Addiction Medicine
and the Primary Care Physician

Alprazolam Use and Dependence
A Retrospective Analysis of 30 Cases of Withdrawal

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From 1986 to 1989, the Chemical Dependency Recovery Program at Kaiser Permanente Hospital, Fontana, California, admitted an increasing number of patients for alprazolam dependence. Severe withdrawal reactions and adverse consequences with use were reported in the literature. In this review of 30 cases of alprazolam dependence and subsequent withdrawal, there was a statistically significant increase in the number of patient hospital days, the subjective symptoms, and staff time spent with patients compared with those in alcoholic controls. Most patients with diagnosed alprazolam dependence used doses in the range recommended by the package information at the time of admission. Patients with low preadmission doses of 1 mg or less per day showed notable withdrawal symptoms. The average duration of use was 29.9 months, considerably longer than suggested effective ranges. Most patients (28) had a chemical dependence history before being placed on alprazolam therapy; 24 had a positive family history of chemical dependence; and 24 had previous or current psychiatric care.

(Dickinson B, Rush PA, Radcliffe AB: Alprazolam use and dependence—A retrospective analysis of 30 cases of withdrawal, *In* Addiction Medicine [Special Issue]. West J Med 1990 May; 152:604-608)

There is increased debate in the literature regarding the appropriate use of benzodiazepines.[1-4] Humans have been using hypnotic-sedative agents for many centuries, the first recorded use of alcohol being documented in Genesis 9. Barbiturates appeared in the 1930s, and the first benzodiazepines were marketed in the early 1960s. Associated with the use of benzodiazepines have been abuse, dependence, and withdrawal sequelae.[5-8]

For the purpose of this review, "abuse" is defined as the use of mind-altering drugs that cause interpersonal, family, job, legal, financial, or health problems in a person's life. "Dependence" is dysfunction (psychological and sometimes physical) resulting from the interaction between human beings and mind-altering drugs characterized by behavioral and other responses that always include a compulsion to take the drug to experience its psychological effects or to avoid the discomfort of its absence. "Addiction" is a state of periodic or chronic intoxication detrimental to persons and society produced by repeated consumption of a drug. Addiction is marked by a compulsion to use, tolerance, and withdrawal signs and symptoms with abstinence.

Reports of abuse, dependence, and addiction to benzodiazepines have periodically sparked debate in an attempt to reach a consensus on the appropriate use of these drugs. The focus of debate is on setting guidelines for prescribing indications, alternative medications, or therapy instead of benzodiazepines; specific time limits for benzodiazepine use; and reevaluation periods that may include being off all medication or changes in medication.[1-4,7-11] Since the early 1960s when chlordiazepoxide was first introduced, many benzodiazepines have been developed and more are in the process. With new agents there is hope that one day there will be a benzodiazepine that does not lead to dependence. To date, this has not been seen. In addition there is evidence that patients with a previous chemical dependence history, especially to other hypnotic-sedative drugs, are at an increased risk for dependence to develop with the use of benzodiazepines.[7-10,12]

In 1981 the Upjohn Company began marketing alprazolam (Xanax). The primary indication for its use was anxiety.[13] As of 1988, alprazolam was the number one selling benzodiazepine ("Upjohn: Bringing Attention to Anxiety in Children," *Medical Advertising News*, October 15, 1988, pp 8, 26). Its use is being suggested with an increasing array of indications in addition to anxiety (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised [DSM-IIIR] codes 300.00, 300.02).[5] Other uses include panic disorder (DSM-IIIR codes 300.01, 300.21),[14] agoraphobia (code 300.22),[14] social phobia (code 300.23),[15] adverse schizophrenic symptoms,[16] and the premenstrual syndrome.[17] Alprazolam is being suggested for treating separation anxiety and generalized anxiety in adolescents. The product circular indicates few side effects as long as dose limits are followed and that dosage reduction should be at a rate of 0.5 mg every three days. In addition, the product circular advises that alprazolam use is not usually indicated for the relief of anxiety or tension associated with the stress of everyday life; effectiveness longer than four months has not been established; and it should not be used in pregnancy or with alcohol.[13] Previous studies of this drug have also indicated low rates of side effects.[14]

