

Optimizing benzodiazepine treatment of anxiety disorders

Understanding the pharmacology of these agents can help guide medication selection and dosing

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Though once the main treatment for anxiety disorders—often as monotherapy¹—benzodiazepines are now primarily used as adjunctive agents.²⁻⁴ Their ability to produce rapid anxiolysis represents a significant therapeutic advantage, but in recent decades their tolerability, class-specific risks, and lack of antidepressant properties contributed to benzodiazepines being largely replaced by selective serotonin reuptake inhibitors (SSRIs) for the pharmacologic treatment of anxiety. This shift within the pharmacologic armamentarium has decreased many clinicians' familiarity with benzodiazepines.

While benzodiazepines continue to have an important role in managing anxiety disorders, particularly treatment-resistant anxiety,⁴ clinicians must consider the limitations of these agents. Benzodiazepines can be associated with abuse and dependence, and overdose risk when combined with opiates.^{5,6} They may cause memory impairment^{7,8} and conflicting data suggest they may contribute to the risk of developing cognitive disorders.⁹⁻¹¹ Benzodiazepines also have been associated with falls and fractures,¹² and worse outcomes in patients with posttraumatic stress disorder.¹³ Some studies of patients with chronic obstructive pulmonary disease (COPD) found benzodiazepines may increase the risk of COPD exacerbations and accidental overdose,¹⁴ though others found that was not always the case.¹⁵ Benzodiazepines may be associated with an increased risk of spontaneous abortion when used early in pregnancy.¹⁶ Prospective research in women who were breastfeeding found benzodiazepines may cause sedation in up to 2% of infants.¹⁷

continued



Benzodiazepines for anxiety

Clinical Point

Benzodiazepine efficacy and tolerability may be related to pharmacodynamic differences in pediatric and adult populations

Despite the potential for adverse effects, benzodiazepine use remains common.¹⁸ These medications have a rapid onset of action, are useful for breakthrough symptoms, may enhance treatment adherence, and alleviate activating symptoms of SSRIs. Like other commonly used medications, benzodiazepines have the potential for both harm and benefit.¹⁹ Similar to other medications with tolerability concerns but established efficacy, particularly in treatment-resistant anxiety disorders, it is important to balance “overprescribing ... to patients at risk and underusing these effective medications when indicated.”¹⁹ Though the use of benzodiazepines has been discouraged and perceptions have shifted, knowledge of benzodiazepines and benzodiazepine pharmacology also has been degraded contemporaneously.

This article provides a synthesis of the clinically relevant pharmacology of benzodiazepines, with a focus on orally administered benzodiazepines, which are more common in outpatient clinical practice. Specifically, this review describes the pharmacology of benzodiazepines, benzodiazepine medication interactions, the relationship between pharmacologic characteristics and treatment response/tolerability, and selection and dosing of oral benzodiazepines (*Table, 20 page 25*).

Benzodiazepine pharmacodynamics

Benzodiazepines act at the gamma-aminobutyric acid (GABA)-A receptor complex and bind allosterically.²¹⁻²³ Comprised of 5 glycoprotein subunits (2 alpha subunits, 2 beta subunits, and 1 gamma subunit), the receptor has 2 distinct sites at which the endogenous inhibitory transmitter GABA binds and 1 benzodiazepine binding site. Benzodiazepines bind within a socket created by the alpha and gamma subunits²² and after binding induce a conformational change in the receptor, which enhances GABA binding. There are 2 types of benzodiazepine receptors: BZ1 and BZ2. The subunits play a critical role in driving the pharmacologic characteristics of the receptor.²⁴ BZ1 and BZ2 receptors bind benzodiazepines, although they are differentially distributed within

the brain. Binding at BZ1 receptors—which are distributed in cortical, thalamic, and cerebellar regions—contributes to sedation and deleterious effects of benzodiazepines on memory (eg, anterograde amnesia). BZ2 receptors (which contain gamma-2 subunits) are responsible for anxiolytic and muscle-relaxing effects. They are distributed throughout limbic regions and motor tracts, including motor neurons and neurons in the dorsal horn of the spinal cord.²⁴

Benzodiazepines—positive GABA-A receptor allosteric modulators—produce phasic inhibition, largely through the alpha and gamma subunits discussed above. In contrast, newer positive allosteric modulators (eg, zuranolone) bind at the alpha/beta subunits.²⁵ Mechanistically, endogenous neuroactive steroids and nonbenzodiazepine GABA-A-positive allosteric modulators such as zuranolone and ganaxolone also differ in their regulation of GABA-A (down-regulated with benzodiazepines and hypothetically upregulated with zuranolone)²⁶ and their synaptic effects (benzodiazepines synaptically vs endogenous neurosteroids and nonbenzodiazepine positive allosteric modulators extrasynaptically).²⁷

From a developmental perspective, benzodiazepines may have less efficacy for anxiolysis and worse tolerability in some pediatric patients,²⁸ although they generally appear effective for immediate use to treat anxiety in acute settings.²⁹ The differences in efficacy and tolerability may be related to pharmacodynamic differences between pediatric populations and adults. GABA receptor expression and function do not reach adult levels until age 14 to 17½ for subcortical regions and age 18 to 22 for cortical regions, although girls reach adult expression of GABA receptors slightly earlier than boys.³⁰ Data from multiple randomized controlled trials of pediatric patients with anxiety disorders do not suggest efficacy as benzodiazepines are poorly tolerated, especially compared to other psychopharmacologic interventions for pediatric anxiety disorders.³⁰

Pharmacology and clinical effects

Benzodiazepine pharmacokinetics are intimately linked with the onset of action and



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Pharmacologic properties of oral benzodiazepines

Medication	Onset of action (min)	Half-life (h)	Tmax (h)	Protein binding	Metabolism
Alprazolam	20 to 30	11	1 to 2	80%	CYP3A4
Chlordiazepoxide	30	24 to 48 for chlordiazepoxide; 14 to 95 for demoxepam (metabolite)	0.5 to 2	96%	CYP3A4 (primary), CYP2C19
Clobazam	30	36 to 42 for clobazam; 71 to 82 for n-desmethyloclobazam	0.5 to 2	80% to 90%	CYP3A4 (primary), CYP2C19, CYP2B6
Lorazepam	20 to 30	12	2	85% to 90%	Nonoxidative
Clonazepam	20 to 40	17 to 60	1 to 4	85%	CYP3A4
Diazepam	15 to 60	44 to 48 for diazepam; 100 for desmethyldiazepam	0.25 to 2.5	98%	CYP3A4 and CYP2C19
Oxazepam	30 to 60	6 to 11	3	96% to 98%	Nonoxidative, glucuronide conjugation
Temazepam	10 to 20	3.5 to 18.4	1.2 to 1.6	96%	Nonoxidative
Triazolam	30	1.5 to 5.5	2	89%	CYP3A4 and glucuronide conjugation

CYP: cytochrome P450
Source: Reference 20

duration of clinical effect and vary based on the route of administration, absorption, and distribution/redistribution.³¹ In this review, we focus on oral administration as opposed to IV, IM, sublingual, or intranasal administration.

