Effects of Alprazolam on Glucose Regulation in Diabetes

Results of a double-blind, placebo-controlled trial

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OBJECTIVE — To determine the effects of alprazolam on glucose regulation in anxious and nonanxious patients with poor glycemic control and establish whether regulatory benefits are related to anxiolytic effects of the medication.

RESEARCH DESIGN AND METHODS — Fifty-eight patients with poor glycemic control, 16 (27.6%) of whom had a symptomatic generalized anxiety disorder, were entered into a randomized, double-blind, placebo-controlled, 8-week trial using alprazolam (up to 2 mg/day) as the active agent. Generalized anxiety disorder was determined in accordance with *Diagnostic and Statistical Manual of Mental Disorders* criteria, and anxiety symptoms were measured using the Hopkins Symptom Checklist. Glycated hemoglobin levels were used to determine glucose regulation. Compliance behavior was assessed using glucometers and medication monitors equipped with electronic memory.

RESULTS — A statistically significant reduction in glycated hemoglobin level was observed in patients treated with alprazolam compared with those receiving placebo (-1.1 vs. -0.3%, $P = 0.04$). This treatment effect was not a function of differences in compliance behaviors. Anxiety symptoms decreased in both alprazolam- and placebo-treated patients with generalized anxiety disorder, but reduction in glycated hemoglobin level was not dependent on alleviation of anxiety.

CONCLUSIONS — A short course of alprazolam improved glucose regulation in patients with a history of poor diabetes control. This effect was not directly related to concomitant changes in anxiety. Alprazolam treatment of anxious patients with poorly controlled diabetes may result in decreased anxiety and improved glucose regulation through independent mechanisms.

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ANCOVA, analysis of covariance; ANOVA, analysis of variance; DIS, National Institute of Mental Health *Diagnostic Interview Schedule-Version Three*; DSM-IIIR, *Diagnostic and Statistical Manual of Mental Disorders*; GAD, generalized anxiety disorder; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; SCL-90-R, revised Hopkins Symptom Checklist.

The Diabetes Control and Complications Trial recently demonstrated that intensive treatment of diabetes can improve glucose regulation and delay the onset and progression of complications of diabetes (1). Efforts to improve glucose regulation may be hampered by active psychiatric illness (2). Generalized anxiety disorder (GAD) affects between 20 and 30% of diabetic individuals at some point during their lifetimes (2–6) and is associated with poor glucose regulation (2–4). The triazolobenzodiazepine alprazolam is an effective treatment for anxiety disorders in nondiabetic individuals (7,8), but its effects on anxiety and glucose regulation in patients with diabetes have not been studied.

In this report we describe the results of a double-blind, placebo-controlled study of the effects of alprazolam on a measure of longer term diabetes control (GHb level) in anxious and nonanxious adults with diabetes. We hypothesized a priori that: *1*) alprazolam would improve glucose regulation in diabetic patients with poor control; 2) its euglycemic effects would be restricted to anxious patients; and 3) in this subgroup, improvements in glucose regulation would parallel improvements in anxiety.

RESEARCH DESIGN AND METHODS

— Studies examining the efficacy of conventional antianxiety and antidepressant medications for poorly controlled diabetes were announced within the Washington University Medical Center community and through various print and media advertisements in the St. Louis metropolitan area. This report focuses on the subset of patients who enrolled in the study examining the efficacy of alprazolam for poor glucose regulation in diabetes. The study was approved by the human studies committee of Washington University School of Medicine. Patients 18–65 years of age with either insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) and having rela-

tively poor control of diabetes (GHb ≥11.5%) were eligible to participate. Patients excluded from participation were those for whom alprazolam therapy was contraindicated. This group included patients who were pregnant or lactating, had a known sensitivity to alprazolam or other benzodiazepines, had clinically significant hepatic disease, had current alcohol or substance abuse disorder, had any suicidal ideation (e.g., active suicidal intent or a history of attempted suicide), gave a history of any psychotic disorder, or currently were taking psychoactive medications.

