Book Review

Changing perspectives on homosexuality

Stein T.S.: in Review of Psychiatry.
(ed.) Oldham J.M., Riba M.B., and Tasman A.
American Psychiatric Press Inc., Chapter 1, Volume 12, 1993

The beginning of the struggle for gay rights is marked by the riots that occurred in New York in 1969. However, a number of homophile groups began working to attain greater acceptance of homosexuality after World War II. They also began to pressure medical and psychiatric associations to "depathologize" homosexuality.

In the atmosphere created by the new social and political forces calling for elimination of homosexuality from the list of psychiatric diagnoses of mental illness, the American Psychiatric Association (APA) decided in the early 1970's to remove it from its classification. This view was reached after a significant review of the considerable research that had been published about the subject since Kinsey et al (1948-1953).

So, it is important to understand the earlier history of scientific views about homosexuality and to appreciate the enormity of the APA decision to declassify homosexuality as a type of mental illness.

Homosexuality first became a subject of medical concern during the 1800's, when it began to be viewed as an illness while in religious and moral teaching it had been considered as a form of depravity.

By the end of the 1800's, several researchers began to explore the origins of homosexuality. During the second half of 19th century, homosexuality became a major focus of psychiatric and medical inquiry with particular interest demonstrated in the question of the extent to which it was an inborn trait or an environmentally determined trait.

This was paralleled to the psychoanalytic view during the 20th century, e.g. Freud believed that heterosexuality was the natural outcome of development. He also described a universal bisexual instinct and defined a variety of origins for adult homosexuality.

Freud recognized both inborn and environmental contributions to the development of homosexuality. He also emphasized that even if homosexuality occurred in the absence of other signs of psychopathology it should not be a cause for exclusion from psychoanalytic training.

"Homosexuality is assuredly no advantage ... but it is nothing to be ashamed of ... it cannot be classifled as an illness. We consider it to be a variation of the sexual function produced by a certain arrest of sexual development; it is a great injustice to consider it as a crime".

Later psychoanalysts, in the 60's, viewed homosexuality as invariably a sign of psychopathology and as a symptom of an underlying fear and rejection of a natural and innate heterosexuality.

In addition, they presented a pathological etiology for homosexuality, "as it is a sign of earlier disturbance of the psychosexual development".

This explanation of homosexuality had a great influence on APA in determining its standard approaches to diagnosis and treatment of homosexuality the decision in 1973 by the APA to declassify homosexuality and delete it from DSM II.

So from the time of DSM I (1952), psychiatry considered homosexuality to be a type of mental illness "in which it is listed as a type of psychopathic personality disorder".

Newer Research Findings. About 3-4 works were particularly important in shifting psychiatric opinion about homosexuality e.g. Kinsey et al. (1948), Ford and Beach (1951).... Evelyn Hooker (1957), Marmor et al, 71 72a 72b Ford and Beach. They reported that in the majority (49) of the 76 cultures they studied, homosexuality in some form was considered normal for at least some individuals. They also showed that homosexuality occurred in monkeys and found that

homosexual behavior could be identified in most animals.

Also, Evelyn Hooker (1957) published the major work that challenged the view of homosexuality as psychopathology. She conducted a study of 30 homosexual non-patient men not from mental hospital but from prison or the military and 30 matched heterosexual men; all men were administered 3 projective tests. The result showed that no difference in adjustment was found between the heterosexual and homosexual group.

Current Perspective. Following these and other researches about homosexuality, the APA decided to depathologize homosexuality, but there were some remnants of the pathological perspective evident in the presence of the diagnostic categories-sexual orientation disturbances and also in DSM-III (1980) " ego dystonic homosexuality that allow psychiatrists to still continue to diagnose persons concerned about their homosexuality as mentally ill until (1987) when all were removed from DSM-III-R". Although the current perspectives considered homosexuality not linked to mental disorder yet the individual psychiattist continued to consider homosexuality as abnormal and dysfunctional.

As a result of eliminating homosexuality from mental illness, a more recent research and interest about homosexuality has occurred outside psychiatry, including sociology, history, .. philosophy...

New development in understanding homosexuaity

How adult sexual desire arises and is oriented. It is clear that homosexuality is the pathway for many men and women.

Recent discussion concerning the question of the development of homosexuality or bisexual orientation has focused on three aspects of maturation.

(1) Homosexuality in children and adolescents;
(2) The coming out process;
(3) How gay, lesbian, bisexual identities are acquired.

I. Homosexuality in children and adolescents.

Most theorists believe that the factors determining adult sexual orientation are established at an early age especially at 2 or 3 years old, but the manner in which these factors interact with other influences throughout the course of a lifetime lead to a great variation in the expression of sexual orientation.

(1) Biological factors.
(2) Genetic factors.
(3) Social and political factors may influence the formation of homosexuality.
(4) Marmor's statement "that homosexuality is multiply determined by psychodynamic socio-cultural, biological, situational factors" is our best guide to the origins.

II. The coming out process

It refers to the most basic level to a state of being clearly and openly gay in contrast to remaining " in the closet" and hiding one's homosexuality, either from oneself or from others.