Absorption

Benzodiazepines are rapidly absorbed after oral administration and quickly enter the systemic circulation. However, absorption rates vary depending on specific aspects of the gastrointestinal milieu and intrinsic properties of the benzodiazepine. For example, alprazolam is more rapidly absorbed than most other benzodiazepines, with a Tmax of 1.8 hours compared to lorazepam, which has a Tmax of approximately 2 hours. These pharmacokinetic effects instantiate differences in tolerability and efficacy. Thus, following single doses of alprazolam and diazepam, self-rated sedating effects and impairment on a task of working memory

suggest that effects have a more rapid onset for alprazolam relative to lorazepam.³² Food and concomitant medications can significantly affect benzodiazepine absorption. A single-dose, 3-way crossover study demonstrated that taking diazepam concomitantly with an antacid (eg, aluminum hydroxide) decreased peak concentrations and prolonged absorption by approximately 30 minutes. However, total absorption of the medication was unaffected.³³ Additionally, administration of diazepam with food significantly slows absorption from 1 hour 15 minutes to approximately 2 hours 30 minutes and increases benzodiazepine absorption by 25% (Figure 1,³⁴ page 26); the fat content of the meal appears important in moderating this effect.³⁵ The impact of food on alprazolam varies by formulation. For example, when administered in an extended-release (XR) formulation with a high-fat meal, alprazolam absorption increases by one-third, while absorption for administration of the

Clinical Point

For certain benzodiazepines, administration with food influences their pharmacology and results in slower absorption



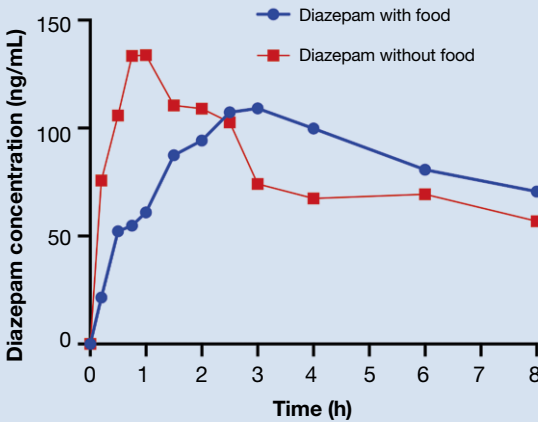
Benzodiazepines for anxiety

Clinical Point

Benzodiazepine response occurs early during treatment and is influenced by pharmacologic properties, including lipophilicity

Figure 1 Effects of food on diazepam concentration time curves

Food significantly slows the absorption of diazepam and results in a decrease in C_{max} and a delay in T_{max} , although the total exposure is unaffected



Source: Adapted from reference 34

orally disintegrating tablet with a high-fat meal increases from 1 hour 30 minutes to 2 hours. Similarly, for lorazepam, administration with a meal delays absorption by approximately 2 hours; however, this effect does not appear present with the XR formulation. Administering benzodiazepines with food can be clinically leveraged to either accelerate the onset of action or decrease peak-associated adverse effects. Thus, when a highly lipophilic benzodiazepine is needed to treat acute anxiety or prior to an expected anxiogenic stimuli, administering the medication without food may produce a faster onset of action.

CNS penetration

Benzodiazepines enter the CNS by passive diffusion. Because of this, lipophilicity at physiologic pH influences the rate at which a benzodiazepine crosses the blood-brain barrier. The rate at which benzodiazepines enter the CNS influences their clinical effects and the speed at which both efficacy (ie, anxiolysis) and adverse effects (ie, sedation, slowed cognition) are observed. In general, more lipophilic medications initiate their anxiolytic effect more quickly. However, by quickly leaving the CNS (through the same mechanism that allowed them to enter the

CNS at such speed), their effects rapidly cease as they redistribute into fat. Thus, highly lipophilic benzodiazepines produce more intense effects compared to less lipophilic benzodiazepines. For these reasons, lipophilicity is more important than half-life for determining the duration of effect in most patients.

Lipophilicity and duration of effect

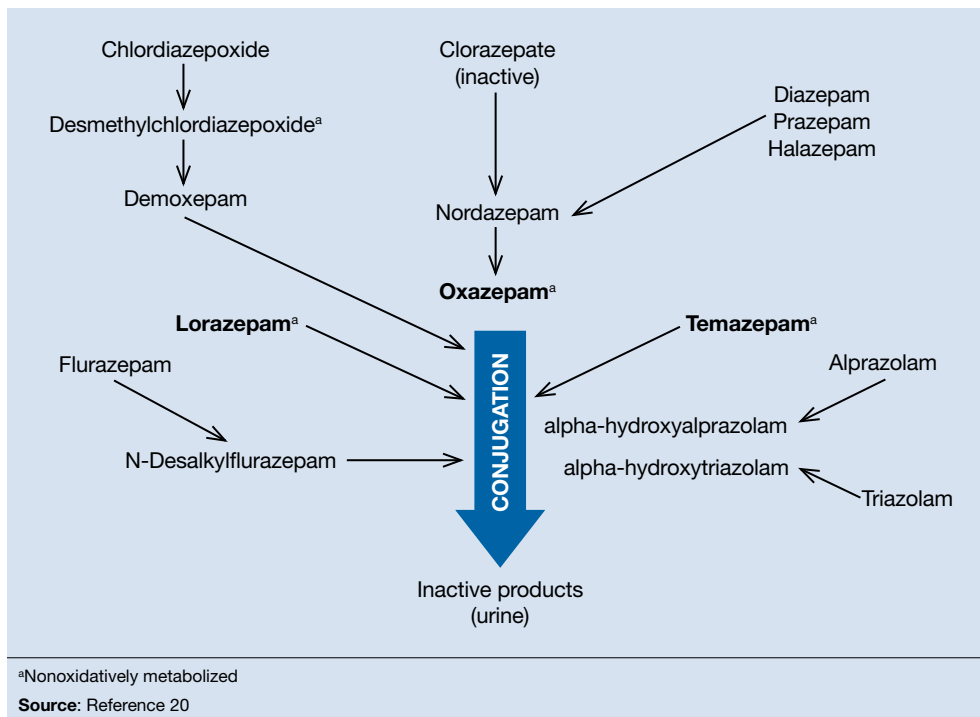
Benzodiazepines and their metabolites tend to be highly protein-bound and distributed in fat- and lipid-enriched areas such as the CNS. As a result, the more lipophilic agents generally have the highest rates of absorption and the fastest onset of clinical effects. The duration of action for many benzodiazepines is determined by the rate and extent of distribution (a function of lipophilicity) rather than by the rate of elimination. For example, diazepam has a longer half-life than lorazepam, but its duration of action following a single dose is shorter. This is because diazepam is more lipophilic and therefore more extensively distributed (particularly to adipose tissue). This results in it leaving the brain and blood and distributing to other tissues. In turn, its CNS effect (ie, anxiolytic effects) are more quickly terminated.

