Handbook of Drug Interactions

A Clinical and Forensic Guide

Edited by

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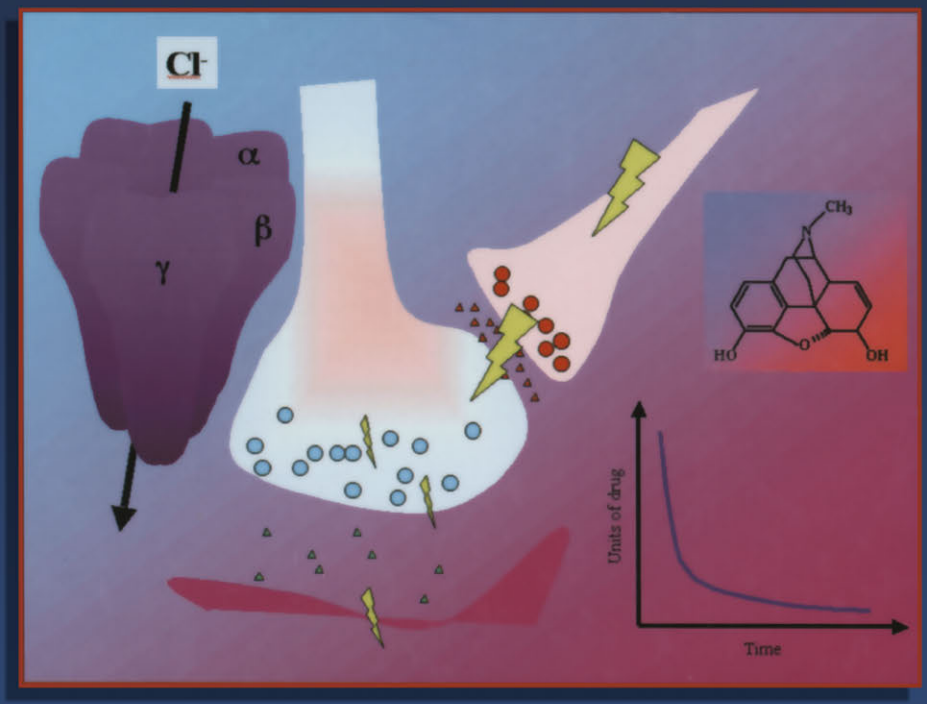

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Handbook of Drug Interactions

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Cover illustration: Two complementary views of drug interactions. The mathematical modeling of the drug is shown as a classic first order kinetic elimination curve and alteration in pharmacokinetics is amongst the best understood potential for undesired effects from combinations of two or more pharmaceuticals. But harder to grasp are the dynamic effects of drugs. The results of binding to target proteins, such as ion channels, can change the overall activity of cells, such as neurons, which in turn impinge on other target tissues. These pharmacodynamic interactions are complex and culminate in the symptomology observed in the patient. Any combination of chemicals in the body, endogenous or not, is a fluid game of competitions, synergies, or antagonisms at the metabolic and functional level. The results may go unseen, may be beneficial, may be harmful or, in some cases, lethal to the subject.

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Preface

Drug interactions and adverse drug effects have received much attention since studies published in daily newspapers have shown that they result in upwards of 100,000 Americans each year being hospitalized or remaining hospitalized longer than necessary, as well as leading to the death of a number of patients. Use of multiple drugs (8–12 on average in hospitalized patients) is common in a number of therapeutic regimens. In addition to multiple drug therapy, a patient may have access to several prescribers, and may have predisposing illnesses or age as risk factors for interactions. Drug interactions may occur between prescription drugs, but also between food and drug, and chemical and drug. Whereas some may be adverse, interactions may also be sought to decrease side effects or to improve therapeutic efficacy.

Combining drugs may cause pharmacokinetic and/or pharmacodynamic interactions. Pharmacokinetic mechanisms of interaction include alterations of absorption, distribution, biotransformation, or elimination. Absorption can be altered when drugs that alter pH or motility are co-administered, as seen with certain antiulcer or antidiarrheal medications, or when drugs are chelators or adsorbents (tetracyclines and divalent cations, cholestyramine, and anionic drugs). Distribution variations can result from competition for protein binding (sulfa drugs and bilirubin binding to albumin) or displacement from tissue-binding sites (digitalis and calcium channel blockers or quinidine). Induction of gene expression (slow), activation or inhibition (much quicker) of liver and extrahepatic enzymes such as P450, and conjugating enzymes have long found a place of choice in the literature describing the potential for adverse drug interactions resulting from altered metabolism. For example, induction is well described with the major anticonvulsant medications phenytoin, carbamazepine, and barbiturates, whereas inhibition can occur with antimicrobials from the quinolone, the macrolide, and the azole families. Finally, excretion can also be modified by drugs that change urinary pH, as carbonic anhydrase inhibitors do, or change secretion and reabsorption pathways, as probenecid does. Pharmacokinetic interactions in general result in an altered concentration of active drug or metabolite in the body, modifying the expected therapeutic response.

A second form of interaction has received little attention because of its modeling complexity and perhaps the poor understanding of basic physiological, biochemical, and anatomical substrates for drug action. Pharmacodynamic interactions involve additive (1 + 1 = 2), potentiating (0 + 1 = 2), synergistic (1 + 1 = 3), or antagonistic (1 + 1 = 0)

effects at the level of receptors. Receptors are mainly proteins, such as enzymes (acetylcholinesterase, angiotensin-converting enzyme, for example), transport proteins (digitalis and Na^+/K^+ ATPase), structural proteins (colchicine and tubulin), or ion channels (Class I antiarrhythmics and voltage-dependent sodium channels). Large families of receptors to drugs involve signal transduction pathways and changes in intracellular second messenger concentrations (autonomic nervous system drugs and α, β, muscarinic receptors, for example). Finally, even less understood are interactions at the level of nucleic acids such as DNA and RNA, which can change the levels of expression of key proteins in target tissues (tolerance, tachyphylaxis of numerous central nervous system drugs).

Handbook of Drug Interactions: A Clinical and Forensic Guide addresses both types of drug interactions, emphasizing explanations when possible, and careful review of the general pharmacology. The result, we hope, will prove useful to health and forensic professionals as well as medical, pharmacy, nursing and graduate students alike.

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Part I
Central Nervous System Drugs

Chapter 1

Drug Interactions with Benzodiazepines

Epidemiologic Correlates with Other CNS Depressants and In Vitro Correlates with Inhibitors and Inducers of Cytochrome P450 3A4

David E. Moody, PhD

1. General Information About Benzodiazepines

1.1. Introduction

The purpose of this chapter is to examine the drug interactions that occur with benzodiazepines and discuss the relevance of these interactions to the field of medicine in general with an emphasis on forensic toxicology. Because of the diverse nature of the benzodiazepines, some time has been taken to introduce this class of drugs. This introductory material has drawn upon some basic reference material and reviews *(1–8)*, and is not otherwise referenced, except for specific points that did not come from these references. The primary literature will be more thoroughly cited in later sections presenting evidence of interactions with other central nervous system (CNS) depressants and specific enzyme involvement in the metabolism of benzodiazepines and drug interactions.

The benzodiazepines are a class of a relatively large number of drugs that share a common chemical structure and have anxiolytic to sedative action on the CNS. Chlordiazepoxide was first introduced in the 1960s, followed by diazepam, flurazepam, and

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oxazepam. Since that time a number of benzodiazepines have been introduced. In the latest edition (1999) of Martindale *(7)*, at least 43 benzodiazepines were listed (Table 1). Most were found in the section on anxyolytic sedatives hypnotics and antipsychotics; one, clonazepam, was listed in the antiepileptics section. Of these 43 benzodiazepines only 12 are cross-listed in the latest edition (2002) of the *Physicians' Desk Reference* (Table 1; *8*); indicating their approval for use in the United States.

Many benzodiazepines are now made by more than one pharmaceutical house, or more than one subsidiary of a pharmaceutical house, and therefore have more than one trade name. A single example of trade names has been listed in Table 1, along with an associated manufacturer.

To understand the importance of drug interactions with benzodiazepines, a basic understanding of their pharmacodynamic action is required, along with the related therapeutic use. In addition, because many of the drug interactions are of a pharmacokinetic nature, the chemical structure and metabolism of the benzodiazepines must be appreciated.

1.2. Pharmacodynamics (Briefly), Uses, and Adverse Effects of Benzodiazepines

Most of the effects of benzodiazepines arise from their action on the CNS. Within the CNS the major molecular targets of the benzodiazepines are inhibitory neurotransmitter receptors directly activated by the amino acid, γ-aminobutyric acid (GABA). Benzodiazepines have been shown to bind and modulate the major GABA receptor in the brain, $GABA_A$, while $GABA_B$ receptors are not altered by benzodiazepines. The $GABA_A$ receptor is an integral membrane chloride channel that mediates most of the rapid inhibitory neurotransmission in the CNS. Benzodiazepines, unlike barbiturates that also bind $GABA_A$, act only in the presence of GABA. Typical benzodiazepine agonists increase the amount of chloride current generated by $GABA_A$ activation, potentiating the effect of GABA throughout the CNS. Bicuculline, an antagonist of $GABA_A$, reduces the behavioral and electrophysiological effects of benzodiazepines, and a benzodiazepine analog, flumazenil, that potently and selectively blocks the benzodiazepine binding site, is used clinically to reverse the effects of high doses of benzodiazepines *(4)*.

These CNS depressive effects result in anxiolytic, muscle relaxant, hypnotic, antigrade amnesia, anticonvulsant, and sedative effects that define the therapeutic uses of benzodiazepines (Table 2). Although the proper dose of any one benzodiazepine will produce many of these effects, some benzodiazepines are more appropriate for certain uses than others. In large part, this is dictated by the therapeutic half-life of the drug. Benzodiazepines are generally classified as short- (0–6 h), intermediate- (6–24 h), or long-acting (>24 h); some texts, however, will just use short- (0–24 h) and long-acting (>24 h) designations. Benzodiazepines used as anticonvulsants are long-acting and have rapid entry into the brain. Short- to intermediate-acting benzodiazepines are favored for treatment of insomnia. Short-acting benzodiazepines are used as preanesthia agents for sedation prior to surgery. Long-acting or multidose shorter-acting benzodiazepines are generally used as anxiolytics. The use of benzodiazepines listed in Martindale, along with their half-life, route(s) of administration, and normal range of doses, is presented in Table 3.

Table 1
Benzodiazepines Listed in the 32nd Edition of Martindale (1999)

Generic Name	Representative Trade Name	Representative Manufacturer	CAS #
Adinazolam	None	Upjohn, USA	37115-32-5
Alprazolam[a]	Xanax (others)	Upjohn, USA	28981-97-7
Bentazepam	Tiadipona	Knoll, Sp	29462-18-8
Bromazepam	Lexotan (others)	Roche, UK	1812-30-2
Brotizolam	Lendormin	B.I., Ger	57801-81-7
Camazepam	Albego	Daker Farmasimos, Sp	36104-80-0
Chlordiazepoxide[a]	Librium (others)	Roche, USA	438-41-5
Cinolazepam	Gerodorm	Great, Aust	75696-02-5
Clobazam	Frisium	Hoechst, UK	22316-47-8
Clonazepam[a]	Klonopin (others)	Roche, USA	1622-61-3
Clorazepate[a]	Tranxene (others)	Abbott, USA	20432-69-3
Clotiazepam	Clozan (others)	Roerig, Belg	33671-46-4
Cloxazolam	Akton (others)	Excel, Belg	24166-13-0
Delorazepam	En	Ravizza, Ital	2894-67-9
Diazepam[a]	Valium (others)	Roche, USA	439-14-5
Estazolam[a]	Prosom (others)	Abbott, USA	29975-16-4
Ethyl Lorazepate	Victan (others)	Clin Midy, Fr	29177-84-2
Etizolam	Depas (others)	Fournier, Ital	40054-69-1
Fludiazepam	Erispan	Sumitomo, Jpn	3900-31-0
Flunitrazepam	Rohypnol (others)	Roche, UK	1622-62-4
Flurazepam[a]	Dalmane (others)	Roche, USA	1172-18-5
Halazepam	Paxipam (others)	Schering-Plough, Ital	23092-17-3
Haloxazolam	Somelin	Sankyo, Jpn	59128-97-1
Ketazolam	Solatran (others)	SmithKline Beecham, Sw	27223-35-4
Loprazolam	Dormonoct (others)	Hoechst Marian Russell, Belg	61197-73-7
Lorazepam[a]	Ativan (others)	Wyeth-Ayerst, USA	846-49-1
Lormetazepam	Loramet (others)	Wyeth, Sw	848-75-9
Medazepam	Rudotel	OPW, Ger	2898-12-6
Metaclazepam	Talis	Organon, Ger	65517-27-3
Mexazolam	Melex	Sankyo, Jpn	31868-18-5
Midazolam[a]	Versed	Roche, USA	59467-96-8
Nimetazepam	Ermin	Suitomo, Jpn	2011-67-8
Nitrazepam	Mogadon (others)	Roche, UK	146-22-5
Nordiazepam	Vegesan (others)	Mack, Sw	1088-11-5
Oxazepam[a]	Serax (others)	Wyeth-Ayerst, USA	604-75-1
Oxazolam	Serenal	Sankyo, Jpn	24143-17-7
Pinazepam	Domar (others)	Teoforma, Ital	52463-83-9
Prazepam	Demetrin (others)	Parke, Davis, Sw	2955-38-6
Quazepam	Doral (others)	Wallace, USA	36735-22-5
Temazepam[a]	Restoril (others)	Sandoz, USA	846-50-4
Tetrazepam	Myolastan (others)	Sanofi Winthrop, Fr	10379-14-3
Tofisopam	Grandaxin	Hung	22345-47-7
Triazolam[a]	Halcion	Upjohn, USA	28911-01-5

Note: Benzodiazepines listed in the 32nd edition of "Martindale The Complete Drug Reference, (1999)" *(7)*. When more than one trade name was listed (noted as "other"), either the U.S. or most common one was chosen; a representative manufacturer was selected for listing.

