Cardiovascular and Symptomatic Reduction Effects of Alprazolam and Imipramine in Patients with Panic Disorder: Results of a Double-Blind, Placebo-Controlled Trial

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Seventy-nine patients with panic disorder were randomized to an 8-week double-blind treatment with alprazolam, imipramine, or placebo. Patients kept daily records of panic attacks, activity, anxiety, sleep, and medication use. Weekly measures of anxiety, depression, somatic symptoms, fears, avoidance, disability, and improvement were obtained. All patients underwent a symptom-limited exercise treadmill and other cardiovascular measures. By physician and patient global assessment, patients receiving alprazolam or imipramine were significantly better than patients on placebo. The alprazolam effects were apparent by week 1; the imipramine effects by week 4. All groups showed significant reductions in anxiety, depression, somatic measures, and panic attack frequency. At 8 weeks, patients in the alprazolam group reported significantly less fear than patients in the other two groups. Subjects in the imipramine group showed a significant increase in heart rate and blood pressure.

PANIC DISORDER is a common and disabling problem. Epidemiologic data indicate that the lifetime prevalence rate for panic disorder is 1–2%.1,2 Until recently, the treatment of panic disorder has focused on the use of tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants. Many studies suggest that imipramine, for instance, is effective in reducing the intensity and frequency of panic attacks and phobic avoidance.3-5 A large multinational trial has established that, compared to placebo, alprazolam is also an effective antipanic and antiphobic agent.6

Although imipramine and alprazolam are both effective, they produce different cardiovascular side effects that might have implications for the long-term treatment of patients. Two studies have reported that patients with panic disorder may have increased cardiovascular mortality.7,8 One explanation for this finding is that panic disorder patients have elevations in one or more cardiovascular risk factors. We have previously reported that patients with panic disorder have higher than expected cholesterol levels9 and a lower level of fitness.10 Improvement in psychological function might be associated with reduced risk factor levels. Although the effects of tricyclics on cardiac rate and rhythm have been well studied, their effect on other cardiovascular risk factors is not known.11

The purposes of this study were (1) to compare the effectiveness of alprazolam, imipramine, and placebo to reduce symptoms associated with panic disorder with or without agoraphobia and (2) to determine and compare the cardiovascular effects of these three treatments.

Methods

Subjects and measurements

Subjects were recruited from the Stanford Anxiety Disorders Clinic and through the mass media for participation in the trial. The methods of recruitment and general characteristics of the population have been reported elsewhere.12 The study followed the methods of the mul-
ticenter trials described elsewhere except as noted be-
low.\textsuperscript{6,12} Subjects who met the following criteria were in-
vited for further evaluation: one panic attack or more per
week, not pregnant or lactating, no previous adequate
treatment with imipramine or alprazolam, no allergic re-
action to benzodiazepines or tricyclic antidepressants, and
willing to stop all psychoactive medications. Informed
consent was obtained from all subjects.

**Clinical assessment.** All interviewers were trained by
senior clinicians familiar with the Structured Clinical In-
terview for Diagnoses–Upjohn version (SCID–UP), fol-
lowing the procedures described elsewhere.\textsuperscript{6} All SCID-
UPs were video or audiotaped. A random sample of SCID-
UPs was reviewed by outside experts to determine that
the SCID-UP procedure was correctly followed. Dis-
agreements or difficulties with diagnosis were resolved
by consensus with senior clinicians. Patients needed to
meet the following criteria: have at least some sponta-
neous panic attacks, have panic attacks with four symp-
toms occurring during an attack, have at least one panic
attack each week for the last 3 weeks, not have an organic
cause for the panic attacks. If patients had a current
major depressive episode, then the panic attacks had to
develop before the current major depressive episode, and
if the patients had a past major depressive episode, then
their panic disorder needed to begin before the past major
depressive episode. Interviewers classified the patients
as having uncomplicated panic disorder if they exhibited
no clinically significant avoidance, panic disorder with
limited phobic avoidance if they had clinically significant
avoidance or endured with dread various situations or
places, or panic disorder with extensive phobic avoidance
if they had any generalized travel restriction, need for a
companion away from home, or markedly altered life-
style. Patients were excluded for a diagnosis of alcohol
or drug abuse or dependence, mania, cyclothymia, psy-
chotic disorder, obsessive-compulsive disorder, or acute
suicidality.

