Chapter 10
Clinical Pharmacokinetics and Pharmacodynamics of Anxiolytics and Sedative/Hypnotics

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Abstract Medications to promote sedation and reduce anxiety and its associated symptoms have been sought since recorded history. The development of the benzodiazepines represented a major therapeutic endeavor due to their safety profile especially when taken in overdose situations compared to the barbiturates and early non-barbiturates such as meprobamate. Benzodiazepines continue to be one of the most commonly prescribed agents available in a variety of dosage formulations used for all age groups. Their pharmacokinetic (PK) and pharmacodynamic (PD) profiles have been extensively studied in adult healthy volunteers, the elderly, and patients with hepatic and renal impairment. Most benzodiazepines are metabolized by the phase I oxidative CYP enzyme system and the remaining agents by the phase II glucuronidation. Many long-acting benzodiazepines are metabolized to an active metabolite desmethyldiazepam. Alprazolam and buspirone were FDA approved for panic and generalized anxiety disorders, respectively. Various sedative-hypnotic non-benzodiazepine agents have been developed that are agonists of the alpha-1 GABA-A subreceptor site and the melatonin receptors type 1 and 2. All of these agents produce common PD effects such as sedation and psychomotor impairment. Benzodiazepines also produce antiepileptic actions, muscle relaxation, and anterograde amnesia. PK-PD modeling has been conducted for benzodiazepines and non-benzodiazepines that mainly focus on sedation and psychomotor impairment. The elderly have more pronounced sedative and psychomotor impairment from these agents compared to the adult population. Gender can be another significant factor as females were found to have significantly higher zolpidem plasma concentrations than males and when given comparative doses also displayed more pronounced psychomotor impairment which led to the FDA recommendation of lower doses prescribed.

Keywords GABA-A receptor • Melatonin receptors • Orexin receptor • CYP metabolism • Benzodiazepines • Diazepam • Desmethyldiazepam • Alprazolam • Buspirone • Zolpidem • Eszopiclone • Zaleplon • Suvorexant • Ramelteon • Tasimelteon

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M. Jann et al. (eds.), *Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents*,
DOI 10.1007/978-3-319-27883-4_10

10.1 Introduction

Drugs used to reduce or relieve the symptoms of anxiety and induce a calmer and more relaxed anticipation of future events are known as anxiolytics. Drugs used to induce, prolong, or improve the quality of sleep, or produce a partial anesthesia, are known as sedative-hypnotics. Often the designation of a drug as having one or more of these therapeutic effects is a function of dosage and differences in the degree of their pharmacodynamic (PD) effects. Evidence suggests that humans have used various plant preparations beginning before recorded history for the purpose of producing antianxiety effects and inducing sleep [1]. Organized drug development over the past century has resulted in the synthesis of thousands of molecules for potential development as safe and effective anxiolytics and sedative-hypnotics. A few have found a place in contemporary therapeutics. The key milestones in this drug development process are listed in Table 10.1 [2].

This chapter will focus on the marketed anxiolytics and sedative/hypnotics that are currently in widespread clinical use. Most of these compounds belong to the benzodiazepine class of drugs. Their disposition has been thoroughly studied and summaries of this voluminous literature are readily available [3, 4]. This discussion will emphasize data that have proven useful in drug selection and dosage regimen design for individual patients [5]. The characteristics of the prototype compounds are summarized and references provided for more detailed discussion of the less widely used drugs.

Table 10.1 Time line for development of sedative-hypnotics and anxiolytics

Prerecorded history	
Hieroglyphics and pottery artifacts document wine from grape cultivation	
Alcohol in various fermented beverages appears in many cultures	
500 BC	
Opium plant products are smoked or taken orally	
1721	London Pharmacopoeia describes products made from opium with camphor similar to paregoric
1800s	Alcohol derivatives are synthesized including paraldehyde and chloral hydrate
1800s	Barbiturates (>2500 derivatives) are synthesized; some become enduring products: amobarbital, butabarbital, pentobarbital, and secobarbital
1950s	Nonbarbiturate sedative-hypnotics are introduced: meprobamate, methaqualone, methyprylon; glutethimide; ethchlorvynol
1955	Synthesis of the first benzodiazepine, chlordiazepoxide; eventual synthesis of hundreds of derivatives
1960	Marketing of chlordiazepoxide
1963	Marketing of diazepam
1963–1980s	Marketing of multiple benzodiazepines with expanding indications
1980s	Non-benzodiazepine benzodiazepine receptor agonists are introduced
2005	Ramelteon approved in the USA as a melatonin receptor agonist for treatment of insomnia

From: Allen et al. [12], Ban [1], Strang et al. [6], Wick [2]

10.2 Historical Development of Anxiolytics and Sedative-Hypnotics

Alcohol may have the most extensive history of drugs being consumed for sedative properties. The history begins with beer-like beverages, or mead, being consumed in China and the Middle East as early as 6000 BC [1]. By 2000 BC, the production of wine from fermented grapes was wide spread. Natural products were cultivated and processed to specifically produce behavioral effects. Opium consumption was proliferating as early as 500 BC [6]. For several subsequent centuries, alcohol and opium preparations were the only available sedative-hypnotics. Drug development during this time was essentially stagnant until solutions of bromide salts appeared in the eighteenth century followed by the availability of paraldehyde and chloral hydrate in the late part of the nineteenth century [7]. In 1864, von Baeyer synthesized malonylurea (barbituric acid) from which thousands of derivatives were synthesized in the twentieth century [8]. Some of these compounds were developed for clinical use and became the barbiturate class of drugs.

