Subject Expectations of Treatment Effectiveness and Outcome of Treatment With an Experimental Antidepressant

Heather V. Krell, M.D., M.P.H.; Andrew F. Leuchter, M.D.; Melinda Morgan, Ph.D.; Ian A. Cook, M.D.; and Michelle Abrams, R.N.

Objective: To evaluate the association between treatment expectations and response in a 9-week, single-blind experimental antidepressant treatment study.

Method: Twenty-five adult subjects meeting DSM-IV criteria for major depressive disorder with Hamilton Rating Scale for Depression (HAM-D) scores of ≥ 17 completed a treatment trial using the experimental antidepressant reboxetine. Following a 1-week placebo lead-in, subjects received single-blind treatment for 8 weeks with reboxetine 8 to 10 mg/day. During the screening visit, subjects were asked to self-rate their expectations of the effectiveness of the study medication. Forced-choice responses were "not at all effective," "somewhat effective," or "very effective." Response to treatment was defined as a final HAM-D score of ≤ 10 at the end of the 9-week trial. Data were collected from October 1999 to July 2001.

Results: Subjects with a higher pretreatment expectation of medication effectiveness had a greater likelihood of response. Of the subjects who reported an expectation that the medication would be very effective, 90.0% (N = 9) responded to treatment, while only 33.3% (N = 5) of those who reported expecting medication to be somewhat effective responded to treatment ($\chi^2 = 7.819$, $p < .005$). There was no association between the level of depression severity, duration of current episode, number of prior episodes, or basic demographic factors and treatment outcome.

Conclusions: These findings indicate that individuals with high baseline expectations of improvement demonstrate a significantly higher level of response to reboxetine than those with lower expectations of improvement with treatment. The data in this study suggest that a subject's expectation of efficacy is associated with the outcome of experimental antidepressant treatment.

(J Clin Psychiatry 2004;65:1174–1179)

Received Nov. 11, 2003; accepted March 23, 2004. From the Laboratory of Behavioral Pharmacology, UCLA Neuropsychiatric Institute, and the Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, Calif.

This work was supported by Research Scientist Development Award K02-MH01165 and grant R01-MH40705 (Dr. Leuchter) and Career Development Award K08-MH01483 (Dr. Cook) from the National Institute of Mental Health, Bethesda, Md. Pharmacia and Upjohn, Inc. provided compound for this study.

Corresponding author and reprints: Heather V. Krell, M.D., UCLA Neuropsychiatric Institute, 760 Westwood Plaza, B8-241, Los Angeles, CA 90024-1759 (e-mail: hkrell@mednet.ucla.edu).

Major depressive disorder (MDD) is a crippling illness, with almost 20% of those with the illness experiencing a chronic, unremitting course.[1] Although many patients show a clinical response to medication, 30% to 50% may not respond to the first medication prescribed.[2,3] Several factors may account for heterogeneity in antidepressant treatment, including genotype[4–6] and brain functional characteristics.[7–9] In addition, limited data suggest a role of patient expectations and attitudes in modulating the rate of response of subjects with MDD to antidepressant medication.[10] A study of 162 patients with MDD as part of the National Institute of Mental Health Treatment of Depression Collaborative Research Program[11] revealed that pretreatment expectations of improvement were a significant predictor of response to pharmacotherapy. Similar findings were reported in a mixed population of depressed subjects examined by Vaz-Leal et al.[12] Peselow and colleagues[13] reported that higher "dysfunctional attitude" scores prior to treatment were negatively associated with response to tricyclic antidepressants, fluoxetine, and placebo in mixed depressed patients. Fava and colleagues,[14] however, did not replicate this finding in MDD subjects treated with fluoxetine only. Although some of these studies focused more on depressive cognitions than on specific negative attitudes toward treatment, such general negative attitudes may in fact reflect negative expectations about treatment. The data on expectation of treatment outcome, although not entirely consistent, warrant further exploration of the role of expectation in medication treatment outcome for MDD.