By contrast, less lipophilic benzodiazepines maintain their CNS concentrations longer; they have a longer duration of action because of their slower redistribution, which culminates in a shorter half-life, and are less extensively distributed to peripheral tissues. In essence, this means that (other things being equal) a less lipophilic benzodiazepine produces a more sustained anxiolytic effect compared to a highly lipophilic benzodiazepine.³⁶

Lipophilicity is also important in predicting some cognitive adverse effects, including amnesia. Benzodiazepines with high lipophilicity have greater absorption and faster onset of action as well as more rapid amnesic effects.^{37,38} These effects may relate to overall efficacy differences for oral benzodiazepines. A recent meta-analysis by Stimpfl et al³⁶ found that less lipophilic benzodiazepines

Figure 2

Oxidative and nonoxidative metabolism of benzodiazepines



Clinical Point

Most benzodiazepines are metabolized through oxidative mechanisms that involve CYP3A4

produced a greater response compared to more lipophilic benzodiazepines.

Metabolism

Regarding cytochrome P450 (CYP) metabolism, polymorphic CYP2C19 and CYP3A4/5 are involved in the metabolism of several benzodiazepines³⁹ and CYP2B6 has been recognized as a contributor to diazepam metabolism. CYP3A5 gene polymorphisms may produce variation in alprazolam metabolism; however, the predominant cytochrome involved in the metabolism of oxidatively metabolized benzodiazepines (ie, benzodiazepines other than lorazepam, oxazepam, and temazepam) is primarily CYP3A4, and most effects on CYP3A4 activity are related to concomitant medications and other non-genetic factors.

Drug-drug interactions

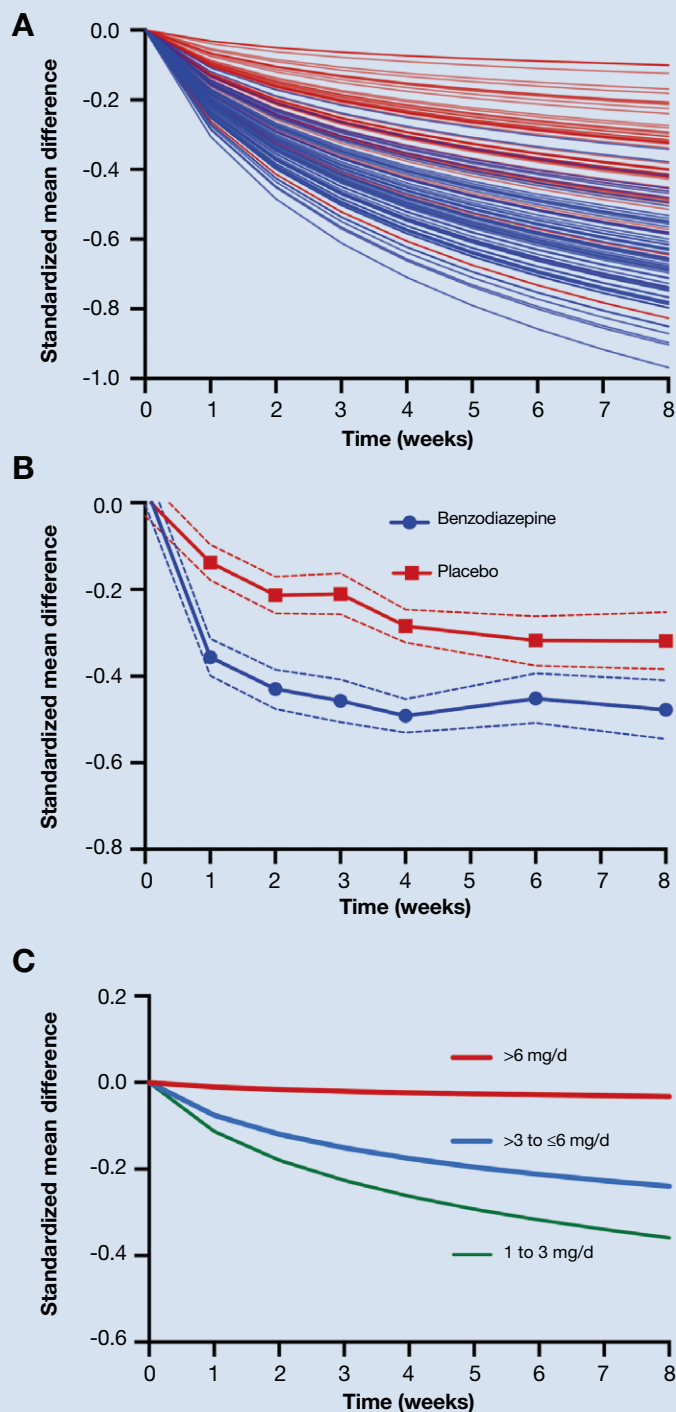
Apart from lorazepam,^{40,41} oxazepam,^{42,43} and temazepam, most benzodiazepines are metabolized through oxidative mechanisms that involve CYP3A4 (Figure 2²⁰).³⁹ As such, their metabolism is influenced by

medications that impact CYP3A4, including antifungals (eg, ketoconazole), calcium channel blockers (eg, verapamil, diltiazem), nefazodone, some protease inhibitors, and macrolide antibiotics. Research has examined the impact of low-dose estrogen oral contraceptives (OCPs) on exposure (eg, plasma concentrations) of several benzodiazepines. The mechanism for this interaction is likely complex and putatively involves multiple pathways, including inhibition of CYP3A4 by OCPs. The effects of OCPs on benzodiazepine pharmacokinetics vary based on the metabolism of the benzodiazepine. In general, medications oxidized and nitroreduced (eg, chlordiazepoxide, alprazolam, diazepam, and nitrazepam) have decreased clearance in patients treated with OCPs. Regarding nonoxidatively metabolized benzodiazepines, data are mixed. Research found no OCP-related effects on the pharmacokinetics of nonoxidatively metabolized benzodiazepines⁴⁴; another study suggested that clearance of these medications—through increased glucuronidation—may be increased.³¹ The effect of smoking on benzodiazepine