Several barbiturates are still widely used. Sodium thiopental is a rapid-onset general anesthetic of the barbiturate class that has been used extensively in surgical practice. It recently drew public attention as a primary component of lethal injections. When shortages of drug supply appeared, its manufacturer became reluctant to continue production [9]. Butabarbital, amobarbital, secobarbital, and pentobarbital as sedative-hypnotics became widely prescribed in medical practice in various oral formulations. A hangover effect of excessive daytime drowsiness is a common problem with barbiturate use for sedation. Solid dosage forms of barbiturates are relatively inexpensive and are used extensively in some countries, especially in Eastern Europe and South America.

Phenobarbital was the first modern anxiolytic and is the prototype barbiturate. It is still widely used in human and veterinary medicine as an antiepileptic compound. It possesses a broad central nervous system (CNS) depressive ability and is capable of producing anxiolytic effects at relatively low dosages. A problem with phenobarbital common to many barbiturates is hepatic enzyme induction resulting in numerous potential drug-drug interactions. Increasingly profound CNS depression occurs with increasing dosage that can ultimately produce anesthesia, coma, respiratory depression, and death [10]. Combining a barbiturate and alcohol produces a synergistic pharmacodynamic depressive effect on the CNS. Numerous accidental deaths have been attributed to normal doses of secobarbital or amobarbital when taken with alcohol [11]. The barbiturate's multiple disadvantages stimulated a search for more effective and less dangerous drugs.

Development of non-barbiturates with a goal of producing similar antianxiety and sedative effects as the barbiturates resulted in marketing of several drugs with diverse structures, some of which remain in limited production. Meprobamate, used since 1955 as an antianxiety drug [12], along with methaqualone, ethchlorvynol, and glutethimide, as sedative-hypnotics, had similar or more profound liabilities than the barbiturates. They were extensively prescribed in the decade preceding the

marketing of the benzodiazepines despite increasing recognition of their lethality. Overdosage with meprobamate proved notoriously difficult to treat [13]. Methaqualone obtained cult status for its ability to produce a dysphoric and disinhibitory emotional state that led to its abuse as a date-rape drug that enabled unwanted sexual assaults [14]. It was removed from the US market by 1985. Other compounds were also removed or production was discontinued due to low sales volume and recognition of their toxicity. These drugs are not discussed further as the benzodiazepines and subsequently developed compounds are far better alternatives.

The availability of efficacious anxiolytics with predictable dose effects was a highly desirable goal of drug development in the middle twentieth century. The discovery of the benzodiazepines was the result of the accidental synthesis of chlordiazepoxide in 1955 by Leo Sternbach at Hoffmann-La Roche [2]. In 1960, it was marketed for agitation associated with acute alcohol withdrawal and was quickly followed by diazepam in 1963. The chemical classification of the benzodiazepines derives from the basic structure of a benzene ring adjacent to a 7-membered diazepam ring. The marketed drugs are designated as having a 1,4 or a 1,5 benzodiazepine structure according to the placement of a nitrogen atom at these two sites on the diazepam ring [15].

Hundreds of benzodiazepines have been synthesized and several developed between1960 and 1980 have had enduring commercial success. The popularity of the benzodiazepines derives from their broad utility and safety. These drugs can be prescribed with more impunity from overdose toxicity than any previously available anxiolytics and sedative-hypnotics and so have become the preferred treatment for most patients. For example, the dose that is lethal for 50 % of the animals in toxicology studies (LD_{50}) requires at least ten times the exposure to diazepam as to secobarbital [16]. The selective serotonin reuptake inhibitors (SSRI) have emerged as effective anxiolytics in the 1990s and are discussed elsewhere in this text.

The World Health Organization (WHO) lists four benzodiazepines on its current biannual List of Essential Medicines [17]. These include midazolam as a preoperative medication and sedative for short-term procedures and lorazepam and diazepam as anticonvulsants. Diazepam is also listed as a medicine for anxiety disorders and under the category of medicines for common symptoms in palliative care. The same three drugs are also regarded as essential drugs for children. A small number of alternatives to the benzodiazepines for use as sedative-hypnotics became available but have not displaced the essential role of benzodiazepines to any substantial degree.

With usage driven by availability in multiple formulations, low toxicity, efficacy in a wide variety of conditions, both medical and psychological, the benzodiazepines are the principle anxiolytics used worldwide. Benzodiazepines have multiple uses outside of their FDA-approved indications and are listed in Table 10.2. The dependence-producing properties and propensity for producing withdrawal syndromes in some patients, discussed below, have limited further widespread use of the benzodiazepines and related drugs. While most anxiety disorders can be managed with a benzodiazepine alone, the antidepressants, discussed elsewhere, are often combined with a benzodiazepine to treat various anxiety disorders.