For patients meeting the screening and SCID-UP di-
agnosis, a history, physical examination, laboratory ex-
amination, and screen benzodiazepine level were ob-
tained. Patients with a history of seizures or head trauma,
or active renal, hepatic, cardiac, pulmonary, endocrine
or collagen disease were excluded.

**Self-report measures.** All subjects were asked to keep
a diary for each day in the study (including at least 1
week of baseline). For each panic attack they had, sub-
jects were asked to record when it occurred, how intense
it was, what symptoms accompanied it, what they were
doing, and when it ended. They were also asked to record
when they went to and got out of bed, and their average
anxiety level for the day on a scale from 0–10 (0 = no
anxiety and 10 = maximum anxiety). Only the total num-
ber of panic attacks per week was analyzed for this paper.

Subjects also kept a diary of any activities above and
beyond their usual activities. The physician reviewed
these diaries each week for completeness and face valid-
ity.

At baseline and each week, patients completed the SCL-
90, the Beck Depression Inventory, and a modified ver-
sion of the Marks/Mathews Fear Questionnaire.\textsuperscript{6} Two
scores were derived from the latter: the patients' main
fears, which represented the patients' rating of how much
fear/anxiety they experienced from their main fears on
a 0–10 scale (where 0 = not at all and 10 = extremely),
and total avoidance, which represented their total avoid-
ance on items similar to the agoraphobia fear scale on the
Marks/Mathews Fear Questionnaire. At 4 and 8 weeks,
patients rated their overall work and social disability on
a five-point scale, for which 1 = no complaint, normal
activity and 5 = symptoms radically change or prevent
normal work or social activities. They also rated their
global improvement since they had begun to take the
medication on a seven-point scale from very much better
(scored as −3) to very much worse (+3).

**Physician measures.** At each physician visit the fol-
lowing self-report measures were obtained: self-report of
panic attacks, classified as spontaneous panic attacks
(sudden anxiety attacks with three or more symptoms
that occur with little or no provocation), minor sponta-
neous attacks (sudden anxiety episodes with only one or
two symptoms that occur with little or no provocation),
situational anxiety episodes (those episodes with one or
two symptoms that occur in anticipation of facing a feared
situation), or situational panic attacks (those attacks with
three or more symptoms occurring while a subject is in
or anticipating a phobic situation). For this study, phy-
sician-obtained self-report measures were only used when
panic attack diaries were not returned (approximately
10% of total encounters). Physicians also completed the
Hamilton Anxiety Rating Scale (HAM-A),\textsuperscript{6} a rating of
the physician's overall impression of the patient from 1
= normal, not at all ill to 7 = among the most extremely
ill patients. After medication was begun, physicians rated
the patient's improvement on a seven-point scale from
very much improved (−3) to very much worse (+3), and
completed a SAFTEE-UP event form\textsuperscript{14} noting any side-
effects.

**Cardiovascular measures.** All eligible subjects under-
went a cardiovascular examination which included an ECG
and a symptom-limited treadmill using a modified Balke
protocol.\textsuperscript{10} These tests were repeated at the end of the
trial. After a 5-minute rest, supine blood pressure was
measured in the right arm. Fifth phase Korotkoff sounds
were used for diastolic pressure. Blood pressure was
measured three times. The average of the second and
third readings was used in all data analyses. Standing
blood pressure was obtained immediately upon standing
using the same criteria. Technicians measuring blood pressure were trained in the proper measurement technique using the American Heart Association method. Heart rate was measured using an R-R wave detection program. The average heart rate represented the heart rate for the last 10 seconds of resting or the last 10 seconds of each stage on the treadmill.

