Anxiolytic and Hypnotic Drugs

OVERVIEW

Disorders involving anxiety are among the most common mental disorders.

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (like a fear that arises from either a known or an unknown source) with physical symptoms in severe anxiety as tachycardia, sweating, trembling, and palpitations) which involve sympathetic activation.

Anxiety types

1- **Mild Anxiety** : Episodes of mild anxiety are common life experiences and do not warrant treatment.
2- **Sever , chronic, debilitating anxiety** may be treated with anti anxiety drugs (sometimes called anxiolytics) and/or some form of psychotherapy. Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleepinducing) agents.

Figure 9.1 summarizes the anxiolytic and hypnotic agents.

Some antidepressants are also indicated for certain anxiety disorders; however, they are discussed with other antidepressants (see Chapter 10).

BENZODIAZEPINES

Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST

Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS

Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone BUSPAR

BARBITURATES

Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS

Antihistamines VARIOUS (SEE CHAPTER 30)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

Figure 9.1
Summary of anxiolytic and hypnotic drugs.

❖ BENZODIAZEPINES

Benzodiazepines are widely used anxiolytic drugs. They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective (Figure 9.2).

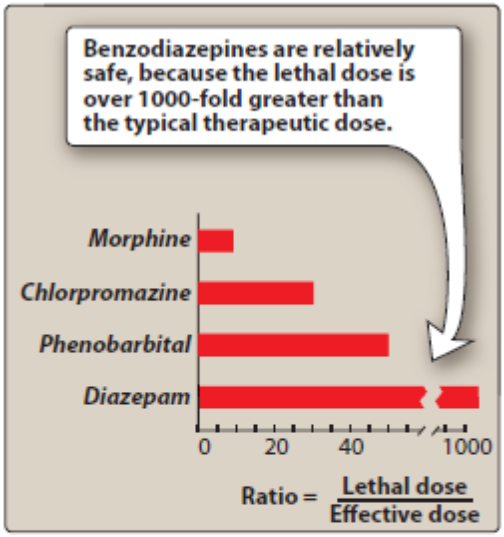


Figure 9.2
Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (an antipsychotic, see Chapter 11), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

Benzodiazepenes (BZD)

Benzodiazepines modulate GABA effects by binding to a specific,

high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor (Figure 9.3).