[a]Also listed in the 2002 edition of the "Physicians Desk Reference" (2002) *(8)*.

Table 2
Uses of Benzodiazepines

1. Anxiety (27)[a]	5. Alcohol Withdrawal (4)
2. Insomnia (26)	6. Muscle Spasms (3)
3. Presurgery / Sedation (8)	7. Panic Disorder (2)
4. Epilepsy / Seizures (7)	8. Depression (2)

[a]The number in parentheses represents the number of benzodiazepines listed in Martindale that are used to treat this disorder.

Drowsiness, sedation, and ataxia are the most frequent adverse effects of benzodiazepine use. They generally decrease on continued administration and arise from the CNS depressive effects of benzodiazepines. Less common adverse effects include vertigo, headache, mental depression, confusion, slurred speech, tremor, changes in libido, visual disturbances, urinary retention, gastrointestinal disturbances, changes in salivation, and amnesia. Rare events include paradoxical excitation leading to hostility and aggression, hypersensitivity reactions, jaundice, and blood disorders. With very high doses, hypotension, respiratory depression, coma, and occasionally death may occur.

Daily benzodiazepine use has been associated with dependence, tolerance, and after discontinuation, withdrawal symptoms in many individuals. Tolerance to the effects of benzodiazepines is a highly debated topic. It appears to occur in some individuals and may not occur in others. The likelihood of dependence appears higher in individuals with a history of drug or alcohol dependence and personality disorders. High doses and intravenous injection are used for their euphoric effects. Because development of dependence cannot be easily predicted, abrupt discontinuation of use is not recommended. Rather the dose should be tapered. Symptoms of withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. If long-term use of benzodiazepines occurs, professional assisted withdrawal is recommended.

1.3. Basic Pharmacokinetics

The benzodiazepines are generally lipophilic drugs. Within the class, however, lipophilicity measured as the oil:water coefficient can differ over a 50-fold range. Due to their lipophilicity the benzodiazepines have relatively high plasma protein binding (70–99%) and relatively large volumes of distribution (0.3–22 L/kg) (Table 4). In general, the percent plasma protein binding and volume of distribution increase as does the oil:water partition coefficient.

The differences in lipophilicity can have a major impact on the pharmacokinetics of the benzodiazepine. Diazepam is regarded as a long-acting benzodiazepine. When diazepam is given as a single dose, however, it rapidly redistributes to nonplasma (lipid) compartments, the α elimination phase. It then slowly distributes back into the plasma compartment at subtherapeutic concentrations with a long terminal elimination half-life. Therefore, single doses of diazepam can be used as a short-term preanesthesia medication, whereas daily dosing will result in accumulation during the terminal elimination phase and provide long-acting therapy.

Table 3
Uses of Benzodiazepines Listed in Martindale

Generic Name	Half-Life (h)[a]	Route(s) of Administration	Usual Dose (mg)	Uses[b]
Adinazolam	short	—	—	1, 8
Alprazolam	11–15	oral	0.75–1.5	1, 8
Bentazepam	—	oral	25	1, 2
Bromazepam	12–32	oral	3–18	1, 2
Brotizolam	4–8	oral	0.25	2
Camazepam	—	oral	10	2
Chlordiazepoxide	5–30, 48–120[c]	oral, iv, im	25–100	1, 2, 3, 5, 6
Cinolazepam	—	—	—	2
Clobazam	18, 42[c]	oral	20–30	2, 4
Clonazepam	20–40	oral, iv	0.25–1	4, 7
Clorazepate	48–120[c]	oral, iv, im	15–90	1, 4, 5
Clotiazapam	4–18	oral	5–60	1, 2
Cloxazolam	long	oral, im	8–12	1, 3
Delorazepam	long	oral, im	0.5–6	1, 2, 3, 4
Diazepam	24–48, 48–120[c]	oral, iv, im	5–30	1, 2, 3, 4, 5, 6
Estazolam	10–24	oral	1–2	2
Ethyl Lorazepate	long	oral	1–3	1
Etizolam	short	oral	3	1, 2
Fludiazepam	short	oral	—	1
Flunitrazepam	16–35	oral, iv	0.5–2	2, 3
Flurazepam	47–100	oral	15–30	2
Halazepam	short	oral	20	1
Haloxazolam	short	oral	5	2
Ketazolam	long	oral	15–60	1
Loprazolam	4–15	oral	1–2	2
Lorazepam	10–20	oral, iv, sl	1–6	1, 2, 3, 4
Lormetazepam	11	oral	0.5–1.5	2
Medazepam	long	oral	10–20	1
Metaclazepam	short	oral	15	1
Mexazolam	—	oral	0.5	1
Midazolam	2–7	iv, im	2.5–7.5	3
Nimetazepam	short	oral	3	2
Nitrazepam	24–30	oral	5–10	2, 4
Nordiazepam	48–120	oral	15	1, 2
Oxazepam	4–15	oral	15–30	1, 2, 5
Oxazolam	long	oral	10	1
Pinazepam	long	oral	5–20	1, 2
Prazepam	48–120[c]	oral	30–60	1
Quazepam	39, 39–73[c]	oral	15	2
Temazepam	8–15	oral	10–40	1, 3
Tetrazepam	—	oral	25–50	6
Tofisopam	—	oral	150	1
Triazolam	1.5–5.5	oral	0.125–5	2

[a] If half-lives were not given, they were often referred to as short- or long-acting.
[b] *See* Table 2 for the number corresponding to different uses.
[c] Half-life for active metabolite.

Table 4
The Percentage of Plasma Protein Binding and Volume of Distribution (V_d) of Some Benzodiazepines

Benzodiazepine	% Bound	V_d (l/kg)	Source
Alprazolam	71	0.7	a
Bromazepam	70	0.9	b
Chlordiazepoxide	96	0.3	a
Clobazam	85	1.0	b,c
Clonazepam	86	3.2	a
Clotiazepam	99	—	c
Diazepam	99	1.1	a
Estazolam	93	—	c
Flunitrazepam	78	3.3	a
Flurazepam	97	22.0	a
Halazepam	—	1.0	b
Lorazepam	91	1.3	a
Midazolam	95	1.1	a
Nitrazepam	87	1.9	a
Nordiazepam	98	0.8	a
Oxazepam	98	0.6	a
Prazepam	—	13.0	b
Quazepam	95	—	c
Temazepam	98	1.1	a
Triazolam	90	1.1	a

The source of information was: a = *(5)*; b = *(6)*; and c = *(7)*.

The benzodiazepines are well absorbed from the gastrointestinal tract, which allows for oral dosing of benzodiazepines (Table 3). As described in more detail in subheading 2.2, most will also undergo extensive first-pass metabolism, some to such an extent that parent drug is detected only at very low concentrations in blood (or blood-derived) samples. The plasma concentration benzodiazepines, or their primary pharmacodynamically active metabolites, correlates well with the dose of benzodiazepine administered (Fig. 1).

As a class, the benzodiazepines share many properties. There are structural differences between them, and these differences will affect the manner in which the benzodiazepine is metabolized, and thereby have an impact on their individual susceptibility to drug interactions.

2. Chemistry and Metabolism of Benzodiazepines

2.1. Chemistry of Benzodiazepines

The classic structure of benzodiazepines (Fig. 2) consists of a benzene (A ring) fused to a seven-membered diazepine (B ring). In all but two of the commercially available benzodiazepines, the nitrogens in the diazepine ring are in the 1,4 position. Clobazam has nitrogens in the 1,5 position of the diazepine ring; tofisopam has nitrogens in the 2,3 position of the diazepine ring (Fig. 3). In addition, most commercially available

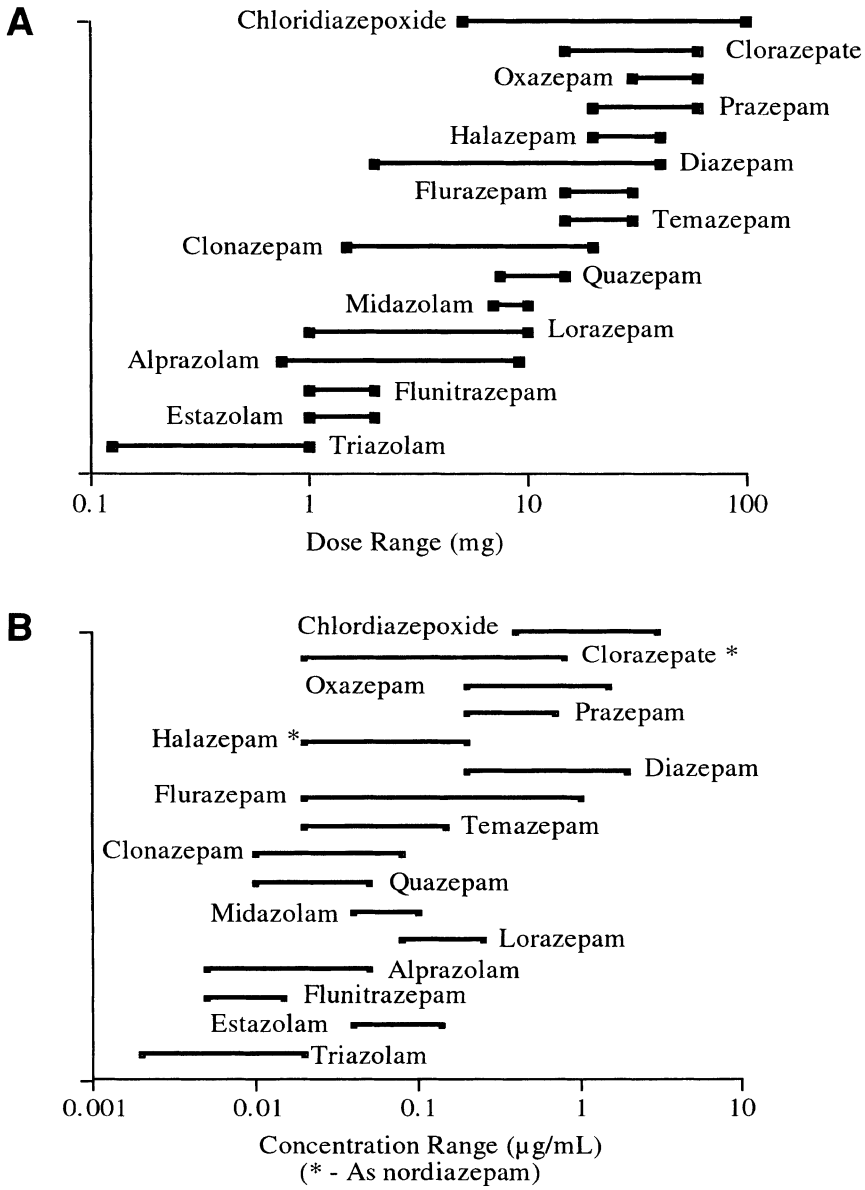


Fig. 1. The range of (**A**) therapeutic doses and (**B**) plasma concentrations of selected benzodiazepines. *In B, these concentrations are for the primary metabolite, nordiazepam.

benzodiazepines have an aryl substituent (C ring) at the 5 position of the diazepine ring. Therefore, with the exception of clobazam and tofisopam, these are 5-aryl-1,4-benzodiazepines.

Following the initial synthesis of chlordiazepoxide by Sternbach in 1957, and its introduction as a therapeutic agent in 1961, a number of benzodiazepines have been introduced onto the market. The initial modifications involved changes in the substituents on the diazepine ring. Modifications along this line first led to the development of diazepam, flurazepam, and oxazepam. These have continued through the years, leading

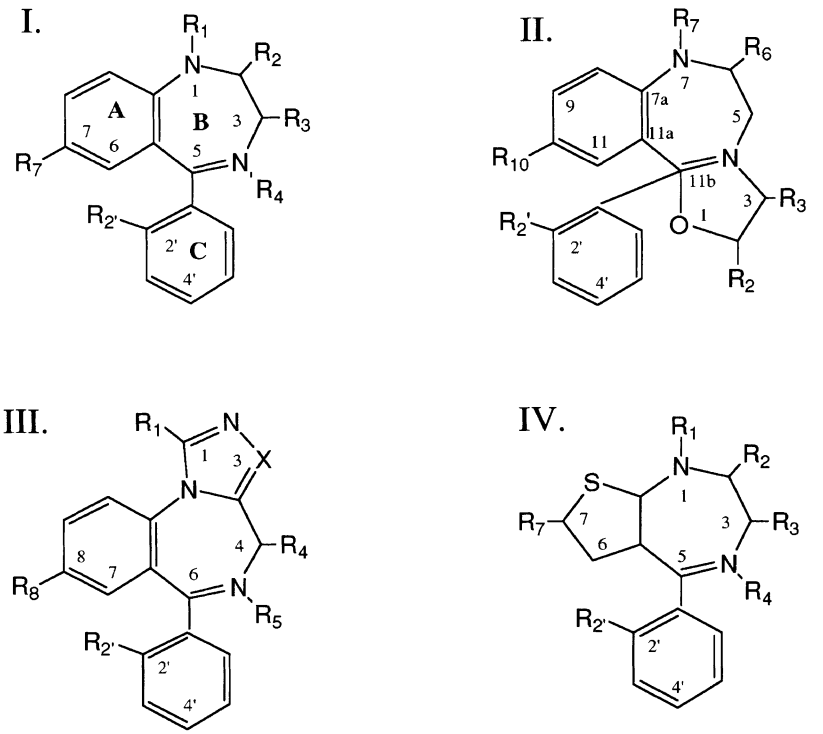


Fig. 2. Basic structure of the 5-aryl-1,4-benzodiazepines (I), 4,5-oxazolo-benzodiazepines (II), 1,2-triazolo- or 1,2-imidazo-benzodiazepines (III), and 1,4-thienodiazepines (IV).

to a number of 1,4-benzodiazepines (Table 5). Substitution of the benzene with a thieno group produced the 1,4-thienodiazepines (Figs. 2 and 3; Table 6). Annelation of an oxazolo (Fig. 2; Table 6) or oxazino group (ketazolam in Fig. 3; Table 6) at the 4,5 position of the diazepine has been used and the newer benzodiazepines have 1,2 anneled triazolo or imidazo groups (Fig. 2; Table 6). While most benzodiazepines have a phenyl substituent at the 5 position of the diazepine ring, bromazepam has a 2-pyridinyl substituent, and tetrazepam has a 1-cyclohexen-1-yl substituent at this position (Fig. 3; Table 6). Bentazepam, with a benzylthieno group fused to the diazepine ring, and brotizolam with both the thieno and triazolo groups are unique 1,4-thienodiazepines (Fig. 3; Table 6).