*Ambulatory heart rate measures.* After the initial screening, medical examination, and treadmill, subjects wore a Vitalog MC-2 Monitor for up to 3 days and nights. This device measures the level of activity and heart rate during the monitoring period. The MC-2 is a solid state microcomputer that measures $4 \times 8 \times 12$ cm, weighs 0.5 kg, and is worn on the belt. The total number of heartbeats/minute during 1-minute periods was stored in one of 64 categories, each representing two beats/minute over a range of 40–160 beats/minute with two additional categories for heart rates <40 and for heart rates >161. At the end of the data collection, the memory was loaded into a minicomputer for storage and analysis. Details of average daily heart rate (HR) and sleep (sleep HR) analysis procedures are reported elsewhere.15

*Plasma lipids.* Fasting plasma lipids were obtained on all subjects before and after treatment. Lipids were analyzed using indirect β quantification.16

*Plasma drug levels.* Plasma drug levels were obtained on all subjects at baseline and just before the 4- and 8-week levels. The analysis included alprazolam,17 imipramine, N-desmethyliimipramine,18 diazepam,19 and desmethyl diazepam.19

*Medications.* Patients were randomized to placebo, alprazolam, or imipramine. Medications were dispensed in identical capsules of placebo, alprazolam 1 mg, or imipramine 30 mg. Medication was increased until patients were free of panic attacks, suffered from unpleasant side effects, or were taking 10 tablets per day.

*Data analysis*

For all subjects who remained in the study for 8 weeks, a one-way ANOVA was done on change scores from baseline to 1 week, 4 weeks, and 8 weeks. When the overall $F$ for the change scores indicated significant ($p < 0.05$) differences among groups, between-group changes were tested separately for each group with a two-tailed $t$-test for independent samples. Thus, dropouts were excluded from the data analysis. In addition, the change scores from baseline to 8 weeks were reanalyzed for only those subjects who did not have evidence for serum benzodiazepine, alprazolam, or imipramine at baseline or did not have serum levels of a drug that should not have been taken at 4 or 8 weeks.

*Subject demographics and dropouts.* Demographic information on the 79 subjects randomized to the trial can be seen in Table 1. There were no significant differences among the three groups on any of the demographic variables. By 8 weeks, 8% (2/26), 19% (5/27), and 23% (6/26) of the subjects in the alprazolam, imipramine, and placebo groups, respectively, had dropped out.

*Medication use.* The eight-week medication use for the three groups was: 3.7 (range, 1–8), 4.9 (range, 1–9), and 6.8 (range, 2–10) pills/day for alprazolam, imipramine, and placebo, respectively. These doses were equivalent to 3.7 (range, 1–8) mg/day of alprazolam and 147 (range, 30–270) mg/day of imipramine. Patients in the placebo group were taking significantly more pills per day than were patients in the alprazolam group.

*Plasma drug levels.* Four- and 8-week alprazolam levels were available on 21 of 26 subjects. Excluding one subject who had a zero level at 8 weeks, the mean 4- and 8-week levels of alprazolam were 40.3 (range, 4–95) and 54.5 (range, 12–184), respectively. Eight-week imipramine and N-desmethyliimipramine levels were available on 20 of 27 subjects randomized to imipramine. The 8-week combined imipramine and N-desmethyliimipramine levels were 96.7 (range, 11–467).

Table 2 provides the baseline and change from baseline for weeks 1, 4, and 8 for the psychological outcome measures. The number of subjects in each of these analyses were 24, 20, and 20 for the alprazolam, imipramine, and placebo groups, respectively. If the overall $F$ indicated significant differences among groups on the change scores, then independent $t$-tests were run between the various groups. Any significant differences are indicated in the table. The overall $F$ for the baseline to 8-week change score was significant for all variables. Furthermore, there was a significant within-group improvement from baseline to week 8 for all groups on all variables except for the frequency of panic attacks per week for the placebo

<table>
<thead>
<tr>
<th>Table 1. Subject demographics</th>
<th>Alprazolam (N = 26)</th>
<th>Imipramine (N = 27)</th>
<th>Placebo (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male (%)</td>
<td>Female (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>70</td>
<td>69</td>
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<tr>
<td>Mean age at screening (years)</td>
<td>35.0</td>
<td>34.1</td>
<td>34.9</td>
</tr>
<tr>
<td>Marital status</td>
<td>Never married (%)</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Married (%)</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Separated/divorced%</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Employment status</td>
<td>Employed (%)</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Unemployed (%)</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Retired (%)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>7.2</td>
<td>5.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Panic disorder (type)</td>
<td>Uncomplicated (%)</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Limited (%)</td>
<td>58</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Extensive (%)</td>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>
group, which did not change significantly from baseline to 8 weeks.