The coming out reflects a complex series of cognitive and affective transformations as well as changes in behavior as:

Adoption of non traditional identity
Alteration of self concept.
Alteration of one's relation with others.
Alteration of one's relation with society.

McDonald identified various events and features correlates to the coming out, including:

Awareness of same - sex attraction 13yrs.
Participation. in same sex acts 15yrs.
Labeling self as homosexual 19 yrs.
Involving in a homosexual relationship 21yrs.
Participation in the gay subculture.
View oneself as having a positive gay identity it also needs a social change and acceptance. Homosexual identity formation.

Two example of such identity development are:

Coleman (1982) described 5 stages.

1. The precoming out
2. The coming out.
3 The exploration.
4 The first relationship.
5. The identity integration.

Cases (1979) described a 6-stage-model for the development process leading to the formation of homosexual identity.

1. Identity confusion.
2. Identity comparison.
3. Identity tolerance.
4. Identity acceptance.
5. Identity pride.
6. Identity synthesis - it involve the merging of personal and public sexual identities and integration of the homosexual identity with other aspects of the self.

Dr. M. Mansour

Current Pharmacy Information

Trade mark
Xanax
Generic name
Alprazolam
Investigational Synonym
U-31, 889
Hospital Formulary Category
Psychotherapeutic Agents (anxiolytics)

Indications and Usage

Xanax is indicated for the treatment of anxiety states (anxiety neuroses) with or without associated symptoms of depression.
Symptoms of anxiety states may variably include anxiety, tension, fear, apprehension, restlessness, concentration difficulties, irritability, insomnia, and/or autonomic hyperactivity, resulting in a variety of somatic complaints. Depressive symptoms occurring in patients with an anxiety state may invariably include depressed or dysphoric mood, loss of interest or pleasure, decreased energy, cognitive disturbances and/or psychomotor agitation.

Xanax is also indicated for the treatment of anxiety states and mixed anxiety-depression associated with other diseases such as the chronic phase of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular, or dermatological disorders.

Xanax is not indicated in patients whose primary symptom of depression is psychomotor retardation, with a diagnosis of bipolar depression or in patients with psychotic symptoms.

The effectiveness of Xanax for long-term use exceeding six months has not been established by systematic clinical trials. The physician should periodically reassess the usefulness of the drug for the individual patient.

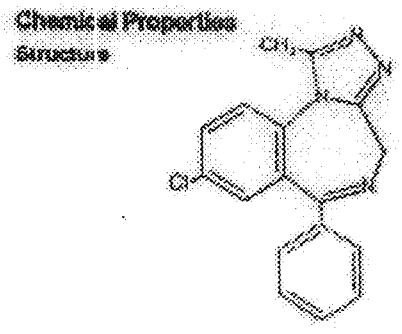
Dosage and Administration

The optimum dosage of Xanax should be individualized based upon the severity of the symptoms and individual patient response. The usual dosage (see table) will meet the needs of most patients. In the few patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquillizers, antidepressants or hypnotics or those with a history of chronic alcoholism. It is recommended that the general principal of using the lowest effective dose be followed in elderly or debilitated patients to preclude the development of over sedation or ataxia.

Indication	Adults	Geriatric patients or in the presence of debilitating disease
Anxiety states or anxiety with symptoms of depression	Usual starting dosage*: 0.25 to 0.5 mg. given three times daily. Usual dosage range: 0.5 to 4.0 mg. daily given in divided doses.	Usual starting dosage*: 0.25 mg. given two to times daily. Usual dosage range: 0.5 to 0.75 mg. daily given in divided doses; to be gradually increased if needed and tolerated.

* If side-effects occur, the dosage should be lowered.

Chemical properties structure



Name

8-chloro-1-methly-6-phenyl- 4H-s-triazolo [4,3-alpha] [1,4] benzo-diazepine

Classification and description

Xanax tablets contain alprazolam, which is a triozolo analogue of the 1,4 benzodiazepine class of central nervous system active compounds. Alprazolam is a white crystalline powder, soluble in methanol or ethanol but with no appreciable solubility in water at physiological pH.

Physical properties

Emperical formula

$C_{17}H_{13}C_1N_4$

Molecular weight

308.76

Melting Point, Solubility

Aloprazolam is supplied as a white, crystalline, micronised powder with a melting point in the range of 228-231°C and is not appreciably soluble in water. It is soluble in methanol, ethanol, methylene chloride and chloroform.

Pharmaceutic and manufacturing factors

Tablet composition

The active ingredient in Xanax is alprazolam, a white crystalline powder. Each Xanax tablet for oral administration contains 0.25 mg. (white), 0.5mg. (peach), or 1.0 mg. (lavender) of alprazolam.

Storage Conditions

Xanax tablets should be stored at controlled room temperature, 15°C (59°F) to 30°C(86°F).

Expiration Dating

Xanax tablets have an expiration period of 36 months. When recommended storage conditions are followed.

Animal pharmacology

An overview of the pharmacology of alprazolam reveals a compound qualitatively similar to diazepam (Valium) but different from this drug in at least three aspects. First, alprazolam is about ten times more potent than diazepam on a weight basis. Second is its low order of acute toxicity. In rodents, it is only slightly more toxic than diazepam, even though it is several times more potent on an overall basis. Third, alprazolam appears to have a flatter dose-response slope than does diazepam.