The relationship between a patient's attitude toward the treatment of his or her illness and treatment outcome

corresponds to the common belief among clinicians that a patient's expectations regarding the success of treatment will influence the patient's clinical outcome.[15] Systematic data, however, are lacking regarding expectations and the outcomes of antidepressant therapy. We report here data on the relationship between research subjects' expectation regarding the effectiveness of an experimental antidepressant (reboxetine) and the likelihood of improvement in the setting of a clinical trial.

METHOD

Subjects

Subjects meeting DSM-IV criteria for MDD without psychotic features, as determined by the Structured Clinical Interview for DSM-IV (SCID),[16] were recruited by advertisement from the community. All subjects were between 18 and 65 years of age and had 17-item Hamilton Rating Scale for Depression (HAM-D)[17] scores of ≥ 17. All subjects were required to be free of another Axis I illness or an Axis II diagnosis of cluster B personality disorder, have no history of significant head trauma or brain surgery, and be taking no other medications that had significant effects on brain function. Thirty-four subjects were recruited from the community. Institutional review board approval for the study was obtained, and all subjects provided written informed consent. Data were collected from October 1999 to July 2001.

Study Procedures

The protocol was a single-blind treatment trial with a 1-week placebo lead-in. Subjects were required to have a HAM-D score of ≥ 17 both at baseline and at the end of the placebo lead-in week. Subjects were informed that they were enrolling in a 9-week treatment trial with an experimental antidepressant and that they would be receiving placebo for 1 week at some time during the trial. After the placebo lead-in, 2 subjects were removed from the protocol for placebo response. Thirty-two subjects were then crossed over to reboxetine treatment at a starting dose of 8 mg/day. After 4 weeks, those not responding were advanced to 10 mg/day. Seven subjects dropped out within the first 2 weeks of reboxetine treatment (because of side effects). Thirteen subjects underwent the dosage increase, with 4 subsequently returning to the original dose (because of troublesome side effects).

During the baseline visit, subjects were asked to rate their expectations for the effectiveness of the study medication. Forced-choice responses were "not at all effective," "somewhat effective," or "very effective." Follow-up ratings using the HAM-D were performed at 7, 9, 14, 21, 35, and 63 days after enrollment in the study. Response to treatment was determined at day 63, with response defined as a final HAM-D score of ≤ 10. We selected this response cutoff because this sample was a treatment-resistant population, many of whom had been depressed for years and had suffered several previous depressive episodes. Subjects were rated by a research nurse or research assistant, who were trained to high interrater reliability and who were blinded to the subjects' expectations regarding treatment.

Data Analysis

Group differences (responders vs. nonresponders) in demographic data including age, years of education, sex, ethnicity, marital status, handedness, number of previous depressive episodes, and length of current episode were assessed with χ^2 tests for categorical variables and independent t tests for continuous variables.

We investigated the relationship between subject expectation and treatment response in 3 ways. First, we used a 2×2 χ^2 analysis by dichotomizing the final HAM-D scores into responders (HAM-D score of ≤ 10) and nonresponders (HAM-D score of > 10). Responses to the expectation question were in only 2 categories because no subjects rated their expectations for the effectiveness of the study medication as not at all effective.

Second, we used a t test with the final HAM-D score as the dependent variable and the expectation variable as the independent variable. After conducting the t test, we also examined several covariates that may have influenced the results. Using regression analysis, we included age, sex, education, medication compliance, baseline HAM-D score, number of prior episodes, and expectation of treatment effectiveness as candidate variables to be entered into the model using the forward stepwise method of entry. In this way, we could assess the relative contribution of these factors to the final HAM-D score.

Third, we used a mixed-effect repeated-measures analysis to assess mood at each timepoint in subjects who expected the treatment to be somewhat effective versus those who expected it to be very effective. There were no missing data in the analysis. The within-group factor was time, with 6 levels (baseline, 48 hours, and 1, 2, 4, and 8 weeks), and the between-group factor was treatment expectation, with 2 levels (somewhat effective vs. very effective). A factorial model was used to assess the within-group effect, the between-group effect, and the time-by-expectation interaction. Box's M test was used to test the null hypothesis of equality of covariance matrices. The p value associated with Box's M was .349, thus indicating that this assumption was valid.