Table 10.2 Major indications of benzodiazepines

Indications and additional uses	Drugs of choice/suitable alternatives
Anxiety disorders	
Generalized anxiety disorder	Diazepam, lorazepam, alprazolam, chlordiazepoxide, oxazepam
Panic disorder	Alprazolam, lorazepam, clonazepam
Social phobia	Diazepam, alprazolam
Other anxious conditions	
Preoperative anxiety	Diazepam
Conscious anesthesia	Midazolam (IV), diazepam (IV)
Critical care ventilation maintenance	Diazepam
Delirious states	Diazepam, lorazepam
Alcohol withdrawal	Chlordiazepoxide, lorazepam
Seizures	Clonazepam (as daily anticonvulsant; diazepam (IV for status epilepticus)
Nausea and vomiting (chemotherapy-related and various etiologies)	Diazepam; any of the medium to longer-acting benzodiazepines
Insomnia	Choice dictated by specific complaint of difficulty falling asleep; difficulty maintaining sleep or early morning awakening; approved benzodiazepines include flurazepam, estazolam, quazepam, temazepam, and triazolam
Akathisia from antipsychotic use	Diazepam

10.3 Pharmacokinetic Properties of Anxiolytics and Sedative-Hypnotics

The benzodiazepines are similar in many physiochemical, pharmacokinetic, and pharmacodynamic characteristics. The drugs are highly lipid soluble with good oral absorption profiles. Most are extensively bound to plasma proteins but this characteristic has not proven to be of major importance for drug selection. Distribution of benzodiazepines is extensive in the body as is expected from drugs that produce CNS effects [18]. This characteristic can occasionally be problematic, for example, for infants of women breast-feeding and receiving high doses of diazepam [19].

The benzodiazepines can be distinguished by different metabolic pathways involved in their metabolism. One group of benzodiazepines is primarily oxidized by phase I enzymes, predominantly the cytochrome P450 enzymes, resulting in demethylated or hydroxylated metabolites. These by-products often possess pharmacological activity. The metabolites are further conjugated by phase II metabolic reactions to glucuronidated metabolites that are inactive and excreted in the urine. A second group of drugs undergoes conjugation reactions as the primary means of elimination from the body. Drugs in the first category include chlordiazepoxide, diazepam, and flurazepam. Drugs in the second category undergoing glucuronidation

as their primary route of elimination include oxazepam, lorazepam, and midazolam. These metabolic characteristics are displayed in Fig. 19.1.

The PD effects of benzodiazepines are the result of enhancing gamma-aminobutyric acid (GABA) neurotransmission [20]. GABA is the main inhibitory neurotransmitter in the CNS. It has three types of receptors but most drug binding involves GABA-A receptors and its various subunits. As a class of drugs with mechanisms of action involving GABA, the benzodiazepines are considered to possess anxiolytic, anticonvulsant, sedative, hypnotic, and skeletal muscle relaxant properties. This complex pharmacology has been the subject of extensive investigation [21]. The drugs decrease the subjective experience of anxiety and, according to the dose, produce a mild sedation that can be increased to the level of anesthesia with sufficient drug administration. An amnestic effect can be produced that is characterized by an anterograde memory impairment [22]. This is an often cited advantage for certain surgical or dental procedures to minimize recall of pain. Some studies have claimed a more favorable anticonvulsant effect with drugs belonging to the 1,5-benzodiazepine structural class. However, effective anticonvulsants have been developed from both the 1,4 (diazepam) and 1,5 (clobazam) categories of benzodiazepines [23].

The choice of a specific drug often involves matching the agent's elimination half-life with the therapeutic PD effects as needed for acute or chronic anxiolytic treatment. A choice can be made to allow dosing just once daily and requiring little tapering upon discontinuation to avoid a return of baseline or rebound symptoms. Further considerations pertaining to individual drugs are given below. A summary of the major benzodiazepine pharmacokinetic properties and clinical pharmacokinetic data of value in clinical practice are presented in Table 19.1.

10.4 Specific Benzodiazepine Anxiolytics

Alprazolam This (1,4)-benzodiazepine in 1981 was the first drug FDA approved specifically for panic disorder. Randomized controlled trials using placebo, tricyclic antidepressants, and monoamine oxidase inhibitors had established its efficacy to reduce the number of panic attacks and also lessen the symptoms of agoraphobia [24]. Experience has shown that the onset of its anxiolytic effects is rapid, within 2 h following oral administration, but the drug demonstrates a fairly limited period of pharmacodynamic effects due to an intermediate elimination half-life. Its development paralleled the increase in public awareness of the dysfunctionality associated with panic disorder [25]. The effective daily dosage is generally higher than that needed to treat generalized anxiety disorder, the FDA-approved indication for most anxiolytic benzodiazepines. Total daily dosage of alprazolam in clinical practice often exceeds 4 mg per day with an occasional patient requiring over 8 mg daily. Unfortunately, this dosage increases the risk and severity of dependence. This is evident by the difficulty some patients experienced in decreasing or discontinuing treatment. Fortunately, evidence for the development of tolerance to the antipanic effects with long-term administration is lacking [26].

Alprazolam quickly became the most widely prescribed benzodiazepine shortly after its marketing. Given its success in treating panic symptoms, other benzodiazepines were tested in clinical trials and several have since received FDA approval. Notably, patients requiring long-term treatment for periods longer than 4–6 months are often switched to clonazepam allowing a reduction in number of doses per day to a single administration [27]. This benefit reflects the longer elimination half-life (range 18–50 h) and slower clearance of clonazepam.

The gastrointestinal absorption rate of alprazolam is rapid, with peak plasma concentrations occurring within 1–4 h after administration so its antianxiety effects are felt almost immediately. Alprazolam was shown to be well absorbed from the buccal mucosa so that patients in stressful situations, when liquids to facilitate oral administration are unavailable, can still obtain anxiolytic effects by placing the drug dose under the tongue for sublingual absorption. Alprazolam has been marketed in multiple formulations and dosage strengths but only for oral administration. Alprazolam can be administered via the sublingual route with similar absorption properties as the oral route [28].