A more detailed evaluation of the pharmacology of alprazolam reveals a compound with anxiolytic, hypnotic, muscle relaxant, and anti-convulsant properties. These properties are shared by all members of the benzodiazepine class, but in different proportions.

Alprazolam has a more rapid onset of activity ,an earlier peak effect, and a shorter duration of action than diazepam in the mouse, rat, and rhesus monkey. Over the dosage range of 3 to 100 mg/kg, brain levels were directly proportional to the administered dose.

Clinical pharmacology

Overview

Following oral administration, the alprazolam in xanax is readily absorbed; peak concentration in the plasma occurs within one to two hours. Plasma levels are proportionate to the dose given . Over the dosage range of 0.5 to 3.0 mg, peak levels of 8.0 to 37ng/ml., were observed. The mean elimination half-life of alprazolam is 12 to 15 hours, and the range for the elimination half-life is six to 20 hours. Alprazolam is classified as having an intermediate half-life. The predominant metabolites are alpha-hydroxy alprazolam and a benzophenone. The biological activity of alpha-hydroxy-alprazolam is approximately half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokintic description. However their half-lives appear to be of the same order of magnitude as alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

Blood levels

Single-dose studies: Single doses of 0.5 mg Xanax. Tablets were given to ten normal male volunteers at 7 AM following overnight fasting. Figure 1 presents the median concentrations of alprazolam serum concentrations as determined by radio immunoassay. Table 1 presents the mean for several pharmacokinetic parameters.

Figure (1): Serum concentration of Alprazolem after 0.5 mg. Doses

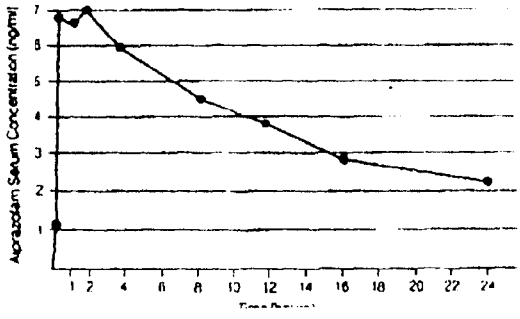


Table (1): Xanax, Single-Dose Pharmacokinetics

Area under curve (AUC) (ng-hrm)	93.8
Maximum serum concentration (C max) (ng/ml)	7.5
Average time to peak concenteration (T max) (hr)	2.0
Elimintation half-life (El t½) (hr).	11.7

Single dose pharmacokinetics of 1.0 mg. Xanax Tablets in non-smokers and smokers: Single dose pharmacokinetics of 1.0 mg. Xanax Tablets given orally were evaluated in ten healthy male volunteers (average 27.3 years); there were five non-smokers and five smokers. Table 2 presents the average values for several pharmacokinetic parameters in the ten subjects after an overnight fast and four hours post-ingestion.

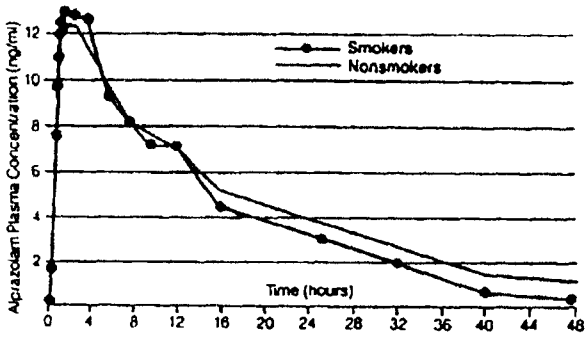
Table (2): Pharmacokinetics of 1.0 mg. Xanax Tablets (alprazolam) in Non-smokers and Smokers

	Non-smokers	Smokers	Average All subjects
AUC 0 to 48 hr (ng-hr/ml)	216.03	201.56	208.80
C_{max} (ng/ml)	13.84	15.40	14.62
T_{max} (hr)	1.55	1.95	1.75
t½ (hr)	12.62	10.69	11.59

No statistically significant differences were found in the plasma concentrations or bioavailability parameters between non-smokers and smokers. Figure 2 shows the average plasma concentrations for non-smokers and smokers.

Figure (2): shows the average plasma concentrations for non-smokers and smokers.

Figure (2) Average Alprazolam Concentration in Smokers and Non-smokers after single 1.0 mg. Xanax Dose*.



* Data on file at the Upjohn Company (CS No. 033).

Effects of age and gender on the pharmacokinetics of alprazolam following a single oral 1.0 mg. dose: A single oral dose of two Xanax 0.5 mg. tablets was administrated to 32 healthy males and females. The results of each group are found in Table 3. The mean alprazolam elimination half-life does not differ significantly between elderly and young females. The elimination half-life was prolonged in elderly males as compared to young males (Figure 3).

