ANXIOLYTICS: CURRENT STATUS

Benzodiazepines are a group of drugs that are most useful in many clinical situations. The following indications for these drugs are most common:

Indications

1) Anxiety - with or without physical disorders
2) Insomnia - preferably after proper diagnosis
3) Muscle relaxation - only in presence of true spasm
4) Adjunct to analgesics - never used alone for pain
5) Alcohol withdrawal - intravenous or oral administration, but not intramuscular
6) Anesthesia - either induction agent or sole anesthetic
7) Anticonvulsant - diazepam intravenously for status epilepticus: clorazepate for minor seizures.

These indications are closely linked to their pharmacological actions.

Pharmacological Actions

a) Sedation with small doses, leading to hypnosis with larger doses leading to anesthesia with still larger doses.
b) Muscle relaxation, in part associated with sedation and in part mediated through their action in the spinal cord.
c) Anticonvulsant effects.

The widest clinical use of these drugs is for treating anxiety/insomnia. This action may be mediated neuroanatomically through a number of major integrating spheres of the brain.

Mode of Action - Neuroanatomical

a) Reticular activating system - decrease sensory input;

b) Limbic system - decrease affective tone;

c) Hypothalamus - reduce somatic responses

d) Median forebrain bundle - increase tolerance for punishment.

Mode of Action - Neurochemical

a) Specific receptors linked to GABA receptors, GABA being an inhibitory neurotransmitter;

b) Glycine receptors in spinal cord;

c) Little direct action on norepinephrine, dopamine or serotonin.

These drugs are, for the most part, highly lipid-soluble. This chemical property allows for rapid absorption from the gut and rapid passage into the brain.

Metabolism

Some members of this class are metabolized to active metabolites.

a) Chlordiazepoxide (Librium) - active metabolites;

b) Diazepam (Valium) - active metabolite, nordiazepam;

c) Prazepam (Verstran) - -)

d) Clorazepate (Tranxene) -) pro-drugs for nordiazepam

e) Flurazepam (Dalmane) - desalkylflurazepam

In general, the drugs with active metabolites are rather long-lived, with effective plasma T½ (counting parent drug and active metabolites) of 24-96 hours.

Other members of this class have already been hydroxylated and need only to be conjugated to be eliminated. These drugs form no active metabolites and tend to have short plasma T½ of about 8-16 hours:

f) Oxazepam (Serax)

g) Lorazepam (Ativan)

These pharmacokinetic differences are of little clinical importance. The drugs do differ in their potency.

Doses (usual single doses)

Flurazepam	15-30 mg
Clorazepate dipotassium	5-10 mg
Prazepam	5-10 mg
Chlordiazepoxide	10-25 mg
Diazepam	2-10 mg
Lorazepam	1-2 mg
Oxazepam	15-30 mg

Dosage Schedules

Although traditionally doses are given equally divided and several times daily, the long-acting benzodiazepines lend themselves very well to single doses given at bed-time. On the other hand, divided doses of the short-acting drugs are usually required to produce a sustained effect.

Other Drugs

Barbiturates have historically had many of the same indications listed above for benzodiazepines. The greater safety and efficacy

of the latter drugs has rendered most barbiturates obsolete, with the exception of phenobarbital as an anticonvulsant and methohexital sodium as a short-acting anesthetic agent. The major disadvantages of the barbiturates are that they induce drug-metabolizing enzymes that can cause serious interactions with other drugs and that they produce severe respiratory depression when taken in overdoses.

Meprobamate and similar drugs have many of the same disadvantages of the barbiturates. In addition, tolerance/dependence may quickly develop to these drugs.

Drugs that are not conventional sedative-hypnotics have also been promoted for some of the same indications as the benzodiazepines. These include sedative antihistamines (hydroxyzine, Atarax or Vistaril), various tricyclic antidepressants (doxepin, Sinequan or other names) and various antipsychotics (trifluoperazine, Stelazine; haloperidol, Haldol). These drugs are disagreeable to patients because the type of sedation is different and is complicated by varying degrees of unwanted autonomic nervous system effects. The latter make these drugs rarely likely to be abused.

Anxiety

Anxiety is one of the most common symptoms seen by primary care physicians. They may see an anxious patient who presents with somatic symptoms, or they may see a patient with some organic disease who presents with secondary anxiety.

Examples of somatic symptoms of anxiety mimicking organic disease are:

1) palpitations, tachycardia, tightness in the chest, breathlessness, vague chest pains, systolic hypertension - may suggest cardio-respiratory disease;
2) indigestion, diarrhea, choking sensations - may suggest gastro-intestinal disease;
3) fatigue, dizziness - may suggest hematologic disease;
4) appetite changes, perspiration - may suggest a metabolic-endocrine disease;
5) other common symptoms, such as headache, muscle aches, insomnia, unreasonable fears, frequent urination, flushing - may suggest involvement of other organ systems.

