Benzodiazepines

Summary

- Benzodiazepines, as a class, have been among the most commonly prescribed of all drugs, with a wide variety of indications, including insomnia, anxiety disorders, seizure disorders, anesthesia and peri-procedural sedation, skeletal muscle relaxation, and alcohol withdrawal.
- Some benzodiazepines, such as lorazepam and diazepam, are used across most of the possible indications, whereas others are much more limited in their usage (e.g., clobazam is an orphan drug indicated only for the treatment of seizures associated with Lennox-Gastaut syndrome).
- Within the class, individual drugs are differentiated primarily by their diverse pharmacokinetic profiles, which reflect large differences in half-life (long-acting, intermediate-acting, and short-acting), onset of action (rapid, intermediate, or slow), and metabolic outcomes (with or without active metabolites).
- The pharmacokinetic profile is a major factor in determining the indications that are suitable to each particular benzodiazepine; for example, temazepam, with an intermediate onset of action, a 6- to 8-hour duration of action, and no active metabolites, is indicated exclusively for insomnia.
- Physiologic dependence, which is accompanied by physical withdrawal symptoms, occurs as a natural consequence of regular use of therapeutic doses of benzodiazepines, without any drug misuse or abuse.
- Psychological dependence is possible; therefore, this class of drugs is best avoided in patients with a history of substance abuse.

Pharmacology

Benzodiazepines act at the level of the limbic, thalamic, and hypothalamic regions of the CNS and can produce any level of CNS depression required, including sedation, hypnosis, skeletal muscle relaxation, and anticonvulsant activity. Extensive evidence indicates that benzodiazepines exert their effects through enhancement of the GABA-benzodiazepine receptor complex. GABA is an inhibitory neurotransmitter that exerts its effects at specific receptor subtypes designated GABA-A and GABA-B. GABA-A is the primary receptor subtype in the CNS and is the primary site of benzodiazepine pharmacodynamic activity.[65276]

Specific benzodiazepine receptor subtypes are thought to be coupled to GABA-A receptors. Three types of benzodiazepine receptors are located in the CNS and other tissues: the BNZ-1 receptors are located in the cerebellum and cerebral cortex, the BNZ-2 receptors in the cerebral cortex and spinal cord, and the BNZ-3 receptors in peripheral tissues. Activation of the BNZ-1 receptor is thought to mediate sleep while the BNZ-2 receptor affects muscle relaxation, anticonvulsant activity, motor coordination, and memory. Benzodiazepines bind nonspecifically to BNZ-1 and BNZ-2, which ultimately enhances the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site opens the chloride channel resulting in a hyperpolarized cell membrane that prevents further excitation of the cell.[50829]

Although benzodiazepines are typically subdivided into short, intermediate, and long half-life agents, the pharmacokinetics of benzodiazepines are more complex. Some benzodiazepines have active metabolites whose pharmacokinetic properties need to be incorporated in the overall evaluation of the parent drug. In addition, benzodiazepines have a 2-compartment pharmacokinetic model of distribution, with a rapid central compartment phase followed by a redistribution phase, primarily to adipose tissue, which ultimately determines the duration of action. One consequence of this model is that lipophilic benzodiazepines, such as diazepam and chlordiazepoxide, are stored in adipose tissue and have extremely long half-lives. A second consequence, however, is that a single dose of a less lipophilic benzodiazepine, such as lorazepam, will remain at therapeutic concentrations at GABA-A receptors longer than the more highly lipophilic compounds that redistribute rapidly to adipose tissue.[50830]

Comparison of Benzodiazepine Pharmacology

Drug	Onset	Duration	Metabolic Pathway	Metabolites
Alprazolam	Rapid	Short	Oxidative via CYP3A4	Minimally active
Chlordiazepoxide	Intermediate	Long	Oxidative via CYP3A4	Active
Clobazam	Slow	Long	Oxidative via CYP3A4 (primary), CYP2C19, and CYP2B6	Active
Clonazepam	Rapid	Intermediate	Oxidative via CYP3A4	Inactive
Clorazepate*	Intermediate	Long	Hydroxylation and glucuronidation	Active
Diazepam	Rapid	Long	Demethylation and hydroxylation via CYP3A4 and CYP2C19	Active
Estazolam	Intermediate	Intermediate	Oxidative via CYP3A4	Minimally active
Flurazepam	Rapid	Long	Oxidative via CYP3A4	Active
Lorazepam	Rapid	Intermediate	Glucuronidation	Inactive
Midazolam	Rapid	Short	Hydroxylation via CYP3A4	Active
Oxazepam	Slow	Intermediate	Glucuronidation	Inactive
Quazepam	Intermediate	Long	Partial CYP3A4	Active
Temazepam	Intermediate	Intermediate	Glucuronidation	Inactive
Triazolam	Rapid	Short	Oxidative via CYP3A4	Inactive