**Total panic attacks per week.** There was a reduction in panic attack frequency for all groups. The only significant difference among the groups was for alprazolam: at week 1, patients in the alprazolam group showed significantly greater reductions in panic attacks than placebo or imipramine. Even though the results were not significantly different, subjects in the placebo group were having four panic attacks per week at week 8, while subjects in the alprazolam and imipramine groups were having about one panic attack per week. Furthermore, during the eighth week, 63% (15/24), 71% (19/21), and 50% (10/20) of the alprazolam, imipramine, and placebo subjects had no panic attacks.

More active patients may be more likely to have panic attacks than less active patients. To adjust for this factor, and to determine if successful treatment increased number of activities, the diaries were analyzed for total number of excursions beyond customary activity recorded each week. There were no differences among the groups at baseline or at 8 weeks for numbers of excursions and there were no significant intragroup changes.

**Anxiety.** On the daily anxiety measure obtained from the diaries, patients in the alprazolam group reported that they had significantly greater reductions in anxiety by week 1 compared with the other groups. This pattern was similar on the HAM-A scale completed by physicians: patients in the alprazolam group had significantly greater reductions in anxiety than the placebo group by week 1.

**Depression.** Changes in depression paralleled those of anxiety but there were no significant differences among the groups. At baseline the mean levels of depression on the Beck were 7.5, 5.8, and 6.5 and on the HAM-A were 11.2, 10.9, and 10.9 for the alprazolam, imipramine, and placebo groups, respectively.

**SCL-90.** In general, there were no differences among the three groups at 8 weeks: all groups showed significant improvement on somatic, obsessive-compulsive, anxiety, and phobic measures. However, at 4 weeks the alprazolam subjects had significantly greater reductions in somatic symptoms than either the imipramine or placebo groups.

**Global improvement.** The greatest differences between medication and placebo were in the patient and physician global impressions of improvements. Patients on alprazolam and imipramine reported significantly greater improvement than patients on placebo at 4 and 8 weeks. Physicians also felt that patients in these groups were significantly better than placebo patients at 4 and 8 weeks. In the alprazolam group, patients also reported being significantly better than the other groups by week 1.

**Disability.** All groups showed significant improvement in work, social, and family disability measures. The alprazolam group reported significantly greater reductions in disability than the placebo group at 4 and 8 weeks. At 8 weeks, subjects in the imipramine and alprazolam groups both reported levels indicating that their symptoms were not interfering with their work, while subjects in the placebo group reported that the symptoms continued to interfere.
Table 3. Treadmill outcome data

<table>
<thead>
<tr>
<th></th>
<th>Alprazolam (24)</th>
<th>Imipramine (20)</th>
<th>Placebo (20)</th>
<th>Overall ANOVA for ( \Delta ) score</th>
<th>Group differences (p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>71.2 ± 10.3*</td>
<td>69.4 ± 9.6</td>
<td>70.9 ± 12.3</td>
<td>90.1 ± 12.4</td>
<td>75.4 ± 11.8</td>
</tr>
<tr>
<td>Standing</td>
<td>86.6 ± 16.6</td>
<td>88.4 ± 17.1</td>
<td>84.4 ± 15.2</td>
<td>105.8 ± 17</td>
<td>88.6 ± 13.4</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Supine</td>
<td>114.4 ± 13.1</td>
<td>109.3 ± 8.3</td>
<td>117.2 ± 13.2</td>
<td>125.9 ± 9.9</td>
<td>119.3 ± 15.6</td>
</tr>
<tr>
<td>Standing</td>
<td>117.6 ± 14.2</td>
<td>109.1 ± 17.0</td>
<td>120.3 ± 14.3</td>
<td>122.9 ± 15.7</td>
<td>125.7 ± 14.2</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>72.9 ± 8.3</td>
<td>71.14 ± 7.08</td>
<td>73.9 ± 8.4</td>
<td>81.18 ± 8.9</td>
<td>79.9 ± 12.0</td>
</tr>
<tr>
<td>Standing</td>
<td>77.2 ± 7.9</td>
<td>85.33 ± 81.7</td>
<td>80.4 ± 9.3</td>
<td>83.07 ± 6.9</td>
<td>83.8 ± 8.5</td>
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<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 METs</td>
<td>120.8 ± 23.4</td>
<td>112.9 ± 17.6</td>
<td>120.6 ± 19.3</td>
<td>127.5 ± 13.1</td>
<td>127.5 ± 22.3</td>
</tr>
<tr>
<td>6 METs</td>
<td>128.3 ± 26.2</td>
<td>128.6 ± 19.3</td>
<td>131.9 ± 18.2</td>
<td>137.9 ± 14.8</td>
<td>138.3 ± 24.6</td>
</tr>
<tr>
<td>8 METs</td>
<td>146.1 ± 28.2</td>
<td>142.9 ± 18.4</td>
<td>148.1 ± 19.5</td>
<td>151.9 ± 17.2</td>
<td>150.1 ± 22</td>
</tr>
<tr>
<td>Max heart rate</td>
<td>171.3 ± 23.1</td>
<td>167.7 ± 23.0</td>
<td>177.1 ± 15.8</td>
<td>176.5 ± 14.4</td>
<td>177.2 ± 13.4</td>
</tr>
<tr>
<td>Max METs</td>
<td>12.4 ± 2.7</td>
<td>13.3 ± 2.6</td>
<td>12.1 ± 2.1</td>
<td>12.4 ± 2.9</td>
<td>11.6 ± 3.7</td>
</tr>
<tr>
<td>Ischemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

