**Anxiolytic and Hypnotic Drugs**

**OVERVIEW**

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from a unknown source). Disorders involving anxiety are the most common mental disturbances. The physical symp- toms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activa- tion. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitat- ing anxiety may be treated with anti-anxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral thera- py or psychotherapy. Because many of the anti-anxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. In addition, some have anticonvul- sant activity. Figure 9.1 summarizes the anxiolytic and hypnotic agents. Though also indicated for certain anxiety disorders, the selective sero- tonin reuptake inhibitors (SSRIs) will be presented in the chapter discuss- ing antidepressants.

**II. BENZODIAZEPINES**

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and meprobamate in the treatment of anxi- ety, because benzodiazepines are safer and more effective (Figure 9.2).

1. **Mechanism of action**

The targets for benzodiazepine actions are the γ-aminobutyric acid (GABAA ) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] These receptors are primarily composed of α, β, and γ subunit families of which a com- bination of five or more span the postsynaptic membrane (Figure 9.3). Depending on the types, number of subunits, and brain region localization, the activation of the receptors results in different phar- macologic effects. Benzodiazepines modulate GABA effects by bind- ing to a specific, high-affinity site located at the interface of the α subunit and the γ2 subunit (see Figure 9.3). [Note: These binding sites are sometimes labeled “benzodiazepine receptors.” Two benzodi- azepine receptor subtypes commonly found in the CNS have been designated as BZ1 and BZ2 receptors depending on whether their composition includes the α1 subunit or the α2 subunit, respectively. The benzodiazepine receptor locations in the CNS parallel those of the GABA neurons. Binding of GABA to its receptor triggers an opening of a chloride channel, which leads to an increase in chloride con- ductance (see Figure 9.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The infl ux of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its fi ring threshold and, thus, inhibits the formation of action potentials. [Note: Binding of a benzodiazepine to its receptor site will increase the affi nity of GABA for the GABA-binding site (and vice versa) without actually changing the total number of sites.] The clinical eff ects of the various benzodiazepines correlate well with each drug’s binding affi nity for the GABA receptor–chloride ion channel complex.

1. **Actions**

The benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not aff ect the autonomic nervous system. All ben- zodiazepines exhibit the following actions to a greater or lesser extent:

1. **Reduction of anxiety**: At low doses, the benzodiazepines are anxi- olytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α2 subunit in their GABAA receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

2. **Sedative and hypnotic actions**: All of the benzodiazepines used to treat anxiety have some sedative properties, and some can produce hypnosis (artifi cially produced sleep) at higher doses. Their eff ects have been shown to be mediated by the α1-GABAA receptors.

3. **Anterograde amnesia**: The temporary impairment of memory with use of the benzodiazepines is also mediated by the α1-GABAA receptors. This also impairs a person’s ability to learn and form new memories.

4. **Anticonvulsant**: Several of the benzodiazepines have anticonvul- sant activity and some are used to treat epilepsy (status epilepti- cus) and other seizure disorders. This eff ect is partially, although not completely, mediated by α1-GABAA receptors.

5. **Muscle relaxant**: At high doses, the benzodiazepines relax the spas- ticity of skeletal muscle, probably by increasing presynaptic inhibi- tion in the spinal cord, where the α2-GABAA receptors are largely located. Baclofen is a muscle relaxant that is believed to aff ect GABA receptors at the level of the spinal cord.

C. **Therapeutic uses**

The individual benzodiazepines show small diff erences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the dura- tion of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

1**. Anxiety disorders:** Benzodiazepines are eff ective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and the extreme anxiety sometimes encountered with specifi c phobias such as fear of fl ying. The benzodiazepines are also useful in treat- ing the anxiety that accompanies some forms of depression and schizophrenia. These drugs should not be used to alleviate the nor- mal stress of everyday life. They should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential. The longer-acting agents, such as clonazepam [kloe-NAZ-e-pam], lorazepam [lor-AZ-e-pam], and diazepam [dye-AZ-e-pam], are often preferred in those patients with anxiety who may require treatment for prolonged periods of time. The anti-anxiety eff ects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic eff ects. [Note: Tolerance (that is, decreased responsiveness to repeated doses of the drug) occurs when used for more than 1 to 2 weeks. Cross-tolerance exists among this group of agents with ethanol. It has been shown that tol- erance is associated with a decrease in GABA-receptor density.] For panic disorders, alprazolam [al-PRAY-zoe-lam] is eff ective for short- and long-term treatment, although it may cause withdrawal reac- tions in about 30 percent of suff erers.