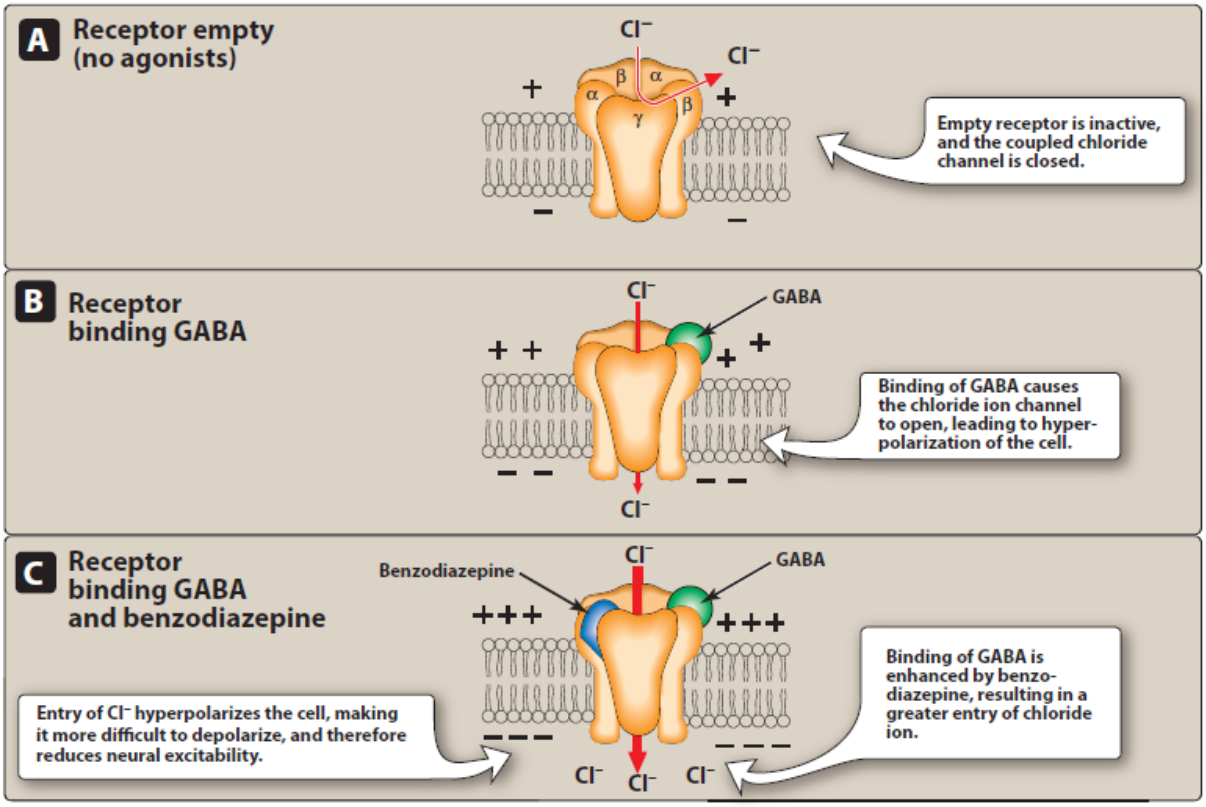


Figure 9.3
Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

Benzodiazepines increase the frequency of channel openings produced by GABA.

[Note: Binding of a benzodiazepine to its receptor site increases the affinity of GABA for the GABA-binding site (and vice versa).]

The clinical effects of the various benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

pharmacological Actions

All benzodiazepines exhibit the following actions to some extent :

1. Reduction of anxiety:

2. Sedative/hypnotic

3. Anterograde amnesia

4. Anticonvulsant

5. Muscle relaxant

C. Pharmacokinetics

1. Absorption and distribution: The benzodiazepines are lipophilic.

They are rapidly and completely absorbed after oral administration, distribute throughout the body and penetrate into the CNS.

2. Duration of action: The half-lives of the benzodiazepines are important clinically, because the duration of action may determine the therapeutic usefulness.

The benzodiazepines can be thoroughly divided into :

short-, intermediate-, and long-acting groups (Figure 9.4).

D- Therapeutic uses & Adverse effects

The individual benzodiazepines show small differences in their relative

anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

Classes of BZD duration of action

- **The longer-acting agents, such as :**
- **Clonazepam [kloe-NAZ-e-pam]**
- **Diazepam [dye-AZ-e-pam]**
- **Flurazepam [flure-AZ-e-pam]**

2. Sleep disorders

Commonly prescribed benzodiazepines for sleep disorders

Include :

- **Intermediate-acting :**
- **Lorazepam [lor-AZ-e-pam]**
- **Temazepam [te-MAZ-e-pam]**
- **Alprazolam**

- **Short-acting :**
- **Triazolam**
- **Oxazepam**

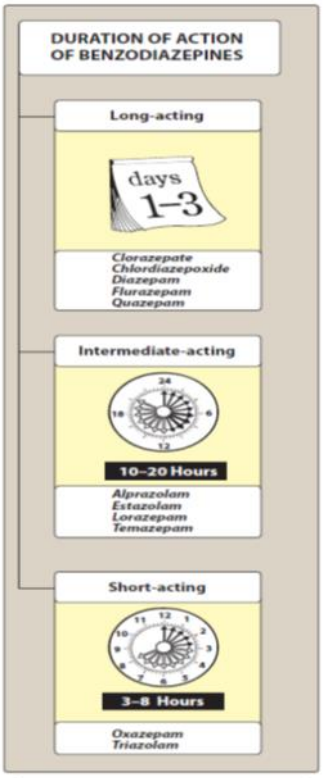


Figure 9.4
Comparison of the durations of action of the benzodiazepines.