* Mean ± SD.

Avoidance. At 8 weeks, patients in the alprazolam group reported significantly greater reductions in their fear of their main phobia than patients in the placebo group. However, there were no significant differences in reported avoidance among the three groups.

Cardiovascular measures

At 8 weeks, subjects in the imipramine group showed a significant and dramatic increase in resting and standing heart rate (Table 3) compared with the other two groups. Compared to alprazolam, imipramine significantly raised systolic and diastolic blood pressure; compared to placebo, imipramine significantly raised diastolic blood pressure.

At 8 weeks, on the exercise treadmill the heart rate at 4 and 6 METs (metabolic units at rest) was significantly higher for imipramine than for any of the other two groups. By max METs, heart rates were not different among the three groups. There were no complex arrhythmias or ST-segment depression at max METs or during recovery for any of the subjects.

There were no significant differences among groups for lipids or triglycerides (Table 4).

As measured by the ambulatory heart rate monitor, there was a significant increase in average daily and sleep heart rate for subjects taking imipramine compared to the other two groups (\( F = 20.0; df = 2, 42; p < 0.0001 \) and \( F = 36.5; df = 2, 40; p < 0.0001 \)). Waking heart rate changes from baseline to 8 weeks for the subsample of patients with complete heart rate data were \(-3.9, +15.5, \) and \(+2.6 \) for alprazolam (18 patients), imipramine (17 patients), and placebo (10 patients), respectively. Sleeping heart rate changes from baseline to 8 weeks were \(-1.4, +14.1, \) and \(-1.4 \) for the same groups and patients respectively.

Prohibited drug use. Of the 24 subjects who completed 8 weeks in the alprazolam group, two were found to be taking prohibited drugs at baseline, 4, or 8 weeks. Of the 22 subjects in the imipramine group, four were found to be taking prohibited drugs at baseline, 4, or 8 weeks, and one had no detectable imipramine levels. Finally, of the 20 subjects in the placebo group, seven were found to be taking prohibited drugs at baseline, 4, or 8 weeks. The analyses of the changes from baseline to 8 weeks were redone with these subjects excluded. On reanalysis, the subjects taking alprazolam now had significantly fewer panic attacks than those taking imipramine or placebo. However, there was no longer a significant difference among the groups on total agoraphobic avoidance. On the treadmill, the imipramine subjects no longer had significantly higher heart rates than the alprazolam group at 6 METs. Otherwise results remained the same for both symptomatic and cardiovascular variables in Tables 1, 2, and 3.