A χ^2 test was used to examine whether expectations were related to subjects' completion of the trial or premature dropout.

RESULTS

Of the 25 subjects completing 9 weeks of treatment, 14 (56%) responded to treatment. Demographic and clinical

Table 1. Clinical and Demographic Characteristics of Subjects Completing 9 Weeks of Antidepressant Treatment With Reboxetine

Characteristic	Responders (N = 14)	Nonresponders (N = 11)	Total (N = 25)	Test Statistic	p Value for Group Differences
Age, mean ± SD, y	41.3 ± 10.8	44.9 ± 11.8	42.9 ± 11.2	t = 0.798	.433
Education, mean ± SD, y	15.7 ± 2.6	15.6 ± 2.8	15.7 ± 2.6	t = 0.072	.943
Gender, male:female, N	4:10	3:8	7:18	χ^2 = 0.005	.943
HAM-D score, mean ± SD					
Baseline	21.9 ± 3.2	24.0 ± 2.6	22.8 ± 3.1	t = 1.814	.083
Final	6.3 ± 2.7	16.2 ± 4.4	10.6 ± 6.1	t = 6.54	.0007
Duration of current episode, mean ± SD, y	11.1 ± 12.1	4.8 ± 6.5	8.1 ± 10.3	t = 1.68	.107
Prior depressive episodes, mean ± SD	4.1 ± 10.5	5.0 ± 7.1	4.5 ± 9.0	t = 0.232	.819
Ethnicity, N (%)				χ^2 = 1.04	.596
Asian/Pacific Islander	1 (7)	0 (0)	1 (4)		
African American	2 (14)	1 (9)	3 (12)		
White	11 (79)	10 (91)	21 (84)		
Marital status, N (%)				χ^2 = 2.23	.694
Currently married	1 (7)	2 (18)	3 (12)		
Divorced	4 (29)	3 (27)	7 (28)		
Never married/single	7 (50)	6 (55)	13 (52)		
Separated	1 (7)	0 (0)	1 (4)		
Widowed	1 (7)	0 (0)	1 (4)		
Handedness, right:left, N	14:0	10:1	24:1		.440[a]

[a]Fisher exact test was used.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

data for responders and nonresponders are shown in Table 1. No significant differences in sociodemographic or clinical variables across groups were detected, with the exception of the final HAM-D score, which by definition was significantly different between responders and nonresponders.

There was a significant relationship between a subject's pretreatment expectation of effectiveness and the subject's actual response as measured by the HAM-D (χ^2 = 7.819, df = 1, p < .005). Of the subjects who expected that the medication would be very effective, 9/10 (90%) responded to treatment, while only 5/15 subjects (33%) who reported an expectation that the medication would be somewhat effective responded (Figure 1).

As shown in Figure 2, there was a significant difference in the mean final HAM-D scores between those subjects who reported that they believed that the treatment was likely to be somewhat effective versus those who reported expecting it to be very effective (12.67 vs. 7.6, respectively; t = 2.2, df = 23, p = .039), with an effect size of .92.

In the regression analysis, the only variable that entered the model was the expectation variable (F = 4.8, df = 1,23; p = .039). The R^2 value was .17, indicating that approximately 17% of the variance in HAM-D score was explained by the subjects' expectations. Illness severity, prior episodes, age, years of education, sex, and medication adherence did not enter the statistical model even if expectation was excluded from the analysis, indicating that these other variables did not account for a significant proportion of the variance.

The repeated-measures analyses resulted in a significant within-group effect (F = 25.42, df = 5,19; p = .0001) and a significant between-group effect (F = 5.17, df = 1,23; p = .033); however, the interaction effect was not significant.

There were no differences in clinical or demographic characteristics (except for final HAM-D score) based on pretreatment levels of expectation (Table 2).