Structure activity studies have demonstrated some essential requirements for the benzodiazepine-mediated CNS effects. An electron-withdrawing group is required at the 7 position of the benzene (or thieno) group (R10 for oxazolo and R8 for triazolo or imidazo). These are generally the halides chloride, and occasionally bromide, or a nitroso group. An electron-withdrawing group at the 2' position of the 5-phenyl substituent is associated with increased potency and decreased half-life. Chloride or fluoride substituents have been used for this purpose.

2.2. Basic Metabolism of Benzodiazepines

Most of the 5-aryl-1,4-benzodiazepines are metabolized by N-dealkylation at the N-1 position and hydroxylation at the 3 position (Fig. 4). The N-dealkylation results

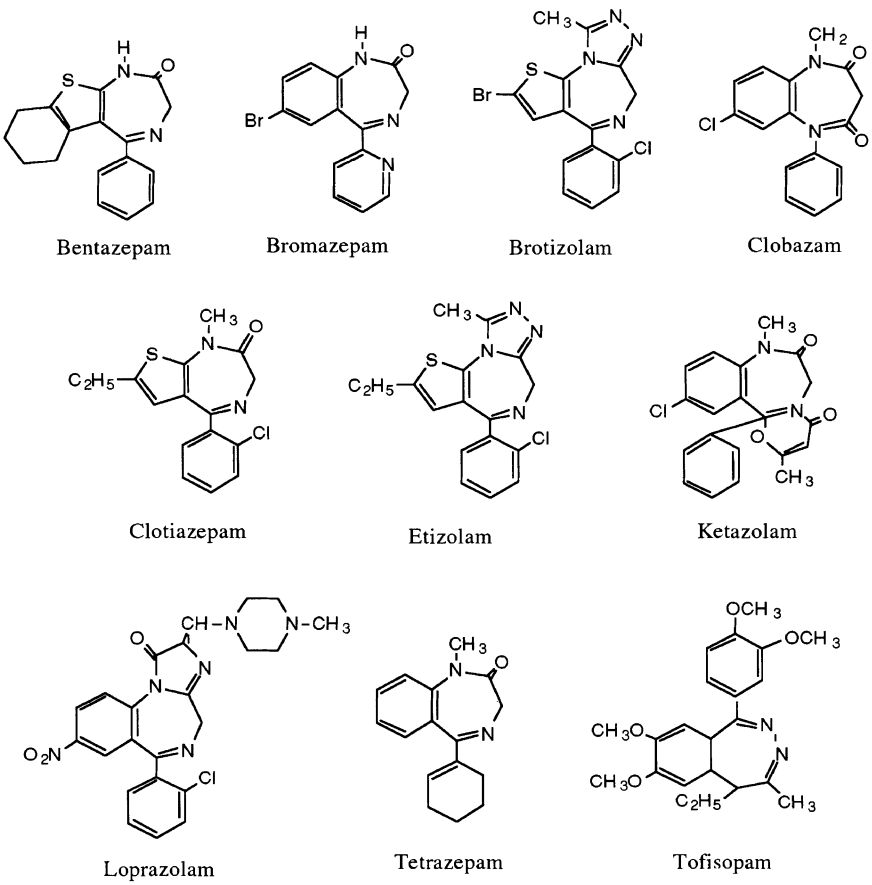


Fig. 3. Structure of "odd" benzodiazepines that could not easily be described in Tables 5 or 6.

in an active metabolite with a longer therapeutic half-life. In many cases the N-dealkyl metabolite is nordiazepam (N-desmethyldiazepam, nordiazam) (Fig. 4). Hydroxylation at the 3 position also results in an active metabolite. The 3-hydroxyl group is then conjugated, usually with glucuronide, resulting in an inactive metabolite. For benzodiazepines with a 3-hydroxyl group, such as temazepam, oxazepam (Fig. 4), lorazepam, and lormetazepam (not shown), conjugation of the 3-hydroxyl group is the major route of metabolism, even when other routes, such as N-dealkylation, may occur. These 3-hydroxyl benzodiazepines are consistently intermediate-acting drugs. Clorazepate is nonenzymatically decarboxylated to nordiazepam at the low pH of the stomach. The 4,5-oxazolo-benzodiazepines, such as ketazolam, oxazolam, and mexazolam, have the 4,5-oxazolo cleaved. It has been postulated by Ishigami et al. *(9)* that P450-mediated hydroxylation of the oxazolo-ring is followed by nonenzymatic cleavage of the ring, as shown for mexazolam (Fig. 5).

The 1,2-triazo- and 1,2-imidazo-benzodiazepines, alprazolam, triazolam, and midazolam, are metabolized by hydroxylation at the alpha (1') methyl group and at the 4 position (same as 3 position for other benzodiazepines). These metabolites are active until they are conjugated. 1'-Hydroxylation is the primary route for triazolam and mid-

Table 5
Structures of the 1,4-Benzodiazepines

Benzodiazipine	R_1	R_2	R_3	R_4	$R_{2'}$	R_7
I. 1,4-Benzodiazepines						
Camazepam	$-CH_3$	=O	$-OCON(CH_3)_2$	-H	-H	-Cl
Chlordiazepoxide	-H	$-NHCH_3$	-H	->O	-H	-Cl
Cinazolam	$-CH_2CH_2CN$	=O	-OH	-H	-F	-Cl
Clonazepam	-H	=O	-H	-H	-Cl	$-NO_2$
Clorazepate	-H	=O	$-COO^-$	-H	-H	-Cl
Delorazepam	-H	=O	-H	-H	-Cl	-Cl
Demoxepam	-H	=O	-H	->O	-H	-Cl
Diazepam	$-CH_3$	=O	-H	-H	-H	-Cl
Ethyl Lorazepate	-H	=O	$-COOC_2H_5$	-H	-F	-Cl
Fludiazepam	$-CH_3$	=O	-H	-H	-F	-Cl
Flunitrazepam	$-CH_3$	=O	-H	-H	-F	$-NO_2$
Flurazepam	$-C_2H_4N(C_2H_5)_2$	=O	-H	-H	-F	-Cl
Flutoprazepam	$-CH_2CH=(CH_2CH_2)$	=O	-H	-H	-F	-Cl
Halazepam	$-CH_2CF_3$	=O	-H	-H	-H	-Cl
Lorazepam	-H	=O	-OH	-H	-Cl	-Cl
Lormetazepam	$-CH_3$	=O	-OH	-H	-Cl	-Cl
Medazepam	$-CH_3$	-H	-H	-H	-H	-Cl
Metaclazepam	$-CH_3$	$-CH_2OCH_3$	-H	-H	-Cl	-Br
Nimetazepam	$-CH_3$	=O	-H	-H	-H	$-NO_2$
Nitrazepam	-H	=O	-H	-H	-H	$-NO_2$
Nordiazepam	-H	=O	-H	-H	-H	-Cl
Oxazepam	-H	=O	-OH	-H	-H	-Cl
Pinazepam	$-CH_2C=CH$	=O	-H	-H	-H	-Cl
Prazepam	$-CH_2-\triangleleft$	=O	-H	-H	-H	-Cl
Quazepam	$-CH_2CF_3$	=S	-H	-H	-F	-Cl
Temazepam	$-CH_3$	=O	-OH	-H	-H	-Cl

azolam, while 4-hydroxylation is the primary route for alprazolam. Cleavage of the diazo-ring of alprazolam has also been described (Fig. 6). Adinazolam is successively N-demethylated at the1-dimethylaminomethyl constituent to N-desmethyladinazolam and didesmethyladinazolam. The first N-demethyl product has a higher area under the curve than the parent drug and higher affinity for the central benzodiazepine receptors. Deamination of N-desmethyladinazolam with eventual 1-hydroxylation to 1-hydroxy-alprazolam or side chain cleavage to estazoalm have been described in the mouse, but does not appear important in humans *(10,11)*. Estazolam is hydroxylated to 1-oxoesta-zolam and to 4-hydroxyestazolam. Although both metabolites have minor activity, they are not formed in sufficient amounts to contribute to the pharmacologic activity of estazolam.

The 7-nitroso-benzodiazepines, clonazepam, flunitrazepam, and nitrazepam, are metabolized by successive reduction of the nitroso-group to the amine and subsequent N-acetylation of the amine to the corresponding acetamido-group (Fig. 7). These are

Table 6
Structures of the Oxazolo-, 1,2-Triazo-, and 1,2-Imidazo- Benzodiazepines

II. Oxazolo-benzodiazepines	R_7	R_6	R_2	R_3	$R_{2'}$	R_{10}
Cloxazolam	-H	=O	-H	-H	-Cl	-Cl
Flutazolam	$-CH_2CH_2OH$	=O	-H	-H	-F	-Cl
Haloxazolam	-H	=O	-H	-H	-F	-Br
Metazolam	-H	=O	-H	$-CH_3$	-Cl	-Cl
Mexazolam	-H	=O	$-CH_3$	-H	-Cl	-Cl
Oxazolam	-H	=O	$-CH_3$	-H	-H	-Cl
III. 1,2-Triazo- or 1,2-Imidazo-Annelated-Benzodiazepines	R_1	X	R_4	R_5	$R_{2'}$	R_8
Adinazolam	$-CH_2N(CH_3)_2$	-N-	-H	-H	-H	-Cl
Alprazolam	$-CH_3$	-N-	-H	-H	-H	-Cl
Clinazolam	$-CH_3$	-CH-	-H	-H	-Cl	-Cl
Estazolam	-H	-N-	-H	-H	-H	-Cl
Midazolam	$-CH_3$	-CH-	-H	-H	-F	-Cl
Triazolam	$-CH_3$	-N-	-H	-H	-Cl	-Cl

V. Odd Structures (*see* Fig. 3)	
Bentazepam	Has thieno-cyclohexyl ring in place of benzyl A ring
Bromazepam	2-Pyridynyl ring at 5 position
Brotizolam	Has thieno ring in place of benzyl A ring along with 1,2-triazo fused ring
Clobazam	A 5-aryl-1,5-benzodiazepine
Clotiazepam	Has thieno ring in place of benzyl A ring
Etizolam	Has thieno ring in place of benzyl A ring along with 1,2-triazo fused ring
Ketazolam	Has a nonoxazolo 4,5-fused ring
Loprazolam	Has an imidazo fused ring with different N configuration / also 7-nitroso
Tetrazepam	Nonaromatic 6-membered ring at 5 position
Tofisopam	A 1-aryl-2,3-benzodiazepine

often the major metabolites present in urine and plasma and are devoid of activity at benzodiazepine receptors. *N*-Dealkylation at the 1 position of the diazo-ring is also a prominent route of metabolism for flunitrazepam. Clonazepam and flunitrazepam can also be hydroxylated at the 3 position of the diazoring. With nitrazepam, oxidative metabolism at the diazo ring results in ring cleavage; this can be followed by hydroxylation of the phenyl (B) ring (Fig. 7).

The routes of metabolism of other benzodiazepines, bromazepam (ring cleavage and 3-hydroxylation), clobazam (N-dealkylation and c-ring hydroxylation), clotiazepam (N-dealkylation and side chain hydroxylation), and loprazolam (N-dealkylation and spontaneous hydrolysis to polar compounds) have been described (Fig. 8). Metaclazepam has a methyl ether at the 2 position of the diazo-ring. This appears to block hydroxylation at the 3 position, with N- and O-demethylations forming the primary metabolites (Fig. 9; *12*). Camazepam has a dimethylcarbamyl group at the 3 position of the diazoring. Successive hydroxylations of the methyl groups followed by N-hydroxymethy-

