often overlooked in ordinary practice. In the present study, only 10 (17%) of 59 patients with an HAD depression score of 8 or more and only 4 (12%) of 32 with panic disorder had any psychiatric diagnosis recorded in their problem list. More of them were receiving psychotropic medication, 18 (31%) of 59 patients for depression and 8 (25%) of 32 for panic disorder, but important psychiatric morbidity may have been overlooked or left untreated in most patients with these problems. When faced with a hypertensive patient who has experienced intolerance to several different drugs, particularly with adverse effects that are not typical for the drugs prescribed, possible psychiatric factors should be considered and explored. Effective treatment of coexistent psychiatric disorders could increase the acceptability of antihypertensive drugs, and thus enhance blood pressure control and reduce the risk for cardiovascular complications. Effective drug treatments for depression, anxiety, and panic disorder are available, and patients may also benefit from cognitive or behavioral therapy, particularly if their medication intolerance extends to psychotropic drugs. Further research is needed to characterize the nature of the psychiatric morbidity in hypertensive patients with nonspecific intolerance to multiple drugs, to determine the mechanisms and to evaluate treatment strategies for this common problem.

Accepted for publication June 18, 2002.

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