3. Amnesia

4. Seizures

5- Alcohol withdrawal

6. Muscular disorders

Adverse effects

- Drowsiness and confusion are the most common side effects of the benzodiazepines.
- Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- Cognitive impairment (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines.

- ✓ **Triazolam** often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety, as well as amnesia and confusion.

Dependence

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given for a prolonged period. All benzodiazepines are controlled substances.

Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures.

Benzodiazepines with a short elimination half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as flurazepam .

BENZODIAZEPINE ANTAGONIST

Flumazenil [floo-MAZ-eh-nill]

OTHER ANXIOLYTIC AGENTS

BARBITURATES

Barbiturate is a drug that acts as a central nervous system depressant, and can therefore produce a **wide spectrum of effects, from mild sedation to total anesthesia. They are also effective as anxiolytics, hypnotics, and anticonvulsants.**

Pharmacological actions :

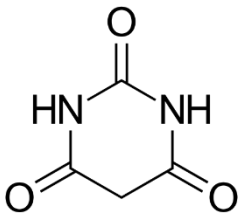
1-Depression of CNS

2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO2, and overdosage is followed by respiratory depression and death.

Barbiturates

A- Class : The name barbiturate originates from the fact that they are all chemical derivatives of barbituric acid .

B- Mechanism of action : barbiturates act as positive allosteric modulators, and at higher doses, as agonists of GABAA receptors. GABA is the principal inhibitory neurotransmitter in the mammalian central nervous system (CNS). Barbiturates bind to the GABAA receptor distinct from the benzodiazepine binding site



Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the GABAA receptor

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep.

The sedative–hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission BY 3 mechanisms :

1- Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings.

2- In addition, barbiturates can block excitatory glutamate receptors.

3- Anesthetic concentrations of pentobarbital also block high-frequency sodium channels.

All of these molecular actions lead to decreased neuronal activity.

Classes of Barbiturate Duration of Action

Barbiturates are classified according to their duration of action (Figure 9.8).

Acts within seconds and has a duration of action of about 30 minutes.

- **Long-acting** : Phenobarbital , has a duration of action greater than a day
- **Short-acting barbiturates** :

  Pentobarbital [pentoe- BAR-bi-tal]

  Secobarbital [see-koe-BAR-bi-tal]

  Amobarbital [am-oh-BAR-bi-tal]

- **Ultra–short-acting thiopental** [thye-oh- PEN-tal]

D-Therapeutic uses

1. Anesthesia

2. Anticonvulsant

3. Sedative/hypnotic

Barbiturates are contraindicated in patients with acute intermittent porphyria.

Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.

OVERDOSE

Severe depression of respiration is coupled with central cardiovascular

depression and results in a shock-like condition with shallow, infrequent breathing.

Treatment includes supportive care and gastric decontamination for recent ingestions.

DEATH

Withdrawal is much more severe than that associated with opiates and can result in death.

Death may also result from overdose.

OTHER HYPNOTIC AGENTS

Non-benzodiazepine drugs, **zolpidem, zaleplon, and ramelton**

- **Zolpidem**
- **Zaleplon**
- **Ramelteon**

Antihistamines

Some antihistamines with sedating properties, such as **diphenhydramine,**

Hydroxyzine , and doxylamine , are effective in treating mild types of situational insomnia. However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines.

Some sedative antihistamines are marketed in numerous over-the-counter products.

Buspirone [byoo-SPYE-rone]

Buspirone : is an anxiolytic drug that is primarily used to treat generalized anxiety disorder (GAD) . It is also commonly used to augment antidepressants in the treatment of major depressive disorder.

Unlike most anxiolytics, the pharmacology of buspirone is not related to that of benzodiazepines, barbiturates (it is not a GABA receptor agonist), and so buspirone **does not carry the risk of physical dependence and withdrawal symptoms for which those drug classes are known**.

Summary of the therapeutic disadvantages and advantagesof some of the anxiolytic and hypnotic drugs.