Of the 180 patients who underwent complete psychiatric evaluation, 66 (33%) were excluded on the basis of the psychiatric interview (e.g., patient had current substance abuse disorder). Of the remaining 114 patients, 19 (16.7%) qualified for diagnosis of GAD, 35 (30.7%) had major depression, and 60 (52.6%) did not meet criteria for any axis I psychiatric disorder. The current study included all 19 patients with GAD and the subset of psychiatrically well patients (n = 47) not assigned to antidepressant therapy. Assignment to treatment was random within psychiatric groups. The likelihood of receiving alprazolam or placebo in the group with GAD was 0.50. By design, the likelihood of receiving alprazolam, an antidepressant, or placebo in the psychiatrically well group was 0.25, 0.25, and 0.50, respectively, resulting in varied cell sizes. The present report is limited to the results of the alprazolam and placebo arms.

Psychiatric diagnosis and measurement of anxiety symptoms

The presence or absence of axis I psychiatric disorder was determined using the National Institute of Mental Health *Diagnostic Interview Schedule-Version Three* (DIS) (9) in accordance with the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IIIR) (10). The DIS is a highly structured psychiatric interview with well-documented reliability and validity in medically well patients (11). There is also evidence for the sensitivity and utility of this diagnostic procedure in diabetes, wherein the somatic manifestations of the medical disease, such as fatigue, weakness, sleep disturbances, and sexual dysfunction, emulate symptoms of psychiatric disorder (12,13). Symptoms of anxiety were measured using the revised Hopkins Symptom Checklist (SCL-90-R) (14). This psychometric instrument was designed to measure psychological symptom patterns of psychiatric and medical patients. Each item is rated on a 5-point scale of distress (0–4), ranging from "not at all" at one pole to "extremely" at the other. The SCL-90-R is scored and interpreted in terms of nine primary dimensions, one of these being the anxiety subscale.

Diabetes assessments

GHb measurement provided an estimate of average blood glucose regulation during the 2-month period preceding entry into the study and during the treatment period (15–17). Total GHb was measured using the Pierce Glyco-Test (Pierce, Rockford, IL), an affinity assay that eliminates interference from hemoglobin variants (e.g., hemoglobin F). The range for normal, nondiabetic subjects at Washington University is 4.4–6.3%.

Compliance assessments

An electronic monitoring device developed and patented by one of the investigators (S.A.E.) was used to measure medication compliance. The device consists of pill-containing blister packs and an electronic memory, both of which are housed in an inconspicuous (18.2 cm × 3.9 cm) dispensing device. The open side of each medication-containing blister is covered by a sheet of paper, which contains loops of electrically conductive material attached to the electronic memory. When a dose of medication is removed (i.e., the paper covering a blister is torn), the conductive material is disrupted and the time and date are recorded. This device has been shown to be a highly reliable and valid method of measuring medication-taking behavior (18–20). Compliance with medication treatment was scored as a percentage equaling the number of days (24-h periods) the patient removed the prescribed number of medication dosages divided by 56 (the total number of days in treatment) times 100%. At the time of recruitment, subjects were informed that the pill dispensing device recorded the time and date of pill removal.

Compliance with self-monitoring of blood glucose was determined using memory glucometers (Ames, Elkhart, IN). These devices recorded the date and time patients tested their blood glucose levels. Patients were instructed to test blood glucose level 4 times per day on 2 nonconsecutive days of the week. Weekly compliance with blood glucose monitoring was computed taking the number of samples measured on the 2 test days divided by 8 (number of tests requested) times 100%.

Study design and statistical analysis

Patients were divided into two groups based upon the psychiatric diagnostic findings: *1*) those with symptomatic GAD; and 2) those judged to be psychiatrically well, i.e., no extant axis I psychiatric disorder per DSM-IIIR. Patients within these two groups were randomly assigned to double-blind treatment with alprazolam or an identical-appearing placebo. The study personnel who prepared the treatment blister packs were not among those who monitored patient progress, and both these groups were distinct from those directly administering treatment. At each measuring point, the research assessments (psychiatric interviews, psychometric measurements, and diabetes evaluations) were administered and scored independently of one another.

Treating physicians were unaware of the patient's psychiatric status. To maintain this experimental blind, these physicians (R.E.C., J.B.M.) did not query the patient regarding current psychiatric symptoms. Alprazolam dosing was guided solely by side effects toward an established target dose thought to be psy-