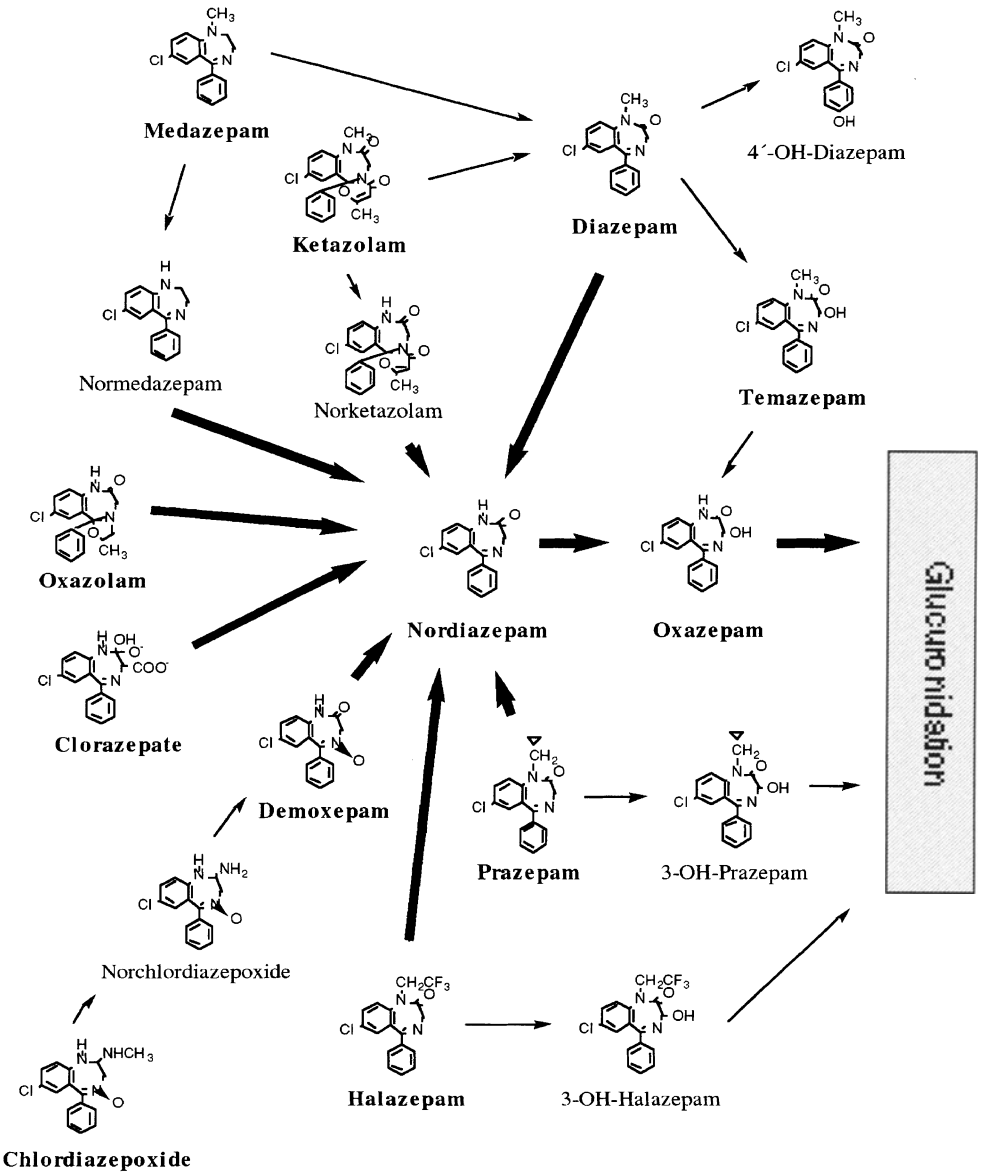


Fig. 4. Common metabolic pathways of 5-aryl-1,4-benzodiazepines. The compounds in bold type are pharmaceutical benzodiazepines. From *(401)*; reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications, a division of Preston Industries, Inc.

lations account for most of the metabolites, along with N-demethylation (Fig. 9; *13*). Tofisopam (tofizopam) is an unusual 2,3-diazepine with hydroxymethyl groups at four positions. O-Demethylation at the R1 and R4 positions has been described as the major routes of tofisopam's metabolism (Fig. 9; *14*). The metabolism of a number of other benzodiazepines has not been described. Based upon the principles discussed above, however, one can speculate on putative pathways of their metabolism (Table 7).

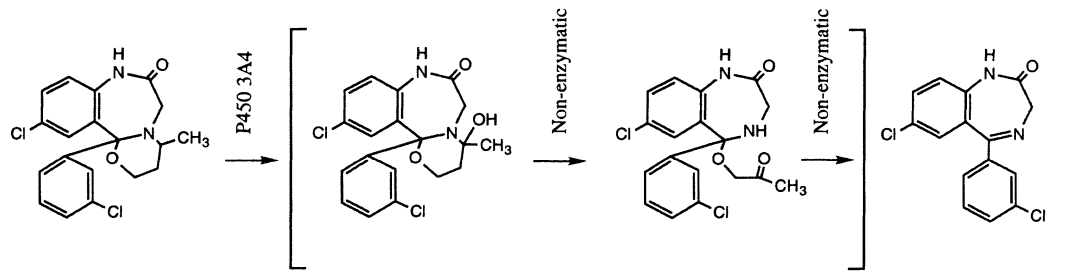
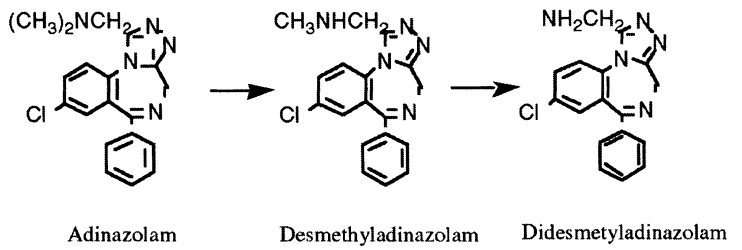


Fig. 5. Metabolism of the 4,5-oxazolone ring as postulated for mexazolam by Ishigami et al. *(9)*.



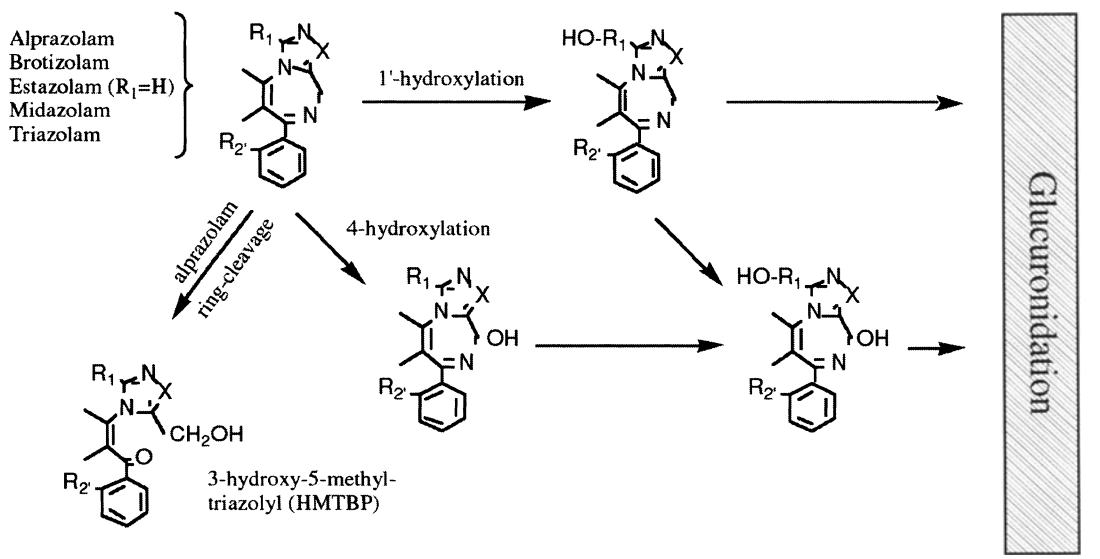


Fig. 6. Metabolic pathways for triazolo- and imidazobenzodiazepines.

2.3. The Role of Specific Enzymes in the Metabolism of Benzodiazepines

2.3.1. Methods Used to Determine Enzyme Involvement in the Metabolic Pathway

The methods for determination of the role of a specific enzyme in the pathway of a drug's metabolism have been developed most thoroughly for the cytochrome P450s

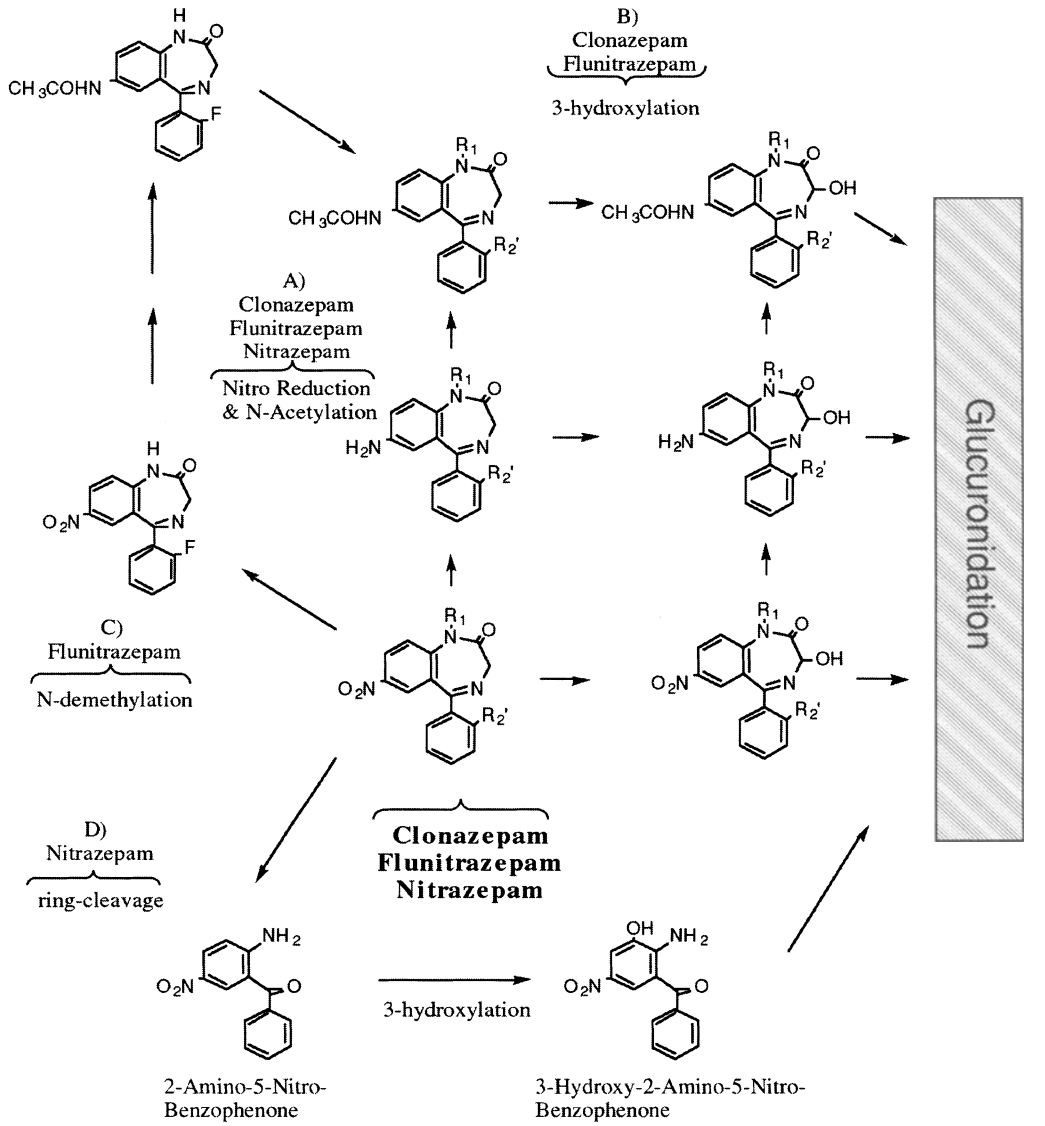


Fig. 7. Common metabolic pathways for 7-nitrobenzodiazepines. From *(401)*; reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications, a division of Preston Industries, Inc.

(P450s) *(15–19)*. Studies are done using human liver tissue that is now usually procured from donor tissue that is deemed unsuitable for transplantation. Most often studies utilize the microsomal cell fraction prepared from differential centrifugation of homogenates of liver tissue *(20)*, but cultured hepatocytes and liver slices are also being used. The methods used include the use of selective inhibitors, selective antibodies, correlation between P450 activities or contents in a number of human liver microsome (HLM) preparations with the pathway in question, and activities with cDNA-expressed P450s (Table 8). Each of these methods has certain strengths and weaknesses; the most convincing studies use most of them in an integrated approach (Table 8).

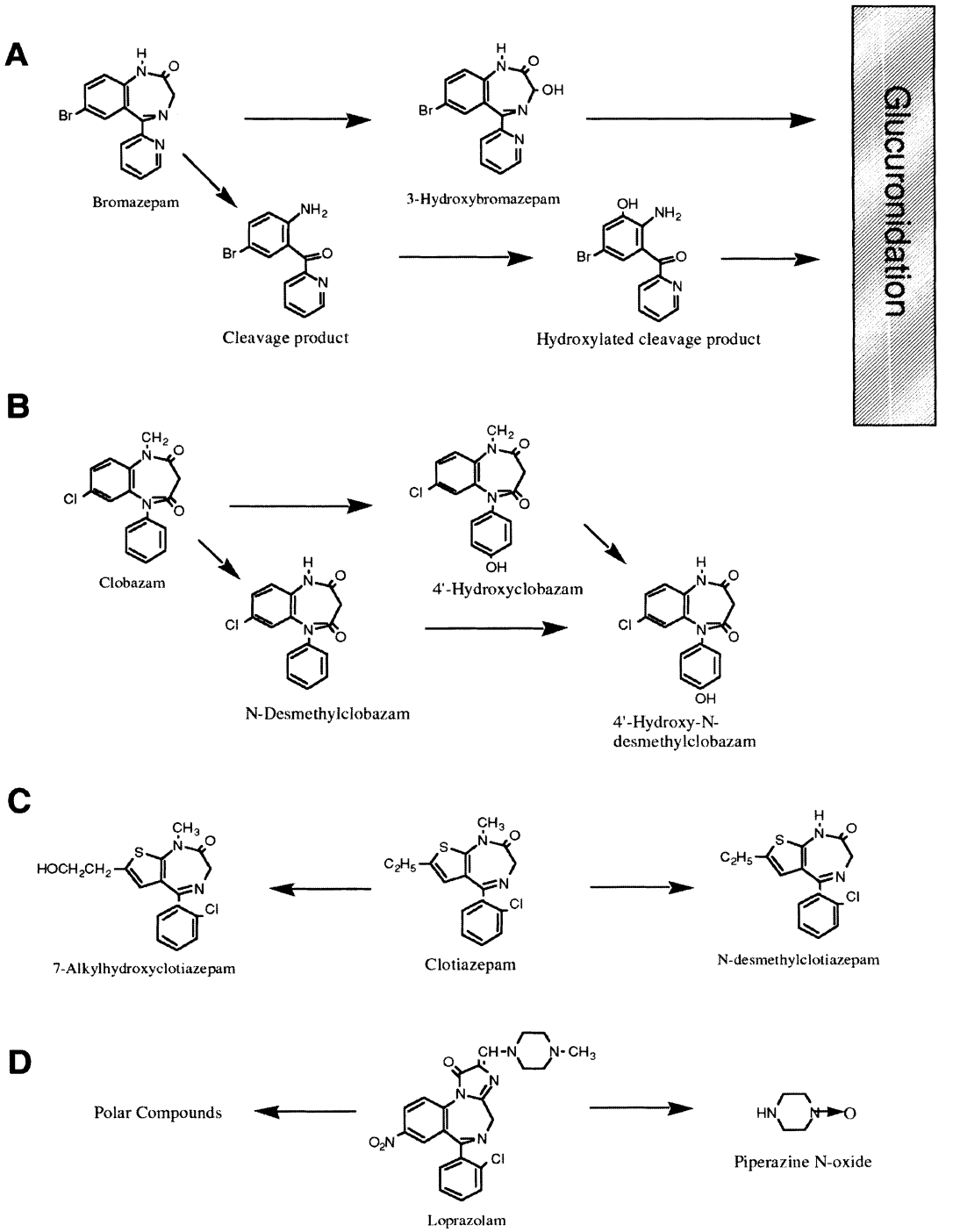


Fig. 8. Metabolic pathways for some other benzodiazepines: (**A**) bromazepam, (**B**) clobazam, (**C**) clotiazepam, and (**D**) loprazolam. From *(401)*; reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications, a division of Preston Industries, Inc.