*Pro-drug which is converted to an active moiety

Comparative Efficacy

Summary

- Alprazolam has not been shown in clinical trials to be superior to comparator benzodiazepines in the treatment of panic disorder, with or without agoraphobia; but it has been associated with high rates of rebound anxiety, withdrawal symptoms, and a propensity for abuse.[48980]
- In a systematic review, intravenous (IV) lorazepam was found to be equivalent in efficacy to IV diazepam and safer; children receiving IV lorazepam had less respiratory depression, fewer admissions to pediatric intensive care unit (ICU), and were less likely to need additional anticonvulsant medication to terminate seizures.[20445]
- A meta-analysis of 6 studies comparing midazolam to diazepam found that midazolam by any route was superior to diazepam for seizure cessation and comparable to IV diazepam for seizure control. [48984]

Comparative Efficacy Trials

Citation	Design/Regimen	Results*	Conclusion
Martin JL, et al. J Psychopharmacol .2007;21:774-782 [41814]	Systematic review and metaanalysis of double-blind, randomized placebo-controlled studies of diazepam (12 trials), lorazepam (7 trials), or alprazolam (4 trials) vs placebo for the treatment of GAD in adults. Duration mode, 4 weeks; 1 study > 8 weeks. n = 1189, benzodiazepine; N=1137, placebo.	**All-cause withdrawal:** RR drug/placebo): 0.78 (95% CI, 0.62 to 1; p = 0.05) **Withdrawal due to lack of efficacy:** RR 0.29 (95% CI, 0.18 to 0.45; p < 0.00001) **Withdrawal due to adverse events:** RR 1.54 (95% CI, 1.17 to 2.03; p < 0.002)	Benzodiazepines are efficacious in the short-term treatment of GAD in clinical trials (as measured by relative risk of withdrawal due to lack of efficacy), but the evidence for effectiveness (as measured by all-cause withdrawal rates) is weaker Comparison between benzodiazepines not meaningful due to study heterogeneity

Moylan S, et al. J Clin Psychopharmacol. 2011;31:647-652 [48980]	Meta-analysis of single- or double-blind, randomized controlled studies of alprazolam vs another benzodiazepine for treatment of panic disorder (DSM-III or DSM-IV) in adults. A total of 8 trials included, n = 631.	**Mean change in panic attack frequency/week(alprazolam - comparator):** 0.6 (95% CI, 0.3 to 1.6) **Mean change in HAM-A (alprazolam - comparator):** 0.8 points (95% CI, 0.5 to 2.1) **Proportion of panic attack-free patients (pooled relative risk, alprazolam vs comparator):** 1.1 (95% CI, 0.9 to 1.4)	The evidence indicates that alprazolam is not superior to other benzodiazepines for the treatment of panic disorder
Amato L, et al. Cochrane Database Syst Rev. 2010(3):CD005063 [48983]	Meta-analysis of randomized controlled trials evaluating benzodiazepines in comparison with placebo, another benzodiazepine, or other drugs in the treatment of alcohol withdrawal. Total of 64 studies, n = 4,309.	**Seizures** Benzodiazepine vs placebo, RR = 0.16 (95% CI, 0.04 to 0.69; p = 0.01) Benzodiazepine vs other drug, RR = 0.52 (95% CI, 0.21 to 1.31) **AEs** Benzodiazepine vs other drug, RR = 1.31 (95% CI, 0.99 to 1.72) **Dropouts** Benzodiazepine vs other drug, RR = 0.93 (95% CI, 0.70 to 1.24) All comparisons of one benzodiazepine to another on all outcome measures were nonsignificant	Benzodiazepine treatment of alcohol withdrawal is highly effective in preventing seizures (vs placebo) and is equivalent to other drugs for most outcome measures; no significant differences noted between benzodiazepines
Appleton R, et al. Cochrane Database Syst Rev. 2008(3):CD001905 [20445]	Systematic review of studies of treatment of tonic-clonic convulsions and status epilepticus in children; only 4 studies met inclusion criteria, only 1 compared IV diazepam with IV lorazepam.	**Seizure cessation, IV lorazepam vs IV diazepam:** RR = 1.09 (95% CI, 0.77 to 1.54) **Seizure recurrence, IV lorazepam vs IV diazepam:** RR = 0.63 (95% CI, 0.27 to 1.46) **Respiratory depression, IV lorazepam vs IV diazepam:** RR = 0.18 (95% CI, 0.02 to 1.37)	IV lorazepam is equivalent in efficacy and appears to produce less respiratory depression than IV diazepam for the treatment of acute tonic-clonic convulsions/status epilepticus in children

McMullan J, et al. Acad Emerg Med.2010;17:575-582 [48984]	Meta-analysis studies comparing non-IV midazolam with diazepam (IV or non-IV) in treatment of status epilepticus in children and young adults. Six studies included, n = 774.	**Seizure cessation failure, diazepam (any route) vs midazolam (any route):** RR 1.52 (95% CI, 1.27 to 1.82; p < 0.00001) **Time to seizure cessation, mean difference,IV diazepam vs non-IV midazolam:** 0.68 minutes (95% CI, -0.03 to 1.39) **Respiratory complicationsdiazepam (any route) vs midazolam (any route):** RR 1.49; 95% CI, 0.25 to 8.72)	Non-IV midazolam is at least as safe and effective as non-IV or IV diazepam for the treatment of status epilepticus in children

Abbreviations: AEs, adverse events; DSM, *Diagnostic and Statistical Manual*; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; IV, intravenous; RR, relative risk.