Secondary anxiety may be seen with:

angina pectoris	cancer
bronchial asthma	myocardial infarction
ulcerative colitis	obstructive pulmonary disease
neurodermatitis	symptomatic hypertension

Basis of pharmacologic treatment of anxiety

Two types of anxiety noted by psychologists:

a) state anxiety - how anxious is the patient at a given moment in time?
b) trait anxiety - how prone is the patient to become anxious under provocations in life experiences?

Trait anxiety is probably an inborn characteristic. High levels of trait anxiety are relatively uncommon. So far as we know, this type of anxiety can not be treated. Such patients tolerate higher levels of anxiety, however, and may obtain symptomatic relief even though still anxious by ordinary standards.

State anxiety can be treated; the goal is to reduce symptoms to a tolerable level, as judged by the patient.

Use of sedative drugs for treating anxiety is thought to be mainly symptomatic. However, the possibility of a more specific action is more plausible now.

Principles in Use of Benzodiazepines to Treat Anxiety

1) Use only for good indications - disabling or discomforting anxiety.
2) Use non-drug approaches whenever feasible.
3) Titrate dose, keep doses flexible.
4) Propose brief treatment periods.
5) Constantly assess efficacy - poor efficacy may indicate a more complicated problem.
6) Avoid in drug abusers.
7) Gradual discontinuation after chronic treatment.

Complications of Treatment

Most common manifestations are simply extensions of known pharmacologic actions of the drugs: lethargy, drowsiness, impaired psychomotor performanc, ataxia, slurred speech.

Respiratory depression is ordinarily not severe with modern drugs but still warrants care in patients with pulmonary failure of varying degrees.

Tolerance/dependence is definitely possible, even with benzodiazepines, but frequency has been exaggerated. Doses should be kept low, courses of treatment short, withdrawal of drug gradual after prolonged treatment.

Disinhibition, with release of aggressive or violent urges, is an idiosyncratic reaction, based on patient's personality. Not specific to a drug.

Paradoxical reactions are manifested by an increase in anxiety, rather than by its relief. Personality of subject plays a major role. Alter dosage schedules.

Depression is unmasked by these drugs, but is not definitely caused by them. Diagnosis of primary anxiety was probably wrong initially.

Suicide is very difficult to accomplish with benzodiazepines in the absence of other drugs.

Major drug interactions are with other central nervous system depressants such as alcohol, with additive sedation and respiratory depression. Enzyme induction is rare. Metabolism of phenytoin may be inhibited.

Allergic, skin, hematologic or hepatic complications are extremely rare.

ANXIETY DISORDERS: A RATIONAL APPROACH TO USING THE BENZODIAZEPINES

Anxiety Disorders: A Rational Approach to Using the Benzodiazepines

The Meaning of Anxiety

Psychiatric disorders comprise only one of the meanings of anxiety.

Historical Aspects of Anxiety Disorders

Only relatively recently has anxiety been claimed by psychiatry from cardiology.

Epidemiology of Anxiety

These disorders affect about 5% of the population.

Classification of Anxiety Disorders

According to DSM-III.

According to treatment options.

ANXIETY DISORDERS: A RATIONAL APPROACH TO USING THE BENZODIAZEPINES (cont'd)

Theories of Anxiety

Psychoanalytic, Biological, Learning, Existential

The Relationship of Anxiety to Depression

These entities are not easily separated clinically.

Aspects of Anxiety

Emotional, Perceptual, Cognitive, Behavioral, Physical

Differential Diagnosis of Illnesses Producing Anxiety

Including Drug Intoxication and Withdrawal, Seizures, Thyrotoxicosis, Pheochromocytoma, Mitral Valve Prolapse

Mechanisms of Medically Induced Anxiety

The Benzodiazepine Receptor

Specific, selective and functionally close to GABA receptor sites.

The possibility of increased anxiolytic specificity.

The search for the endogenous benzodiazepine.

Pharmacological Approaches to Anxiety

Benzodiazepines have replaced the barbiturates and propanediols.

Indication for Benzodiazepines

Ranging from Anxiety Disorders to Epilepsy, Muscle Spasm, PCP toxicity, and night terrors.

Predictors of Good Response to Benzodiazepines

Better in patients without primary depression or obsessive-compulsive disorders; good improvement in first week and adequate plasma levels also predict.

The Grouping of Benzodiazepines by Half-Life

Benzodiazepines half-lives range from 2 to 120 hours or more. This is the most important pharmacokinetic difference among them.

Short Half-Life Benzodiazepines

These have less accumulation but more sudden and intense withdrawal syndromes. They are useful in brief anxiety attacks and may be excreted more rapidly by cirrhotics and by the elderly. As hypnotics, they may produce rebound insomnia.