The number of reports of problems with alprazolam

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during both treatment and withdrawal is increasing. Hostility,[18,19] rebound insomnia,[20] major depression,[21] amnesia, aggressive and violent behavior, mania, hepatitis, hepatomegaly, jaundice, and altered liver function have all been reported during treatment.[14] Severe withdrawal symptoms reported have included seizures,[22-25] rebound anxiety greater than before being placed on alprazolam therapy,[22,26,27] delirium,[24,28] psychosis,[22] mania,[29] paranoia,[29] and increased panic attacks compared with pretreatment levels.[30] Increased cortisol levels have also been seen.[26] Many cases involving generalized benzodiazepine withdrawal symptoms have been reported.[22,24,26,27,31-35] Several reports indicate that standard withdrawal measures, especially substituting other benzodiazepines for alprazolam, have not been effective in treating alprazolam withdrawal.[23,28,33,36] It has been theorized that alprazolam and other triazolobenzodiazepines may work at varying sets or subsets of receptor sites other than those of other benzodiazepines.[22,23,28,33,36] This helps to explain incomplete cross tolerance and may provide insight into the causes of more difficult withdrawal in alprazolam patients. Some reports indicate that patients with a previous history of chemical dependence prefer alprazolam over diazepam.[37,38]

During the past year, the staff at our treatment center have noted that patients in withdrawal from alprazolam have a longer detoxification time, more severe withdrawal symptoms, and require more staff time than other patients. These observations seem to correlate with findings in the medical literature.[26,30,34,39] During the period January 1989 to May 1989, there was a greatly increased number of admissions for alprazolam withdrawal. This has also been seen at some treatment centers.[32]

The following report summarizes 30 cases of alprazolam withdrawal seen from October 1986 through May 1989. Cases of alprazolam withdrawal before October 1986 were not included because our computer data base does not list cases specifically for alprazolam before that date.

Patients and Methods

In this review we retrospectively analyze 30 cases of alprazolam withdrawal in patients who were admitted for detoxification from October 1986 until May 1989. All cases had a discharge diagnosis of alprazolam dependence (DSM-IIIR codes 292.00, 304.10). Treatments used include supportive counseling, group therapy, and continuing medical regimens used before admission for chronic disorders—such as antihypertensive drugs, asthma treatments, and the like. Pentobarbital substitution and gradual withdrawal were frequently used to minimize physical signs and symptoms of benzodiazepine withdrawal (hypertension, tachycardia, and seizures). In this 32-month period, 1,595 patients were admitted to the inpatient unit at the Chemical Dependency Recovery Program, Kaiser Permanente Hospital, Fontana, California. Patients were referred to the recovery program by other services or departments within the health plan. These 30 cases represent 1.9% of all admissions. All medical records were reviewed by one examiner (B.D.). Information was collected on the admission date, age, sex, race, source of initial alprazolam prescribed, the primary indication for alprazolam use when initially prescribed, chemical dependence history before alprazolam use, family history of chemical dependence, psychiatric history, subjective and physical signs of withdrawal, number of detoxification days, initial prescribed dosage of alprazolam, maximum alprazolam dose used in one 24-hour period, alprazolam dose per day being used at the time of admission, and the duration of use.

The severity of withdrawal was estimated in several areas. The number of patient days spent in primary detoxification were counted. The Chemical Dependency Recovery Program uses predominantly inpatient services for detoxification. This is followed by an intensive outpatient program where the patient spends 9 to 12 hours a day in therapy at the recovery program for an additional one to two weeks. Patients are observed medically during this time and may continue to have some minor withdrawal symptoms. No data from this intensive outpatient program are included in this study. Only primarily detoxification days were counted. The number and type of both subjective and physical withdrawal signs and symptoms were recorded. The number of staff entries per day was noted. Both the withdrawal signs and symptoms and the staff entries are recorded in the patient's chart either during routine general patient monitoring of all patients several times each day or when a patient seeks out the staff because of specific complaints. All entries by the staff attempt to accurately reflect both the patients' specific words and the staff's observations and vital signs measurements.