Table 1—*Demographic characteristics of study sample*

Characteristic	Alprazolam			Placebo		
	GAD	Well	All	GAD	Well	All
n	7	14	21	9	28	37
Age (years)	39.1 ± 9.0	58.0 ± 9.9*	51.7 ± 13.1	48.1 ± 12.1	50.9 ± 14.1	50.2 ± 13.6
Female	5 (71)	2 (14)*	7 (33)	5 (56)	12 (43)	17 (46)
Race						
White	7 (100)	10 (71)	17 (81)	9 (100)	23 (82)	32 (86)
Black	0 (0)	3 (21)	3 (14)	0 (0)	5 (18)	5 (14)
Other	0 (0)	1 (7)	1 (5)	0 (0)	0 (0)	0 (0)
Marital status						
Married	5 (71)	11 (79)	16 (76)	5 (56)	18 (64)	23 (62)
Single	1 (14)	0 (0)	1 (5)	0 (0)	2 (7)	2 (5)
Divorced	0 (0)	3 (21)	3 (14)	1 (11)	4 (14)	5 (14)
Never married	1 (14)	0 (0)	1 (5)	3 (33)	4 (14)	7 (19)
Monthly income (dollars)	2,860 ± 1,827	2,136 ± 1,032	2,306 ± 1,291	2,012 ± 432	1,828 ± 1,199	1,856 ± 1,111
Education (years)	13.9 ± 2.9	14.1 ± 2.7	14.0 ± 2.7	13.9 ± 2.5	14.0 ± 2.8	14.0 ± 2.7

Data are means ± SD or *n* (%). *$P < 0.05$ compared with GAD group.

chiatrically therapeutic (2.0 mg/day). Alprazolam dosing began at 0.25 mg/day with incremental adjustments to the target in divided doses. Patients were provided medication packs that always involved three times daily dosing, and the packs were prepared using alprazolam or identical placebos to maintain the blind. Except at the initiation of treatment, patients receiving active drug were given doses throughout the day.

To detect changes in glucose regulation related to anxiolytic therapy, diabetes management regimens remained fixed over the period of the study unless clinically contraindicated. Patients remained on their pre-enrollment treatment (diet, oral hypoglycemic agents, and insulin) throughout the study. Patients on sliding scale insulin regimens were allowed to continue this practice without new instruction. At the beginning of each study visit, the patient's interim glucometer data were reviewed by the study nurse. Two fasting blood glucose levels <90 mg/dl or a mean weekly value >300 mg/dl were considered potential indications for diabetes treatment adjustment. If these thresholds were passed or if a patient complained of hypo- or hyperglycemic symptoms, physicians were given the glucometer data to review in formulating a decision regarding diabetes treatment.

Differences in demographic and clinical characteristics between subjects receiving alprazolam or placebo and within a psychiatric group (GAD or psychiatrically well) were determined using Fisher's exact test for categorical data and two-way analyses of variance for continuous data. Analysis of variance (ANOVA) techniques were used to judge the effects of treatment on compliance with blood glucose monitoring and treatment. A two-way analysis of covariance (ANCOVA) (psychiatric status [GAD or well] by treatment status [alprazolam or placebo]) on post-treatment GHb level, with pretreatment GHb level used as the covariate, was used to determine the effect of alprazolam on blood glucose regulation. Dropouts were not included in the data analysis because they were relatively few in number ($n = 8$) and equally distributed between the alprazolam and placebo arms of the study. A similarly constructed ANCOVA was used to test the effects of treatment on anxiety symptoms. The pretreatment SCL-90-R anxiety score was used as the covariate in this analysis. The anxiolytic effects of treatment were further studied within the GAD subset by analyzing pre-post changes in anxiety using Student's *t* tests. Continuous variables are reported as means ± SD.

RESULTS

Demographic and clinical characteristics

Of the 66 study patients, 19 (28.8%) met psychiatric diagnostic criteria for current GAD (referred to herein as the "anxious" patients). The remaining 47 (71.2%) patients gave a history unremarkable for any axis I psychiatric disorder. These patients formed the psychiatrically well group. Eight (12.1%) of the 66 patients did not complete the protocol. Of these eight patients, four (50%) were taking alprazolam and four (50%) were receiving placebo. Seven (87.5%) of these eight patients discontinued participation because of perceived intolerance to the study treatment (four were taking alprazolam, and three were receiving placebo) and one withdrew because of an intercurrent medical problem. Selected demographic and clinical characteristics of the 58 patients who completed the 8 weeks of treatment are