Table (3): Pharmacokinetics of 1.0 mg. Xanax Tablets Related to Age and Gender

	Young Males (31 yr)+	Elderly Males (70 yr)	Young Females (28 yr)	Elderly Females (69 yr)
C_{max} (ng/ml)	20.10	19.90	15.70	25.90*
T_{max} (hr)	1.44	1.16	1.75	0.56**
t½ (hr)	11.10	19.00***	10.80	13.50

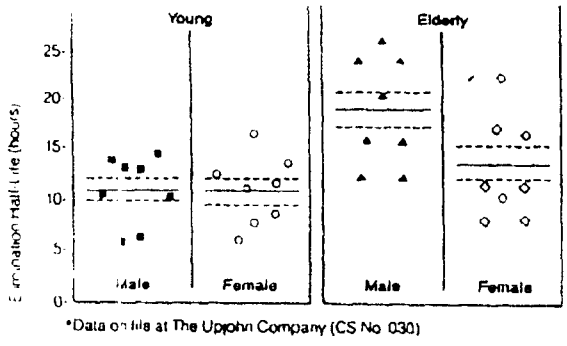
t (average age of the group)

* $p < 0.01$ between young and elderly females

** $p < 0.01$ between young and elderly females

*** $p < 0.01$ between young and elderly males

Figure (3): Alprazolam Elimination Half-Life in Relation to Age and Sex*



* Data on file at The Upjohn Company (CS No. 030).

Effect of food on the bioavailability of alprazolam following a single oral 1.0 mg. dose: In a randomized, two-way, crossover-designed study, the bioavailability of a single oral 1.0 mg. Dose of Xanax (alprazolam) was assessed in 16 healthy males when Xanax was given immediately following a meal or a 12-hour fast. Table 4 provides the pharmacokinetic values obtained from the study.

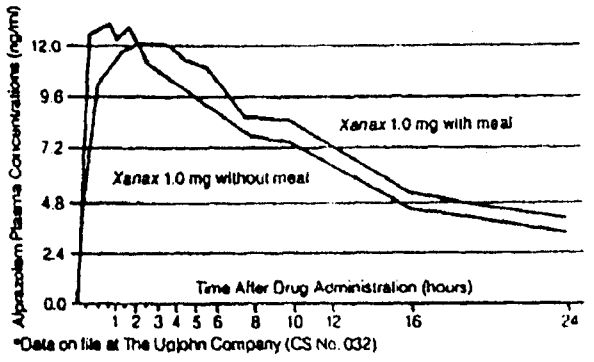
Table (4): Pharmacokinetics of 1.0 mg. Xanax Tablets in Fasting and Food Conditions

		Fasting	Food
AUC (ng-hr/ml)	0 to 2.5hr	26.04*	19.96
	0 to 24hr	164.25	172.68
C_{max} (ng/ml)	0 to 2.5hr	14.21*	12.64
	0 to 24hr	14.26	13.26
T_{max} (hr)		1.61	2.47
t½ (hr)		13.17	13.42

*P < 0.25

The results demonstrate no significant differences between treatment in average area under the curve (AUC), time to peak concentration (Tmax), peak concentration (Cmax), or elimination half-life (t½). Figure 4 shows the plasma levels of alprazolam. This study demonstrates that the administration of Xanax after a meal decreases the average rate of absorption, as compared with fasting subjects, but does not affect the extent of alprazolam absorption.

Figure (4): Plasma Concentration after 1.0 mg. of Xanax in Fasting and Food Conditions*.



* Data on file at the Upjohn Company (CS No. 032).

Effects of alcoholic liver disease on the pharmacokinetics of Xanax 1.0 mg. tablets. A single oral dose of Xanax 1.0 mg. tablets was administrated to 34 patients, 17 with alcoholic liver disease. The time to maximum serum concentration (T_{max}), elimination half-life (t½), and clearance of the drug were all prolonged in the alcoholic liver disease patients as compared with the normal controls (Table 5). The maximum concentration (C_{max}) did not differ between the two groups. The changes in elimination half-life and clearance indicate that the metabolism of alprazolam is slowed in patients with alcoholic liver disease.

Table (5): Pharmacokinetics of 1.0 mg. Xanax Tablets in Alcoholic Liver Disease Patients

	(N=17) Liver disease	(N=17) Normal
T_{max} (hr)	3.34*	1.47
t½ (hr)	19.70**	11.40
C_{max} (ng/ml)	17.30	18.40
Clearance	0.56***	1.22

*P < 0.02 **P < 0.01 ***P < 0.001

Effect of obesity on the pharmacokinetics of Xanax 1.0mg. tablets: In 24 patients, 12 obese and 12 pair-matched normals, a single 1.0mg. Dose of Xanax was administered. Table 6 shows that obese patients had a greater volume of distribution (Vd) and elimination half-life (t½) as compared with normals. There was no difference between the groups in clearance. Alprazolam should accumulate more slowly with chronic dosing in obese patients and should not accumulate to any greater extent in obese patients.

Table (6): Pharmacokinetics of 1.0 mg. Xanax Tablets (alprazolam) in Obese Patients

	Obase	Normal
Vd	113.5*	73.1
Clearance	66.4	88.0
t½	21.8*	10.6

* Statistically significant difference.

Multiple dose study

Multiple-dose pharmacokinetics of Xanax in non smokers and smokers: A 0.5mg. dose of Xanax was administered every eight hours for six days to ten healthy males (five non-smokers and five smokers). Aloprazolam plasma levels were determined after the first dose on day seven and througout the next 48 hours.