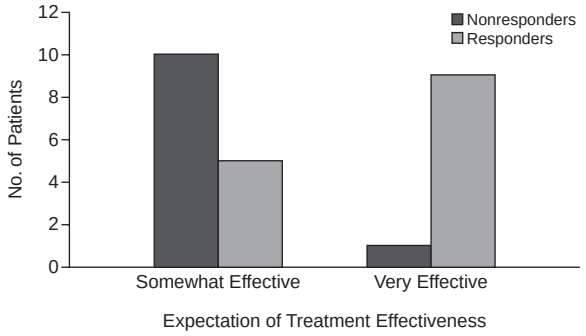
Pretreatment expectation did not identify those subjects who were likely to drop out of treatment. Of the 9 subjects who dropped out of the study, 5 subjects expected that treatment would be somewhat effective and 4 subjects expected the treatment would be very effective (χ^2 = 0.054, df = 1, p = .816). Expectation also appears to be unrelated to adherence to the medication treatment regimen. Of the 25 subjects who completed treatment, 20 subjects adhered to the medication regimen. Five subjects missed more than 2 doses of medication during 1 week of the study, and there was not a significant relationship between adherence and expectation of effectiveness (χ^2 = 0.00, df = 1, p = 1.0).

DISCUSSION

Our findings are consistent with literature indicating that a patient's pretreatment expectation of treatment outcome is related to treatment response.[15] In our study, those individuals presenting with stronger positive expectations regarding experimental medication effectiveness responded at a higher rate than those with lesser expectations. In the present sample, the relationship between treatment response and pretreatment expectation was independent of symptom severity, number of prior episodes, and demographic factors.

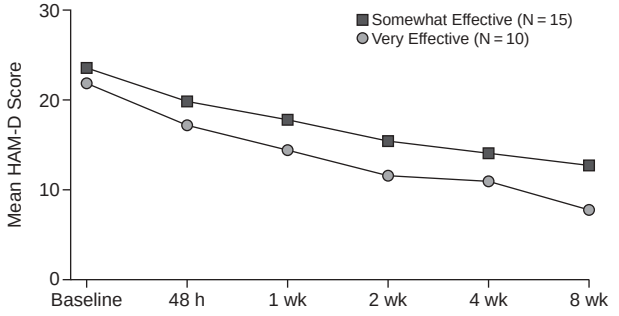
The present findings are consistent with a growing body of literature that relates expectations to treatment outcomes for general illnesses. Mondloch and col-

Figure 1. Pretreatment Expectation of Medication Effectiveness and Treatment Response in Patients Treated With an Experimental Antidepressant[a]



[a]p < .039 for somewhat effective vs. very effective at week 8.

Figure 2. HAM-D Scores Over Time According to Pretreatment Expectation of Medication Effectiveness



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 2. Patients' Expectation of Treatment Effectiveness and Demographic Characteristics

Characteristic	Somewhat Effective (N = 15)	Very Effective (N = 10)	Total (N = 25)	Test Statistic	p Value for Group Differences
Age, mean ± SD, y	41.6 ± 10.8	44.8 ± 12.0	42.9 ± 11.2	t = 0.693	.495
Education, mean ± SD, y	15.3 ± 2.6	16.2 ± 2.7	15.7 ± 2.6	t = 0.798	.433
Gender, male:female, N	3:12	3:7	6:19	χ^2 = 0.329	.566
HAM-D score, mean ± SD					
Baseline	23.5 ± 2.5	21.8 ± 3.7	22.8 ± 3.1	t = 1.35	.189
Final	12.7 ± 6.2	7.6 ± 4.7	10.6 ± 6.1	t = 2.191	.039
Duration of current episode, mean ± SD, y	8.9 ± 12.1	6.7 ± 6.9	8.1 ± 10.3	t = 1.68	.107
Prior depressive episodes, mean ± SD	3.1 ± 4.5	6.7 ± 13.2	4.5 ± 9.0	t = 0.492	.421
Ethnicity, N (%)				χ^2 = 2.78	.627
Asian/Pacific Islander	0 (0)	1 (10)	1 (4)		
African American	1 (7)	2 (20)	3 (12)		
White	14 (93)	7 (70)	21 (84)		
Marital status, N (%)				χ^2 = 3.54	.472
Currently married	2 (13)	1 (10)	3 (12)		
Divorced	3 (20)	4 (40)	7 (28)		
Never married/single	9 (60)	4 (40)	13 (52)		
Separated	0 (0)	1 (10)	1 (4)		
Widowed	1 (7)	0 (0)	1 (4)		
Handedness, right:left, N	15:0	9:1	24:1		.400[a]