Table 2—*Illness characteristics of study sample*

Characteristic	Alprazolam			Placebo		
	GAD	Well	All	GAD	Well	All
n	7	14	21	9	28	37
Type of diabetes						
IDDM	3 (43)	4 (29)	7 (33)	2 (22)	8 (29)	10 (27)
NIDDM	4 (57)	10 (71)	14 (67)	7 (78)	20 (71)	27 (73)
Duration of diabetes (years)	13.9 ± 2.9	12.6 ± 9.0	13.0 ± 6.4	12.6 ± 8.5	11.2 ± 11.4	11.5 ± 10.7
Glycated hemoglobin (%)	12.0 ± 2.3	12.0 ± 2.3	12.0 ± 2.2	12.4 ± 3.0	12.0 ± 3.6	12.1 ± 3.4
Complications of diabetes						
Nephropathy	1 (14)	2 (14)	3 (14)	0 (0)	0 (0)	0 (0)*
Retinopathy	2 (29)	3 (21)	5 (24)	4 (44)	5 (18)	9 (24)
Neuropathy	2 (29)	8 (57)	10 (48)	6 (67)	17 (61)	23 (62)
SCL-90R anxiety score	1.5 ± 0.8	0.2 ± 0.1*	0.8 ± 0.9	0.6 ± 0.4	0.2 ± 0.3*	0.4 ± 0.3

Data are means ± SD or number (%). *$P < 0.05$ compared with GAD group.

shown in Tables 1 and 2. There was no statistically significant difference between patients in the placebo and alprazolam arms with regard to pretreatment GHb levels (12.0 + 2.2 vs. 12.1 + 3.4%, $t = 0.12$, $P = 0.90$). These groups were also similar in age, sex, race, martial status, monthly income, education, type of diabetes, duration of diabetes, and prevalence of diabetes complications (nephropathy, retinopathy, or peripheral neuropathy). There were also no significant differences in pretreatment GHb levels between patients with IDDM and those with NIDDM.

The demographic and clinical characteristics of GAD and psychiatrically well patient subsets (nested within treatment group) were also statistically compared (Tables 1 and 2). As expected, within both active and placebo treatment groups, anxious patients had higher pretreatment anxiety scores than their well counterparts. Within the alprazolam group, psychiatrically well patients were significantly older and preponderantly male. There were no other significant differences between anxious and nonanxious patients on the measured demographic and illness characteristics. Of the patients who received alprazolam, there was no significant difference in the mean daily dose achieved by anxious and nonanxious patients (1.70 ± 0.47 vs. 1.53 ± 0.53 mg/day, $t = -0.71$, $P = 0.49$). Increases in diabetes management regimens occurred in only two subjects (one placebo and one alprazolam) and decreases in six subjects (three placebo and three alprazolam). Alterations in management regimens by treatment group were not significantly different ($\chi^2 = 0.66$, $P = 0.41$).

Effect of treatment on measures of compliance

The compliance data reported herein are intended to determine whether differences in compliance might have affected the outcome of the trial. All study patients practiced using a memory glucometer for 1 week before initiation of treatment. Analysis of these pretreatment glucometer data showed no significant differences between alprazolam- and placebo-treated patients (87.6 ± 22.1 vs. 81.9 ± 27.9%, $t = 0.80$, $P = 0.43$). Separate ANOVAs were used to test the effects of treatment and psychiatric status on compliance during the 8 weeks of study. The ANOVA of compliance with blood glucose monitoring revealed no statistically significant effect of treatment ($F = 0.17$, $P = 0.68$), initial psychiatric status ($F = 0.85$, $P = 0.36$), or the interaction of treatment and psychiatric grouping ($F = 0.07$, $P = 0.79$). The results of the ANOVA of compliance with medication monitoring were similar, showing no significant effect of treatment ($F = 0.84$, $P = 0.36$), initial psychiatric status ($F = 0.02$, $P = 0.90$), or the interaction between treatment and psychiatric status ($F = 0.31$, $P = 0.58$). Taken together, these data suggest that patients in the alprazolam- and placebo-treated groups were equally compliant at the beginning of treatment and that during the 8 weeks of treatment, compliance with the medication regimen and with blood glucose monitoring did not differ as a function of treatment received.

