Should Anxiety and Insomnia Influence Antidepressant Selection: A Randomized Comparison of Fluoxetine and Imipramine

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Background: The more sedating antidepressants are often recommended for patients presenting with anxiety or insomnia. We examine whether baseline anxiety or insomnia symptoms (1) show differential response to fluoxetine or imipramine or (2) predict differences between drugs in overall clinical response or likelihood of medication discontinuation.

Method: 336 health maintenance organization primary care patients beginning antidepressant treatment for depression were randomly assigned to an initial prescription for fluoxetine or imipramine. All subsequent care (medication dosage, change, or discontinuation) was managed as usual by the primary care physician. The 17-item Hamilton Rating Scale for Depression (HAM-D) and the Hopkins Symptom Checklist (SCL) anxiety and depression subscales were administered prior to randomization and 1 month later.

Results: Rates of improvement in insomnia (HAM-D insomnia items), agitation (HAM-D agitation item), and anxiety (SCL anxiety subscale) were essentially identical in the two treatment groups. Baseline level of insomnia did not predict significant differences between randomization groups in improvement in overall HAM-D score ($p = .44$) or SCL depression subscale ($p = .44$). Similarly, baseline level of anxiety did not predict significant differences in improvement in HAM-D ($p = .19$) or SCL depression subscale ($p = .31$). Patients assigned to fluoxetine were significantly less likely to change or discontinue antidepressant medication during the first month, but this difference did not vary according to baseline level of insomnia ($p = .68$) or anxiety ($p = .25$).

Conclusion: Among patients with moderate depression, baseline levels of insomnia or anxiety should not influence the choice of fluoxetine or imipramine as an initial antidepressant.

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Experimental comparisons of different antidepressant drugs typically find equal efficacy for relief of depressive symptoms.[1,2] The absence of mean differences among treatments in randomized trials, however, does not necessarily imply equal benefit for individuals. Because a significant minority of patients initiating antidepressant treatment either discontinue treatment due to adverse events[3] or fail to respond,[1,2] selection of an initial antidepressant drug deserves considerable attention. Expert guidelines typically advise that initial drug choice should be guided by prior treatment history and expected side effects.[4,5] Guidelines and expert recommendations have often recommended a more sedating drug (such as a tricyclic antidepressant) for patients with significant anxiety or insomnia.[5,6]

While selection of an antidepressant drug based on sedating or activating effects may be reasonable, little experimental evidence is available to support this recommendation. In studies conducted during the tricyclic drug era,[7,8] baseline anxiety symptoms have not predicted differential response to more sedating or activating drugs. Tollefson and colleagues[9] analyzed pooled data from 19 randomized trials comparing fluoxetine with placebo or tricyclic antidepressants. In the comparison of fluoxetine with tricyclic antidepressants, the presence of baseline anxiety symptoms did not predict differential efficacy or differential rates of treatment discontinuation due to adverse events. In a second report,[10] Tollefson and colleagues compared response to fluoxetine and imipramine among outpatients with agitated depression. The two treatments produced similar rates of symptomatic improvement, but more patients discontinued imipramine because of adverse events.

In a randomized comparison of fluoxetine and trazodone, Beasley and colleagues[11] reported clear differences in adverse event profiles (more frequent activating effects for fluoxetine, more frequent sedating effects for trazodone), but no differences in treatment discontinuation rates because of activating or sedating effects.

Data from conventional randomized trials, however, may not necessarily generalize to everyday practice. Typical randomized trial procedures, such as strict eligibility criteria and placebo washout, select patients who are more severely depressed, younger, less medically ill, and more likely to comply with treatment than those seen in primary care or community psychiatric practice. Frequent follow-up visits and specific treatment protocols may reduce the influence of adverse events on dose adjustment or treatment discontinuation. Differences in side effect profiles may have greater impact in everyday practice where follow-up is less intensive and treatment discontinuation more frequent.[3,12,13]

This report will use data from a large primary care–based randomized trial to examine how initial symptom patterns predict early response to fluoxetine or imipramine. Specific questions to be addressed include:

1. Does initial prescription of fluoxetine or imipramine lead to different effects on insomnia or anxiety symptoms?
2. Do baseline levels of insomnia or anxiety predict differences in overall response of depressive symptoms to fluoxetine or imipramine?
3. Do baseline levels of insomnia or anxiety predict differential discontinuation of treatment with fluoxetine or imipramine?