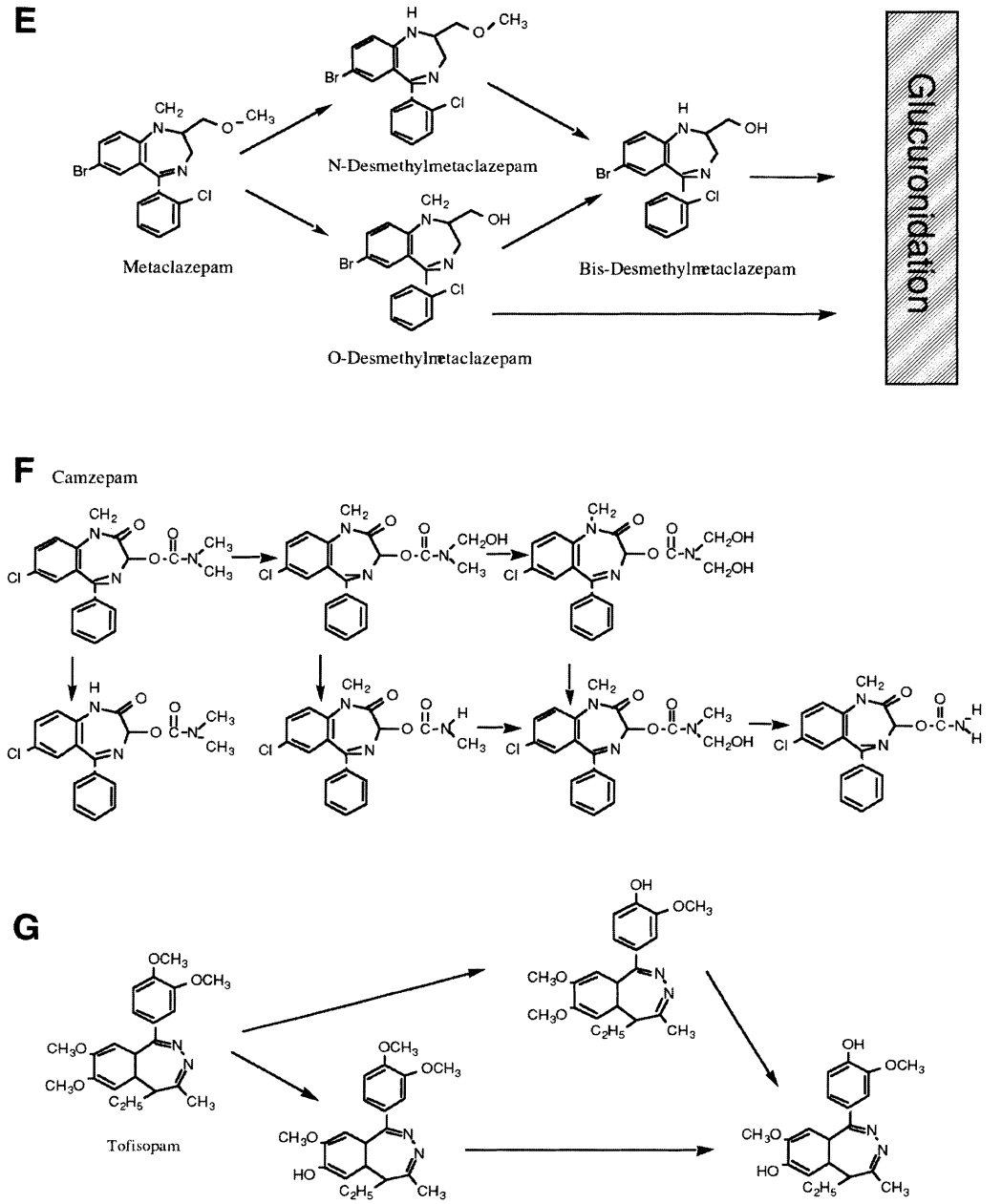


Fig. 9. Metabolic pathways for some other benzodiazepines (con'td.): (**E**) metaclazepam, (**F**) camazepem, and (**G**) tofisopam.

Selective inhibitors are often the easiest reagents to obtain and perform studies with. The results from their use, however, must be interpreted with care, as selectivity either is not complete, or is lost as the concentration of the inhibitor is increased. Recent studies have compared the ability of commonly used selective inhibitors to inhibit marker substrate P450 activities in either HLM or cDNA-expressed P450s *(21–23)*. A summary of their results is presented in Table 9. These comparisons can be useful in interpreting

Table 7
Speculation on Putative Metabolic Pathways for Benzodiazepines that Have Not Had Metabolites Defined

5-Aryl-1,4-Benzodiazepines	
Cinolazolam	conjugation of 3-hydroxyl; N-dealkylation
Delorazepam	3-hydroxylation → conjugation
Ethyl Lorazepate	3-ester hydrolysis → conjugation
Fludiazepam	3-hydroxylation → conjugation; N-dealkylation
Pinazepam	3-hydroxylation → conjugation; N-dealkylation
Tetrazepam	3-hydroxylation → conjugation; N-dealkylation
7-Nitroso-5-Aryl-1,4-Benzodiazepines	
Nimatazepam	amine reduction → N-acetylation 3-hydroxylation → conjugation; N-dealkylation
4,5-Oxazolo-Benzodiazepines	
Cloxazolam	cleavage of 4,5-oxazolo-ring; 3-hydroxylation → conjugation
Haloxazolam	cleavage of 4,5-oxazolo-ring; 3-hydroxylation → conjugation
Mexazolam	cleavage of 4,5-oxazolo-ring; 3-hydroxylation → conjugation
1,2-Triazo-Benzodiazepine	
Etizolam	α-hydroxylation → conjugation; 4-hydroxylation

Table 8
Tools Used to Determine Involvement of Specific Enzymes in Xenobitotic Metabolism

1. Selective inhibitors
   - Relatively easy to get and most are relatively inexpensive
   - Selectivity is concentration dependent
   - Using titration can help determine % involvement in a pathway
   - Mechanism-based and metabolite intermediate complex inhibitors require 10–15 min preincubation before addition of test substrate

2. Selective antibodies
   - Either expensive or require collaboration with laboratory that produces them
   - Selectivity often limited to family of enzyme
   - Using titration can help determine % involvement in a pathway

3. Correlation
   - Requires a phenotyped HLM bank, the more HLM the better
   - Requires selective assays for all enzymes monitored
   - Selectivity is rarely perfect
   - If marker assay is not evenly distributed, high activity HLMs may bias result

4. cDNA-expressed enzymes
   - Excellent to determine if enzymes can carry out metabolism
   - Activities have improved over time
   - Newer studies are employing scaling techniques to help estimate % involvement. This requires a phenotyped liver bank

Table 9
Selectivity of P450 Inhibitors (% Inhibition)

Inhibitor	μM	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Fur[a]	5[b]	90				—		—	15	—
	5[d]	20–90	—	—	—	—	—	—	—	—
	100[b]	90				—		—	15	—
	100[d]	30–95	—	20–30	—	15–30	15–30	—	0–15	0–25
	200[c]	90	—	—	45	30		65	30	50
7,8-BF	1[c]	95	—	—	20	—		—	—	—
	10[b]	75				—		+20	+30	—
	100[b]	80				60		—	+90	30
α-NF	1[d]	20–95	—	—	+200	15	25	—	—	0–+50
	100[d]	90–95	0–65	—	+300	25–35	30–45	—	—	0–+1000
Orph	100[d]	—	—	0–20	0–25	—	—	0–70	—	0–25
	500[d]	0–70	—	70–75	65–70	25–30	0–65	55–90	30–40	35–70
Tran	1000[c]	60	100	100	80	90		—	60	65
Sulf	10[b]	—				65		—	—	—
	10[c]	—	—	—	100	90		15	—	—
	20[b]	—				75		20	—	—
	20[d]	0–20	—	—	—	90	—	—	—	10–30
	100[b]	—				85		—	—	—
	100[d]	0–30	—	20–35	20–30	90	—	—	15–25	20–25
Quin	0.5[c]	—	—	—	—	45		95	—	—
	0.5[d]	—	—	—	—	—	—	60–70	—	—
	1[b]	—				—		60	—	—
	10[b]	—				—		85	—	—
	10[d]	—	—	—	—	—	—	85–95	—	0–20
DDC	10[b]	—				—		—	50	—
	20[d]	—	20–35	—	—	15–35	0–50	—	35	—
	100[b]	20				20		30	75	20
	100[d]	10–30	50–70	10–40	15–45	30–60	35–80	20	70–75	20
	200[c]	—	90	30	35	40		50	90	25
3-MP	50[b]	—				—		65	70	—
	500[b]	35				40		80	75	20
	500[c]	—	20	50	—	60		75	80	35
Keto	1[d]	—	—	—	0–25	—	—	—	—	10–90
	2[b]	—				—		—	—	82
	5[d]	—	—	20–40	50–55	25	—	—	—	90–100
	10[c]	40	35	85	—	60		65	85	100
	50[b]	45				70		60	—	100

(continued)

Table 9 (*continued*)

Inhibitor	μM	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
TAO	50[b]	—				—		—	—	80
	50[d]	—	—	—	—	—	—	—	—	25–50
	500[d]	—	0–20	0–20	20–30	—	—	—	15–30	75–80
	1000[c]	20	25	30	30	50		40	10	100

Note: "—" means less than 15% inhibition was observed; a blank spot indicates that P450 was not studied.

[a]The abbreviations used for inhibitors are listed along with the P450 it is commonly believed specific for in parentheses: Fur, furafylline (1A2); 7,8-BF, 7,8-benzoflavone (1A2); α-NF, α-naphthoflavone (1A2); Orph, orphenadrine (2B6); Tran, tranylcypromine (2C); Sulf, sulfaphenazole (2C9); Quin, quinidine (2D6); DDC, diethyldithiocarbamate (2E1); 3-MP, 3-methylpyrazole (2E1); Keto, ketoconazole (3A4); and TAO, troleandromycin (3A4).

[b]Data from Newton et al. *(21)*, who used four HLM with 15-min preincubation for studies with Fur, DDC, and TAO, and no preincubation for all other inhibitors.

[c]Data from Ono et al. *(22)*, who used cDNA-expressed P450s with 5-min preincubation for all inhibitors.

[d]Data from Sai et al. *(23)*, who used cDNA-expressed P450s with 10-min preincubation for Fur, DDC, and TAO, and 5-min preincubations for all other inhibitors.

results presented in this and other chapters of this book, and when researching the primary literature.

Selective antibodies are powerful tools, but their selectivity must be carefully determined. The most common limitation is their inability to distinguish P450s of the same family (e.g., 3A4 vs 3A5). A common feature of selective inhibitors and selective antibodies is that they can be used to titrate the activity in liver tissue preparations and provide an estimate of the percent involvement. Selective antibodies can also be used to quantitate the amount of a particular P450 or P450 family in liver tissue.