Figure 3

Benzodiazepine response in adults with anxiety disorders

In prospective randomized controlled trials of adults with anxiety disorders, benzodiazepines are consistently superior to placebo (A), although the magnitude and trajectory of response vary considerably. In meta-analyses, the average response to benzodiazepines emerges early in treatment (B). Variation in benzodiazepine response in prospective controlled trials relates to dose with doses ≤ 3 mg/d producing the greatest improvement (C).



Source: Adapted with permission from Stimpfl JN, Mills JA, Strawn JR. Pharmacologic predictors of benzodiazepine response trajectory in anxiety disorders: a Bayesian hierarchical modeling meta-analysis. *CNS Spectr*. 2023;28(1):53-60. doi:10.1017/S1092852921000870

concentration has been well documented. Smoking increases the clearance of orally administered diazepam,⁴⁵ but not IV diazepam, midazolam, or lorazepam, suggesting that this represents a first-pass effect.⁴⁶ For alprazolam, plasma concentrations are reduced by 15% to 30% in smokers and total body clearance is 24% greater compared to nonsmokers, which results in an approximately 50% increase in half-life in nonsmokers compared to smokers.⁴⁷ The most notable interaction between benzodiazepines and SSRIs is seen with fluvoxamine. Because fluvoxamine moderately inhibits CYP2C19 and CYP3A4 and potentially inhibits CYP1A2,⁴⁸ the clearance of oxidatively metabolized benzodiazepines is reduced.⁴⁹ Additionally, the effects of grapefruit juice—a potent inhibitor of CYP3A4—has been evaluated for several benzodiazepines. Yasui et al⁵⁰ found grapefruit juice did not alter alprazolam plasma concentrations. However, in separate research, grapefruit juice tripled diazepam exposure, increased peak concentrations 1.5-fold, and prolonged absorption.⁵¹

Hepatic disease

Exposure to benzodiazepines—other than lorazepam, oxazepam, and temazepam—is influenced by intrinsic hepatic disease and requires dose adjustment in individuals with significant hepatic impairment. The impact of hepatic disease on the clinical pharmacology of benzodiazepines may relate to 2 factors: protein binding and metabolism. In a study of individuals with cirrhosis, lorazepam binding was decreased, although its metabolism and clearance were largely unaffected.⁴⁰

Aging and benzodiazepine metabolism/clearance

Aging is associated with myriad physiologic changes (eg, decrease in renal clearance after age 40, changes in body fat distribution, changes in activity of cytochromes) that are relevant to benzodiazepine pharmacology. They may underlie differences in the tolerability of benzodiazepines and other clinically relevant characteristics (eg, duration of action, accumulation).

Several studies have evaluated the impact of aging on the clearance and

disposition of selected benzodiazepines. The respective half-lives of chlordiazepoxide and diazepam increase from 4- to 6-fold from age 20 to 80. Further, with chronic dosing, highly lipophilic benzodiazepines may require additional attention in geriatric patients. In a study that included individuals up to age 78, steady-state plasma concentrations of diazepam and its metabolite, desmethyldiazepam (DMDZ), were 30% to 35% higher in older patients compared to younger individuals.⁵² In this study, the half-lives for the young and older patients were 31 hours and 86 hours, respectively, for diazepam, and 40 hours and 80 hours, respectively, for the active metabolite. The half-life of diazepam is increased by “1 hour for each year of age beginning with a half-life of 20 hours at 20 years of age, as the volume of distribution is increased, and clearance is decreased.”⁵² Clinically, this implies that in older adults, clinicians should expect lower peak concentrations (C_{max}), higher trough concentrations (C_{min}), and that diazepam will take longer to reach steady-state concentrations. Taken together, these findings raised concern that “slow accumulation and delayed washout of diazepam and DMDZ is probable.”⁵² These findings—which may have more clinical relevance than those of single-dose studies—suggest that the effects related to diazepam would also take longer to resolve in older patients. Finally, lorazepam clearance or distribution does not appear to be affected by aging, at least in patients age 15 to 73.⁴⁰ Alprazolam is more slowly cleared in geriatric patients and its effects may be potentiated by reduced protein binding.

Obesity

The distribution of medications, including benzodiazepines, is altered in patients who are obese because of increased adipose tissue.^{53,54} This increase in the volume of distribution can attenuate the onset of action, increase medication accumulation in fat, and potentiate the duration of action.^{55,56}

Obesity may also affect hepatic metabolism by induction of CYP1A2, CYP2C9, and CYP2C19, and inhibition of CYP3A4.⁵⁷ Triazolam, which is metabolized by CYP3A4,

is associated with a greater exposure (ie, plasma concentrations) in individuals who are obese.⁵⁸ However, when considering differences in benzodiazepine pharmacokinetics in patients who are obese, clinicians must remember that elimination half-life depends on both volume of distribution and clearance. In patients who are obese (compared to patients who are not obese), the half-lives are increased for alprazolam (22 hours vs 11 hours, $P < .001$)⁵⁹ and diazepam (82 hours vs 32 hours, $P < .005$).⁶⁰ In a pharmacokinetic study of diazepam in individuals who were obese and individuals who were not obese, total metabolic clearance did not differ. Rather, the increased half-life was related to a tripling of the volume of distribution in obese patients (228 liters vs 70 liters, $P < .01$). This indicates that patients who are obese may experience a much slower onset of maximal effect compared to patients who are not obese because the accumulation of the medication is delayed. Additionally, for benzodiazepines that are conjugated (lorazepam and oxazepam), clearance is significantly enhanced in patients who are obese. For example, lorazepam clearance is 102 mL/min in individuals who are obese compared to 63 mL/min in individuals who are not obese; for oxazepam, clearance is 181 mL/min in patients who are obese compared to 98 mL/min in individuals who are not obese.⁶¹ These differences are attributed to increased uridine diphosphate glucuronyl transferase in obesity and to increases in liver size in obesity.⁵³

How quickly do benzodiazepines work?