METHOD

Data for this report were drawn from a large randomized trial comparing the effectiveness and cost of fluoxetine, imipramine, and desipramine among health maintenance organization (HMO) primary care patients. Methods of the trial are described in detail elsewhere[14,15] and will be summarized here.

Patients were enrolled from selected primary care clinics of Group Health Cooperative of Puget Sound, a staff-model HMO. Enrollment procedures were designed to select participants broadly representative of patients treated for depression in primary care. At participating clinics, all primary care physicians were asked to refer any adult patient beginning antidepressant treatment for depression if both physician and patient would consider random assignment of the initial medication. Need for antidepressant treatment was based strictly on the referring physician's judgment regardless of medical comorbidity or severity of depression. Study personnel were immediately available (on-site or by telephone) to assess the following exclusion criteria: use of antidepressants in the prior 90 days, current alcohol abuse, current psychotic symptoms, history of mania, current pregnancy, or medical conditions or use of medications that might contraindicate use of a tricyclic antidepressant. After complete description of the study to potential participants, written informed consent was obtained.

Eligible and consenting patients were randomly assigned to begin treatment with either desipramine, fluoxetine, or imipramine, and randomization was stratified according to presence/absence of current major depression by using the Structured Clinical Interview for DSM-III-R (SCID) (see below). Neither patients nor referring physicians were blinded to treatment assignment, as blinding would preclude typical clinical management in primary care.

All decisions regarding antidepressant management (initial dose, dosage changes, treatment discontinuation, switch to a different antidepressant) were made by patients and treating physicians as in usual practice.

Baseline assessment (conducted prior to randomization) included (1) a structured interview rating of the 17-item version of the Hamilton Rating Scale for Depression (HAM-D)[16] adapted from Williams.[17] (While this instrument has demonstrated test-retest reliability at least equal to that of the traditional clinician-rated scale,[18] the telephone version may yield somewhat lower scores than the traditional unstructured HAM-D.[18]) and (2) anxiety and depression subscales of the Hopkins Symptom Checklist (SCL), a standard self-rated measure of current psychiatric symptoms.[19] Each measure was repeated at 1, 3, 6, 9, 12, 18, and 24 months after randomization. Because activating or sedating effects of antidepressants were believed to have their greatest potential impact during early treatment, this report focuses on data from the 1-month follow-up assessment. Follow-up interviewers were blinded to initial treatment assignment and current medication use during assessment of outcome data reported here. After the assessment of clinical and functional outcomes, interviewers did inquire about current antidepressant use and possible adverse events.

Approximately 16% of baseline assessments and 97% of follow-up assessments were conducted by telephone (with the remainder conducted in person). A test-retest reliability study found excellent agreement between in-person and telephone administration of depression measures using independent, blinded raters.[18]

Primary comparisons in the report presented here include patients initially assigned to treatment with fluoxetine or imipramine. Those assigned to desipramine were excluded in order to allow a clearer comparison of a drug (imipramine) thought to be more sedating with a drug (fluoxetine) thought to be more activating.