Effect of alprazolam on glucose regulation

The results of the ANCOVA showed that there were significant effects for the covariate (pretreatment GHb, $F = 221.9$, $P < 0.001$) and for the treatment group ($F = 4.4$, $P = 0.04$). Patients treated with alprazolam evidenced a significantly greater reduction in GHb level than those receiving placebo (−1.1 vs. −0.3%, $P = 0.04$). The largest improvement in GHb level (−1.4%) was seen in GAD patients treated with alprazolam, although differences between psychiatric groups did not reach statistical significance. Post-treatment mean GHb levels, adjusted for ini-

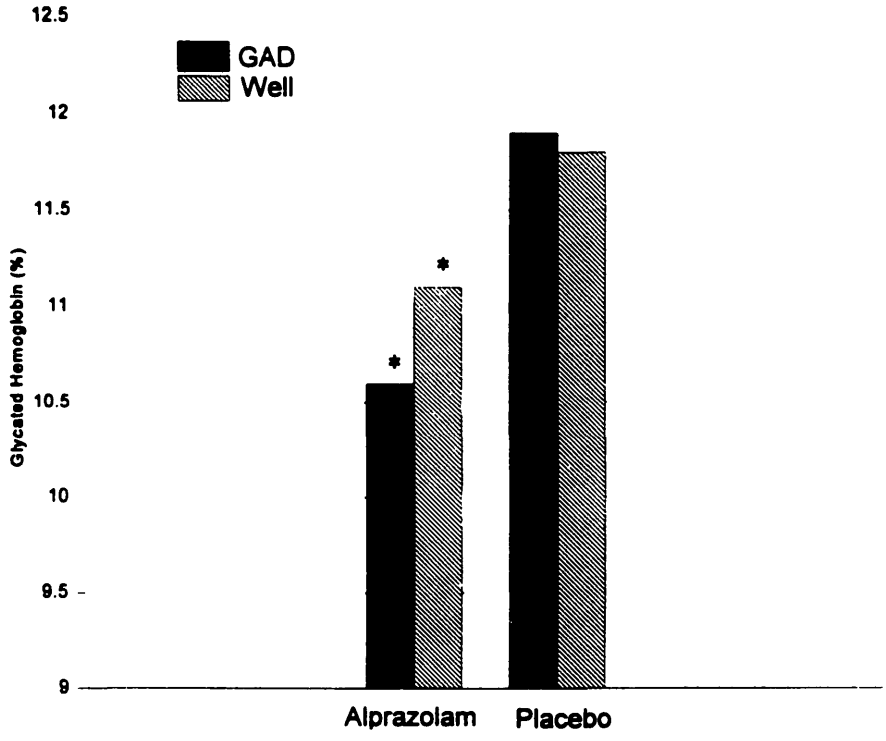

Figure 1—*Post-treatment mean GHb levels by group, statistically adjusted (ANCOVA) for initial differences in GHb among groups. GAD, those with generalized anxiety disorder; Well, those without a psychiatric disorder. *P < 0.05 compared with the placebo-treated group.*

tial between-group differences (i.e., covariate-adjusted means), are displayed in Fig. 1. Treatment had no effect on weight ($F = 0.07$, $P = 0.79$, comparing weight change by treatment), and the change in GHb level was poorly correlated with mean daily dose of alprazolam ($r = 0.13$, $P = 0.36$).

Effect of alprazolam on anxiety

A similar ANCOVA was used to examine the effects of treatment and initial psychiatric group on anxiety, with the pretreatment anxiety score used as the covariate. The overall model was statistically significant ($F = 6.4$, $P = 0.0005$), and the effect of the covariate was significant as well ($F = 8.2$, $P = 0.007$). There were no significant effects for psychiatric diagnostic group or for the interaction between treatment and psychiatric group. Likewise, within the whole sample the effect of alprazolam treatment on anxiety was not statistically significant ($F = 1.21$, $P = 0.28$). This test of the effect of treatment on anxiety may have been biased because it included both anxious and nonanxious patients. We had not expected an anxiolytic effect of alprazolam in nonanxious patients and measured anxiety in this group to assess untoward psychiatric effects of alprazolam treatment. Over the 8 weeks of treatment, no change in anxiety was observed in the nonanxious group. These patients had virtually identical low levels of anxiety (per SCL-90-R anxiety scale score) before and after treatment (0.22 ± 0.19 vs. 0.23 ± 0.27, $t = 0.19$, $P = 0.85$).

Further statistical testing, confined to the group of patients with GAD, was used to assess the anxiolytic effects of treatment. Within this group, a significant reduction in anxiety was observed during the study period (-0.5 ± 0.6, $t = -3.5$, $P = 0.003$). Within the subgroups of GAD patients, those treated with placebo evidenced a significant reduction in anxiety (-0.34 ± 0.3, $t = -3.65$, $P = 0.007$), and a trend toward significance was observed in those who received alprazolam (-0.7 ± 0.8, $t = -2.3$, $P = 0.058$). There was no significant difference between alprazolam- and placebo-treated patients in terms of the observed anxiolytic effects. Pre- and post-treatment means on the SCL-90-R anxiety scale are displayed according to psychiatric and medication status in Fig. 2.