Benzodiazepines act quickly. Meta-analyses³⁶ suggest that improvement in anxiety symptoms compared to placebo is greatest initially and then the rate of improvement slows over successive weeks. Research on benzodiazepines reveals statistically significant differences between benzodiazepines and placebo within the first week of treatment, with >80% of the expected improvement by Week 8 of treatment emerging by Week 4 (*Figure 3*,³⁶ page 28). The rapid reduction in anxiety symptoms seen with benzodiazepines has

Clinical Point

Aging is associated with decreased clearance and longer duration of action for oxidatively metabolized benzodiazepines



Benzodiazepines for anxiety

Clinical Point

High-dose benzodiazepines produce a slower response and less improvement compared to other doses

important treatment implications, given that traditional psychotherapeutic and antidepressant treatments are slow to produce improvements. Consistent data suggesting that benzodiazepines work faster than other treatments support that they may have a role during the initiation of other treatments.

What is the 'best' dose?

As seen with other classes of psychotropic medications,⁴ the relationship between benzodiazepine dose and response is complex. In a recent meta-analysis of 65 placebo-controlled trials of benzodiazepines in adults with anxiety disorders, there was a superior response over time for low-dose benzodiazepines (<3 mg/d in lorazepam equivalents) compared to a medium dose (3 to 6 mg/d; $P = .042$); high-dose benzodiazepines (>6 mg/d) yielded less improvement compared to medium doses ($P = .001$).³⁶ A study of adults with panic disorder similarly found the greatest responses with alprazolam plasma concentrations of 20 to 40 ng/mL, with no additional benefit at <20 ng/mL or >40 ng/mL.⁴⁹ As plasma concentrations increase, adverse effects such as sedation also increase, which may confound the observed loss of a dose-response relationship at higher doses and plasma concentrations.⁶² This may, in part, account for the observation that higher doses of benzodiazepines are associated with greater depressive symptoms and disrupted sleep.⁶³ As such, low doses may represent a delicate equipoise between efficacy and tolerability, yielding the most optimal clinical response.

Which benzodiazepine should I prescribe?

Comparing benzodiazepines is difficult, given the differences in dosing and disorders studied and differences in how each individual clinical trial was conducted. A meta-analysis by Stimpfl et al³⁶ that used Bayesian hierarchical modeling, which allowed some of this heterogeneity to be addressed, found that relative to the reference benzodiazepine (lorazepam), clonazepam had the greatest trajectory/magnitude

of response (other specific benzodiazepines did not statistically differ from lorazepam) (Figure 4,³⁶ page 31).

Another aspect of the superiority of clonazepam in some research relates to its pharmacokinetic properties, particularly when compared with benzodiazepines that have very short half-lives. Short half-life benzodiazepines have been associated with rebound anxiety, which is defined as "the relative worsening of symptoms on discontinuation of treatment as compared to baseline symptoms" and is distinct from withdrawal.⁶⁴ While it is difficult to assess this in clinical trials, Herman et al⁶⁵ provided insight into the contribution of rebound anxiety in a study of patients with panic disorder treated with alprazolam who experienced "interdose anxiety symptoms." Of the 48 patients in this study, 41 switched to clonazepam, and most who switched (82%) experienced improvement. The improvement was attributed to the decreased frequency of clonazepam (vs alprazolam) administration and lack of interdose anxiety. When selecting an oral benzodiazepine, consider the duration, onset of action, and differences in metabolism that produce varying levels of effectiveness for individual patients. In situations where rapid onset is desired, a short-acting benzodiazepine may be preferable, while a longer-acting benzodiazepine would be preferable in situations where the patient needs sustained effects.

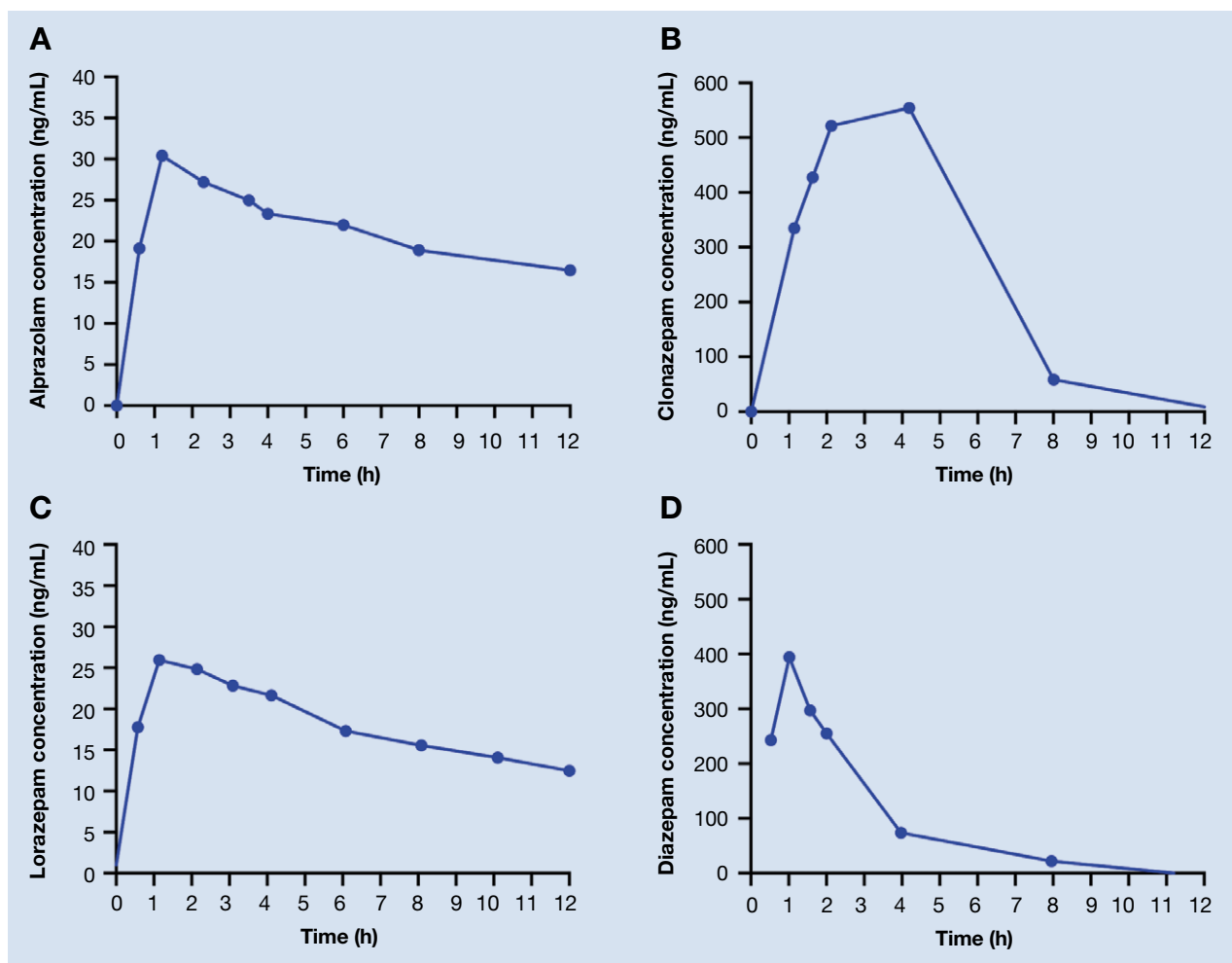
Regarding lipophilicity, differences among benzodiazepines could contribute to differences in psychological dependence and differential utility in some situations. For example, alprazolam rapidly enters the CNS, producing an immediate anxiolytic effect. However, its egress from the CNS is equally rapid, and its anxiolytic effects disappear quickly. This may be desirable for addressing acute, predictable anxiety, but could have unintended consequences in treating chronic anxiety, where it could facilitate psychological dependence.