As a CYP3A4 substrate, alprazolam is subject to drug-drug interactions from multiple metabolic inducers or inhibitors to increase or decrease clearance [29]. It has an intermediate elimination half-life in adults, and treatment of panic disorder often requires the drug to be administered two to three times a day in order to maintain relatively stable plasma drug concentrations. Once-daily dosing may create a situation of excessive drowsiness for a short period of time after drug administration with breakthrough anxiety occurring near the end of an 8–12 h dosage interval. Clinical trials that established the efficacy of alprazolam in panic disorder showed that 6–12 mg/day in treatment-resistant patients could reduce multiple daily panic attacks to a frequency of only a few attacks a week.

Plasma concentration ranges have not been defined that serve as guidelines for target dosing. Adjustment of daily dosing to achieve the optimal efficacy is empirical, allowing enough time for a new steady state to occur between adjustments to evaluate therapeutic effects. A problem that became apparent with alprazolam after several years of experience was the difficulty in withdrawing some patients from high daily dosing regimens when a reduction in dosage or discontinuation was desired [30].

General guidelines that have become widely accepted to reduce the total daily dose include a recommendation to reduce no faster than one-fourth of the total dose each week. With this approach, a patient desiring to eliminate alprazolam would reduce a 4 mg/day dosing regimen by 1 mg per day for 1 week, followed by a second reduction of an addition mg to 2 mg/day the second week and continuing until a satisfactory goal was reached or until breakthrough anxiety and panic attacks defined the minimum maintenance dose. Alternatively, many patients can be switched to a benzodiazepine with a longer elimination half-life to prevent or minimize a withdrawal syndrome. Clonazepam has been a favorite choice [31].

Alprazolam was briefly investigated in clinical trials during the 1980s for antidepressant effects as its safety in overdosage is far superior to the tricyclic antidepressants, the other drug category used for the treatment of panic disorder during this

time. This would be an advantage in suicidal patients [32]. However, evidence for antidepressant effects has not been convincing and subsequently tested benzodiazepines such as adinazolam were not found to be any better for depression.

Chlordiazepoxide As previously described, chlordiazepoxide was the first compound synthesized in the benzodiazepine class and the first marketed, initially with a primary indication for use in alcohol withdrawal. Chlordiazepoxide and diazepam were further differentiated by their manufacturer, Hoffmann-La Roche, by marketing in different formulations. Chlordiazepoxide was formulated into capsules while diazepam was formulated in tablets. The latter eventually became available in sustained-release capsules, oral solution, parenteral form, and suppository form for rectal administration. Chlordiazepoxide became part of the standard of care for alcohol withdrawal and has retained this recommendation [33]. Intramuscular (IM) injection of 25–100 mg every 8 h has been the recommended dose to minimize agitation, promote sleep, and suppress epileptiform withdrawal seizures. An advantage of chlordiazepoxide is its relatively long elimination half-life so that it contributes to a smooth course of alcohol withdrawal. Oral doses may be similar on a daily basis divided into several administrations. A pharmacokinetic study demonstrated oral absorption was reasonably rapid and complete suggesting that oral administration could be as useful as IM dosing [34].

With an elimination half-life of medium duration, chlordiazepoxide is a versatile drug for anxiety if immediate relief of symptoms is not needed due to its relative slow absorption profile. It has multiple pathways of elimination that do not produce pharmacologic active metabolites.

Also, use in liver disease, old age, and situations where CYP induction/inhibition would be problematic, chlordiazepoxide is an advantageous choice [35].

Clobazam This (1, 5)-benzodiazepine has been marketed since the mid-1970s in many countries outside the USA for the treatment of epilepsy. It is only available orally and has the claimed advantage of producing less sedation than clonazepam [36, 37]. Such differences may be due to affinity for two different subunits of the GABA-A receptor complex [38]. However, tolerance to its anticonvulsant effects has been a disadvantage, and animal studies showed it to be more susceptible to development of tolerance than clonazepam [39]. Tolerance to the anticonvulsant effects develops more quickly to both clobazam and clonazepam than to valproate which may account for a lack of popularity of the benzodiazepines for this use.

Clonazepam An anticonvulsant effect is a characteristic common to several benzodiazepines, notably diazepam in addition to clonazepam and clobazam. Clonazepam has found a role in substituting for alprazolam when a longer-acting antipanic effect is desired, and diazepam has the advantage as an anticonvulsant in being available in parenteral dosage forms. This becomes important when an anticonvulsant effect is needed urgently for indications such as status epilepticus.

Clorazepate This orally administered drug is rapidly converted to desmethyldiazepam, the same molecular entity that is the long-acting metabolite of diazepam.

Lacking any intrinsic pharmacological activity, clorazepate is a prodrug for desmethyldiazepam and should be expected to have many of the same qualities as this metabolite with a long elimination half-life of 20–179 h.

Diazepam Diazepam is the prototype 1,4-benzodiazepine. Early in its development, it was found to be more potent than chlordiazepoxide as a sedative, anticonvulsant, and muscle relaxant [40]. However, the pharmacologic effects of the benzodiazepines are quite similar across drugs and what often determines their preferred use has been differences in dosage, their pharmacokinetic characteristics in the intended population, and the availability of evidence for efficacy. The anxiolytic effects are mediated by alpha-2 GABA-A receptors, while the sedative effects and antiepileptic effects appear to involve alpha-1 GABA-A receptors [20]. Myorelaxant actions of diazepam appear to arise from actions at alpha-2 or alpha-3 GABA-A receptors. Diazepam, in comparison to chlordiazepoxide, was developed more extensively by Hoffmann-La Roche for multiple indications that covered the entire life span. These included anxiety during labor and delivery, childhood epilepsy, and symptoms of anxiety in adult and elderly patients with both acute and chronic symptoms. Diazepam became the most prescribed drug in the USA from 1969 to 1982 [41].