Long Half-Life Benzodiazepines

Fewer daily doses are needed, and withdrawal is less intense. These are useful in sustained anxiety episodes.

Factors Altering Benzodiazepines Kinetics

Those biotransformed by oxidation are more sensitive to alteration than those metabolized by glucuronide conjugation. The factors include age, sex, race, smoking, drugs, or the presence of liver disease.

Benzodiazepines in the Elderly

While safer than other drugs, all benzodiazepines accumulate over time, may cause increased sedation, diminished libido and energy, and may worsen depression, dementia or delirium. The usual initial dose must be much less in the elderly.

Benzodiazepine Side-Effects

These include drowsiness, irritability, withdrawal and dependence, Withdrawal has numerous presentations varying from psychotic be-

havior to grand mal convulsions. The possibility of dependence has probably been exaggerated, but requires alertness on the part of the physician.

Benzodiazepine Interactions

Among these are interaction with phenytoin, digoxin, disulfiram, antacids, cimetidine, food, and alcohol.

The Clinical Use of Benzodiazepines

These must be used only in severe anxiety, under careful supervision, and in low doses. Brief benzodiazepine holidays, gradual discontinuation, and observation for withdrawal and rebound anxiety are imperative. Adjunctive psychotherapeutic methods should not be overlooked.

ANTIANXIETY DRUGS: A CLINICAL UPDATE

The purpose of this lecture is to acquaint the student with the antianxiety drugs. I will review the proper indications for their use, their pharmacology (with a special emphasis on the benzodiazepines), their unwanted effects (side effects), the epidemiology of their use, and finally attempt to put these findings into perspective. In relating this information, I will follow the following model:

A. Anxiety is a symptom seen as a reaction to normal stress, can represent a transient pathological state, or may represent the core symptomatology seen in some psychiatric or medical disorders (e.g., anxiety neurosis or hyperthyroidism). Establishing the proper diagnosis is the key to proper use of these medications.

B. Antianxiety drugs are best used in the treatment of transient anxiety states (for both transient anxiety and insomnia), as a muscle relaxant for a wide variety of problems, and as anticonvulsants.

C. Prior to the last decade bromide and barbiturate type drugs were used as "sedatives". For the last 10 to 20 years the three types of drugs most often prescribed as antianxiety medications are the carbamates (for example Miltown - drugs to be avoided whenever possible for their addiction lability and overdose lethality), beta-blockers (propanalol - still experimental in the treatment of anxiety states), and the benzodiazepines (e.g., Librium, Valium, etc.). This last named group of drugs forms the basis for the majority of the material presented here.

D. The benzodiazepine drugs share many common properties and , usually, no one medication is totally better than any other. The specific drug prescribed should depend upon the careful establishment of the balance between the specific pharmacological properties (e.g., half-life), the side effects, and the balance between anxiety reducing, anticonvulsant, and muscle relaxant properties. It is probable that all benzodiazepines exert their effect through actions on benzodiazepine receptors in the brain and the neurotransmitter GABA in addition to other unknown mechanisms. As a group, the benzodiazepines have relatively low potencies in overdosage and relatively low addiction lability.

E. As a result of these properties benzodiazepines are useful for many conditions. Their anxiety reducing properties make them important for some forms of psychotherapy, to decrease cardiac anxiety, in treating hypertension, etc.; their muscle relaxant properties make them useful for strained muscles, dystonias, spasticities, the treatment of tetanus, etc.; their anticonvulsant properties make them important in the treatment of status epilepticus, and petit mal, myoclonic, and psychomotor epilepsies; they are also used as hypnotics, as adjuncts for carrying out various surgical and medical procedures, and as useful medications for treating withdrawal states experienced after the abuse of many CNS depressing drugs.

F. As is true with any class of drugs, there are dangers to the benzodiazepines. The most common problems involve CNS depression with

heightened problems surrounding driving, difficulties in the elderly, and interaction with other CNS depressing drugs. Additional difficulties include rebound anxiety and insomnia, hostility as a reaction to the medication, drug involvement in overdoses (seldom lethal unless the benzodiazepines are mixed with other drugs) and the possibilities of psychological and even physical dependence.

G. It is not surprising that drugs with such a wide variety of indications and relative (although certainly not absolute) safety are widely prescribed. These drugs are the most frequently prescribed medications in the United States and western Europe with almost two billion tablets of Valium alone being sold per year in the late 1970s.

H. While the benzodiazepines occupy a solid place in the treatment of acute anxiety, muscle tensions, and convulsive disorders they should be prescribed most carefully. As the physician you should invoke such medication only when they meet a specific indication, utilize short term treatment for anxiety and insomnia, and only rarely give prescription refills; never by phone.

I. The benzodiazepines are a very useful and valuable group of drugs. As with all useful instruments we must guard to be sure that they are used in a manner in which their assets outweigh their liabilities.