Analyses of clinical outcomes were based on initial medication assignment or intent to treat.[20] Patients discontinuing treatment or switching to a different antide-

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Fluoxetine (N = 160)	Imipramine (N = 176)
Median age (range), y	41 (19–83)	42 (18–82)
% Female	74%	70%
Mean HAM-D-17 score (SD)	13.33 (2.54)	13.23 (2.85)
% With DSM-III-R major depression	67%	70%
Mean SCL depression score (SD)	2.08 (0.80)	2.03 (0.78)
Mean SCL anxiety score (SD)	1.14 (0.78)	1.17 (0.79)

pressant were analyzed according to initial randomization and were not excluded, since we view these events as consistent with our goal of examining all consequences of initial medication choice. Stated otherwise, these analyses examine the outcomes of an *initial prescription* for fluoxetine or imipramine—not the outcomes of continued treatment with either of these drugs. Univariate comparisons were performed using t tests for semicontinuous variables and chi-square for categorical variables. The presence of differential treatment effect was examined using an interaction term (presenting symptoms-by-treatment assignment) in the appropriate statistical model (linear regression for semicontinuous variables, logistic regression for dichotomous variables).

RESULTS

Study Sample

During a 28-month enrollment period, 621 patients were referred by participating physicians, 42 were ineligible, and 43 refused to participate, yielding a final sample of 536 patients randomly assigned to desipramine (N = 181), fluoxetine (N = 173), or imipramine (N = 182). Of the 355 randomly assigned to fluoxetine or imipramine, 336 (95%) completed the 1-month follow-up assessment (160 assigned to fluoxetine and 176 assigned to imipramine). Those failing to complete the follow-up assessment did not differ significantly from completers in age, gender, or baseline HAM-D score. Noncompleters did have significantly lower baseline scores on the SCL depression subscale (p = .002) and marginally lower scores on the SCL anxiety subscale (p = .06).

Baseline characteristics of patients assigned to fluoxetine and imipramine are displayed in Table 1; the two groups did not differ significantly in demographic characteristics or symptom severity. At the baseline assessment, 68% satisfied SCID criteria for current major depression, and an additional 7% satisfied criteria for dysthymia. Approximately 35% reported a duration of illness greater than 6 months, and 19% reported a duration of greater than 2 years. Approximately 75% reported previous episodes of depression, 33% reported previous treatment with antidepressant medications, and 7% reported prior hospitalization for depression.

Antidepressant doses were examined in two ways. First, we compared the proportion receiving at least 30 days of treatment at doses exceeding minimum levels recommended by the Agency for Health Care Policy and Research Depression Guideline Panel.[4] In the entire study sample, this proportion was 70% for those assigned to fluoxetine and 59% for those assigned to imipramine ($\chi^2 = 3.78$, p = .05). We next examined daily doses among those continuing the original antidepressant medication at the 1-month assessment (excluding those who stopped or discontinued the original medication). Mean daily doses were 21 mg for those assigned to fluoxetine and 104 mg for those assigned to imipramine.

Table 2. Short-Term Improvement (Baseline to 1-Month) in Insomnia, Agitation, and Anxiety Symptoms According to Initial Treatment Assignment

	Fluoxetine (N = 160)		Imipramine (N = 176)		t Test for Fluoxetine = Imipramine	
Assessment	Mean	SD	Mean	SD	t	p
HAM-D insomnia items						
Baseline	2.23	0.97	2.32	0.90		
1-Month	1.81	1.14	2.00	1.12		
Improvement	0.41	1.25	0.32	1.30	0.35	.55
HAM-D agitation item						
Baseline	1.12	1.04	1.12	1.16		
1-Month	0.96	1.26	0.97	1.16		
Improvement	0.16	1.49	0.16	1.59	0.01	.98
HAM-D anxiety factor						
Baseline	4.92	1.61	4.73	1.85		
1-Month	3.53	1.88	3.75	1.98		
Improvement	1.39	2.22	0.98	2.5	1.55	.12
SCL anxiety subscale						
Baseline	1.16	0.79	1.18	0.79		
1-Month	0.44	0.54	0.54	0.65		
Improvement	0.71	0.73	0.65	0.77	.68	.41

Do insomnia or anxiety symptoms show a differential response?

Our first set of analyses examined the course of insomnia and anxiety symptoms among patients initially treated with fluoxetine or imipramine. These comparisons included the total HAM-D insomnia score (sum of initial insomnia, middle insomnia, and late insomnia items), the HAM-D agitation item, the HAM-D anxiety factor,[21] and the SCL anxiety subscale. Table 2 displays mean values for each of these measures at the baseline and 1-month assessments. All measures showed a statistically significant (p < .05) improvement between the baseline and 1-month assessments, and rates of improvement were similar in the fluoxetine and imipramine groups. A similar pattern was seen for each of the individual HAM-D insomnia items.