The benzodiazepines have physiochemical properties of lipid solubility and pKa values corresponding to non-ionization at physiological pH suggesting absorption should be relatively unhindered by physiological barriers. Diazepam has a rapid absorption through the gut wall and then through the cerebral capillaries, producing a potent CNS drug concentration within minutes after oral absorption. This rapid distribution results in immediate pharmacodynamic effects. However, the same physiological chemical properties that lead to an immediate pharmacologic effect also contribute to a rapid distribution throughout the body that effectively reduces the CNS concentration in favor of increasing drug concentrations in other tissues. As this process continues, hepatic metabolism of diazepam is forming desmethyldiazepam (DMD), a metabolite with similar pharmacological activity. As DMD increases in the body, pharmacodynamic effects are prolonged due to the slow elimination half-life of DMD.

Diazepam is the prototype benzodiazepine and likely the most important drug of its class due to its historical significance. The oral bioavailability is nearly complete. Depending upon the patient's previous experience with the drug, the initial perception of pharmacodynamic effects after oral administration may be felt as a diminution of anxiety, a slight sedative effect, or a slight dysphoric effect. The metabolism of diazepam is by CYP2C19 and CYP3A. Upon dosing to steady state, the DMD metabolite eventually assumes a higher plasma concentration than the parent drug. The metabolite is eliminated much more slowly with an average half-life of 36–96 h. For forensic investigations, the presence of DMD in the plasma is consistent with the patient having taken a diazepam dose sometime in the past 3–4 days.

When plasma albumin concentration is low, as often occurs in elderly patients, usual daily doses of diazepam can produce exaggerated pharmacologic effects and adverse events [42]. Standard dosage increases should proceed cautiously in the

elderly with low albumin to avoid increased drug intolerance. Whenever diazepam is discontinued, the possibility of withdrawal symptoms should be kept in mind. The sudden loss of receptor occupancy can result in a return or relapse of symptoms and occasional rebound of anxiety more intense than that originally experienced before treatment. This situation requires that drug withdrawal occur slowly, sometimes over weeks or months, to avoid any withdrawal syndrome.

Lorazepam Lorazepam has the distinction of being a benzodiazepine available in both oral and parenteral dosage forms and being metabolized by phase II glucuronidation. These characteristics contribute to its versatile anxiolytic and antiepileptic actions with low concern for use in patients with hepatic diseases. Lorazepam is used extensively by intramuscular, intravenous, and oral administration.

Midazolam Midazolam is well absorbed by various routes of administration but is only available in the USA in a parenteral formulation. It has proven to be useful for producing a state called "conscious anesthesia" allowing procedures such as endoscopy to be performed without pain and limited recall memory for the actual procedure. The level of vital sign monitoring usually provided by anesthesiologists in surgical settings is often unnecessary. Other uses include maintenance of mechanical ventilation, treatment of intractable seizures, and palliative sedation [43]. The drug's clinical utility is facilitated by a pharmacokinetic profile of a short elimination half-life and a lack of active metabolites. Midazolam is subject to numerous drug-drug interactions from induction or inhibition of CYP3A4 [44].

Oxazepam Oxazepam is a metabolite of diazepam that was developed as a separate drug. Following diazepam administration, oxazepam is usually formed to such a minor extent that it is not quantifiable in plasma and likely contributes minimally to the therapeutic effects of diazepam. It is further metabolized to a glucuronide conjugate and excreted in the urine. By developing the drug separately as a preformed product, a major distinguishing feature of both oxazepam and lorazepam is that they are metabolized by phase II enzymes to glucuronides and then largely renally excreted as highly water-soluble compounds. This route of elimination and the characteristics of lower lipid solubility confer several major differences between the drugs. Metabolism by phase II enzymes typically means less susceptibility to drug interactions compared to drugs metabolized by phase I oxidative enzymes such as CYP3A4. Oxazepam is available in oral form. Lorazepam or oxazepam may be preferred in elderly patients or those with coexisting hepatic dysfunction as their metabolism is less affected by age and liver disease due to a metabolic profile that mostly involves glucuronidation by liver enzymes [35, 45].

10.5 Non-benzodiazepine Anxiolytics

Buspirone This drug was introduced into clinical practice in 1986 to treat generalized anxiety disorder and quickly became widely prescribed as the first non-dependence-producing anxiolytic with comparative efficacy to the benzodiazepines

[46]. The FDA approval was for generalized anxiety disorder and the drug was shown to be ineffective for panic disorder. The initial impression of its effectiveness was not sustained as it appeared that patients who were benzodiazepine naive responded better than those who were switched from a benzodiazepine to avoid an adverse drug event (drowsiness, dependence). The elimination half-life of buspirone is only about 2 h which is short for use in treating chronic anxiety and therefore the drug must be dosed multiple times per day. The drug has found other uses including reduction of marijuana use dependence and in reducing tobacco smoking. Because it lacks a perceptible antianxiety effect upon immediate administration, patients and clinicians must wait for several weeks to fully evaluate its benefits in chronic anxiety disorders. Unlike the benzodiazepines, there is less concern for pharmacodynamic interactions with dependence-producing drugs. Buspirone is often used as an alternative anxiolytic in patients who are at risk to escalate dosage and become dependent. However, this population, sometimes with an extensive history of benzodiazepine use, has reported that the therapeutic effects of buspirone are disappointing or nonexistent. For this reason, buspirone may be a good choice for patients with mild anxiety who are benzodiazepine naive.