A common feature of liver tissue preparations is that there is usually large interindividual variation between preparations. This arises in part from true individual differences and from differences in tissue preparation. When a number of HLMs have been phenotyped by immunoquantitation and/or by determining P450 selective activities, they can be used for correlational studies. The metabolic pathway in question is measured in the different preparations and plotted as a scatter gram against the marker activities or contents. High and low correlation coefficients provide supportive evidence of the enzymes' positive or negative involvement, respectively. As with any correlation experiments the distribution of activities should be carefully examined to assure no heterogenous scatter is creating a biased result *(24)*.

cDNA-expressed P450s provide a means of measuring the pathway in question in a purified and reconstituted system. By themselves, they can only determine the ability of the enzyme to perform the reaction. Comparison of different P450s is complicated by differences in their membrane lipid contents, and the contents of the other enzymes involved in P450-mediated monooxygenations, NADPH cytochrome P450 reductase, and cytochrome b_5 *(18)*. In more recent experiments, scaling techniques have been employed to estimate the relative contributions of P450s using the results of experiments in cDNA-expressed P450s. The relative contribution of the enzyme (f_i) is calculated from: $f_i = [A_i v_i(s)] / [\Sigma A_i v_i(s)]$, where A_i is the relative abundance of the P450

Table 10
Involvement of Specific Enzymes in the Metabolism of Benzodiazepines

Drug	Pathway	P450	Level of Evidence[a]	References
Diazepam	3-Hydroxylation	3A4, 3A5 >> 2C19	1, 2, 4	*26–30*
	N-Demethylation	2C19, 3A4, 3A5 >> 2B6	1, 2, 4	*26–30*
Nordiazepam	3-Hydroxylation	3A4 >> 3A5	4	*27,28*
Temazepam	N-Dealkylation	3A4, 2C19 > 3A5 >> 2B6	4	*27,28*
Midazolam	1'-Hydroxylation	3A5 > 3A4 >> 2B6	1, 2, 3, 4	*31–42*
	4-Hydroxylation	3A4, 3A5 >> 2B6	1, 2, 3, 4	*32,33,35,37,38,41*
Triazolam	1'-Hydroxylation	3A	1, 2, 3	*32,41,207*
	4-Hydroxylation	3A	1, 2, 3	*32,41,207*
Alprazolam	1'-Hydroxylation	3A5 > 3A4	1, 2, 3, 4	*44,45*
	4-Hydroxylation	3A4, 3A5	1, 2, 3, 4	*43–45*
Adinozalam	N-Demethylation	3A4 > 2C19	1, 4	*46*
	2nd N-Demethylation	3A4 > 2C19	1, 4	*46*
Flunitrazepam	3-Hydroxylation	3A4	1, 2, 4	*47–49*
	N-demethylation	3A4, 2C19	1, 2, 4	*47–49*
Brotizolam	Utilization	3A4	4	*50*
	1'-Hydroxylation	3A4	1, 2	*50*
	4-Hydroxylation	3A4	1, 2	*50*
Mexazolam	Oxazolo-ring cleavage	3A4	2	*9*

[a]Level of evidence refers to the types of experiments with the same number listed in Table 8.

and $v_i(s)$ is the concentration velocity function of the P450. Abundance has been alternatively estimated from immunoquantitation of P450s in HLM *(25)* or from relative activity factors (RAFs) calculated from the ratio of activity of enzyme-specific pathways in HLM to that in cDNA-expressed P450s *(18)*. These methods are well described in the recent work of Venkatakrishnan et al. *(19)*.

2.3.2. Involvement of Specific P450s in the Metabolism of Benzodiazepines

The metabolism of a number of benzodiazepines has been studied using the methods described above. The results of these studies are summarized in Table 10. The P450 3A family has been implemented in all of these metabolic pathways that include: diazepam 3-hydroxylation and N-demethylation *(26–30)*, nordiazepam 3-hydroxylation *(27, 28)*, temazepam N-dealkylation *(27,28)*, midazolam 1'- and 4-hydroxylation *(31–42)*, alprazolam 1'- and 4-hydroxylation *(43–45)*, the first and second N-demethylations of adinazolam *(46)*, flunitrazepam 3-hydroxylation and N-demethylation *(47–49)*, brotizolam 1'- and 4-hydroxylation *(50)*, and the oxazolo-ring cleavage of mexazolam *(9)*.

In human liver there are two members of the 3A family, 3A4 and 3A5. P450 3A4 is the most abundant P450 in most livers, while 3A5 is detected in only approximately 20% of livers *(51)*. In a few of the studies cited above, 3A4 and 3A5 mediated activities have been compared. Equivalent activities were found for diazepam 3-hydroxylation and N-demethylation *(27,29)*, and for midazolam 4-hydroxylation *(33,35)*. P450 3A4

was more active than 3A5 for nordiazepam 3-hydroxylation and temazepam N-dealkylation *(27,28)*. In contrast, P450 3A5 was more active than 3A4 for midazolam 1'-hydroxylation *(33,35,42)*. Gorski et al. *(44)* indirectly suggest that 3A5 is more involved in the 1'-hydroxylation of alprazolam based upon correlation differences between livers that contain both 3A4 and 3A5 vs those containing only 3A4. As some differences have been observed in the response of 3A4 and 3A5 to inhibitors *(22)*, the differential metabolism of benzodiazepines by these two members of the 3A family may play a factor in susceptibility to certain drug interactions.

P450 2C19 appears to play a role in the N-demethylation of diazepam, temazepam, adinazolam, N-desmethyladinazolam, and flurazepam. For diazepam, this involvement has been confirmed from studies comparing extensive and poor 2C19 metabolisors *(52)*. For 3 poor metabolizers, compared to 13 extensive metabolizers, the clearance of diazepam was reduced by 50%, and the elimination half-life was increased twofold *(52)*. This study is consistent with the in vitro findings that show considerable diazepam N-demethylation activity with cDNA-expressed 2C19, inhibition of diazepam N-demethylation in HLM with omeprazole, and with anti-2C family antibodies *(26–30)*. In the same study, Bertilsson et al. *(52)* compared the elimination of nordiazepam in poor and extensive 2C19 metabolizers. With nordiazepam also, the clearance was reduced by 50%, and the elimination half-life was increased twofold *(52)*. This suggests that 2C19 can also be involved in some 3-hydroxylation reactions, which was not readily apparent from the results of the in vitro studies *(27)*.

P450 2B6 may have a minor role in the N-demethylations of diazepam and temazepam *(27–29)*, as well as the 1'- and 4-hydroxylations of midazolam *(39,41,42)*. Whether this role of 2B6 will have clinical significance has yet to be determined. In part, this will depend upon the relative content of 2B6 in human livers. Earlier studies on specific P450 content suggested that 2B6 did not exceed 1–2% of total P450 *(51)*, but a more recent one showed 100-fold variation in 2B6 content in 19 HLM from 0.7 to 71.1 pmol/mg protein. Assuming an average P450 content of 500 pmol/mg protein, this is a range of 0.14–14.2% of total P450. If high 2B6 content is coupled with low 3A4 and 3A5 content, then the likelihood of 2B6's contribution to the metabolism of some benzodiazepines may be increased.

In summary, P450 3A4 (and 3A5) are extensively involved in many pathways of oxidative metabolism of benzodiazepines. P450 2C19 is involved in many of the N-demethylation reactions, and may play a role in some other oxidative pathways. P450 2B6 may also have a role in certain oxidative pathways. Though a number of metabolic pathways of benzodiazepines have been studied, many have not. Little is known of the role of specific uridine diphosphate glucuronosyl transferases or sulfotransferases in conjugation of benzodiazepines or of the enzymes involved in reduction and subsequent acetylation of the nitroso-benzodiazepines.

3. Benzodiazepine Drug Interactions

3.1. General Considerations

Both pharmacodynamic and pharmacokinetic mechanisms have been observed for drug interactions concerning benzodiazepines. Most pharmacokinetic drug interactions involve either the inhibition or induction of specific P450s involved in the metab-

olism of benzodiazepines. They are the most common and the better documented of drug interactions with benzodiazepines. Most, however, result in either an increased (inhibitors) or decreased (inducers) activity of the benzodiazepine. When therapeutic doses are used these interactions may have clinical and forensic, if carried into driving or other machine-operating environments, but rarely lethal consequences. Pharmacokinetic drug interactions with benzodiazepines are specific for certain benzodiazepines depending upon the enzyme(s) involved in their metabolism. Some of these interactions were reviewed in the mid-1980s *(53,54)*. A more recent review was restricted to alprazolam, midazolam, and triazolam *(55)*.

Pharmacodynamic drug interactions with other CNS depressants are more likely to have lethal, as well as clinical and forensic, consequences. These drugs, which include ethanol, opioids, and barbiturates, also cause respiratory depression, and their combined use can have additive, and has been described in some cases, even synergistic effects. The potential for pharmacodynamic interactions exists for all benzodiazepines regardless of route of metabolism; synergistic interactions, however, may involve a combined pharmacodynamic and pharmacokinetic interaction that is specific for certain benzodiazepines. A number of reviews have considered the interactions of benzodiazepines and ethanol *(56–59)*. None were located addressing interactions with opioids or barbiturates.

The tables presenting pharmacokinetic and pharmacodynamic results of clinical studies (Tables 14–30) are structured in a similar format with consistent abbreviations. A key to these tables is presented at the end of the chapter in Table 31.

3.2. Epidemiological Occurrences of Benzodiazepines, Ethanol, and Opioids

3.2.1. The Occurrence of Other Drugs or Ethanol in Benzodiazepine-Associated Deaths

The epidemiologic record presents circumstantial evidence for the importance of drug interactions of benzodiazepines with ethanol and opioids. A number of studies have examined deaths linked to benzodiazepines. Those that investigated the involvement of other drugs and/or ethanol in the deaths are listed in Table 11A. In general, deaths linked to benzodiazepine use often, but not always, also have evidence of ethanol and/or other drug use. Some studies investigated only the involvement of ethanol *(60,61)*, or other drugs *(62)*, in addition to benzodiazepines. It is therefore difficult to get an exact estimate of how often only benzodiazepines were identified. In one study carried out in the United States and Canada that investigated deaths involving diazepam, only 2 of 914 deaths were identified with only diazepam *(63)*. In another study carried out in Sweden, benzodiazepines were identified in 144 of 702 deaths without other drugs or ethanol *(64)*. A sufficient dose of benzodiazepines can be lethal, but this appears to be exacerbated when other drugs are involved.

3.2.2. The Occurrence of Benzodiazepines in Opioid-Associated Deaths: The Buprenorphine Story

Benzodiazepines are also apparent in some opioid related deaths (Table 11B). Three studies were identified that investigated heroin-linked deaths. Benzodiazepines

Table 11
The Presence of Alcohol and Other Drugs in Benzodiazepine Poisonings

Year	Population	Location	Reference
A) The occurrence of other drugs or ethanol in benzodiazepine-associated deaths			
1979	914 diazepam-positive fatalities 912 & other drug or EtOH; 51 EtOH; 295 EtOH and other drug; 566 other drug; propoxyphene > opiates > barbiturates	USA and Canada	*63*
1980	2723 overdoses 1071 benzo positive; 726 & other drugs (EtOH apparently not studied)	Toronto, Canada	*62*
1989	3430 overdoses 702 benzo positive; 144 benzo; 200 benzo & EtOH; 254 benzo & other drug; 104 benzo, other drug & EtOH	Stockholm, Sweden	*64*
1993	1576 benzodiazepine-associated deaths 891 single benzo; 591 single benzo & EtOH; 94 more than one benzo ± EtOH	Great Britain	*60*
1995	303 benzodiazepine-associated overdoses 303 total; 114 & EtOH	Newcastle, Australia	*61*
B) The occurrence of benzodiazepines in opioid-associated deaths			
1976	114 heroin-related deaths 9 benzo positives	Orange Co., CA	*65*
1977	268 heroin-related deaths 12 diazepam positive	Wayne Co., MI	*66*
1994	21 heroin-related deaths 2 benzo positive	Baltimore, MD	*67*
1998	Unknown no. of buprenorphine-related deaths 6 benzo positive cases	France	*69*

were also found in 5–10% of these deaths *(65–67)*. Opioids are well recognized for their respiratory depressant effects; that a combination with another CNS depressant that also causes respiratory depression may exacerbate the situation is not too suprising.

Buprenorphine has been used for years as an analgesic or for treatment of chronic pain at doses 0.3–0.8 mg. More recently, buprenorphine has been used in substitution therapy for opioid dependence. For the latter, doses of 8–32 mg are used. Buprenorphine is known as a partial μ agonist that appears to have ceiling effects in regard to its μ-activities such as respiratory depression *(68)*. Recently in France, however, six cases of deaths involving buprenorphine were also found to involve benzodiazepine use (*69*; Table 11B). That buprenorphine may interact with benzodiazepines was suggested in a series of letters to the editor in the journal *Anaesthesia*. Papworth *(70)* first reported four cases of prolonged somnolence and bradypnoea with combinations of buprenorphine and lorazepam. Forrest *(71)* then described a case, also with buprenorphine and lorazepam, that had prolonged somnolence, bradypnoea, and the need for assisted respiration. This was followed shortly thereafter by a report from Faroqui et al. *(72)* that found 11 subjects out of 64 that were premedicated with diazepam and had anesthesia induced with buprenorphine required assisted ventilation. This was not observed in 24 patients receiving diazepam and fentanyl.

This combined effect of buprenorphine and a benzodiazepine, midazolam, has now been reproduced in an animal model. Gueye et al. *(73)* have shown that rats given

Table 12
Benzodiazepine Use Among Opioid Users: Survey of Studies in 1990s

Year	Population	Location	Reference
1990	272 polydrug users (75% heroin) 28% were also using temazepam (use of other benzos not mentioned).	Northwest England	*368*
1990	249 male opiate addicts Greater than 50% used benzos, with flunitrazepam most common.	Penang, Malaysia	*369*
1991	323 methadone treatment subjects Daily, few times per week, and a few times per month benzo use was 14, 15, and 39% in those who did not share needles and 25, 18, and 24% in those who did share needles.	Philadelphia and New Jersey	*370*
1992	1245 injecting drug users 36.6% used benzos	Sydney, Australia	*371*
1992	103 methadone treatment subjects All had used heroin and benzodiazepines, relative liking of cocaine > cannabis >> stimulates ≈ benzos. Flunitrazepam and diazepam were the most favored.	Innsbruck, Austria	*372*
1993	313 applicants for methadone treatment 42% reported a benzo habit (37% of males; 56% of females).	Kensington, Australia	*373*
1993	973 admittees for inpatient opiate detoxiciation 80.2% history of benzo use; 68.5% current; 43.1% daily. Flunitrazepam > clorazepate > diazepam.	Barcelona, Spain	*374*
1993	222 methadone treatment subjects 36.5% use in the past month; 26.6% daily; and 11.3% five or more pills a day.	Kensington, Australia	*375*
1994	208 subjects (82.2% for opiate use) 90% had used benzos, 49% by injection.	clinics in seven cities in Britain	*376*

buprenorphine alone (30 mg/kg, iv) had a mild increase in $PaCO_2$ at 60 min. Rats given midazolam alone (160 mg/kg, ip) had a mild decrease in arterial pH at 90 min and increase in $PaCO_2$ at 60 min. When the doses were combined, there was a prolonged respiratory depression with the changes in blood pH and $PaCO_2$ noted within 20 min, with delayed hypoxia at 120 and 180 min.