Practical considerations

When prescribing benzodiazepines, consider a myriad of patient- and medication-specific factors, as these have clinically relevant

Figure 4

Concentration time curves for select orally administered benzodiazepines



Source: Reference 36

implications on treatment response. This information, taken together, supports the importance of an individualized approach to benzodiazepine use. Before selecting a benzodiazepine and during treatment, important elements of the patient's history must be considered, including age, body weight, concomitant medication use (eg, antacids, CYP3A4 inhibitors, OCPs), smoking status, and history of hepatic or renal disease.

Patients age <18 are unlikely to have full expression of GABA receptors in the brain³⁰ and therefore benzodiazepines may not be as efficacious for anxiolysis in this population. Moreover, compared to younger patients, older patients may experience higher steady-state concentrations of benzodiazepines, especially lipophilic

agents, due to an increased volume of distribution and decreased clearance. In patients treated with OCPs, some benzodiazepines may take longer to reach steady-state, and dose adjustments may need to be considered. In patients who smoke, clearance of some oral benzodiazepines is also accelerated, potentially decreasing half-life by up to 50%.

When dosing and titrating benzodiazepines, consider the patient's body weight, particularly if they are obese. The effects of obesity on benzodiazepine pharmacokinetics are complex. For glucuronidated benzodiazepines, clearance is increased in patients who are obese; however, the volume of distribution is also increased in such patients, meaning it will take longer for



Benzodiazepines for anxiety

Clinical Point

Obesity affects the clearance and distribution of benzodiazepines

Related Resources

- Weber SR, Duchemin AM. Benzodiazepines: sensible prescribing in light of the risks. *Current Psychiatry*. 2018;17(2):22-27.
- Balon R. Benzodiazepines for anxious depression. *Current Psychiatry*. 2018;17(8):9-12.

Drug Brand Names

Alprazolam • Xanax	Ganaxolone • Ztalmey
Chlordiazepoxide • Librium	Ketoconazole • Nizoral
Clobazam • Onfi	Lorazepam • Ativan
Clonazepam • Klonopin	Midazolam • Versed
Clorazepate • Gen-Xene	Temazepam • Restoril
Diazepam • Valium	Triazolam • Halcion
Diltiazem • Cardizem	Verapamil • Calan
Fluvoxamine • Luvox	

benzodiazepines to achieve steady-state in these individuals compared to patients who are not obese. These effects suggest it may take longer to achieve a response at a given dose in patients who are obese compared to individuals who are not obese.

The properties of individual benzodiazepines should also be considered when selecting a benzodiazepine treatment. If circumstances necessitate rapid symptom relief, a lipophilic benzodiazepine, such as diazepam, may be preferred for quick onset and offset of action. Onset of action may also be hastened by taking the benzodiazepine without food; conversely, if peak adverse effects are problematic, concurrent consumption of a high-fat meal may help decrease peak concentration and prolonging absorption. In other circumstances, such as if sustained anxiolysis is desired, a clinician may opt for a less lipophilic benzodiazepine, such as clonazepam. Finally, in terms of general treatment response, benzodiazepines separate from placebo in the first week of treatment, which supports the idea they may be useful during the introduction of other

medications (eg, SSRIs) that take a longer time to achieve clinical effect.