The usual daily dose is divided into two dosage intervals using a total dose of 10–15 mg initially and not exceeding 60 mg daily. Several weeks of continuous therapy may be needed to produce full benefits at a given dosage level. Buspirone's clearance is subject to inhibition by CYP3A4 inhibition so interactions with strong inhibitors of this enzyme should be anticipated or avoided. Studies of buspirone's plasma concentration in relation to clinical effects have not found drug concentration ranges that serve as biomarkers of effect, i.e., dosage is titrated according to clinical effects. It is possible that a therapeutic plasma concentration range exists, but plasma concentrations from usual doses of buspirone are generally in the low ng/ml range, making it difficult to conduct well-designed concentration versus effect studies.

10.6 Benzodiazepine Sedative-Hypnotics

Estazolam This (1,4)-benzodiazepine was developed in the 1970s for oral administration as a sedative-hypnotic with a relatively long elimination half-life (range 8–31 h, mean of 19 h [47]. Because of this characteristic, estazolam has a liability for producing a hangover effect the morning after administration [48]. Thus, it has not been as well received as similar drugs without the carryover effect.

Flurazepam This benzodiazepine was the first specifically marketed for insomnia and was therefore highly successful, especially when considered against the major sedative-hypnotics available in the 1970s (glutethimide, ethchlorvynol, methaqualone). Flurazepam is rapidly absorbed from the gastrointestinal tract producing its maximum concentration in plasma within 30–60 min. It behaves similarly to diazepam with plasma drug concentration rapidly rising and then falling to be replaced

by active metabolites that sustain and prolong the sedative effects of the parent drug. The elimination half-life of flurazepam is short, less than 2 h, but its active metabolites, *N*-1-hydroxyethylflurazepam and desalkylflurazepam have half-lives of 2–4 h and 36–100 h, respectively. The overall pharmacodynamic profile becomes one of rapid sedative effects with an intermediate metabolite to sustain sleep and a long-acting metabolite that minimizes or prevents any early morning awakening. While this profile sounds ideal, for many patients, including most elderly patients, the slow accumulate of the desalkyl metabolites causes a morning after cognitive impairment. Patients can awaken with difficulty arising due to an excessive sedation.

Temazepam Temazepam, like oxazepam, is another minor metabolite of diazepam that has been developed as a separate drug [49]. However, it has no pharmacologically active metabolites so the pharmacodynamic effects theoretically relate to only the parent drug concentration in the CNS. An initial formulation for oral administration released the drug too slowly to be effective at reducing the time to sleep onset, but this deficit was corrected to take advantage of the drug's rapid absorption in subsequent formulations [50]. Following rapid absorption, temazepam undergoes conjugation with a minor degree of demethylation giving the drug an overall elimination half-life of 3–15 h. It's clinical trial data support efficacy for both promoting sleep onset and prolonging total sleep time [51].

Triazolam This benzodiazepine is characterized by a short half-life, approximately 1.5 h, like flurazepam, but it doesn't possess long-acting metabolites. This gives it a unique profile of being able to hasten sleep onset but not provide effective sedation during the night for patients who either have middle of the night awakening or need to prolong total sleep time. This is an advantage for situations such as jet lag when only a brief treatment of insomnia is needed but presents problems if the patient must take the drug for more than a few days. Problems include development of tolerance, rebound insomnia, and dependence [52, 53]. In addition, some patients have reported a disinhibition and amnestic effect from taking triazolam. For patients naive to this drug, it is advisable to try a test dose at home or under familiar circumstances before taking a dose to induce sleep while flying or in an unfamiliar setting where awakening with disorientation may be hazardous. As triazolam is metabolized by CYP3A4, inhibitory drug-drug interactions are potential hazardous [54].

Quazepam Like other (1, 4)-benzodiazepines, quazepam was developed in the 1970s as a sedative-hypnotic. It has multiple metabolites that produce a combined pharmacodynamic profile of rapid-onset and sustained effects [55]. It is partially metabolized to desalkylflurazepam which creates a potential disadvantage of accumulation upon chronic dosing to contribute to daytime sedation [56]. This characteristic can be undesirable for some patients, especially the elderly [57]. Thus, its commercial value has been less successful than other sedative-hypnotics. Nevertheless, it has a useful profile that should be applicable to many patients. In a sleep laboratory study comparing quazepam to triazolam [58], both drugs increased total sleep time but withdrawal favored quazepam which produced less rebound

insomnia. Similar to the non-benzodiazepines (zolpidem), its onset of sedative effects can be significantly impaired or eliminated if taken with food which decreases both the rate and extent of absorption [59].

10.7 Non-benzodiazepine Sedative-Hypnotics

The pharmacokinetic properties of these agents are presented in Table 10.3. Overall, these agents are rapidly absorbed with a T_{max} of under 2.0 h and possess an elimination half-life less than 3 h except for eszopiclone and suvorexant which are about 6 h and 12 h, respectively.