[a]Fisher exact test was used.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

leagues[15] reviewed the literature on 16 different medical and psychiatric conditions and found that 15/16 studies showed that "positive" expectations were associated with better treatment outcome. Expectations have been most clearly shown to influence medication effects in subjects suffering from pain.[18–20] In a series of studies using experimental pain paradigms, Benedetti and colleagues[21,22] showed that there was a strong effect of expectation *in addition to* drug conditioning in modulating the effectiveness of placebo-induced analgesia. The effects of expectation in experimental pain appear to translate into the clinical setting. In patients with chronic pain, the tolerance for future episodes of pain appears to be influenced significantly by expectancy regarding its severity.[23] The role of expectation in outcomes from pharmacologic treatment has also been shown for post-chemotherapy nausea, in which severity is directly related to patients' pretreatment expectations of developing nausea independently of prior treatment.[24]

The effects of expectation may extend beyond immediate drug effects to longer-term functional outcomes. The success rates of renal transplantation[25] and the recovery and 1-year outcomes from prostate surgery[26] were significantly higher in patients with positive expectations regarding the treatment they would be receiving. Furthermore, expectation regarding recovery from painful injury has been shown to influence duration of disability.[27] There are few data available on the relationship between expectation and long-term outcomes in depression. Expectations of treatment outcome in depression could be shaped

by many factors, including the nature and success of previous treatments, as well as personality and other factors. One factor that has not been systematically examined is the role of the therapeutic alliance in forming expectations. One recent study by Joyce and colleagues[28] suggests that the relationship between expectancy and outcome in psychotherapy may in part be mediated by the therapeutic alliance. Further research would be needed to identify the major determinants of expectations for treatment outcome of pharmacotherapy in depression.

One limitation of our dataset is that no subject reported negative expectations regarding treatment outcome, which could reflect either the positive attitudes of the subjects or a hesitancy on the part of the subjects to report negative expectations. A relationship between negative expectations and treatment outcome has been suggested by Barsky and colleagues, who found that "patients who expect distressing side effects before taking a medication are more likely to develop them. Such negative expectations make the individual more likely to notice and attend to new or unwelcome sensations; interpret preexisting, ambiguous, and vague sensations unfavorably and attribute them to the medication; and overlook positive changes and evidence of symptom remission."[29(p624)] The relatively limited 3-item, forced-choice self-report measure that we used in this study may have limited our ability to detect negative expectations. In future studies, other instruments to measure expectations that provide a wider range of possible responses to detect negative expectations should be considered.

While the present results help to elucidate further the relationship between antidepressant treatment response and expectation, the findings may not be generalizable to the clinical treatment setting. Treatment was conducted using an experimental antidepressant, and it is possible that subjects bring unique expectations to treatment with a novel agent. Furthermore, the efficacy of reboxetine as an antidepressant is still unknown, as it has not been approved for clinical use in the United States, and expectations may differ for agents with proven robust efficacy. Expectations also may have been altered because subjects knew that they were going to receive a placebo at some point in the course of the clinical trial. In addition, the limited sample size may have resulted in recruitment of a group of subjects who were not representative of depressed patients who would present for general treatment. It is therefore important that the current results be replicated in a larger sample of subjects from a general clinical setting before conclusions are drawn regarding the role of expectation in antidepressant treatment. The current findings support the importance, however, both of developing valid methods for measuring subject expectations in antidepressant treatment and of examining the relationship between these expectations and treatment outcome in depression.

Drug name: fluoxetine (Prozac and others).