Alprazolam-dependent patients were compared in each of the preceding areas with a control group. The controls came from a stratified random sample of patients admitted for alcohol dependence between October 1986 and July 1989. Control patients were matched to the alprazolam group on the basis of sex, age, and race.

Results

Admission Date

Three patients were admitted during 1986, nine patients during 1987, nine patients during 1988, and nine patients from January through May 1989. Of the 30 patients, 9 (30%) were admitted during the last five months of the study. As a point of interest but not included in this study, 3 additional patients in alprazolam withdrawal were admitted during June 1989, giving a total of 12 patients admitted for alprazolam withdrawal in the first six months of 1989.

Age

The average age of admission for the alprazolam cases and controls was 43.7 and 44.4 years, respectively. The age range was 20 to 73 years for the alprazolam group and 25 to 67 for controls. For the study group, 26 patients (87%) were between 30 and 59 years of age compared with 24 (80%) for controls. The difference in mean age between the two groups was not statistically significant ($t = -0.26$, $P > .05$).

Sex

In the study group, 22 (73%) patients were female and 8 (27%) were male. This was identical to controls.

Race

Of the 30 patients, 25 (83%) were white, 4 (13%) were hispanic, and 1 (3%) was black. This was identical to controls.

Chemical Dependence History

Of the 30 patients, 28 (93%) had a chemical dependence by history before being started on alprazolam therapy.

Family History of Chemical Dependence

Patients had a family history of chemical dependence as reported by 24 patients (80%) in the alprazolam group and 27 (90%) in the alcohol group. The difference was not significant ($\chi^2 = 1.18$, $P > .05$).

Psychiatric History

Of the 30 patients, 24 (80%) had a history of psychiatric care either before or during their alprazolam use. Psychiatric care was reported by 8 (27%) of the controls.

Initial Dosage of Alprazolam

In all cases where data were available (29/30), alprazolam was prescribed in the therapeutic dose range at initial use. Data were not available in one case regarding the initial dosage prescribed. The initial dosage ranged from 0.25 mg to 4.0 mg per day.

Maximum Alprazolam Dose Used in a 24-Hour Period

The range of maximum dosage used was 0.75 mg to 20.0 mg per day. In 24 patients the dosage was 4.0 mg per day or less and therefore in the therapeutic dose range according to the Xanax product circular. Two patients used 5 mg per day, one used 6 mg per day, two used 8 mg per day, and one patient reported using 20 mg per day.

Alprazolam Dose per Day at Time of Admission

The range of the alprazolam dosage used at the time of admission was 0.5 mg to 7.0 mg per day; 27 (90%) patients were at 4.0 mg per day or less. These patients were therefore in the therapeutic dose range listed in the product circular. Patients reported trying to cut down on their use of alprazolam before admission: 21 (70%) had a daily dose of less than their maximum dose at the time of admission. In addition, 9 (30%) patients experienced signs and symptoms of withdrawal from using 1.0 mg per day or less.

Duration of Use

The average duration of use was 29.9 months with a range of 4 to 84 months. Five patients (17%) used the drug for ten months or less, two (7%) used it for only four months.

Source of Initial Use

Of 26 patients, 19 (73%) received alprazolam from a psychiatrist and 7 patients (27%) received alprazolam from a primary care physician. In the remaining four cases, the original source could not be ascertained.

Primary Indication for Initial Use

In 26 cases, alprazolam was used for general anxiety, panic attacks, or agoraphobia. In the remaining four cases, the original indication for beginning alprazolam use was unknown.

Patient Days

The average number of days for a patient to have withdrawal signs and symptoms from alprazolam was 8.8; the range was 5 to 18 days. Four patients from the study group and three from the control group left against medical advice. Their patient days were not counted in the average. In comparison, patients undergoing withdrawal from alcohol took an average of 5.9 days to go through most of their withdrawal signs and symptoms. The range for alcoholic patients was 4 to 8 days. Thus, alprazolam withdrawal patients took an average of 2.9 days longer to go through the major part of detoxification than the patients undergoing alcohol withdrawal. The difference was statistically significant ($t = 4.70$, $P = .0001$).