References

1. Rickels K, Moeller HJ. Benzodiazepines in anxiety disorders: reassessment of usefulness and safety. *World J Biol Psychiatry*. 2019;20(7):514-518. doi:10.1080/15622975.2018.1500031
2. Stevens JC, Pollack MH. Benzodiazepines in clinical practice: consideration of their long-term use and alternative agents. *J Clin Psychiatry*. 2005;66(Suppl 2):21-27.
3. Pollack MH, van Ameringen M, Simon NM, et al. A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. *Am J Psychiatry*. 2014;171(1):44-53. doi:10.1176/appi.ajp.2013.12101353
4. Strawn JR, Geraciotti L, Rajdev N, et al. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. *Expert Opin Pharmacother*. 2018;19(10):1057-1070. doi:10.1080/14656566.2018.1491966
5. Karaca-Mandic P, Meara E, Morden NE. The growing problem of co-treatment with opioids and benzodiazepines. *BMJ*. 2017;356:j1224. doi:10.1136/bmj.j1224
6. Bachhuber MA, Hennessy S, Cunningham CO, et al. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061
7. Bentué-Ferrer D, Akwa Y. Benzodiazepines: Effects on memory functioning. In: Pandi-Perumal SR, Verster J, Monti J, et al, eds. *Sleep Disorders: Diagnosis and Therapeutics*. CRC Press; 2008:104-114. doi:10.3109/9780203091715-15
8. Pomara N, Facelle TM, Roth AE, et al. Dose-dependent retrograde facilitation of verbal memory in healthy elderly after acute oral lorazepam administration. *Psychopharmacology (Berl)*. 2006;185(4):487-494. doi:10.1007/s00213-006-0336-0
9. Gray SL, Dublin S, Yu O, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ*. 2016;352:i90. doi:10.1136/bmj.i90
10. Biétry FA, Pfeil AM, Reich O, et al. Benzodiazepine use and risk of developing Alzheimer's disease: a case-control study based on Swiss claims data. *CNS Drugs*. 2017;31(3):245-251. doi:10.1007/s40263-016-0404-x
11. de Gage SB, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ*. 2014;349:g5205. doi:10.1136/bmj.g5205
12. Shah R, Raji MA, Westra J, et al. Association of co-prescribing of opioid and benzodiazepine substitutes with incident falls and fractures among older adults: a cohort study. *BMJ Open*. 2021;11(12):e052057. doi:10.1136/bmjopen-2021-052057
13. Guina J, Rossetter SR, DeRhodes BJ, et al. Benzodiazepines for PTSD: a systematic review and meta-analysis. *J Psychiatr Pract*. 2015;21(4):281-303.
14. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, et al. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*. 2014;348:g445. doi:10.1136/bmj.g445
15. Donovan LM, Malte CA, Spece LJ, et al. Center predictors of long-term benzodiazepine use in chronic obstructive

Bottom Line

The pharmacokinetics of benzodiazepines are intimately linked with the onset of action and duration of clinical effect and vary based on individual absorption and distribution/redistribution. Benzodiazepines' clinical profile derives from their pharmacokinetic differences and is influenced by many factors, including age, body weight, concomitant medication use, smoking status, and hepatic or renal disease. Consider these factors to individualize the approach to using benzodiazepines and optimize tolerability and efficacy.

- pulmonary disease and post-traumatic stress disorder. *Ann Am Thorac Soc.* 2019;16(9):1151-1157. doi:10.1513/AnnalsATS.201901-0480C
16. Sheehy O, Zhao JP, Bérard A. Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion. *JAMA Psychiatry.* 2019;76(9):948-957. doi:10.1001/jamapsychiatry.2019.0963
 17. Kelly LE, Poon S, Madadi P, et al. Neonatal benzodiazepines exposure during breastfeeding. *J Pediatr.* 2012;161(3):448-451. doi:10.1016/j.jpeds.2012.03.003
 18. Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States. *JAMA Netw Open.* 2019;2(1):e187399. doi:10.1001/jamanetworkopen.2018.7399
 19. Hirschtritt ME, Olfson M, Kroenke K. Balancing the risks and benefits of benzodiazepines. *JAMA.* 2021;325(4):347-348. doi:10.1001/jama.2020.22106
 20. Brunton LL, Hilal-Dandan R, Knollman BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics.* McGraw-Hill Education; 2018.
 21. Nutt DJ, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. *British J Psychiatry.* 2001;179:390-396. doi:10.1192/bjp.179.5.390
 22. Sigel E. Mapping of the benzodiazepine recognition site on GABA(A) receptors. *Curr Top Med Chem.* 2002;2(8):833-839. doi:10.2174/1568026023393444
 23. Savić MM, Huang S, Furtmüller R, et al. Are GABAA receptors containing alpha5 subunits contributing to the sedative properties of benzodiazepine site agonists? *Neuropsychopharmacology.* 2008;33(2):332-339. doi:10.1038/sj.npp.1301403
 24. Smith TA. Type A gamma-aminobutyric acid (GABAA) receptor subunits and benzodiazepine binding: significance to clinical syndromes and their treatment. *Br J Biomed Sci.* 2001;58(2):111-121.
 25. Althaus AL, Ackley MA, Belfort GM, et al. Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABAA receptor positive allosteric modulator. *Neuropharmacology.* 2020;181:108333. doi:10.1016/j.neuropharm.2020.108333
 26. Jacob TC, Michels G, Silayeva L, et al. Benzodiazepine treatment induces subtype-specific changes in GABA(A) receptor trafficking and decreases synaptic inhibition. *Proc Natl Acad Sci U S A.* 2012;109(45):18595-18600. doi:10.1073/pnas.1204994109
 27. Nicholson MW, Sweeney A, Pekle E, et al. Diazepam-induced loss of inhibitory synapses mediated by PLCδ/Ca2+/calcineurin signalling downstream of GABAA receptors. *Mol Psychiatry.* 2018;23(9):1851-1867. doi:10.1038/s41380-018-0100-y
 28. Dobson ET, Bloch MH, Strawn JR. Efficacy and tolerability of pharmacotherapy for pediatric anxiety disorders: a network meta-analysis. *J Clin Psychiatry.* 2019;80(1):17r12064. doi:10.4088/JCP.17r12064
 29. Kuang H, Johnson JA, Mulqueen JM, et al. The efficacy of benzodiazepines as acute anxiolytics in children: a meta-analysis. *Depress Anxiety.* 2017;34(10):888-896. doi:10.1002/da.22643
 30. Chugani DC, Muzik O, Juhász C, et al. Postnatal maturation of human GABAA receptors measured with positron emission tomography. *Ann Neurol.* 2001;49(5):618-626. doi:10.1002/ana.1003
 31. Jochemsen R, Breimer DD. Pharmacokinetics of benzodiazepines: metabolic pathways and plasma level profiles. *Curr Med Res Opin.* 1984;8(Suppl 4):60-79. doi:10.1185/03007998409109545
 32. Greenblatt DJ, Harmatz JS, Dorsey C, et al. Comparative single-dose kinetics and dynamics of lorazepam, alprazolam, prazepam, and placebo. *Clin Pharmacol Ther.* 1988;44(3):326-334. doi:10.1038/clpt.1988.158
 33. Shader RI, Georgotas A, Greenblatt DJ, et al. Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther.* 1978;24(3):308-315. doi:10.1002/cpt1978243308
 34. Greenblatt DJ, Allen MD, MacLaughlin DS, et al. Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther.* 1978;24(5):600-609. doi:10.1002/cpt1978245600
 35. Yamazaki A, Kumagai Y, Fujita T, et al. Different effects of light food on pharmacokinetics and pharmacodynamics of three benzodiazepines, quazepam, nitrazepam and diazepam. *J Clin Pharm Ther.* 2007;32(1):31-39. doi:10.1111/j.1365-2710.2007.00795.x
 36. Stimpf J, Mills JA, Strawn JR. Pharmacologic predictors of benzodiazepine response trajectory in anxiety disorders: a Bayesian hierarchical modeling meta-analysis. *CNS Spectr.* 2023;28(1):53-60. doi:10.1017/S1092852921000870
 37. Griffin CE 3rd, Kaye AM, Bueno FR, et al. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J.* 2013;13(2):214-223.
 38. Buffett-Jerrott SE, Stewart SH. Cognitive and sedative effects of benzodiazepine use. *Curr Pharm Des.* 2005;8(1):45-58. doi:10.2174/1381612023396654
 39. Fukasawa T, Suzuki A, Otani K. Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. *J Clin Pharm Ther.* 2007;32(4):333-341. doi:10.1111/j.1365-2710.2007.00829.x
 40. Kraus JW, Desmond PV, Marshall JP, et al. Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther.* 1978;24(4):411-419. doi:10.1002/cpt1978244411
 41. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet.* 1981;6(2):89-105. doi:10.2165/00003088-198106020-00001
 42. Walkenstein SS, Wiser R, Gudmundsen CH, et al. Absorption, metabolism, and excretion of oxazepam and its succinate half-ester. *J Pharm Sci.* 1964;53(10):1181-1186. doi:10.1002/jps.2600531010
 43. Shull HJ, Wilkinson GR, Johnson R, et al. Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med.* 1976;84(4):420-425. doi:10.7326/0003-4819-84-4-420
 44. Abernethy DR, Greenblatt DJ, Ochs HR, et al. Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther.* 1983;33(5):628-632. doi:10.1038/clpt.1983.85
 45. Greenblatt DJ, Allen MD, Harmatz JS, et al. Diazepam disposition determinants. *Clin Pharmacol Ther.* 1980;27(3):301-312. doi:10.1038/clpt.1980.40
 46. Ochs HR, Greenblatt DJ, Knüchel M. Kinetics of diazepam, midazolam, and lorazepam, in cigarette smokers. *Chest.* 1985;87(2):223-226. doi:10.1378/chest.87.2.223
 47. Smith RB, Gwilt PR, Wright CE 3rd. Single- and multiple-dose pharmacokinetics of oral alprazolam in healthy smoking and nonsmoking men. *Clin Pharm.* 1983;2(2):139-143.
 48. Figgitt DP, McClellan KJ. Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders. *Drugs.* 2000;60(4):925-954. doi:10.2165/00003495-200060040-00006
 49. Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam. Therapeutic implications. *Clin Pharmacokinet.* 1993;24(6):453-471. doi:10.2165/00003088-199324060-00003
 50. Yasui N, Kondo T, Furukori H, et al. Effects of repeated ingestion of grapefruit juice on the single and multiple oral-dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology (Berl).* 2000;150(2):185-190. doi:10.1007/s002130000438
 51. Özdemir M, Aktan Y, Boydağ BS, et al. Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet.* 1998;23(1):55-59. doi:10.1007/BF03189827
 52. Greenblatt DJ, Harmatz JS, Zhang Q, et al. Slow accumulation and elimination of diazepam and its active metabolite with extended treatment in the elderly. *J Clin Pharmacol.* 2021;61(2):193-203. doi:10.1002/jcph.1726
 53. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans: an update. *Clin Pharmacokinet.* 1986;11(3):199-213. doi:10.2165/00003088-198611030-00002
 54. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet.* 2010;49(2):71-87. doi:10.2165/11318100-000000000-00000
 55. Bauer LA. Drug Dosing in special populations: renal and hepatic disease, dialysis, heart failure, obesity, and drug interactions. In: Weitz M, Thomas, CM, eds. *Applied Clinical Pharmacokinetics.* 3rd ed. McGraw-Hill Education; 2014. <https://accesspharmacy.mhmedical.com/book.aspx?bookid=1374>
 56. Kendrick JG, Carr RR, Ensom MHH. Pharmacokinetics and drug dosing in obese children. *J Pediatr Pharmacol Ther.* 2010;15(2):94-109. doi:10.5863/1551-6776-15.2.94