2. **Muscular disorders**: Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spas- ticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

3. **Amnesia:** The shorter-acting agents are often employed as premed- ication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. They also cause a form of conscious sedation, allow- ing the person to be receptive to instructions during these proce- dures. Midazolam [mi-DAY-zoe-lam] is a benzodiazepine also used for the induction of anesthesia.

4. **Seizures**: Clonazepam is occasionally used in the treatment of cer- tain types of epilepsy, whereas diazepam and lorazepam are the drugs of choice in terminating grand mal epileptic seizures and sta- tus epilepticus (see p. 184). Due to cross-tolerance, chlordiazepoxide [klor-di-az-e-POX-ide], clorazepate [klor-AZ-e-pate], diazepam, and oxazepam [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures.

5. **Sleep disorders**: Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. They tend to decrease the latency to sleep onset and increase Stage II of nonrapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to bal- ance the sedative effect needed at bedtime with the residual seda- tion (“hangover”) upon awakening. Commonly prescribed benzodi- azepines for sleep disorders include long-acting flurazepam [flure- AZ-e-pam], intermediate-acting temazepam [te-MAZ-e-pam], and short-acting triazolam [trye-AY-zoe-lam].

a. **Flurazepam**: This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakenings, and it increases the duration of sleep. Flurazepam has a long- acting effect (Figure 9.4) and causes little rebound insomnia. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. Flurazepam and its active metabolites have a half-life of approximately 85 hours, which may result in daytime sedation and accumulation of the drug.

b. **Temazepam**: This drug is useful in patients who experience frequent wakening. However, because the peak sedative effect occurs 1 to 3 hours after an oral dose it should be given 1 to 2 hours before the desired bedtime.

c. **Triazolam**: This benzodiazepine has a relatively short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia. Whereas temazepam is useful for insomnia caused by the inability to stay asleep, triazolam is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription or higher dose. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

D**. Pharmacokinetics**

1. **Absorption and distribution**: The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration and distribute throughout the body.

2. **Durations of action**: The half-lives of the benzodiazepines are very important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (see Figure 9.4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical durations of action do not always correlate with actual half-lives (otherwise, a dose of diazepam could conceivably be given only every other day or even less often given its active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution elsewhere.

3. **Fate**: Most benzodiazepines, including chlordiazepoxide and diaz- epam, are metabolized by the hepatic microsomal system to com- pounds that are also active. For these benzodiazepines, the appar- ent half-life of the drug represents the combined actions of the par- ent drug and its metabolites. The drugs’ eff ects are terminated not only by excretion but also by redistribution. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites. All the benzodiazepines cross the placental barrier and may depress the CNS of the newborn if given before birth. Nursing infants may also become exposed to the drugs in breast milk.

E. **Dependence**

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insom- nia, tension, and (rarely) seizures. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. 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 fl urazepam (Figure 9.5).

F**. Adverse eff ects**

1. **Drowsiness and confusion**: These eff ects are the two most com- mon side eff ects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fi ne 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, one of the most potent oral benzodiaz- epines with rapid elimination, often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety as well as amnesia and confusion.

2. **Precautions**: Benzodiazepines should be used cautiously in treat- ing patients with liver disease. These drugs should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic eff ects of the benzodi- azepines. Benzodiazepines are, however, considerably less danger- ous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol, are taken concurrently.

III**. BENZODIAZEPINE ANTAGONIST**

Flumazenil [fl oo-MAZ-eh-nill] is a GABA-receptor antagonist that can rapidly reverse the eff ects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but duration is short, with a half- life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. Administration of fl umazenil may precipitate withdrawal in dependent patients or cause seizures if a benzo- diazepine is used to control seizure activity. Seizures may also result if the patient ingests tricyclic antidepressants (TCAs). Dizziness, nausea, vomiting, and agitation are the most common side eff ects.