Subjective Symptoms of Withdrawal

Alprazolam withdrawal patients had an average of 7.6 different types of complaints described per patient. The following is a breakdown of the percentage of alprazolam withdrawal charts containing specific subjective symptoms: anxiety, 70%; headache, 50%; agitation, 47%; tearful, 47%; nausea and vomiting, 40%; feeling shaky, 37%; nervous, 37%; insomnia, 33%; muscle aches, 33%; restlessness, 27%; fatigue, 27%; mood swings, 27%; anger, 23%; pacing, 20%; fear, 20%; stomach cramps, 20%; isolation, 17%; dizziness, 17%; and panic, 10%. Subjective complaints were not compared against those of control subjects.

Physical Signs of Withdrawal

In all, 28 (93%) of the 30 alprazolam patients and 21 (70%) of the 30 alcoholic patients had physical signs of withdrawal. The difference in proportions was statistically significant ($\chi^2 = 5.46$, $P = .02$). In the alprazolam group, these included elevated systolic and diastolic blood pressures, 20; tachycardia, 20; tremors, 15 (50%); and sweating, 1 (3%).

Staff Entries per Day

As an assessment of staff time used during withdrawal, the number of staff charting entries per day was measured for each patient. Alprazolam patients had an average of 8.5 staff entries per day with a range of 5.2 to 17.4. Alcoholic patients averaged 7.3 entries per day with a range of 4.3 to 9.8. Alprazolam patients averaged 1.2 more staff entries per day compared with alcoholic patients, the difference being statistically significant ($t = 2.48$, $P = .02$).

Discussion

There was a pronounced increase in the number of admissions to the Kaiser Chemical Dependency Recovery Program for alprazolam withdrawal in the period from October 1986 through May 1989. This correlates with other studies.[32]

In all, 27 of our patients (90%) admitted for alprazolam withdrawal reported increasing their use of alprazolam over time. This has been seen in previous studies.[39] Of the patients who were admitted, 21 (70%) had tried to cut down on their alprazolam use before admission but were only able to do so slightly. Patients often told the staff at the recovery program that they were unable to reduce their use of alprazolam further, and this was one reason they were convinced of their dependence on the drug. An interesting finding in this review was that 24 patients (80%) were taking alprazolam at dosages within the listed therapeutic dose range at the time of their maximal use and 27 patients (90%) admitted for alprazolam withdrawal were taking alprazolam in a dosage suggested in the package literature at the time of admission. A dependence on low or therapeutic doses of benzodiazepines and an associated low-dose withdrawal syndrome has been described previously in the medical literature.[1,6] This review correlates with those previous findings, suggesting that more caution should be used when prescribing alprazolam because dependence may develop at recommended therapeutic levels. As

reported by Ayd, Rashid and co-workers have recommended that the maximum dose for a 24-hour period should be 1 mg or less.[39] Even at this level, 9 patients (30%) in this study had significant withdrawal signs and symptoms.

The product insert for alprazolam states that "the effectiveness of Xanax for long-term use, that is, more than four months, has not been established by systematic clinical trials." In this study, the average duration of use of 29.9 months greatly exceeded the demonstrated efficacious time listed in the product circular. Considering that 90% of the patients with alprazolam withdrawal were within the suggested dosage range at the time of admission, it is reasonable to suspect that an extended duration of use also contributes to the development of alprazolam dependence. Similar information has already been published for other benzodiazepines.[1,3,6,7,11] Ayd reported that Rashid and associates clearly state that four months should be the maximum length of time for alprazolam use.[39] Other studies have echoed this caution.[1,3,4,7,8,11] In one published report alprazolam withdrawal was described after only eight weeks of use.[35]

Withdrawal from alprazolam has been described as a tedious process[3,34] and unresponsive to standard medical withdrawal regimens.[23,28,33,34,36] Although the product circular recommends reducing the dose of alprazolam at a rate of 0.5 mg every three days, there is little if any support for this procedure in the literature. Most studies have recommended a much slower rate.[3,26,34] One recommended an outpatient reduction of no more than 0.25 mg every two weeks.[3] The information in this study confirms previous reports of severe withdrawal signs and symptoms from alprazolam. Patient days in withdrawal, the number and type of physical signs of withdrawal, and the amount of staff time needed for each patient with alprazolam withdrawal were all notably increased over those in patients with alcohol withdrawal.