Eszopiclone Three similar drugs, zolpidem, zopiclone, and eszopiclone, were all marketed after the benzodiazepines and are all specific agonists at the benzodiazepine GABA-A alpha-1 subreceptor site. This confers the sedative-hypnotic properties but not anticonvulsant effects from GABA-A affinity. These drugs are all short acting and used exclusively as sedative-hypnotics. The S-enantiomer of zopiclone, eszopiclone, has about 50 times the affinity at the GABA-A receptor-binding complex than the racemic compound. It is highly metabolized, producing several active metabolites from biotransformation mediated by CYP3A4 and CYP2E1 [60]. It is well absorbed orally, but when taken with food, its absorption rate slows and is mirrored by a lesser effect on deceasing sleep onset. The dosage recommended is between 1 and 2 mg at bedtime [61].

Ramelteon This is the first successful melatonin receptor agonist to be marketed for the treatment of insomnia in 2005. While melatonin had been discovered in the early part of the twentieth century, its receptor was not cloned until the 1990s [62]. Multiple receptors are found in the central nervous system with some in the suprachiasmatic nucleus involved in circadian rhythm and sleep [62]. Ramelteon has been especially recommended for its effects on decreasing the time to sleep onset. Ramelteon is primarily metabolized by the CYP1A2 and to a minor extent, CYP2C

Table 10.3 Pharmacokinetic properties of the non-benzodiazepine sedative-hypnotics [60, 64, 67, 68–70]

Drug	T_{max} (h)	Metabolism	*V/F* (L)	T1/2 β (h)
Eszopiclone	1.6	CYP3A4, CYP2E1	132	6.0
Ramelteon	1.6	CYP1A2	N.R.	1.3
Suvorexant	2.0	CYP3A4, CYP2C19	49	12
Tasimelteon	2.0	CYP1A2, CYP3A4	56–126	1.3–3.7
Zaleplon	1.4	Aldehyde oxidase	285	1.0
Zolpidem	1.4	CYP3A4	70	2.1

T_{max} time to maximum plasma concentration, *CYP* cytochrome P450, *V/F* distribution, *L* liters, *T1/2* β elimination half-life

and CYP3A4. The recommended dosage is 8 mg about 30 min before the desired bedtime [63]. Age but gender was reported to significantly affect drug clearance as the elderly had a much lower ramelteon mean clearance (384 ± 84 ml/min/kg vs. 883 ± 175 ml/min/kg, $p < 0.01$) [64].

Suvorexant This agent is the first in class as a distinct pharmacologic for the treatment of insomnia. Suvorexant is an orexin receptor antagonist where orexin neurons have been located in the lateral hypothalamus. Receptor antagonism is suggested to promote sleep by blocking the brain's orexin-mediated wake system, enabling transition to sleep [65]. Suvorexant pharmacokinetic properties are shown in Table 10.3. The FDA recommended cautious dose escalation in obese females with a noted increase in suvorexant area under the plasma concentration time curve (AUC) and C_{max} by 46 % and 25 %, respectively [66]. Suvorexant 40 and 150 mg lacked significant effects on respiration during sleep as measured by oxygen saturation and promoted sleep efficiency [65].

Tasimelteon A slight change in the structure of ramelteon results in tasimelteon. This drug is a melatonin receptor MT1 and MT2 agonist specifically recommended for a diagnosis of disturbances in the sleep-wake cycle [67]. This agent is available only in a 20 mg capsule and is metabolized extensively by CYP1A2 and CYP3A4 and prone to many significantly drug-drug interactions. When taken with a high-fat meal, the agent's T_{max} and C_{max} was increased by and reduced by 1.75 h and 44 %, respectively. Therefore, tasimelteon is recommended to be taken without food [66]. Hepatic or renal impairment was shown not to significantly alter tasimelteon disposition, and dosage adjustments were not suggested [68].

Zaleplon With a biological half-life of only 1–1.5 h, zaleplon is used primarily to reduce difficulty in falling asleep. It can be expected to be less effective or not effective at eliminating early morning awakening or prolonging sleep time. Zaleplon is metabolized by the aldehyde oxidase and CYP3A4 [70]. Its potency and rapid onset of effects are reasons to use lower doses in the elderly and only administer for bedtime use [61].

Zolpidem With a biological half-life of 2–3 h, zolpidem should be nearly as effective as zaleplon at reducing sleep latency but also provide some degree of benefit for middle of the night awakening. Zolpidem is metabolized by CYP3A4 and other CYP enzymes [71]. Like triazolam, zolpidem has numerous anecdotal reports of causing disinhibition reactions and loss of memory for the time around drug administration. These problems seem to be present in a greater degree in women and in the elderly [72]. Females were found to have zolpidem concentrations significantly greater than males C_{max}/dose ($p < 0.001$) and AUC/dose ($p < 0.001$), but weight-normalized clearance and elimination half-life did not reach significance [72]. A lower dosage recommendation for females was FDA approved.

10.8 Clinical Pharmacodynamic Modeling

Benzodiazepines produce these PD effects of antiepileptic and anxiolytic actions, muscle relaxation, and sedation [61]. Benzodiazepines also can cause anterograde amnesia but each benzodiazepine may produce different dose-dependent effects on various memory parameters such as immediate versus delayed recall [22]. Benzodiazepines also produce physical dependence, tolerance, and withdrawal symptoms [73]. Non-benzodiazepine sedative-hypnotics are designed for sleep disorders such as insomnia and non-24 h sleep-wake disorder. Except for physical dependence and antiepileptic activity, benzodiazepines and non-benzodiazepine agents have been extensively modeled for their PD effects.