Exploratory data analysis procedures (21,22) were performed to determine whether improvement in GHb level is associated with improvement in anxiety. Noninferential Spearman rank-order correlations were computed first for the entire sample and then within the GAD group by treatment. There was no association in the overall sample or in the psychiatrically well group between change in anxiety and change in GHb level. In contrast, these outcomes were positively correlated in the GAD group treated with alprazolam ($r_s = 0.34$).

CONCLUSIONS— The following conclusions can be drawn from the data analyses: *1*) glucose regulation was improved by alprazolam but not by placebo; 2) this effect was not restricted to the subjects with GAD; 3) both alprazolam and placebo similarly improved anxiety among patients with GAD because the placebo response was significant; and *4*) the effect of alprazolam on GHb level was not dependent upon improvement in anxiety. Improvement in GHb level correlated with improvement in anxiety in the GAD group, but alprazolam also improved GHb level in the nonanxious patient group. Thus, it appears that alprazolam has a direct, beneficial effect on blood glucose regulation in diabetes, an effect not mediated solely through improvement in anxiety.

Some data are available from which one can speculate the mechanisms by which alprazolam affects glucose regulation. One potential mechanism might operate through a dampening of the neu-

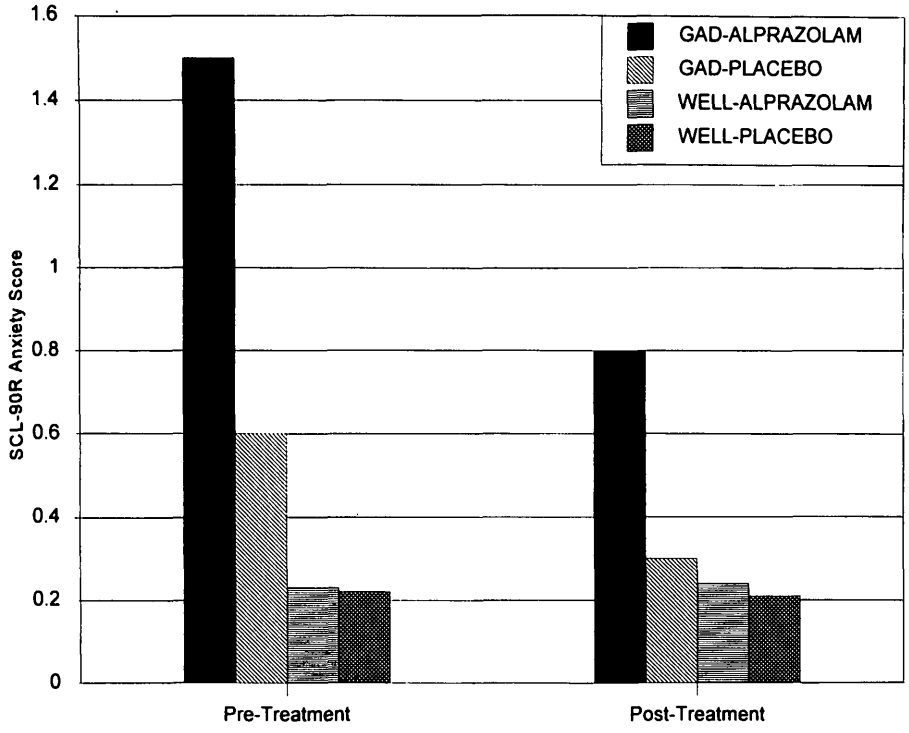

Figure 2—*Change in anxiety symptoms during treatment. Post hoc comparisons indicated that the pre- to post-treatment changes in the GAD groups were only significant for placebo (P = 0.007; compared with alprazolam, P = 0.058).*

rohormonal response to stress. Filinger et al. (23) reported that diazepam reduced by ~50% the release of noradrenaline and acetylcholine after preganglionic stimulation of isolated superior cervical ganglion in the cat. Owens et al. (24) and Kalogeras et al. (25) demonstrated the ability of alprazolam to suppress the hypothalamic-pituitary-adrenal axis via its effects on corticotropin-releasing factor. Using an animal model of NIDDM diabetes, Surwit et al. (26) demonstrated that alprazolam modified the hyperglycemic effect of stress, significantly increased plasma insulin, and significantly reduced plasma corticosterone. These reports are representative of studies, predominantly in animal models, suggesting that benzodiazepine treatment may blunt the neurotransmitter/neurohormonal responses to stressors, which may otherwise produce hyperglycemia via glucocorticoid hypersecretion (27–30).