Although the medical literature describes seizures occurring in a significant percentage of alprazolam withdrawal patients,[22-25] we found no seizures during the treatment of withdrawal.

Conclusion

Many studies have concluded that patients with a history of chemical dependence are at an increased risk to become dependent on benzodiazepines.[7-10,12,37,38] One study showed that alprazolam produced more euphoria and drug-induced behavioral changes in alcoholics than in nonalcoholics.[37] Another study found that patients who had a history of benzodiazepine dependence liked to use and sought to use alprazolam instead of diazepam.[38] In light of this, our case reviews found that 28 of 30 patients (93%) with alprazolam withdrawal admitted to the Chemical Dependency Recovery Program had a history of chemical dependence. This history was not always known by the physicians who initially prescribed the alprazolam, and this finding reinforces the need to be extremely cautious in prescribing this drug to patients with such a history. Ciraulo and colleagues have shown evidence that parental alcoholism is a risk in benzodiazepine abuse.[40] We found that 24 of these patients (80%) had a family history of chemical dependence, which supports their conclusion. A family history for dependence should also be obtained and considered before prescribing alprazolam. In addition, we found that 80% of patients (24) admitted for alprazolam withdrawal had a previous or concurrent history of psychiatric illness. This correlates with the finding in this review that a psychiatrist was the source of the initial use of alprazolam in 22 patients (73%) admitted for alprazolam withdrawal. It is known that patients with chemical dependence issues often have a concurrent psychiatric diagnosis. Many of these are related to the dependence or abuse of drugs and alcohol. Both anxiety and panic can accompany use and withdrawal from a variety of substances.

We found that in 100% of the cases, the primary indication for alprazolam use was generalized anxiety, panic attacks, or both. It would therefore seem important to obtain a chemical dependence history and a family history for chemical dependence in any patient under psychiatric care. This will help facilitate the appropriate use of alprazolam, especially to use caution in prescribing for patients with this type of history.

REFERENCES

1. Woods JH, Katz JL, Winger G, et al: Use and abuse of benzodiazepines. JAMA 1988; 260:3476-3480

2. Lin S, Morse RM, Finlayson RE, et al: Abuse of benzodiazepines. JAMA 1989; 261:2956-2957

3. Bystritsky A: Benzodiazepine withdrawal. South Calif Psychiatr Soc Newslett 1989; 37:10

4. Yates WR, Wesner RB: Advances in anxiety management. J Am Board Fam Pract 1989; 2:38-42

5. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed Revised. Washington, DC, American Psychiatric Association, 1987

6. Smith DE, Wesson DR: Benzodiazepine dependency syndromes. J Psychoactive Drugs 1983; 15:85-95

7. WHO Review Group: Use and abuse of benzodiazepines. Bull WHO 1983; 61:551-562

8. Dietch J: The nature and extent of benzodiazepine abuse: An overview of recent literature. Hosp Community Psychiatry 1983; 34:1139-1145

9. Ciraulo DA, Sands BF, Shader RI: Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psychiatry 1988; 145:1501-1506

10. Schuckit MA, Morrissey ER: Drug abuse among alcoholic women. Am J Psychiatry 1979; 136(4B):607-611

11. Chiefs of Psychiatry: Guidelines for the Treatment of Insomnia, Anxiety and Panic Disorders in the Primary Care Setting. Pasadena, Calif, Southern California Permanente Medical Group Publication, March 1989

12. Ayd FJ: The abuse liability of alprazolam. Int Drug Ther Newslett 1989; 24:4

13. Product Insert, Xanax. Kalamazoo, Mich, Upjohn Company, 1985

14. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial. Arch Gen Psychiatry 1988; 45:423-428