The pharmacokinetic data from the study are found in Table 7. None of the differences between non-smokers and smokers were statistically significant.

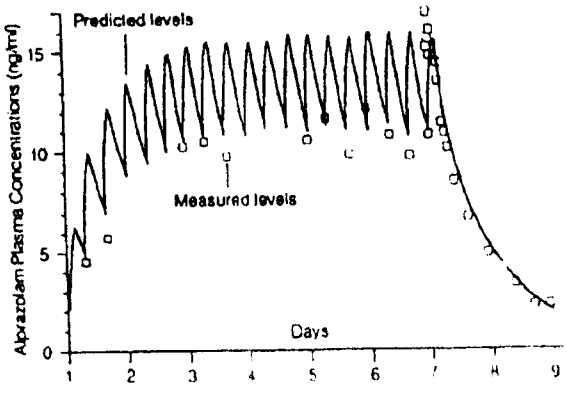
Table (7): Multiple-Dose Pharmacokinetics with 0.5 mg. Xanax Tablets (alprazolam) in Non-smokers and Smokers (Day 7)

	Non-smokers	Smokers	All study subjects
AUC 0 to 8 hr (ng-hr/ml)	117.70	94.15	105.92
C_{max} (ng/ml)	19.88	16.68	18.38
T_{max} (hr)	1.00	1.40	1.20
t½ (hr)	14.20	9.54	11.41

The average plasma concentration on day 7 was approximately 15% to 30% lower in smokers compared with non-smokers due to faster clearance in smokers. The average washout elimination half-life in all volunteers was 11.41 hours, which is almost identical to that after the single dose administration.

Figure 5 represents the predicted plasma concentration (solid line) from the single dose 1.0 mg. study, and the squares represent the observed average concentrations after 0.5 mg. Alprazolam t.i.d.

Figure (5): Predicted and Actual Plasma concentrations of Alprazolam 1.0 mg*



* Data on file at The Upjohn Company (CS No. 033).

Distribution

Tissue distribution:

Tissue distribution of alprazolam ^{14}C radioactivity was studied in the mouse by whole body section autoradiography, with estimation of tissue ^{14}C content by densitometry and/or combustion and counting of excised tissue segments. Single doses of 2.23 mg/kg were given to males, po and IV to females, and po to pregnant females; animals were sacrificed at times ranging from one minute to 24 hours after dosing. Alprazolam and/or metabolites were rapidly and widely distributed throughout the body, reaching maximum levels in most tissues within one hour after dosing and decreasing rapidly thereafter.

Drug-related material entered the central nervous system rapidly, reaching an apparent maximum concentration within one minute of intravenous administration and 15 minutes after oral administration. The concentration of drug-related material in the brain was equal to that in the blood up to 15 minutes following drug administration but thereafter disappeared from the brain more rapidly than from the blood. Nevertheless, the brain concentration of drug related material was reasonably well reflected by the blood concentration.

Drug-related material was absorbed by the myocardium rapidly and extensively. Concentrations at all times were greater (usually much greater) than in the blood. The concentration of drug-related in the spleen, although lower than in the myocardium, exceeded that in the blood at all times except one.

The liver absorbed drug-related material as rapidly as did the myocardium and at higher concentrations. The concentration of drug related material in the gall bladder reached a maximum concentration somewhat later than in the liver but persisted at high concentrations throughout the study, indicating that biliary secretion and, likely, enterohepatic recirculation are important routes for this drug's elimination by the mouse.

The high concentrations of drug-related material in the stomach following intravenous administration of the drug indicate rather rapid excretion into the lumen of the stomach. The somewhat slower appearance of drug-related material in the small and large intestines - following intravenous drug administration most likely results from biliary secretion as well as material passing from the stomach.

Low levels of drug related material appeared in the eye soon after drug administration. No drug was detected in the vitreous humour. Low but detectable levels persisted in the area of the lens, however. A moderate but persistent concentration of drug-related material was found in the Harder's gland, located just behind the eye.

The adrenals rapidly attained high concentrations of drug-related material, which disappeared relatively rapidly. The adrenal cortex invariably had considerably higher concentrations than did the medulla.

The kidney also rapidly attained high levels of drug-related material, and the cortex showed higher concentrations than did the medulla. The bladder showed delayed appearance of drug-related material which was consistent with significant elimination of the drug via urine. The ovary and the testicle usually showed low to moderate levels of drug-related material following drug administration.

The brown fat showed somewhat, but not substantially, greater concentrations of drug-related material than did skeletal muscle. Both tissues absorbed the drug rapidly. Concentrations of drug-related material in the lung were similar to those in brown fat and skeletal muscle.

Low, but significant, concentrations of drug-related material were found in the foetus 15 minutes and eight hours following oral adminstration of the drug to pregnant mice. This material was uniformly distributed in the foetus, with concentrations similar to those in the brain of the mother. Since placental transport of drugs and metabolites from mother to foetus is a common occurrence, placental transport of alprazolam and/or metabolites presumably also will occur in humans.