This effect is apparently not due to an inhibition of the benzodiazepine metabolism. Kilicarslan and Sellers *(74)* have shown that metabolism of flunitrazepam to 3-hydroxy-flunitrazepam in HLMs was not inhibited by norbuprenorphine, and while inhibited by buprenorphine, the K_i of 118 μM was suggestive of only 0.1–2.5% inhibition in vivo. The converse situation, inhibition of buprenorphine metabolism by benzodiazepines, has not yet been addressed.

Although the percentage of opioid-associated deaths that also show benzodiazepine use is relatively low (Table 11B), it is still a concern due to the potential for the pharmacodynamic interaction resulting in additive (or synergistic) effects on respiratory depression. Further epidemiological data substantiate the risk. Surveys conducted in the early 1990s in various parts of the world demonstrate that use of benzodiazepines is quite common in opioid-dependent subjects (Table 12). Regular benzodiazepine use ranged from 27 to 50%, whereas most had used benzodiazepines at one time. A great majority reported intravenous use of the benzodiazepines.

3.2.3. The Occurrence of Benzodiazepines, with or Without Ethanol or Other Drugs in Motor Vehicle Investigations

One other area in which epidemiological data point to potential interactions between benzodiazepines and ethanol or other drugs is within motor vehicle investigations. Studies that clearly indicated benzodiazepine and ethanol and/or other drug use were reveiwed and are listed in Table 13. These studies can be divided into three types: (a) studies on fatalities where in most studies drug use was determined in all cases, (b) studies on impaired driving where in most studies only cases with ethanol below a certain cutoff were tested for drugs, and (c) random testing where participants volunteered for inclusion in the drug-testing part of the study. These differnet protocols may have an impact on the drug findings.

In studies on driving fatalities, the presence of benzodiazepines ranged from 1.3 to 10.2%. Benzodiazepine positives were found in conjuction with ethanol in 25 to 78% of the cases. For impaired driving cases the presence of benzodiazepines ranged from 1 to 30% with the additional finding of ethanol ranging from 22 to 100%. Studies that focused on profession transportation reported very low incidences of benzodiazepine use. In a study on 168 track-driver fatalities, no benzodiazepines were detected *(75)*. In the two random studies, only commercial truck drivers were included. In one study, only 1 of 317 participants (88% compliance) was benzodiazepine positive and had a prescription for its use *(76)*. In the other study, none of the 822 (81% compliance) participants was positive for benzodiazepines *(77)*. In 1398 mandatory postaccident cases studied for the Federal Railroad Association, only 2 benzodiazepine positive cases were detected, 1 with prescription for its use *(78)*. Benzodiazepine use in vehicle-related investigations varies widely. This may be due in part to geographic and temporal differences in the studies. In 7 of the 10 studies that did not include commercial drivers, ethanol was a cofactor in greater than 50% of the cases.

Benzodiazepine-positive findings along with other drugs were described in a few of these studies. In a study of impaired drivers in California published in 1979, 14 of the 56 cases positive for chlordiazepoxide also had phenobarbital *(79)*. In a study of ethanol-negative-impaired drivers in St. Louis published in 1987, 10 and 8 of the 30 benzodiazepine-positive cases were also positive for barbiturates or opiate analgesics, respectively *(80)*. Two studies focused on cases positive for a specific drug(s). In a study in Sweden published in 2000 of 486 impaired drivers that had tested positive for codeine or dextropropoxyphene, 346 were also positive for a benzodiazepine *(81)*. In a study from Washington state published in 2001, 4 of 29 zolpidem-positive cases were also positive for benzodiazepines *(82)*. As with mixtures of benzodiazepines with ethanol, their mixture with other CNS depressant drugs is common in vehicle-irregularity-related studies.

3.3. Clinical Studies on Drug Interactions of Benzodiazepines with Other CNS Depressants

3.3.1. Pharmacodynamic and Pharmacokinetic Interactions with Analgesics and Anesthetics

Clinical studies on drug interactions between benzodiazepines and opioids, or other CNS depressants, have been mostly limited to interactions between the two benzodiaz-

Table 13
The Occurrence of Benzodiazepines with or Without Ethanol (or Other Drugs) in Motor Vehicle Investigations

Year	Population	Location	Reference
A) Fatalities			
1977	127 driving fatalities 23 drug positive; 13 diazepam, 7 & EtOH	Dallas, Co., TX	*377*
1980	401 motor vehicle fatalities 64 drug positives; 15 benzos; 12 diazepam, 3 & EtOH, 4 & other drugs	Ontario, Canada	*378*
1986	1518 driving fatalities 32 benzo positive, 25 & EtOH	Alabama	*379*
1987	200 driving fatalities, survivors, or blood tested (resticted to EtOH < 0.05) 34 drug positive; 9 benzo, 7 & EtOH	Tasmania, Autralia	*380*
1993	168 trucker fatalities no benzos identified	USA	*75*
1996	318 driving fatalities 61 drug positive; 4 benzo, 2 & EtOH	Washington	*381*
B) Impaired situations			
1969	180 overt intoxication, but BAC ≤ 0.15% 38 drug positive; 2 chlordiazepoxide (BAC) 1 (0-< 0.05); 1 (0.10-0.15)	Santa Clara Co, CA	*382*
1979	765 drug positive-impaired driving 171 diazepam, 40 & EtOH; 56 chlordiazepoxide, 9 & EtOH, 14 & phenobarbital	California	*79*
1979	425 under influence (EtOH < 0.08 in 282) Drugs present in 115 cases; benzos in 90 (80 diazepam), 85 & EtOH	Northern Ireland	*383*
1981	71,937 impaired driving, but BAC ≤ 0.10% 684 benzos (571 dizepam), 310 & EtOH	Orange Co., CA	*384*
1984	56 impaired driving (saliva) 10 drug positive; 4 diazepam, 4 & EtOH	Ottawa, Canada	*385*
1987	184 impaired driving, negative EtOH 30 benzo positive; 10 & barbiturates, 8 & opiates analgesics	St. Louis, MO	*80*
1991	1398 mandatory railroad postaccident testing 85 drug positives; 2 benzos, 0 & EtOH	USA	*78*
1998	19,386 first road-traffic accidents Based on prescription data, use of benzos had a 1.52 risk factor (8.15 & EtOH) compared to 0.30 (1.0) with tricyclics and 0.51 (0.89) with SSRIs.	Tayside region, UK	*386*
2000	486 impaired drivers study restricted to dextropropoxyphene or codeine positive samples; 346 benzo	Sweden	*81*
2001	29 zolpidem positive impaired drivers 4 benzo positive; 1 & EtOH	Washington	*82*
C) Random testing			
1988	317 (88% compliance) random truck drivers 1 benzo positive with prescription	Tennessee	*76*
2002	822 (81% compliance) random truck drivers no benzos identified	Oregon/Washington	*77*

epines used as anesthetics, diazepam and midazolam, with other anesthetic or analgesic agents (Tables 14 and 15). One exception is a study on the effect of diazepam on methadone maintenance. In an initial paper, Preston et al. *(83)* demonstrated that a combination of diazepam and methadone produced subjective opioid effects greater than either drug alone (Table 14). In a follow-up report, these investigators studied the effect of

Table 14
Effect of Analgesics and Anesthetics on Benzodiazepine Pharmacodynamics

Benzodiazepine	Dose	Agent Dose	Agent Time	N	Reference
Methadone					
Diazepam	20 & 40, or 40 mg diazepam and 150% maintenance dose induced changes in pupil constriction and subjective opioid effects greater than those by either drug alone.	100 & 150% maintenance	0 h	5m	*83*
Papaveretum					
Midazolam	0.15–0.5/kg, iv Sedative effect of midazolam was potentiated by opiate.	15–20 mg, im	0 h	37/29	*86*
Pethidine					
Midazolam	0.15–0.5/kg, iv Sedative effect of midazolam was potentiated by opiate.	50–75 mg, im	0 h	47/29	*86*
Diazepam	10, iv No difference in sedation noted, but patients more comfortable with procedure.	50–75 mg	0 h	50/50	*87*
Morphine					
Midazolam	0.01–0.03/kg, iv Dose response: additive effect on visual analog determination of sedation.	0.006–0.12 mg/kg, iv	–10 min	5/dose	*88*
Fentanyl					
Diazepam	0–0.5/kg, iv Dose response of diazepam: caused significant reduction in arterial pressure and systemic vascular resistance associated with decreases in (nor)epinephrine.	50 μg/kg	4 min	5/dose	*90*
Midazolam	≈0.35/kg, iv Combination caused greater respiratory depression than midazolam alone.	50 μg, iv	–1 min	30/44	*89*
Midazolam	0.3/kg, iv Fentanyl decreased onset time for midazolam anesthesia and % asleep at 3 min.	50 or 100 μg, iv	–2 min	52/100	*91*
Midazolam	0.05/kg, iv Synergistic increase in apnea and hypoxemia, no further reduction in fentanyl-reduction of ventilatory response to CO_2.	2 μg/kg, iv	0 h	12m	*92*
Midazolam	0.02–0.37/kg, iv Synergistic increase in inability to open eyes in response to command (anesthesia).	1.9–8.5 μg/kg, iv	1 min	10f/dose	*93*
Alfentanyl					
Diazepam	0.125/kg, iv Diazepam reduced the numbers responding to voice at 5 min (10 to 1, 5 to 1), increased heart rate, increased reductions in blood pressure, and increased number (1 to 5) with inadequate postoperative ventilation.	100 or 200 μg/kg, iv	5 min	10/dose	*94*
Midazolam	0.3/kg, iv Alfentanyl decreased onset time for midazolam anesthesia and % asleep at 3 min.	150 or 300 μg, iv	–2 min	40/100	*91*
Midazolam	0.07–0.35/kg, iv Dose response; found synergistic response of response to verbal command (sedation).	0.02–0.18 mg/kg, iv	1 min	5/dose	*95*

(continued)

Table 14 (*continued*)

Benzodiazepine	Dose	Agent Dose	Agent Time	*N*	Reference
Alfentanyl *(continued)*					
Midazolam	0.023–0.2/kg, iv	0.016–0.15 mg/kg, iv	0 h	10/dose	*96*
	Dose response, response to verbal command (hypnosis), and response to tetanic stimulus (anesthesia) are synergistically enhanced.				
Naltrexone					
Diazepam	10, or	50 mg	−1.5 h	8f, 18m	*103*
	Negative mood states (sedation, fatique) were increased and positive mood states (friendliness, feeling high) were decreased by naltrexone.				
Propofol					
Midazolam	0.1–0.2/kg, iv	0.7–2.5 mg/kg, iv	0 h	10/dose	*106*
	Dose response: response to command was synergistically influenced; midazolam reduced dose of propofol required for response to tetanic stimuli.				
Midazolam	0.1–0.4/kg, iv	0.4–2.8 mg/kg, iv	2 min	10/dose	*107*
	Dose response: response to command was synergistically influenced.				
Thiopental					
Midazolam	0.03–0.37/kg, iv	0.7–3.6 mg/kg, iv	1 min	5/dose	*104*
	Dose response: response to command was synergistically influenced.				
Midazolam	0.04–0.2/kg, iv	0.7–4.5 mg/kg, iv	2.5 min	20/dose	*105*
	Dose response: response to command was synergistically influenced; midazolam reduced dose of thipopental required for response to electrical stimuli.				

Table 15
Effect of Analgesics and Anesthetics on the Pharmacokinetics of Benzodiazepines

Benzodiazepine	Dose	*N*	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	Reference
Methadone	100% of maintenance dose							
Diazepam	20, or	5m				0.95		*84*
Diazepam	40, or	5m				0.91		*84*
Methadone	150% of maintenance dose							
Diazepam	20, or	5m				1.28		*84*
Diazepam	40, or	5m				1.24		*84*
Propoxyphene	65 mg, 4/d, multidose							
Alprazolam	1, or	6f,2m	3.46	0.94	1.58*		0.62*	*85*
Diazepam	10, iv	2f,4m			1.14		0.87	*85*
Lorazepam	2, iv	1f,4m			0.99		1.10	*85*
Fentanyl	Patients undergoing orthopedic surgery ±200 μg, iv							
Midazolam	0.2/kg, iv	15/15			1.49*	1.54*	0.70*	*97*
Naltrexone	50 mg at −1.5h							
Diazepam	10, or	8f,18m	1.80*	0.93	1.05*	0.95		*103*
Propofol	Patients undergoing elective sugery ±2 mg/kg bolus, 9 mg/kg/h infusion							
Midazolam	0.2/kg, iv	12/12			1.61*	1.58*	0.63*	*108*

methadone on the pharmacokinetics of diazepam. Although not significant, a combination of 150% of the maintenance dose of methadone with either 20 or 40 mg oral diazepam resulted in an approximately 25% increase in the area under the curve (AUC) of diazepam (*84*; Table 15).

Propoxyphene is an extensively used analgesic; its coadministration with benzodiazepines would not be uncommon. In a single study, subjects took three different benzodiazepines, oral alprazolam and intravenous diazepam and lorazepam, each one twice. In one setting, no other drug was taken; in the other, propoxyphene was administered every 6 h from 12 h prior to the benzodiazepine and then for the duration of the study *(85)*. Coadministration of propoxyphene significantly inhibited the elimination of alprazolam; there was a slight, but nonsignificant inhibition of diazepam; and no effect on the pharmacokinetics of lorazepam (Table 15). No information was found on the in vitro inhibition of P450s by propoxyphene, but these data would support an inhibitory effect of propoxyphene on P450 3A4 that spares P450 2C19. No data were presented on the effect of propoxyphene on the pharmacodynamics of benzodiazepines.

When midazolam or diazepam is combined with the opioids papaveretum, pethidine, or morphine during anesthesia, potentiation of the sedative or subjective effects is consistently found (*86–88*; Table 14). Pharmacokinetic interactions between these drugs were not studied.