15. Reich J, Yates W: A pilot study of treatment of social phobia with alprazolam. Am J Psychiatry 1988; 145:590-594

16. Csernansky JG, Riney SJ, Lombrozo L, et al: Double-blind comparison of alprazolam, diazepam, and placebo for the treatment of negative schizophrenic symptoms. Arch Gen Psychiatry 1988; 45:655-659

17. Smith S, Rinehart JS, Ruddock VE, et al: Treatment of premenstrual syndrome with alprazolam. Obstet Gynecol 1987; 70:37-43

18. Rosenbaum JF, Wood SW, Groves JE, et al: Emergence of hostility during alprazolam treatment. Am J Psychiatry 1984; 141:792-793

19. Rapaport M, Braff DL: Alprazolam and hostility (Letter). Am J Psychiatry 1985; 142:146

20. Kales A, Bixler EO, Vela-Bueno A, et al: Alprazolam: Effects on sleep and withdrawal phenomena. J Clin Pharmacol 1987; 27:508-515

21. Lydiard RB, Laraia MT, Ballenger JC, et al: Emergence of depressive symptoms in patients receiving alprazolam for panic disorder. Am J Psychiatry 1987; 144:664-665

22. Browne JL, Hauge KJ: A review of alprazolam withdrawal. Drug Intell Clin Pharm 1986; 20:837-841

23. Kantor SJ: A difficult alprazolam withdrawal. J Clin Psychopharmacol 1986; 6:124-125

24. Levy AB: Delirium and seizures due to abrupt alprazolam withdrawal. J Clin Psychiatry 1984; 45:38-39

25. Breier A, Charney DS, Nelson JC: Seizures induced by abrupt discontinuation of alprazolam. Am J Psychiatry 1984; 141:1606-1607

26. Mellman TA, Uhde TW: Withdrawal syndrome with gradual tapering of alprazolam. Am J Psychiatry 1986; 143:1464-1466

27. Vital-Herne J, Brenner R, Lesser M: Another case of alprazolam withdrawal syndrome (Letter). Am J Psychiatry 1985; 142:1515

28. Zipursky RB, Baker RW, Zimmer B: Alprazolam withdrawal delirium unresponsive to diazepam. J Clin Psychiatry 1985; 46:344-345

29. Bleich A, Grinspoon A, Garb R: Paranoid reaction following alprazolam withdrawal. Psychosomatics 1987; 28:599-600

30. Fyer AJ, Leibowitz MR, Gorman JM, et al: Discontinuation of alprazolam treatment in panic patients. Am J Psychiatry 1987; 144:303-308

31. Patterson JF: Alprazolam dependency—Use of clonazepam for withdrawal. South Med J 1988; 81:830-836

32. Juergens SM, Morse RM: Alprazolam dependence in seven patients. Am J Psychiatry 1988; 145:625-627

33. Alprazolam withdrawal. Mass Gen Hosp Newslett Biol Ther Psychiatry 1987; 10:11

34. Ayd FJ: Alprazolam withdrawal. Int Drug Ther Newslett 1986; 21:28

35. Noyes R, Clancy J, Coryell WH, et al: A withdrawal syndrome after abrupt discontinuation of alprazolam. Am J Psychiatry 1985; 142:114-116

36. Votolato NA, Batcha KJ, Olson SC: Alprazolam withdrawal (Letter). Drug Intell Clin Pharm 1987; 21:754-755

37. Ciraulo DA, Barnhill JG, Greenblatt DJ, et al: Abuse liability and clinical pharmacokinetics of alprazolam in alcoholic men. J Clin Psychiatry 1988; 49:333-337

38. Schmauss C, Apelt S, Emrich HM: The seeking and liking potentials of alprazolam (Letter). Am J Psychiatry 1988; 145:128

39. Ayd FJ: Problems associated with alprazolam therapy. Int Drug Ther Newslett 1988; 23:29-31

40. Ciraulo DA, Barnhill JG, Ciraulo AM, et al: Parental alcoholism as a risk factor in benzodiazepine abuse: A pilot study. Am J Psychiatry 1989; 146:1333-1335