Do baseline insomnia or anxiety symptoms predict differences in overall response?

We next examined whether higher levels of insomnia at the baseline assessment predicted differential improvement in overall depressive symptoms. Patients were di-

Table 3. Short-Term Improvement (Baseline to 1-Month) in Depressive Symptoms According to Initial Treatment Assignment and Baseline Insomnia Level

Change in Group Scores	Fluoxetine (N = 160) Mean	SD	Imipramine (N = 176) Mean	SD	Difference	Interaction	95% CI	t[a]	p
HAM-D-17									
Low insomnia	3.33	4.08	2.18	4.28	1.15				
High insomnia	3.79	3.74	3.35	4.63	0.45	0.71	–1.09 to +2.51	.77	.44
SCL depression									
Low insomnia	1.38	0.80	1.11	0.81	0.27				
High insomnia	1.39	0.78	1.25	0.87	0.14	0.14	–0.21 to +0.49	.78	.44

[a]t test for the hypothesis that interaction = 0.

Table 4. Short-Term Improvement in Depressive Symptoms According to Initial Treatment Assignment and Baseline Anxiety Level

Change in Group Scores	Fluoxetine (N = 160) Mean	SD	Imipramine (N = 176) Mean	SD	Difference	Interaction	95% CI	t[a]	p
HAM-D-17									
Low anxiety	3.67	3.87	2.24	4.64	1.43				
High anxiety	3.41	3.99	3.20	4.28	0.21	1.22	–0.58 to +3.02	1.32	.19
SCL depression									
Low anxiety	1.14	0.65	1.02	0.76	0.13				
High anxiety	1.63	0.84	1.33	0.89	0.30	–0.18	–0.15 to +0.51	1.01	.31

[a]t test for the hypothesis that interaction = 0.

vided into approximately equal groups according to total HAM-D insomnia ratings at baseline (insomnia rating 2 or less vs. 3 or more). This resulted in 178 patients in the low insomnia group (85 assigned to fluoxetine and 93 to imipramine) and 158 in the high insomnia group (75 assigned to fluoxetine and 83 to imipramine).

Table 3 displays mean change in HAM-D-17 score and SCL depression subscale score according to baseline insomnia level and initial treatment assignment. Overall improvement in the fluoxetine group was slightly greater than that in the imipramine group. For both measures, this slight advantage for fluoxetine was greater among patients with lower levels of insomnia at baseline (the column in Table 3 labeled "Difference"). The significance of these differences was examined in a pair of linear regression models that predicted change in depressive symptoms (one model for HAM-D-17, one model for SCL depression subscale score) as a function of baseline insomnia (high vs. low insomnia groups defined above) and initial treatment assignment. In these models, the size of a differential effect (i.e., the "difference of differences") is indicated by the interaction between baseline insomnia group and treatment group (the column in Table 3 labeled "Interaction"). For both HAM-D-17 and SCL depression subscale, this interaction term was greater than zero, indicating a greater advantage for fluoxetine in the low insomnia group. In neither case, though, was the interaction coefficient significantly different from zero (i.e., the difference between fluoxetine and imipramine did not differ significantly according to level of insomnia at baseline).

Analyses of HAM-D remission rates (defined as HAM-D score of 7 or less at the 1-month assessment) yielded similar results. The difference in remission rates was greater among those with low baseline insomnia (38% for fluoxetine vs. 23% for imipramine) than among those with high baseline insomnia (21% for fluoxetine vs. 16% for imipramine). In a logistic regression model, however, the coefficient associated with the interaction of insomnia level and treatment group was not significantly different from zero (interaction coefficient = 0.35, SE = 0.53, p = .51).