Protein binding

Alprazolam is bound (80%) to human serum protein in vitro. Binding of alprazolam to serum protein at 37C was measured by a modified ultrafiltration technique at drug concentrations ranging from 30 to 10()0 ng/ml, with the following results:

Protein Source	% Bound
Human serum	79.5
Dog serum	74.8
Rat serum	74.0
Human serum albumin	68.4

Binding was extensive and concentration. independent in all three species, and most of the binding by human serum probably was accounted for by albumin. The serum proteins are not saturated with Xanax at 1000 ng/ml, a concentration 42 times higher than the average steady-state levels after 0.5 mg. t.i.d. and 25 times higher than the average peak level after a single 3 mg. dose. Thus, large amounts of Xanax would have to be ingested before a significant increase in the free fraction of alprazolam would occur.

Lacteal secretion

Four lactating rats were given a 0.3 mg/kg oral dose of alprazolam-14C. The mean concentration of -^{14}C in milk specimens obtained six and 12 hours after dosing were 17.4 ng/ml ± 5.6 SDM and 18.3 ng/ml ± 5.6 SDM, respectively, expressed as alprazolam equivalents. Since lacteal secretion of drugs and their metabolites is a characteristic common to various species, it is presumed that lacteal secretion of alprazolam and / or metabolites also will occur in humans.

Metabolism

Extracts of enzymatically hydrolysed urine from humans, dogs, and rats given alprazolam ^{14}C orally were analyzed for metabolites by thin layer chromatography and by chromatography on Sephadex LH 20 followed by high-pressure liquid chromatography. Un-metabolised drug was found in human and rat urine but not in dog urine; however, alprazolam was extensively metabolized by all three species. Evidence was obtained for 29 metabolites in humans, 47 in dogs, and 19 in rats.

An important route of metabolism in humans involves hydroxylation of the 1-methyl group, which demonstrates the hydroxy-methyl analogue of

alprazolam, alpha-HA (Figure 6), and accounts for 14.96% of the urinary ^{14}C. Further sequential oxidation of alpha-HA to the aldehyde and carboxilic acid (unstable), followed by decarboxylation, indicates that the 1 hydrogen is the analogue of alprazolam, 1-DA. This route of metabolism also occurs in dogs and rats.

Another pathway of metabolism apparently involves hydrolysis of the azomethine to yield the corresponding benzophenone, which contains a methyl and an amino methyl group on the triazole ring. Oxidation of the 1° amine would yield the aldehyde which would be reduced to give HB. This pathway is present in all three species. The corresponding mono-methyl-triazole which would result from oxidation of the aldehyde and subsequent decarboxylation, has not been identified.

A small amount of the 4-hydroxy analogue of alprazolam (4-HA) was found in human urine but not in dog or rat urine. The expected dihydroxy analogue, alpha, 4-HA, was not found in human urine, which suggests that the amount formed was very low and/or it was formed as expected but rapidly converted to one or more other metabolites. However, alpha, 4-HA was found in dog urine, but 4-HA was not. The hypothesis that alpha, 4-HA is formed only from alpha-HA is no more likely than the hypothesis that the conversion of 4-HA to alpha, 4-HA is a faster reaction than that a to 4-HA, leading to no excretion of 4-HA or to excreted levels of 4-HA, which cannot be measured. Considering the multiple sites for metabolism (e.g., triazole moity, diazepine ring, and 5-methyl ring, as well as the corresponding series of benzophenone structures), the apparent difference among species suggested (i.e., divergent pathways) might reflect common pathways with many intermediate metabolites formed but not excreted or excreted in quantities too small to be detected.

On the basis of the extant data, metabolism of alprazolam in dogs is more similar to humans than is metabolism in rats. Nine metabolites found in humans were not seen in dogs; one of these was 4-HA (described earlier). In man, these nine metabolites accounted for a combined total of only 1.57% of the urinary radioactivity, or 1.24% of the administered dose. However, on the basis of metabolites that have been identified to date, it is suggested that humans and dogs have common pathways of alprazolam metabolism.

Excretion In Humans

Urinary and faecal excretion

Urinary and faecal excretion of drug-related materials (^{14}C) were followed up for two weeks after a single dose 2mg. tablet dose of alprazolam- ^{14}C in six male subjects. The mean ± SDM recoveries of ^{14}C and estimated excretion half-lives were as follows:

	% Recovery	Excretion t½ (hr)
Urine	78.8 ± 2.1	13.7 ± 0.5 (n=6)
Faeces	7.0 ± 0.6	21.7 + 2.5 (n=6)
		46.8 + 4.6 (n=6)

Excretion occurred predominantly in the urine and ranges from 70.9% to 85.7% of the dose; faecal excretion accounted for only 5.4% to 9.9% of the dose. Both urinary and faecal excretion were slow. Excretion in urine could be described with a single exponential, with half-lives ranging from 11.1 to 15.4 hours. These values were close to the estimated ^{14}C plasma half-life values. Excretion was slower in faeces, with the excretion curve approximating a biexponential process in five subjects. The initial excretion half lives in faeces ranged from 15 to 30 hours. The terminal half-lives ranged from 31 to 60 hours; however, this terminal excretion phase accounted for only about 0.1% of the dose and was apparent one week after dosing.