REFERENCES

1. Muller TI, Leon AC. Recovery, chronicity, and levels of psychopathology in major depression. Psychiatr Clin North Am 1996;119:85–102
2. Ballas C, Staab JP, Evans DL. Strategies for treatment-resistant depression. Psychopharmacol Bull 2002;36:39–62
3. Thase ME, Ninan PT. New goals in the treatment of depression: moving toward recovery. Psychopharmacol Bull 2002;36:24–35
4. Kim DK, Lim SW, Lee S, et al. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 2000;11:215–219
5. Rausch JL, Johnson ME, Fei YJ, et al. Initial conditions of serotonin transporter kinetics and genotype: influence on SSRI treatment trial outcome. Biol Psychiatry 2002;51:723–732
6. Yu YW, Tsai SJ, Chen TJ, et al. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. Mol Psychiatry 2002;7: 1115–1119
7. Brody AL, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry 2001;58: 631–640
8. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential of treatment response. Neuroreport 1997;8: 1057–1061
9. Cook IA, Leuchter AF, Witte E, et al. Neurophysiologic predictors of treatment response to fluoxetine in major depression. Psychiatry Res 1999;85:263–273
10. Brown C, Schulberg HC, Prigerson HG. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. Gen Hosp Psychiatry 2000;22:242–250
11. Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 1991; 148:997–1008
12. Vaz-Leal FJ, Salcedo-Salcedo MS, Silvestre-Garcia M. Expectations of the patient and attitudes toward treatment as predictive factors in the clinical course of affective disorders [in Spanish]. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1989;17:215–222
13. Peselow ED, Robins C, Block P, et al. Dysfunctional attitudes in depressed patients before and after clinical treatment in normal control subjects. Am J Psychiatry 1990;147:439–444
14. Fava M, Bless E, Otto MW, et al. Dysfunctional attitudes in major depression: changes with pharmacotherapy. J Nerv Ment Dis 1994; 182:45–49
15. Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you'll do? a systematic review of evidence for a relation between patients' recovery expectations and health outcomes. CMAJ 2001;165:174–179
16. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (SCID-I/P, version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1994
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
18. Price DD, Barrel JJ. Some general laws of human emotion: interrelationships between intensities of desire, expectation, and emotional feeling. J Pers 1984;52:389–409
19. Price DD, Fields HL. The contribution of desire and expectation to placebo analgesia: implications for new research strategies. In: Harrington A, ed. The Placebo Effect. Cambridge, Mass: Harvard University Press; 1999:117–137
20. Price DD, Milling LS, Kirsch I, et al. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain 1999;83:147–156
21. Benedetti F, Arduino C, Amanzio M. Somatotopic activation of opioid systems by target directed expectations of analgesia. J Neurosci 1999;19: 3639–3648
22. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 1999;19:484–494
23. Cipher DJ, Fernandez E. Expectancy variables in predicting tolerance

and avoidance of pain in chronic pain patients. Behav Res Ther 1997;35:437–444
24. Roscoe JA, Hickok JT, Morrow GR. Patient expectations as predictor of chemotherapy-induced nausea. Ann Behav Med 2000;22:121–126
25. Pommer W, Diederichs P, Hummel M, et al. Patients' expectations from renal grafting and transplantation outcome. Psychother Psychosom 1985; 71:297–305
26. Flood AB, Lorence DP, Ding J, et al. The role of expectations in patients' reports of post-operative outcomes and improvement following therapy. Med Care 1993;31:1043–1056
27. Cole DC, Mondloch MV, Hogg-Johnson S. Listening to injured workers: how recovery expectations predict outcomes: a prospective study. CMAJ 2002;166:749–754
28. Joyce AS, Ogrodniczuk JS, Piper WE, et al. The alliance as mediator of expectancy effects in short-term individual therapy. J Consult Clin Psychol 2003;71:672–679
29. Barsky AJ, Saintfort R, Rogers MP, et al. Nonspecific medication side effects and the nocebo phenomenon. JAMA 2002;287:622–627