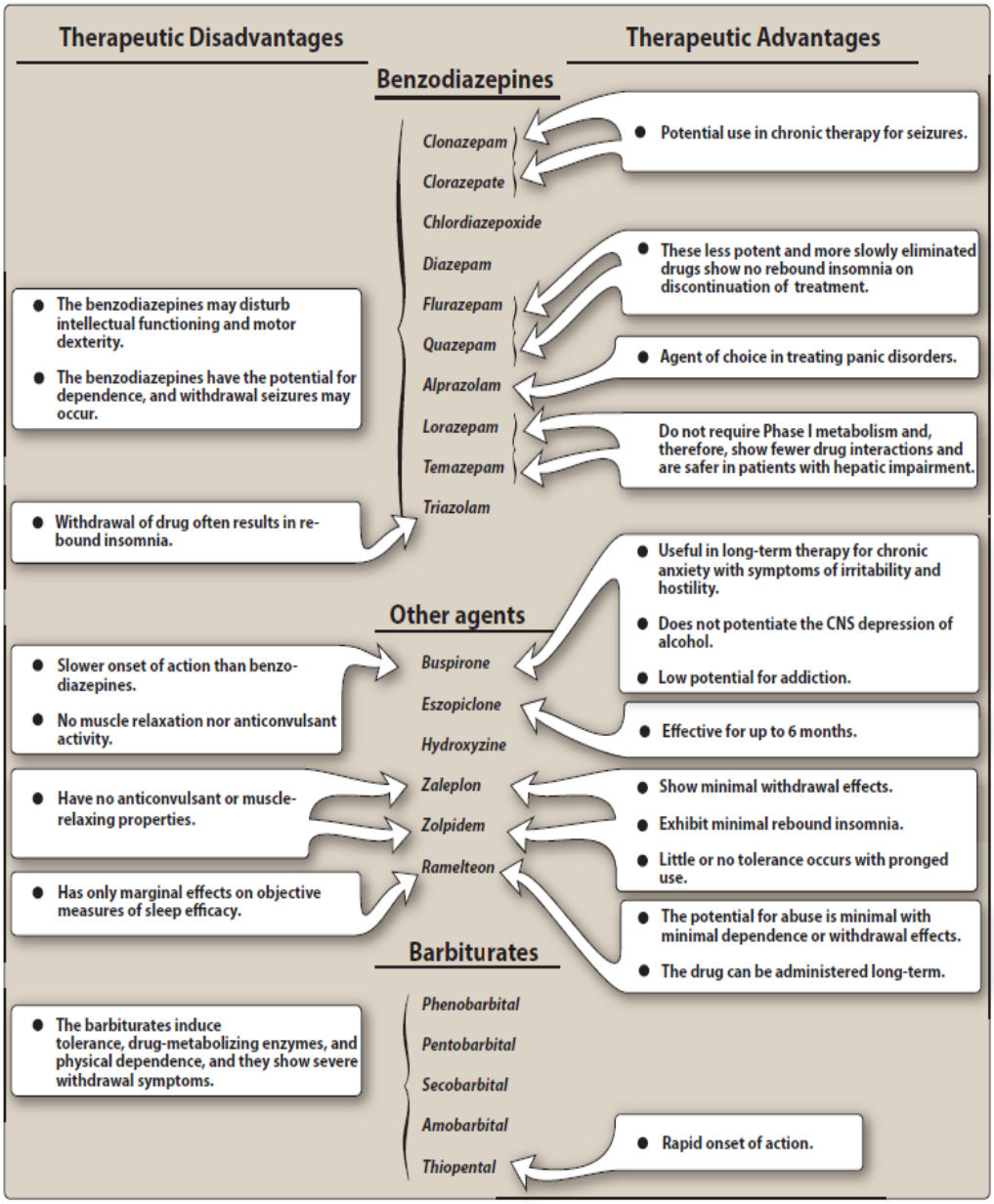


Figure 9.11
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.