Renal clearance

Renal clearance of alprazolam was calculated from urinary alprazolam, and nonprotien bound alprazolam in plasma obtained from the six subjects discussed above. The values obtained ranged from 237 to 503 ml/hr; mean = 371ml/hr: ± 38 SDM. Compared to an average glomerular filtraration rate of 7500 ml/hr for a normal adult, the data suggest that the mechanism of alprazolam excretion involves glomerular filtration with extensive reabsorption. The data do not allow assessment of tubular secretion.

Drug interactions

The ability of Xanax to induce human hepatic enzyme systems has not yet been determined; however, this is not a property of benzodiazepines in general. Further, Xanax did not affect the prothrombin or plasma levels of sodium warfarin given orally to male volunteers.

Effect of a Xanax 1.0 mg. tablet dose with and without cimetidine 5:

A single 1.0 mg. dose of a Xanax tablet was administered on two separate occasions once with cimetidine and once without cimitidine - to 18 healthy male and female volunteers. A 300 mg. dose of cimetidine was administrated every six hours for 48 hours, beginning 12 hours prior to ingestion of the Xanax. The results show that the coadministration of Xanax with cimetidine did not affect the peak plasma concentration (C_{max}) and time to peak concentration.

The elimination half-life (t½) and clearance of alprazolam were extended during cimetidine administration.

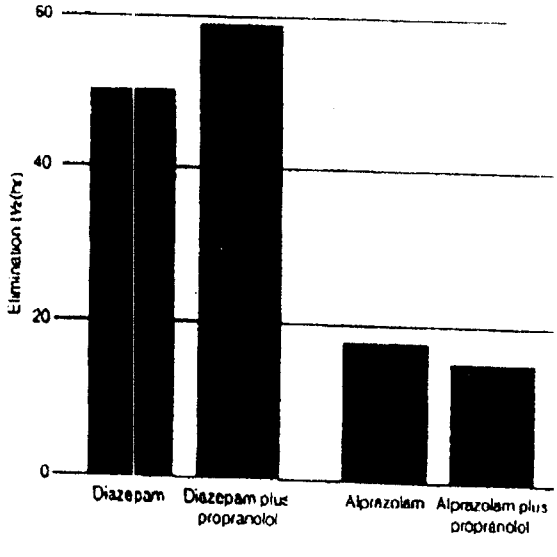
	Control Period	With Cimetidine
C_{max} (ng/ml)	15.50	16.00
Time to peak concentration (hr)	1.10	1.10
t½ (hr)	12.40	16.60*
Clearance (ml/min/kg)	1.66	1.05*

*P < 0.005

In studies on the effect of alprazolam on the kinetics of digoxin and creatinine clearance, no significant difference was found between the control and alprazolam groups in digoxin volume of distribution, elimination half-life, or total clearance from the serum. Alprazolam co-administration slightly reduced the mean 96-hour urinary excretion of digoxin in but there was no significant difference between treatment conditions in projected total cumulative excretion of digoxin or in renal clearance of digoxin. Creatinine clearance did not differ between the control and alprazolam groups. Thus, daily doses up to 1.5 mg. of alprazolam do not significantly alter digoxin clearance in healthy men.

The extent of interaction of propranolol, a widely used beta-adrenergic receptor blocker, with diazepam and alprazolam has been studied. Twenty-four healthy men and women participated in a series of two-way, single-dose crossover studies. In one trial, a single dose of a benzodiazepine derivative was taken in the control state without propranolol. For the second trial, subjects took propranolol 80 mg. three times a day, beginning 48 hours before taking diazepam or alprazolam.

Figure (6): Interaction of Propranolol with Diazepam and Alprazolam



Drug serum concentrations and elimination rates were recorded. Results showed that propranolol induced a small but significant reduction in the clearance of diazepam but had no significant effect on the elimination or clearance of alprazolam (Figure 6). The clinical importance of the interaction of propranolol with diazepam was not established.

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.

Contra-indications

Xanax is contra-indicated in patients with known sensitivity to the benzodiazepines. Xanax may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contra-indicated in acute narrow angle glaucoma.

Warnings

Xanax is not recommended for use in patients whose primary diagnosis is schizophrenia.

Although no withdrawal symptoms were observed in patients in whom Xanax was abruptly discontinued after six months of therapy, such symptoms have been reported following abrupt withdrawal of other benzodiazepine drugs. Individuals who are prone to abuse drugs, such as alcoholics and known drug addicts, should be under careful surveillance when receiving benzodiazepines because of the predisposition of such patients to habituation and dependence.

Precautions

As with other CNS active drugs, patients receiving Xanax should be advised not to operate motor vehicles or dangerous machinery until it is established that they do not become drowsy or dizzy while receiving Xanax.

The dosage of Xanax tablets should be terminated gradually, since abrupt withdrawal of any anti-anxiety agent may result in symptoms similar to those for which patients are being treated. Signs and symptoms of withdrawal may include anxiety, agitation, irritability, tension, insomnia, and occasionally, convulsions.

The usual precautions for treating patients with impaired renal or hepatic function should be observed.

The safety and efficacy of Xanax in children less than 18 years of age has not been established.