Discussion

A striking finding of this study was the improvement in all three groups across a number of psychological domains. By 8 weeks, subjects in all three groups were experiencing significantly fewer anxiety symptoms, less avoidance and disability, and a large reduction in the frequency of panic attacks. However, on both physician and patient global measures of improvement, subjects taking alprazolam or imipramine were judged as doing better than subjects taking placebo. Furthermore, when
subjects taking the drugs they were not supposed to are eliminated, alprazolam had a significantly greater effect on reducing number of panic attacks than did placebo, and the results for both alprazolam and imipramine remained generally the same. These results are consistent with those of studies that have evaluated alprazolam or imipramine independently or together.\(^3\)\(^-\)\(^6\)

The strong placebo effects on reducing panic attack frequency have been reported by other authors.\(^6\)\(^-\)\(^8\) This placebo response might be due to subject selection: patients recruited largely by the mass media may not be as symptomatic as other patients and our strict diagnostic and inclusion criteria may have excluded more impaired patients. The intensive medical and psychological examination of patients and the use of daily self-report logs might also have contributed to their improvement. Although subjects in the placebo group did improve, they continued to have more disability and impairment from their symptoms than did the other two groups. Furthermore, analysis of drug levels revealed that 30% of subjects in the placebo group took prohibited medication during treatment.

At 8 weeks there were few significant differences between imipramine and alprazolam on any of the psychological measures, although patients on alprazolam reported less anxiety or disability than did patients on imipramine. In comparing alprazolam and imipramine, it appears that alprazolam had a more rapid onset of effect. Subjects on alprazolam judged themselves to be significantly less anxious by week 1. The mean dosage of prescribed medication (147 mg) is lower than reported in some studies. However, several reports have suggested that very low doses or plasma concentrations of imipramine and N-desmethylinimipramine can be effective in alleviating avoidance and panic attacks.\(^21\)\(^-\)\(^24\) Furthermore, 71% of subjects in the imipramine group were panic-attack-free at 8 weeks, compared, for instance, to 73% in a study where the mean dosage was 193 mg and the total imipramine and N-desmethylinimipramine was 147 mg.\(^25\)

Imipramine had a significant effect on a number of cardiovascular variables. Although the effects of imipramine on increasing heart rate are well known, the magnitude of changes is greater here than has been previously reported.\(^26\) Compared to alprazolam or placebo, heart rate was significantly increased at resting, standing, and at 4 and 6 METs. By 8 METs the heart rates were no longer significantly different, presumably because sympathetic stimulation had overwhelmed the anticholinergic effects of the imipramine.

Imipramine also raised both systolic and diastolic blood pressures. This blood pressure finding is somewhat surprising. Imipramine has previously been reported to produce orthostatic hypotension in a subgroup of patients and to have no effect on blood pressure in patients without this complication.\(^26\) A preliminary analysis of the resting blood pressure of the patients not taking prohibited medications and having serum evidence of taking the prescribed medication was obtained in our psychophysiology laboratory. Four blood pressure measurements were obtained 4.5 minutes apart using an automated blood pressure reading device (Accuror 2, Datascope Corporation) on each subject. Subjects taking imipramine had significantly higher blood pressures posttreatment than subjects in the alprazolam or placebo groups on all measures. The higher blood pressures on standing in all groups both pre- and posttreatment is also an unusual finding in a young, predominantly female population. Cardiovascular dysregulation has been noted previously in this patient population and a subgroup of patients has been noted to have a significant reaction to imipramine even at very low doses.\(^25\) This reaction is characterized by increased signs and symptoms suggestive of sympathetic arousal. During such reactions, blood pressure is usually elevated. In most studies, 25% or more patients report this reaction to imipramine and most studies have a higher dropout rate in the imipramine group than reported in this study. Therefore, it is possible that subjects with an exaggerated sympathetic response to imipramine remained in this study, thus accounting for the blood pressure elevation.

The lack of change in lipids between pre- and posttreatment is also of interest. Panic disorder patients have been shown to have a higher-than-expected prevalence of hyperlipidemia\(^26\) and one would expect that symptomatic improvement would be associated with reduction in lipids.

Our data further complicate the already complex issue...
of which medications should be used to treat panic disorder. Alprazolam and imipramine are clearly effective, yet placebo effects are striking. Psychological interventions mediating the placebo effects need to be developed and evaluated. Alprazolam seems to have little effect on the cardiovascular system; imipramine may increase blood pressure and has a dramatic effect on heart rate. Cardiovascular risk factors need to be evaluated in all panic disorder patients. The heart rate and blood pressure of patients on imipramine need to be carefully monitored.

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