The data indicate that the beneficial effect of alprazolam on glucose regulation was not related to selective improvement of diabetes treatment compliance. There were no pretreatment differences in compliance with blood glucose monitoring between patients who received alprazolam and those who received placebo. There were also no differences on either measure of compliance as a function of treatment. Rates of compliance were uniformly high at the beginning of the study and, as is common in treatment studies, declined somewhat over the course of the experimental trial. The effect of alprazolam was also unrelated to changes in diabetes treatment regimens or to weight alterations during the trial, but other influences on diabetes regulation (e.g., exercise or dietary intake) were not monitored.

Clinically significant anxiety (GAD) is associated with poor glucose regulation in diabetes (2–4), and we hypothesized that treatment of anxiety would improve glucose control. Alprazolam was selected for study because of its recognized ability to induce rapid anxiolytic change. Although alprazolam improved GHb levels in both anxious and nonanxious patients, the largest gain was observed in patients with GAD. A similar observation was made by Lane et al. (31) who reported that the diabetic patients most likely to show improved glucose control with behavioral anxiolytic treatment were those with pronounced trait anxiety. Thus, there may be multiple mechanisms by which alprazolam can affect GHb levels in anxious patients. The euglycemic effect may relate to alprazolam's anxiolytic effect, to its physiological effects, or to the interaction of these effects. Additional studies incorporating multiple indexes of anxiety (psychological and physiological) should be undertaken to clarify the anxiolytic mechanisms responsible for, and their precise contribution to, improvements in diabetic regulation.

The extent to which the treatment gains found in this study are generalizable to clinical practice, durable, or achievable with other psychoactive agents remains to be determined, and our conclusions were based on a relatively small number of subjects. Treating medical problems with psychoactive agents in patients with a comorbid psychiatric disorder is not unique to diabetes. For example, tricyclic antidepressants may be given for pain when pain and depression are coprevalent. These medications have both analgesic and antidepressant effects that operate independently (31,33). The potential improvement in glucose control attributable to alprazolam treatment should be weighed carefully against the risk of dependence or withdrawal symptoms associated with benzodiazepines (34,35). These concerns are particularly relevant here given that poor regulation in diabetes is often a chronic problem.