Clinical Point

If rapid symptom relief is necessary, a lipophilic benzodiazepine may be preferred for quick onset and offset of action

57. Brill MJE, Diepstraten J, van Rongen A, et al. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet*. 2012;51(5):277-304. doi:10.2165/11599410-000000000-00000
58. Derry CL, Kroboth PD, Pittenger AL, et al. Pharmacokinetics and pharmacodynamics of triazolam after two intermittent doses in obese and normal-weight men. *J Clin Psychopharmacol*. 1995;15(3):197-205. doi:10.1097/00004714-199506000-00008
59. Abernethy DR, Greenblatt DJ, Divoll M, et al. The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. *Clin Pharmacokinet*. 1984;9(2):177-183. doi:10.2165/00003088-198409020-00005
60. Abernethy DR, Greenblatt DJ, Divoll M, et al. Prolonged accumulation of diazepam in obesity. *J Clin Pharmacol*. 1983;23(8-9):369-376. doi:10.1002/j.1552-4604.1983.tb02750.x
61. Abernethy DR, Greenblatt DJ, Divoll M, et al. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. *J Lab Clin Med*. 1983;101(6):873-880.
62. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Alprazolam pharmacokinetics, metabolism, and plasma levels: clinical implications. *J Clin Psychiatry*. 1993;54 Suppl:4-11.
63. Chen YT, Liu CY, Chang CM, et al. Perceptions, clinical characteristics, and other factors associated with prolonged and high daily dose of benzodiazepine use among patients with anxiety or depressive disorders. *J Affect Disord*. 2020;271:215-223. doi:10.1016/j.jad.2020.03.077
64. Herman JB, Brotman AW, Rosenbaum JF. Rebound anxiety in panic disorder patients treated with shorter-acting benzodiazepines. *J Clin Psychiatry*. 1987;48(Suppl): 22-28.
65. Herman JB, Rosenbaum JF, Brotman AW. The alprazolam to clonazepam switch for the treatment of panic disorder. *J Clin Psychopharmacol*. 1987;7(3):175-178.

Clinical Point

Before prescribing a benzodiazepine, consider the patient's age, body weight, concomitant medication use, and smoking status