We next examined the influence of baseline anxiety level on differential treatment response using a set of analyses parallel to those described immediately above. Patients were classified according to SCL anxiety subscale score at baseline (cutoff score = 1.0). This resulted in 166 patients in the low anxiety group (80 assigned to fluoxetine and 86 to imipramine) and 170 patients in the high anxiety group (80 assigned to fluoxetine and 90 to imipramine). Results are displayed in Table 4.

For both measures, the pattern of results was quite similar to that seen for the influence of insomnia. Patients assigned to fluoxetine showed slightly greater short-term improvement. For HAM-D scores, this difference was greater among those with lower levels of anxiety at baseline, while a small difference in the opposite direction was seen in the analysis of SCL depression scores (the column in Table 4 labeled "Interaction"). In a pair of linear regression models (one for HAM-D-17, one for SCL depression subscale) that predicted improvement in depressive

Figure 1. Frequency of Medication Change or Discontinuation During First Month of Treatment According to Initial Treatment Assignment and Baseline Insomnia Level

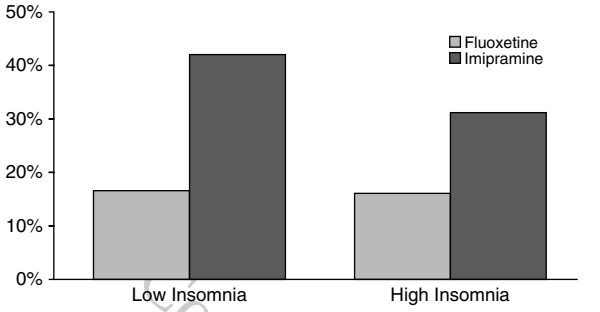
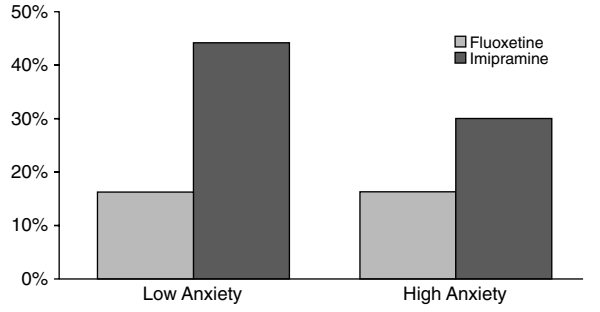


Figure 2. Frequency of Medication Change or Discontinuation During First Month of Treatment According to Initial Treatment Assignment and Baseline Anxiety Level



symptoms, neither interaction term was significantly different from zero. The likelihood of remission on the HAM-D (defined as a score of 7 or less) was slightly higher in the fluoxetine group, and this difference was larger in those with low anxiety at baseline (39% vs. 24%) than in those with high anxiety (21% vs. 14%). In a logistic regression model predicting likelihood of remission, the difference in remission rates (fluoxetine vs. imipramine) did not differ significantly according to baseline anxiety level (interaction coefficient = 0.20, SE = 0.53, p = .70).

Do baseline insomnia or anxiety symptoms predict differential treatment discontinuation?

Our final set of analyses examined the influence of initial anxiety or insomnia on the likelihood of either discontinuing the original antidepressant or switching medications prior to the 1-month assessment. Figure 1 displays the likelihood of medication change or discontinuation according to treatment assignment and baseline insomnia level. The likelihood of change or discontinuation was significantly higher for the imipramine group regardless of level of insomnia. In a logistic model predicting likelihood of change or discontinuation, the interaction of treatment assignment with insomnia level was associated with a coefficient of 0.19 (SE = 0.48), which was not significantly different from zero (p = .68). Figure 2 displays the likelihood of medication change or discontinuation according to treatment assignment and baseline anxiety level. Again the likelihood of change or discontinuation was markedly higher for the imipramine group regardless of baseline anxiety level. In a parallel logistic model, the interaction of treatment group with baseline anxiety level was again not significantly different from zero ($\beta = 0.61$, SE = 0.53, p = .25).

