

# NIH Tightens Ethics Rules for All Employees

BY MARY ELLEN SCHNEIDER  
Senior Writer

Officials at the National Institutes of Health are tightening restrictions on outside consulting arrangements with industry after more than a year of investigations turned up potential conflicts of interest.

“Nothing is more important to me than preserving the trust of the public in NIH,” Elias A. Zerhouni, M.D., NIH director,

said in a statement announcing the new ethics rules. “It is unfortunate that the activities of a few employees have tainted the stellar reputation of the many thousands of NIH scientists who have never compromised their integrity and have selflessly served the nation with great distinction through their discoveries.”

The new policy bars all NIH employees from engaging in compensated or uncompensated employment or consulting relationships with those organizations that

are substantially affected by NIH decisions. Such organizations include pharmaceutical manufacturers, biotechnology companies, support research institutions, health care providers and insurers, and related trade and professional associations.

The policy also prohibits NIH employees from participating in compensated teaching, speaking, writing, or editing with these affected organizations.

Further, NIH employees are prohibited

from self-employment activities that involve the sale or promotion of services or products from these organizations.

However, employees are allowed to teach courses that require multiple presentations and are part of an established curriculum at a university or college. They can also teach, speak, or write as part of a continuing education program. However, if the funding for the program comes from a substantially affected organization, like a drug company, it must be funded by an unrestricted grant.

NIH employees can also author articles, chapters, and textbooks that are subject to peer review provided that funding from affected organizations is in the form of unrestricted contributions.

Under the new policy, NIH employees are also allowed to continue clinical care to individual patients.

The new regulation also takes aim at stock ownership. NIH employees who are required to file financial disclosure statements are prohibited from acquiring or holding financial interests in affected organizations including biotechnology, pharmaceutical, and medical device companies. All other NIH employees are subject to a \$15,000 cap on such holdings.

“This new policy is an extension of a profession-wide examination of physicians’ relationships to industry,” said William E. Golden, M.D., professor of medicine and public health at the University of Arkansas in Little Rock.

Medical schools are likely to be the next major institutions to seek out greater transparency in the relationships between their faculty members and industry, Dr. Golden predicted.

The interim final regulation was developed by the Department of Health and Human Services with the Office of Government Ethics and went into effect immediately.

The new policy comes after about a year of internal NIH investigations as well as congressional inquiries into consulting arrangements between NIH employees and outside companies. NIH officials had previously proposed a 1-year moratorium on all outside consulting arrangements.

The new policy was praised by the Association of American Medical Colleges. “The rules are clear and unambiguous and will enhance the public’s confidence in the integrity and dedication of NIH employees and scientists,” AAMC President Jordan J. Cohen, M.D., said in statement.

“We also firmly support NIH’s plan to assess the impact of these new rules within 1 year. Given the sweeping changes being made and the possibility of unintended consequences, it is prudent for the agency to undertake a thorough review after full implementation so that appropriate modifications can be made, if necessary,” he said.

Officials at NIH also announced a new policy aimed at speeding the public’s access to scientific articles that result from NIH-funded research. Under the policy, the agency is calling on scientists to voluntarily release manuscripts supported by NIH to the public within a year of peer-reviewed publication. ■