Clinically significant drug interactions: The benzodiazepines, including Xanax, produce addictive

CNS depressant effects when co-adminstered with observed in rates during a 24-month study with Xanax.

Pregnancy: An increased risk of congenital malformations associated with the minor tranquillizers, such as chlordiazepoxide, diazepam, and meprobamate during the first trimester of pregnancy has been suggested in several studies.

Because the use of these drugs is rarely a matter of urgency, the use of Xanax during this period should almost always be avoided. The possibility that a woman of child-bearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Nursing Mothers: As a general rule, nursing should not be undertaken while a patient is on drugs, since many drugs are excreted in human milk.

Side-effects

Side-effects, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. The most common side-effect of Xanax was drowsiness. Less common side-effects were light-headedness, blurred vision, coordination disorders, various gastrointestinal symptoms, and autonomic manifestations. As with other benzodiazepines, paradoxical reactions such as stimulation, agitation, concentration difficulties, confusion, hallucinations, or other adverse behavioral effects, may occur in rare instances and in a random fashion.

Overdosage

Manifestations of overdosage of Xanax include extensions of its pharmacologic activity, namely ataxia and somnolence. Induced vomiting and/or gastric lavage are indicated. As in all cases of drug overdosage, respiration, pulse and blood pressure should be monitored and supported by general measures when necessary.

Interavenous fluids may be adminstered and an adequate airway maintained.

Experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of Xanax (over 195 mg/kg; > 2000 times the maximum usual daily human dose). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of levarterenol.

Other animal experiments have suggested that forced diuresis or haemodialysis are probably of little value in treating overdosage. As with the management of any overdosage, the physician should bear in mind that multiple agents may have been ingested.

References

l. Greenblatt DJ, et al (1981): BR. J. Clin. Pharmacol. 11:115.

2. *Greenblatt DJ, et al (1981):* Arch. Gen. Psychiatry 40:287.

3. Data on file at The Upjohn Company (CS No 034)

4. *Abernathy DR, et al (1983):* Clin. Pharmacol. Ther. 33 (2): 247

5. *Abernathy DR, et al (1983):* Psychopharmacology 80:275

Supplied

Xanax is available as 0.25 mg. (white), 0.5 mg. (peach), and 1 mg. (lavender) scored, ovoid-shaped tables in bottles of 100.

APPENDIX

Updating Scientific Information

Epilepsy, Major Risk Factor

- Age less than 10 years old, and more than 50 years old.
- Males more than females .
- Poor health care in prenatal period .
- Head trauma.
- Poor socio-economic status.
- First degree epileptic relatives.
- Other conditions such as:
  Diseases of the central nervous system.
  Illness of gravid women.
  Febrile convulsions.
  Maternal age at parturition.

The International Classification of Epilepsies

I. Localization-related (focal ,local, partial) epilepsies and syndromes:
Idiopathic
Symptomatic
Cryptogenic

II. Generalized epilepsies and syndromes:
Idiopathic
Cryptogenic or symptomatic
Symptomatic

III. Epilepsies and Syndromes undetermined focal or generalized:
With both generalized and focal seizures cases with generalized tonic clonic seizures in which clinical and EEG findings do not permit classification.

IV. Special syndromes:
Situation related seizures (Gelegenheits anafalle)

Treatment Initiation

1. Patients having one single attack: Postpone treatment if patient has no evidence of cerebral lesion.
2. Patients having more than one attack within previous twelve months: Start treatment immediately.

The commonly used anti-convulsant drugs

Seizure type	First line						Second line		
	carbama zapine	Phenytoin	Phenobar bitone	Valp rocte	Primidone	Ethosux imide	Valproate	Benzodi a Zapine	Ethosux imide
Partial:									
Simplex	+	+	+	-	-	-	+	+	-
Complex	+	+	+	-	-	-	+	+	-
2ry gen.	+	+	+	-	-	-	+	+	-
Generalized:									
Tonic Clonic	+	+	+	+	+	+	-	+	-
Absence	-	-	-	+	-	+	-	+	-
Myoclonic	-	-	-	+	-	-	-	-	+
Tonic	+	+	+	+	+	+	-	+	-
Clonic	+	+	+	+	+	+	-	+	-
Atonic	+	+	+	=	+	+	-	+	-

The Principal Strategy for Initiation of Anti-convulsant Treatment:

How to start anticonvulsant therapy

1. Start treatment with one drug i.e. monotherapy. Monotherapy has the advantage of being:
a) Highly effective.
b) Minimal side-effects.
c) Compliance is improved.
d) Lesser cost.

2. Use first line anti-convulsant drug with simplified dosage regimen i.e. given once or twice daily.

3. Start drug treatment with a small dose and build-up over a period of weeks.

4. Gradually increase dosage to minimum maintenance dose, achieving complete seizure control without toxic effects.

Measures to minimize therapeutic failure:

a. **Good compliance:** Explain to the patient the diagnosis, prognosis, and that treatment has to be taken over years and must be strictly regular.
b. Anticonvulsants need a steady level to achieve a consistent effect.
c. Keep stock of medication at home.
d. Use a pill-box divided into seven daily sections to be refilled once a week.
e. Intermittent therapy is worse than none at all.