The combination of midazolam or diazepam with fentanyl has also been consistently found to result in potentiation of the sedative and in some cases respiratory depressant effects of the drugs *(89–93)*. In the latter two studies, which used midazolam, statisitical evaluation of dose responses suggested that the drugs interacted in a synergistic manner *(92,93)*. A similar finding was found for combined use of diazepam or midazolam with alfentanil, including the synergistic response with midazolam (*91,94–96*; Table 14). With fentanyl it has been shown that its combination with midazolam results in a significant increase in the terminal elimination half-life ($t_{1/2}$) and AUC and significant decrease in the clearance of midazolam (*97*; Table 15). A similar pharmacokinetic study has not been done with alfentanil, but both are P450 3A4 substrates *(98–101)* and may have similar potential to inhibit midazolam metabolism, as has been found in vitro for fentanyl *(102)*.

The interaction between naltrexone, an opioid μ receptor antagonist, and diazepam is another exception to the studies between anesthetics. Naltrexone was found to increase the negative mood states such as sedation, and decrease the positive mood effects such as friendliness of diazepam (Table 14), with no effect on its pharmacokinetics (Table 15; *103*).

The interaction of the structurally unique anesthetic propofol or the barbiturate thiopental with midazolam has also been reported to have synergistic effects on the sedative effects of the drugs (Table 14; *104–107*). A pharmacokinetic study has been performed on the interaction of midazolam and propofol, and propofol was found to significantly increase the $t_{1/2}$ and AUC of midazolam (Table 15; *108*). This is consistent with the in vitro inhibition of midazolam metabolism by propofol *(109)*.

Clinical studies confirm that additive interactions occur between the opioids and other anesthetic agents. These have sometimes been found to be synergistic in their response. The synergistic response appears to occur when there is also a pharmacokinetic interaction resulting in the inhibition of the benzodiazepines' clearance.

Table 16
Effect of Ethanol on Benzodiazepine Pharmacodynamics

Benzodiazepine	Dose (mg)	Ethanol Dose	Ethanol Time	*N*	Reference
Alprazolam	0.5, or	0.8 g/kg	3 h	10m	*116*
	No effect on measures of side effects, tracking skills, angle recognition or free recall; diminished choice reaction time.				
Alprazolam	2, or	0.8 g/kg	3 h	10m	*116*
	No effect on measures of side effects, tracking skills, angle recognition, or free recall; diminished choice reaction time.				
Alprazolam	1, or	0.5 g/kg,	0.75 h	12/12	*110*
	Produced predictive additive effects on sedation, unsteadiness, dizziness, tiredness and psychomotor performance.				
Bromazepam	6, or 3/d × 14 d	0.5 g/kg	0 h	20m	*387*
	Enhanceed impairment of learning skills, but not short-term memory.				
Bromazepam	6, or 3/d × 14 d	0.5 g/kg	0 h	1f,16m	*113*
	No effect on reaction time or mistakes; enhanced effects on coordination skills, attention and propioception.				
Brotizolam	0.25, or	24 mL	0 h	13m	*120*
	Subjective perceptions of sedation were enhanced, but psychomotor performance was not.				
Chlordiazepoxide	5, or 3/d × 2 d	45 mL		6f,12m	*388*
	Subjects were tested on mental and then psychomotor performance starting at +1h. No significant difference ± ethanol.				
Chlordiazepoxide -lactam	10, or 3/d × 14 d	0.5 g/kg	0h	20	*115*
	No effect on reaction time; enhanced coordination mistakes at fixed and free speed and impairment of attention and propioception.				

(continued)

3.3.2. Pharmacodynamic and Pharmacokinetic Interactions with Ethanol

The effect of combined use of ethanol on pharmacodynamic end points has been studied with a large number of benzodiazepines (Table 16). In general, ethanol has a potentiating effect on some of the psychomotor and subjective measures, but rarely affects all such measures in any one study. In part because the studies were not designed to detect it, synergistic effects were not noted. Because of the diverse end points in the studies, there was no apparent general set of pharmacodynamic end points that ethanol consistently had an effect upon. For example, reaction time was a common end point. Ethanol was reported as enhancing impairment of reaction time for alprazolam *(110)*, clobazam *(111)*, diazepam *(112)*, and tofisopam *(112)*, whereas it had no effect on reaction time with bromazepam *(113)*, loprazolam *(114)*, oxazepam *(115)*, nordiazepam *(115)*, and temazepam *(115)*. Few of the studies compared benzodiazepines under the same conditions. It is therefore difficult to draw conclusions about some benzodiazepines being more susceptable to the interactive effects with ethanol.

Table 16 (*continued*)

Benzodiazepine	Dose (mg)	Ethanol Dose	Ethanol Time	*N*	Reference
Clobazam	20, or	77 g	0–1.5 h	8m	*111*
	Enhanced impairment of reaction errors and time, deviations of two-hand coordination and body sway.				
Clorazepate	20, or	1 g/kg		14m	*389*
	Enhance alcohol acute euphoric effects and decreased dysphoric effects in the following morning.				
Diazepam	5, or 3/d × 3 d	42 mL	0 h	20	*390*
	Measured ability for cancellation of letters, digit substition, addition and pegboard placement begining at +75 min. Performance under diazepam, ± EtOH, was slightly poorer than with placebo tablet.				
Diazepam	2, or 3/d × 2 d	45 mL		6f,12m	*388*
	Subjects were tested on mental and then psychomotor performance starting at +1 h. Ethanol enhanced the effects on two of nine mental tests; no effect on psychomotor tests.				
Diazepam	10, or /70 kg	0.75 mL/70 kg	0 h	8m	*129*
	Starting at +90 min, no effect on mirror tracing; slight enhancement of attention and time evaluation; significant with attempted letter cancellations, sorting, flicker fusion, complex coordination and clinical symptoms.				
Diazepam	10, or	0.5 g/kg		10/10	*117*
	Simulated driving by professional drivers from +30–70 min. Enhanced number of collsions and driving off the road instances.				
Diazepam	10, 20, or 40, or	0.5 g/kg	0 h	6m	*391*
	Markedly enhanced the effects on coordination and mood.				
Diazepam	10, or	0.8 g/kg	–0.5 h	10	*127*
	Enhanced impairment of tracking skills and oculo-motor coordination; enhanced nystagmus.				
Diazepam	10, iv	at 0.8–1.0 g/L	–1–8 h	6m	*128*
	Enhanced impairment of pursuit rotor performance and intoxication indices and visual analog scale.				
Diazepam	10, or/d × 2 d	0.8 g/kg		12m	*112*
	Enhanced impairment on coordination, reaction, flicker fusion, maddox wing and attention tests.				
Diazepam	10, or	at 0.5 g/L	–1.5–2.5 h	12m	*392*
	Produced additive effects on subjective alertness and measures of performance; synergistic effect on smooth pursuit eye movements.				
Diazepam	5, or	at 0.5 g/L	–1.5–4 h	8m	*393*
	Produced additive effects on adaptive tracking, smooth pursuit, DSST and body sway; did see supra-additive effects in 2 subjects.				
Diazepam	10, or	0.8 g/kg	3 h	10m	*116*
	No effect on measures of side effects, tracking skills, choice reaction time, angle recognition, or free recall.				
Flunitrazepam	2, or	0.8 g/kg	–0.5 h	12m	*124*
	Alcohol did not effect impairment of tracking skills at +1h, but did enhance impairment the following morning.				

(continued)

Table 16 (*continued*)

Benzodiazepine	Dose (mg)	Ethanol Dose	Ethanol Time	*N*	Reference
Flurazepam	30, or/d × 14 d	0.5 g/kg	10 h	7f,33m	*394*
	No effect on reaction time, reaction mistakes or attention; enhanced effects on coordination skills.				
Loprazolam	1, or	0.7 g/kg	0 h	8m	*114*
	No effects on simple reaction time; alleviated lopraz-impairment of manual dexterity; both alone impaired tracking, but not together; memory impaired by lopraz, improved by EtOH, not affected together.				
Oxazepam	10, 20, or 40, or	0.5 g/kg	0 h	6m	*391*
	Slightly enhanced the effects on coordination and mood.				
Oxazepam	15, or 3/d × 14 d	0.5 g/kg	0 h	20	*115*
	No effect on reaction time, attention or propioception; enhanced coordination mistakes at fixed and free speed.				
Midazolam	0.1/kg, iv	0.7 g/kg	4 h	16m	*395*
	Midazolam did not add to the +5h or +7h effects of EtOH.				
Nitrazepam	10, or/d × 14 d	0.5 g/kg	10 h	3f,17m	*396*
	No effect on reaction times; enhanced choice reaction and coordination mistakes and impaired attention.				
Nordiazepam	5, or 3/d × 14 d	0.5 g/kg	0 h	20	*115*
	No effect on reaction time, attention or propioception; enhanced coordination mistakes at fixed speed, no effect at free speed.				
Prazepam	20, or	0.5 g/kg	0 h	12m	*125*
	Enhanced impairment in auditory reaction and DSST; reduced reaction to auditory stimuli and cancellation test and enhanced drowsiness.				
Temazepam	20, or 3/d × 14 d	0.5 g/kg	0 h	20	*115*
	No effect on reaction time or attention; enhanced coordination mistakes at fixed speed, but not at free speed; enhanced impairment of propioception.				
Tofisopam	100, or × 3	0.8 g/kg		12m	*112*
	Enhanced impairment on coordination, reaction, flicker fusion, maddox wing and attention tests.				
Triazolam	0.25, or	at 0.8–0.95 g/L	–0.5–7.5 h	1f,6m	*122*
	Enhanced impairment of free recall, postural stability, and hand–eye coordination.				

The timing of the administration of ethanol was an important factor. When ethanol was given 3 h after alprazolam, only minimal effects were found *(116)*. When ethanol was given only 45 min after alprazolam, however, it had additive effects on most of the end points measured *(110)*. Similarly, combining ethanol with diazepam at the same time led to enhanced impairment of reaction time *(112)*, whereas giving the ethanol 3 h after diazepam did not *(116)*.

Ethanol, therefore, does appear to enhance the impairing effects of benzodiazepines in an additive fashion. In the one study that measured driving skills, diazepam and ethanol were taken together and the stimulated driving of professional drivers was

Table 17
Effect of Ethanol on the Pharmacokinetics of Benzodiazepines in Nonalcoholics

Benzodiazepine	EtOH Dose	EtOH Dose	Time	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	Reference
Alprazolam	0.5, or	0.8 g/kg	+3 h	10m			no change			*116*
Alprazolam	2, or	0.8 g/kg,	+3 h	10m			no change			*116*
Brotizolam	0.25, or	24 mL	0 h	13m	0.95	1.23*	1.18*		0.84*	*120*
Chlordiazepoxide	25, or	0.8 g/kg	0 h	5m	1.67	1.48*				*121*
Clobazam	20, or	39 g		8m	1.00	1.59*		1.55*		*111*
Clotiazepam	5, or	24 mL	0 h	11			1.21		0.93	*123*
Diazepam	10, or	0.8 g/kg	0 h	5m	1.25	1.03				*121*
Diazepam	0.14/kg, or	0.75 mL/kg	0 h	8m	3.0	1.19				*129*
Diazepam	0.07/kg, iv	15 mL	0 h	1f,6m	1.42	1.58*				*126*
Diazepam	5, or	17 mL	0 h	2f,4m	2.27	0.94		1.00		*130*
Diazepam	10, or	0.8 g/kg (b)	−0.5 h	10	0.38	1.58*		1.15		*127*
Diazepam	10, ore	0.8 g/kg (wh)	−0.5 h	10	0.50	1.16		1.07		*127*
Diazepam	10, or	0.8 g/kg (wi)	−0.5 h	10	1.00	1.57*		1.21*		*127*
Diazepam	10, iv	0.8–1.0 g/L	−1–8 h	6m				1.31		*128*
Diazepam	5, or	24 mL	−0.5 h	2f,4m	3.94	0.84	1.23	1.04		*131*
N-desmethyl					1.00	1.10		1.00		
Diazepam	5, or	24 mL	0 h	2f,4m	2.11	0.87	1.21	1.07		*131*
N-desmethyl					1.12	1.00		0.94		
Diazepam	10, or	0.8 g/kg	3 h	10m	≈ 35% higher					*116*
Diazepam	10, or	0.5 g/L	−1.5–2.5 h	12m	1.23	1.15		1.12		*392*
Flunitrazepam	2, or	0.8 g/kg	-0.5 h	12m	0.98	1.02	0.81	1.05		*124*
Prazepam	20, or	0.5 g/kg	0 h	12m	0.83	1.09		0.92		*125*
Triazolam	0.25, or	0.8–0.95 g/L	−0.5–7.5 h	1f,6m		1.08	1.22*	0.84*		*122*

Table 18
Effect of Ethanol on the Pharmacokinetics of Benzodiazepines in Chronic Alcoholics

Benzodiazepine	Dose	Condition	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	Reference
Chlordiazepoxide	50, or	acute vs 7 d abst	5	1.87	1.01	1.52	2.35		*133*
N-desmethyl				2.60	0.71				
Chlordiazepoxide	50, im	acute vs 7 d abst	5	2.41	1.94	1.85	3.35		*133*
N-desmethyl				1.70	1.02				
Chlordiazepoxide	25, or (md)	2 vs 6 d abst	6		2.1ss*				*134*
N-desmethyl					1.91ss*				
demoxepam					0.15ss*				
Diazepam	10, or	1–11 d abst	11/14	1.00	0.43*				*135*
Diazepam	10, iv	1–3 d abst	14/13				0.71*		*136*
N-desmethyl							0.65*		
Diazepam	6	1 d vs 6 d abst	7			0.83		0.67	*137*

studied. The combined use of ethanol and diazepam resulted in increased numbers of collisions and driving off the road instances *(117)*.

Ethanol is known to affect the metabolism of many drugs. In general, acute use of ethanol is associated with the inhibition of drug metabolism; chronic use induces metabolism *(118,119)*. Therefore, examination of the effect of ethanol on benzodiazepine pharmacokinetics should differentiate between studies on acute exposure in nonalcoholics (Table 17) and studies in alcoholics (Table 18).