## NIRAVAM™ (alprazolam orally disintegrating tablets)

0.25 mg • 0.5 mg • 1.0 mg • 2.0 mg

### Brief Summary of Prescribing Information

#### Rx Only

**CONTRAINDICATIONS.** NIRAVAM™ is contraindicated in patients with known sensitivity to this drug or other benzodiazepines. NIRAVAM™ may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow-angle glaucoma. NIRAVAM™ is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see WARNINGS). **WARNINGS. Dependence and Withdrawal Reactions, Including Seizures.** Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure. Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4.0 mg per day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day. **The importance of dose and the risks of alprazolam as a treatment for panic disorder.** Because the management of panic disorder often requires the use of average daily doses of alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-treated patients. Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline. In a controlled clinical trial in which 63 patients were randomized to alprazolam and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal. In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71% - 93% of patients treated with alprazolam tapered completely off therapy compared to 89% - 96% of placebo-treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. Seizures attributable to alprazolam were seen after drug discontinuation or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24 - 72 hours after discontinuation. **Status Epilepticus.** The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. **Interdose Symptoms.** Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with panic disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations. **Risk of Dose Reduction.** Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of NIRAVAM™ should be reduced or discontinued gradually. **CNS Depression and Impaired Performance.** Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam. **Risk of Fetal Harm.** Benzodiazepines can potentially cause fetal harm when administered to pregnant

women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug. **Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P450 3A.** The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class. The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A. **Potent CYP3A Inhibitors.** Azole antifungal agents—Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS). **Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs).** Nefazodone— Coadministration of nefazodone increased alprazolam concentration two-fold. Fluvoxamine— Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance. Cimetidine— Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%. **Other drugs possibly affecting alprazolam metabolism.** See complete prescribing information. **PRECAUTIONS. General. Suicide.** As with other psychotropic medications, the usual precautions with respect to administration of the drug and the size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. **Mania.** Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression. **Uricosuric Effect.** Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam. **Use in Patients with Concomitant Illness.** It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam. **Information for Patients.** See complete prescribing information. **Laboratory Tests.** Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice. **Drug Interactions. Use with Other CNS Depressants.** If NIRAVAM™ is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression. **Drugs Affecting Salivary Flow and Stomach pH.** Because NIRAVAM™ disintegrates in the presence of saliva and the formulation requires an acidic environment to dissolve, concomitant drugs or diseases that cause dry mouth or raise stomach pH might slow disintegration or dissolution, resulting in slowed or decreased absorption. **Use with Imipramine and Desipramine.** The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam in doses up to 4 mg/day. The clinical significance of these changes is unknown. **Drugs that inhibit alprazolam metabolism via cytochrome P450 3A.** See CONTRAINDICATIONS, WARNINGS and the complete prescribing information for drugs of this type. **Drugs demonstrated to be inducers of CYP3A.** Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam. **Drug/Laboratory Test Interactions.** Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** No evidence of carcinogenic potential was observed during 2-year bioassay studies in rats and in mice. Alprazolam was not mutagenic in the rat micronucleus test, *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay. Alprazolam produced no impairment of fertility in rats. **Pregnancy. Teratogenic Effects.** Pregnancy Category D: (See WARNINGS section). **Nonteratogenic Effects:** It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory

problems have been reported in children born of mothers who have been receiving benzodiazepines. **Labor and Delivery.** NIRAVAM™ has no established use in labor or delivery. **Nursing Mothers.** Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use NIRAVAM™. **Pediatric Use.** Safety and effectiveness of NIRAVAM™ in individuals below 18 years of age have not been established. **Geriatric Use.** The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of NIRAVAM™ should be used in the elderly to preclude the development of ataxia and oversedation. **ADVERSE REACTIONS.** Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or lightheadedness. The following data are estimates of outward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of alprazolam in patients with panic disorder, with or without agoraphobia. **Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders.** The incidence of treatment-emergent adverse events that occurred during placebo-controlled trials in 85% of alprazolam patients treated for anxiety disorders (n=565) vs placebo-treated patients (n=505) were: Drowsiness (41.0% vs 21.6%); Lightheadedness (20.8% vs 19.3%); Depression (13.9% vs 18.1%); Headache (12.9% vs 19.6%); Confusion (9.9% vs 10.0%); Insomnia (8.9% vs 18.4%); Dry Mouth (14.7% vs 13.3%); Constipation (10.4% vs 11.4%); Diarrhea (10.1% vs 10.3%); Nausea/Vomiting (9.6% vs 12.8%); Tachycardia/Palpitations (7.7% vs 15.6%); Blurred Vision (6.2% vs 6.2%); Nasal Congestion (7.3% vs 9.3%). See the complete prescribing information for other reported adverse events. **Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder.** The incidence of treatment-emergent adverse events that occurred during placebo-controlled trials in 85% of alprazolam patients treated for panic disorder (n=1,388) vs placebo-treated patients (n=1,231) were: Drowsiness (76.8% vs 42.7%); Fatigue and Tiredness (48.6% vs 42.3%); Impaired Coordination (40.1% vs 17.9%); Irritability (33.1% vs 30.1%); Memory Impairment (33.1% vs 22.1%); Lightheadedness/Dizziness (29.8% vs 36.9%); Insomnia (29.4% vs 41.8%); Headache (29.2% vs 35.6%); Cognitive Disorder (28.8% vs 20.5%); Dysarthria (23.3% vs 6.3%); Anxiety (16.6% vs 24.9%); Abnormal Involuntary Movement (14.8% vs 21.0%); Decreased Libido (14.4% vs 8.0%); Depression (13.8% vs 14.0%); Confusional State (10.4% vs 8.2%); Muscular Twitching (7.9% vs 11.8%); Increased Libido (7.7% vs 4.1%); Change in Libido (Not Specified) (7.1% vs 5.6%); Weakness (7.1% vs 8.4%); Muscle Tone Disorders (6.3% vs 7.5%); Decreased Salivation (32.8% vs 34.2%); Constipation (26.2% vs 15.4%); Nausea/Vomiting (22.0% vs 31.8%); Diarrhea (20.6% vs 22.8%); Abdominal Distress (18.3% vs 21.5%); Increased Salivation (5.6% vs 4.4%); Nasal Congestion (17.4% vs 16.5%); Tachycardia (15.4% vs 26.8%); Chest Pain (10.6% vs 18.1%); Hyperventilation (9.7% vs 14.5%); Blurred Vision (21.0% vs 21.4%); Tinnitus (6.6% vs 10.4%); Sweating (15.1% vs 23.5%); Rash (10.8% vs 8.1%); Increased Appetite (32.7% vs 22.8%); Decreased Appetite (27.8% vs 24.1%); Weight Gain (27.2% vs 17.9%); Weight Loss (22.6% vs 16.5%); Micturition Difficulties (12.2% vs 8.6%); Menstrual Disorders (10.4% vs 8.7%); Sexual Dysfunction (7.4% vs 3.7%). See the complete prescribing information for other reported adverse events. **Adverse Events Reported as Reasons for Discontinuation in Treatment of Panic Disorder in Placebo-Controlled Trials.** In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received alprazolam, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo-treated group were as follows: Insomnia (29.5%); Lightheadedness (19.3%); Abnormal involuntary movement (17.3%); Headache (17.0%); Muscular twitching (6.9%); Impaired coordination (6.6%); Muscle tone disorders (5.9%); Weakness (5.8%); Anxiety (19.2%); Fatigue and Tiredness (18.4%); Irritability (10.5%); Cognitive disorder (10.3%); Memory impairment (5.5%); Depression (5.1%); Confusional state (5.0%); Nausea/Vomiting (16.5%); Diarrhea (13.6%); Decreased salivation (10.6%); Weight loss (13.3%); Decreased appetite (12.8%); Sweating (14.4%); Tachycardia (12.2%); Blurred vision (10.0%). See complete prescribing information for further information. **Post Introduction Reports:** See complete prescribing information. **DRUG ABUSE AND DEPENDENCE. Physical and Psychological Dependence.** Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including alprazolam. While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day. (see WARNINGS). Psychological dependence is a risk with all benzodiazepines, including NIRAVAM™. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. **Controlled Substance Class.** Schedule IV.

Please see full Prescribing Information for additional information about Niravam™ available at [www.NIRAVAM.com](http://www.NIRAVAM.com).

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