The kinetics of a PD response has been previously described as a link from a drug's pharmacokinetic properties where the E_{max} and sigmoidal E_{max} models evolved with hysteresis loops for drug efficacy and tolerance developed [74]. Diazepam free plasma concentrations were correlated to the digit symbol substitution test (DSST), and wheel tracking indicated a tolerance hysteresis loop development which matches its memory impairment and sedative action [75]. A further extensive study reported that alprazolam and diazepam but not lorazepam showed development of acute tolerance that was related to the drug concentrations [76]. Alprazolam single doses of 2, 4, 8, and 10 mg were given to healthy volunteers and the medication displayed linear pharmacokinetic properties. Alprazolam's PD effects reported a concentration-effect curve to a clockwise hysteresis loop related to the distribution rate into the systemic circulation [77]. Pharmacokinetic and PD models have been evaluated with various benzodiazepines [78–80]. Lorazepam PD was reported to have significant effects on memory impairment in the elderly without significant actions on mood, sedation, or anxiety [81]. Benzodiazepines, when used in the elderly, should be prudently prescribed with a careful assessment of their risks and benefits.

Both zaleplon and zolpidem were found to have dose and concentration-dependent PD effects on the DSST scores and other psychomotor actions in adult healthy volunteers [82]. Zaleplon, zolpidem, and eszopiclone were reported to have a lesser effect than the benzodiazepines on memory impairment [70]. Significantly greater zolpidem concentrations were reported for elderly males and females compared to adult healthy volunteers (AUC 40 %, elderly females and 31 % elderly males, $p < 0.01$) [83]. A recent survey in emergency departments reported that persons >65 years taking zolpidem had the highest rates of adverse events when evaluated in the emergency room [84]. As previously indicated, adult females also had significantly higher zolpidem serum concentrations than adult males [72]. The PD effects were assessed by the DSST, reaction times, and memory tests. Zolpidem doses of 1, 1.75, and 3.5 mg led to dose-dependent impairment in all PD effects, and these enhanced PD actions (e.g., reduced DSST scores) were more pronounced in the female group compared to the male group. Based upon the pharmacokinetic and PD effects of zolpidem on females, the FDA recommended that lower doses be

prescribed in the package insert. Therefore, both age and gender play a significant role in zolpidem disposition and PD actions. Careful patient monitoring is needed for these agents when used in females and the elderly population.

10.9 Conclusions and Future Directions

The value of pharmacokinetics and PD are often conceived as deriving from knowing a desired plasma drug concentration range is a target for designing drug dosage regimens. This is particularly useful when linearity of metabolism is maintained with increasing total amount of daily dose. Substantial experimental evidence exists for linear pharmacokinetics of benzodiazepines across the usual daily dose range. Under these conditions, if half the desired plasma concentration is produced from a given dose, then the target concentration should be achieved by doubling the dose. However, for the anxiolytics and sedative-hypnotics, the results of plasma concentration versus PD effect studies have not identified rigorous target concentration ranges associated with optimal therapeutic effects.

However, there remains value in knowing the general characteristics of a drug's pharmacokinetics. Knowledge of metabolic pathways and a drug's affinity for inhibiting or inducing drug-metabolizing enzymes can be valuable in avoiding drug-drug interactions. The elimination half-life is especially useful in guiding the time between dosage adjustments that are necessary for the patient to reach a new steady state following either an increase or decrease in daily drug dosage.

The necessity of sleep for maintenance of health appears to be an absolute requirement in all members of the animal kingdom. The variability in the temporal patterns of sleep is broad, from quick naps to hibernation. The species variability can be astounding. What appears to be a universal characteristic is that deprivation of sleep eventually leads to a deterioration of the organism's functioning and if maintained for a sufficient period, can even lead to death. However, the ability to go for long periods without sleep is beneficial for the survival of many organisms, but eventually sleep must occur. During the past two centuries, humans have been drawn to and have exploited chemical means of both increasing and decreasing sleep, usually for the purpose of improving performance or promoting health.

The use of prescription and nonprescription drugs to treat sleep disorders is extensive in the USA and most countries around the world. As the FDA requires that new drugs introduced into the market in the USA be safe and effective, then a substantial research effort is expended to develop these compounds. The proper use of these drugs requires an extensive knowledge of pharmacology, physiology, medicine, and other aspects of health that are influenced by the ingestion of the sedative-hypnotics. They are certainly not without potential harm and have been a favorite for suicide attempts by drug overdose historically.

The specific indications for use of benzodiazepine drugs shown in Table 10.2 have developed as a result of specific marketing efforts by manufacturers in a

desire to differentiate products when more than one benzodiazepine were developed by the same company. Other influences included the period of time in the development of the drug class when a new molecule appeared and the desire to expand the market with new drugs for new indications rather than repurposing existing drugs for additional uses. The specificity has also been guided to some extent by the differences in metabolism of a few drugs. For example, flurazepam and oxazepam which are glucuronidated after absorption as their major pathway for disposition from the body confers some stability in the range of clearance for patients with hepatic disease, advanced alcohol abuse, or aging. Also, the presence of pharmacologically active metabolites has served as a basis for choosing one drug over another. Finally, the inherent rate at which some drugs are absorbed from the gastrointestinal tract may be faster than others thus conferring a more desirable profile as a sedative-hypnotic.

Although the benzodiazepines' dominance of the market for conditions requiring antianxiety effects or sedation has been overwhelming, a few compounds have been developed that have found a place in pharmacotherapy. These include buspirone as an oral anxioloytic and suvorexant, ramelteon, and tasimelteon for sedation. The "Z" drugs, eszopiclone, zaleplon, and zolpidem, have gained wide acceptance for their use in the treatment of acute and chronic insomnia.

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