Secondary Analyses

Because the full study sample included patients with dysthymia and minor depression, we repeated each of the analyses in the subgroup of patients satisfying SCID criteria for DSM-III-R major depressive episode at baseline (N = 234) and for the subgroup with baseline HAM-D scores of 17 or more (N = 93). For both of these subgroups, the same pattern of results was seen. While most measures showed small differential effects (i.e., greater advantage for fluoxetine among those with lower baseline levels of anxiety or insomnia), none of these differential effects reached statistical significance (i.e., interaction terms not significantly different from zero).

Each of the above analyses was also repeated using data from the 3-month follow-up assessment. On average, both groups showed continued improvement in depressive symptoms. Otherwise, these analyses yielded results quite similar to those based on 1-month data. In general, any indicators of differential effect seen in the 1-month data were less apparent at the 3-month follow-up.

We also repeated the above analyses comparing patients classified as both high insomnia and high anxiety at baseline (N = 95) to those with scores below the median on both measures (N = 105). These analyses excluded patients with higher scores on one measure and lower scores on the other. The pattern of results was essentially identical. Most measures showed small differential effects (greater advantage for fluoxetine in patients with lower anxiety or insomnia), but none of these differential effects were statistically significant.

Because any influence of anxiety or insomnia symptoms might be masked by coadministration of anxiolytic or hypnotic drugs, we examined use of benzodiazepines and trazodone during the first month of treatment. The proportion filling any benzodiazepine or trazodone prescription was 7.6% (13 of 172) among those assigned to fluoxetine and 7.7% (14 of 182) among those assigned to imipramine. Exclusion of these 27 patients had no appreciable effect on any of the analyses reported above.

As mentioned above, these data were collected as part of a larger study that randomly assigned primary care patients to initial treatment with either desipramine, fluoxe-

tine, or imipramine. The analyses above focus on patients assigned to either imipramine (the most sedating of the three choices) or fluoxetine (the most activating). As reported elsewhere,[15] short-term outcomes in the desipramine group were intermediate between (and not significantly different from) those in the fluoxetine and imipramine groups. The series of analyses described above were also performed with patients assigned to desipramine. First, short-term changes in insomnia and anxiety symptoms among patients assigned to desipramine did not differ significantly from outcomes of patients assigned to imipramine or fluoxetine. Second, baseline insomnia or anxiety did not predict differential treatment response when the desipramine group was compared with either of the other groups. Third, likelihood of continuing the originally assigned medication in the desipramine group was similar to that in the imipramine group and significantly lower than that in the fluoxetine group. There was, however, no interaction between treatment assignment and baseline level of insomnia or anxiety. Details of these analyses are available on request.

DISCUSSION

In this randomized trial, presence of insomnia or anxiety symptoms at baseline did not predict significant differences in response to treatment with fluoxetine or imipramine. The two treatments led to similar short-term decreases in insomnia, anxiety, and agitation symptoms. Differences in overall relief of depressive symptoms between the fluoxetine and imipramine groups were not significantly related to baseline insomnia or anxiety symptoms. Similarly, differences in likelihood of continuing the originally assigned antidepressant were not related to initial insomnia or anxiety.

While this trial incorporated a number of unusual features, such a design is well suited to examining the consequences of initial drug selection in "real world" practice. Antidepressant treatment was managed as usual by treating physicians with no restrictions on doses, duration of treatment, or medication switches. Neither patients nor treating physicians were blinded to initial treatment assignment. Data analysis considered patients to be members of the initial randomization group regardless of subsequent medication changes or discontinuation. While these design features would not be appropriate in a study of drug efficacy (i.e., How do fluoxetine and imipramine compare when used under ideal conditions?), they are necessary to accurately study real world effectiveness (i.e., How does initial choice of antidepressant medication influence subsequent processes and outcomes of care?).