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References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Lustman PJ, Griffith LS, Clouse RE, Cryer PE: Psychiatric illness in diabetes: relationship to symptoms and glucose control. *J Nerv Ment Dis* 174:736–742, 1986
3. Lustman PJ: Anxiety disorders in adults with diabetes mellitus. *Psychiatr Clin North Am* 11:419–432, 1988
4. Turkat ID: Glycosylated hemoglobin levels in anxious and nonanxious diabetic patients. *Psychosomatics* 23:1056–1058, 1982
5. Popkin, MK, Callies AL, Lentz RD, Colon EA, Sutherland DE: Prevalence of major depression, simple phobia, and other psychiatric disorders in patients with long-standing type 1 diabetes mellitus. *Arch Gen Psychiatry* 45:64–68, 1988
6. Wells KB, Golding JM, Burnam MA: Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. *Gen Hosp Psychiatry* 11:320–327, 1989
7. Jonas JM, Cohon MS: A comparison of the safety and efficacy of alprazolam versus other agents in the treatment of anxiety, panic, and depression: a review of the literature. *J Clin Psychiatry* 54:25–45, 1993
8. Kravitz HM, Fawcett J, Newman AJ: Alprazolam and depression: a review of risks and benefits. *J Clin Psychiatry* 54:78–84, 1993
9. Robins LN, Helzer JE, Croughan J: *The NIMH Diagnostic Interview Schedule: Version 3*. Washington, DC, U.S. Public Health Service, 1981
10. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC, American Psychiatric Association, 1987
11. Robins LN, Helzer JE, Croughan J, Ratcliff KS: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry* 38:381–389, 1981
12. Lustman PJ, Harper GW, Griffith LS, Clouse RE: Use of the Diagnostic Interview Schedule in patients with diabetes. *J Nerv Ment Dis* 174:743–746, 1986
13. Lustman PJ, Freedland KE, Carney RM, Hong BA, Clouse RE: Similarity of depression in diabetic and psychiatric patients. *Psychosom Med* 54:602–611, 1992
14. Derogatis LR: *The SCL-90-R Administration, Scoring and Procedures Manual I*. Baltimore, MD, Clinical Psychometric Research, 1977
15. Goldstein DE, Little RR, Wiedmeyer H, England JD, McKenzie EM: Glycated hemoglobin: methodologies and clinical applications. *Clin Chem* 32:B64–B70, 1986
16. Santiago JV, Davis JE, Fisher F: Hemoglobin A_{1c} levels in a diabetes detection program. *J Clin Endocrinol Metab* 47:578–580, 1978
17. Ladenson JH, Chan KM, Kilzer P: Glycated hemoglobin and diabetes. *Clin Chem* 31:1060–1067, 1985
18. Eisen SA, Hanpeter JA, Kreuger LW, Gard M: Monitoring medication compliance: description of a new device. *J Compliance Health Care* 2:131–141, 1987
19. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR: The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 150:1881–1884, 1990
20. Eisen SA, Woodward RS, Miller D, Spitznagel E, Windham CA: Effect of medication compliance on the control of hypertension. *J Gen Intern Med* 2:298–305, 1987
21. Tukey JW: *Exploratory Statistical Analyses*. Reading, MA, Addison-Wesley, 1977
22. Smith AF, Prentice DF: Exploratory data analysis. In *A Handbook for Data Analysis in the Behavioral Sciences*. Keven L, Lewis C, Eds. Hillsdale, NJ, Lawrence Erlbaum, 1993
23. Filinger EJ, Elgoyhen AB, Adler-Graschinsky E: Benzodiazepines decrease the release of [^{3}H]noradrenaline and of [^{3}H] acetylcholine in the cat superior cervical ganglion. *Neurosci Lett* 105:195–199, 1989
24. Owens MJ, Bissette G, Nemeroff CB: Acute effects of alprazolam and adinazolam on the concentrations of corticotropin-releasing factor in the rat brain. *Synapse* 4:196–202, 1989
25. Kalogeras KT, Calogero AE, Kuribayiashi T, Khan I, Gallucci WT, Kling MA, Chrousos GP, Gold PW: In vitro and in vivo effects of the triazolobenzodiazepine alprazolam on hypothalamic-pituitary-adrenal function: pharmacological and clinical implications. *J Clin Endocrinol Metab* 70:1462–1471, 1990
26. Surwit RS, McCubbin JA, Kuhn CM, McGee D, Gerstenfeld D, Feinglos MN: Alprazolam reduces stress hyperglycemia in ob/ob mice. *Psychosom Med* 48:278–282, 1986
27. Gaumann DM, Yaksh TL, Tyce GM: Effects of intrathecal morphine, clonidine, and midazolam on the somato-sympathoadrenal reflex response in halothane-anesthetized cats. *Anesthesiology* 3:425–432, 1990
28. Kimura T, Shimamura T, Satoh S: Effects of pirenzepine and hexamethonium on adrenal catecholamine release in responses to endogenous and exogenous acetylcholine in anesthetized dogs. *J Cardiovasc Pharmacol* 20:870–874, 1992
29. Sapolsky RM, Krey LC, McEwen BS: The neuroendocrinology of stress and aging. *Endocr Rev* 7:284–301, 1986
30. Surwit RS, Feinglos MN, Livingston EG, Kuhn CM, McCubbin JA: Behavioral manipulation of the diabetic phenotype in *ob/ob* mice. *Diabetes* 33:616–618, 1984
31. Lane JD, McCaskill CC, Ross SL, Feinglos MN, Surwit RS: Relaxation training for NIDDM. *Diabetes Care* 16:1087–1094, 1993
33. Max MB, Lunch SA, Muir J, Shoaf SE, Smoller B, Dubner R: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326:1250–1256, 1992
34. Petursson H, Lader M: *Dependence on Tranquilizers*. New York, Oxford Univ. Press, 1984
35. Fyer AJ, Liebowitz MR, Gorman JM, Campeas R, Levin A, Davies SO, Goetz D, Klein DF: Discontinuation of alprazolam treatment in panic patients. *Am J Psychiatry* 144:303–308, 1987