Interpretation of these findings must consider several limitations. First, this sample reflects the characteristics of an HMO primary care population: primarily middle-class patients with mild-to-moderate depression. Few patients in this sample were as severely ill as those typically enrolled in specialty clinic trials. These results may not necessarily generalize to a more severely ill or socioeconomically deprived sample. Second, we have no data on changes in depressive symptoms during the first few weeks of treatment. Consequently, we cannot exclude a significant differential treatment response at 1 or 2 weeks. Third, the doses of tricyclic antidepressants and the intensity of follow-up care in this sample are typical of those used in primary care and differ considerably from those recommended by specialists. Differential treatment effects might have emerged with higher doses. Frequency of medication changes or discontinuation might have been lower with more frequent follow-up contact. We would argue, however, that these data are relevant to the bulk of real world antidepressant treatment in primary care. Fourth, we are unable to examine the effects of specific anxiety disorders (e.g., panic disorder, generalized anxiety disorder) on differential treatment response. Fifth, these results might not generalize to other sedating antidepressants. Finally, these data do not address other clinical characteristics that may predict differential response to antidepressant drugs such as the presence of atypical depressive symptoms, psychotic symptoms, or comorbid medical illness.

These data cannot exclude the possibility of a small differential treatment response. For three of the four measures of overall improvement (Tables 3 and 4), the difference between the fluoxetine and imipramine groups was consistent with a differential effect (e.g., no difference between fluoxetine and imipramine in those with high insomnia/anxiety and a slight—but not significant—difference favoring fluoxetine in those with low insomnia/anxiety). Were our sample size four times as large, some of these differences would have approached statistical significance at the .05 level. Based on the estimates from this sample (e.g., difference of 1.2 points on the 17-item HAM-D), it is unlikely that any differential response would be clinically important. While some of our findings may suggest a slight differential effect, we found no clinical subgroup in which imipramine appeared superior to fluoxetine. For example, Figure 1 suggests that patients with higher levels of insomnia or anxiety were less likely to discontinue imipramine than were patients presenting with lower levels of insomnia or anxiety. Figure 1 also shows, however, that patients assigned to fluoxetine were less likely to discontinue medication regardless of presenting symptoms.

We should emphasize that our analyses include those patients discontinuing or switching from the originally assigned medication. The substantial minority of patients switching from imipramine to other antidepressants (including fluoxetine) were analyzed according to initial assignment. While this strategy may appear at first unusual, it is necessary to avoid significant bias. Because likeli-

hood of medication switches or discontinuation was significantly higher in the group beginning treatment with imipramine, exclusion of dropouts or crossovers would selectively remove the more difficult-to-treat patients from the imipramine group. Our design views medication changes or discontinuation as important consequences of initial treatment choice rather than sources of contamination. Because traditional clinical trials typically exclude these dropouts and crossovers, such studies cannot accurately examine the consequences of initial medication choice in real world practice. While our strategy may be well suited to the study of real world treatment decisions, it may not be appropriate for study of pure pharmacologic effects. We have performed secondary analyses in the sample of patients continuing the originally assigned medication. These analyses addressed our first two study questions and yielded results quite similar to those reported above: no differential improvement in anxiety or insomnia symptoms and no significant interaction between treatment group and baseline level of anxiety or insomnia.

Our findings do not support the historic recommendation[5,6] that the presenting symptoms of insomnia or anxiety should guide initial antidepressant selection in primary care. These findings are consistent with those of Tollefson et al.[9] in moderately to severely depressed psychiatric outpatients. Symptoms of insomnia, agitation, and anxiety showed essentially identical early improvement in the two treatment groups. Among the subgroups for whom the more sedating medication has been recommended[5,6] (high baseline insomnia or anxiety), overall clinical improvement among those assigned to fluoxetine was equal to or slightly better than for those assigned to imipramine. The likelihood of changing or discontinuing antidepressant medication was significantly less likely among those assigned to fluoxetine regardless of baseline insomnia or anxiety levels. While side effects may be an important consideration in antidepressant selection, we cannot demonstrate a significant interaction between presenting anxiety or insomnia symptoms and subsequent response to antidepressants that have activating or sedating effects.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), trazodone (Desyrel and others).

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