*p-value only shown if significant

Drug Interactions

CNS depressants, including Alcohol and Opioids

A boxed warning in the labels for all benzodiazepines warns about the risks of coadministration of benzodiazepines and opioids. Concomitant use of benzodiazepines and opioids increases the risk of respiratory depression, low blood pressure, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and prescription durations to the minimum required, and monitor patients for signs and symptoms of respiratory depression and sedation.[61143]

Concomitant administration of benzodiazepines with other CNS depressant drugs, including alcohol, also generally produces additive CNS depressant effects. Patients should be advised to avoid ingestion of alcoholic beverages during treatment with a benzodiazepine. In addition to alcohol, medications such as psychotropic medications, anticonvulsants, sedating antihistamines, and many other medications that produce CNS sedation may have additive effects with the benzodiazepines.[62827]

Drugs that inhibit or induce CYP 450 isozymes

Many benzodiazepines are metabolized by CYP450 enzymes, particularly CYP3A4 and/or CYP2C19, and may require dosing adjustments when prescribed to patients receiving inhibitors or inducers of the relevant CYP450 enzymes for that benzodiazepine. For example, triazolam is a sensitive CYP3A4 substrate, and coadministration with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, nefazodone, lopinavir, ritonavir) is contraindicated. Dose reductions of up to 50% may be required when alprazolam, a CYP3A4 substrate, is given concomitantly with CYP3A4 inhibitors. Dosage reductions of

clobazam, a CYP2C19 substrate, may be required when used concomitantly with CYP2C19 inhibitors. Diazepam is also a moderately sensitive CYP2C19 substrate. Increased monitoring of benzodiazepines metabolized by CYP450 enzymes is recommended when used with CYP450 inhibitors or inducers. [41538][41543][46370][56579]

Grapefruit juice

Grapefruit juice is a clinically significant inhibitor of CYP3A4. Benzodiazepines that are metabolized by CYP3A4 include midazolam, diazepam, and triazolam. The drug concentrations of the benzodiazepine may increase when consuming grapefruit juice. Consideration should be given to not drinking grapefruit juice when taking these medications. Also, alprazolam is metabolized by CYP3A4 but does not appear to be affected by grapefruit juice.[28040][30935][44717][41543][53391]

Oral contraceptives

Oral contraceptives and other moderate to weak CYP450 inhibitors may increase concentrations of benzodiazepines metabolized via oxidative metabolism. Oral contraceptives also increase glucuronidation, which may decrease concentrations of benzodiazepines metabolized by glucuronidation.[30723][41538]

Appendix A

Therapeutic Use Table

Indications	Alprazolam	Chlordiazepoxide Hydrochloride	Clobazam	Clonazepam	Clorazepate Dipotassium	Diazepam	Estazolam	Flurazepam Hydrochloride	Lorazepam	Midazolam Hydrochloride	Oxazepam	Quazepam	Temazepam	Triazolam
Renal Impairment Dosing Adjustment		Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes		Yes		
Hepatic Impairment Dosing Adjustment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes
absence seizures				Yes										
agitation									Yes †	Yes †				
alcohol withdrawal		Yes			Yes	Yes			Yes †	Yes †	Yes			
amnesia induction						Yes			Yes	Yes				
anxiety	Yes	Yes			Yes	Yes		Yes †	Yes	Yes	Yes			
benzodiazepine withdrawal						Yes †								
general anesthesia induction										Yes				
general anesthesia maintenance										Yes				
generalized anxiety disorder (GAD)	Yes				Yes		Yes †							
insomnia				Yes †		Yes †	Yes	Yes	Yes		Yes †	Yes	Yes	Yes
Lennox-Gastaut syndrome			Yes	Yes										
muscle spasm						Yes								
myoclonic seizures				Yes										
panic disorder	Yes			Yes										
partial seizures					Yes	Yes								
rapid-sequence intubation										Yes †				
sedation induction									Yes					

sedation maintenance									Yes †	Yes				
seizure prophylaxis									Yes †					
status epilepticus						Yes			Yes	Yes †				
tetanus						Yes								
tonic-clonic seizures						Yes								

Yes – Labeled

Yes † – Off-label

Appendix B

Top 20 Adverse Reactions / Side Effects Table

Adverse Reaction / Side Effect	Alprazolam	Chlordiazepoxide Hydrochloride	Clobazam	Clonazepam	Clorazepate Dipotassium	Diazepam	Estazolam	Flurazepam Hydrochloride	Lorazepam	Midazolam Hydrochloride	Oxazepam	Quazepam	Temazepam	Triazolam
appetite stimulation	7 - 32.7%		2 - 5%	0.1 - 1%		32.1%	0.1 - 1%							
ataxia	7.2%	1 - 10%	2 - 10%	1 - 30%	Reported	2 - 5%	<0.1%	1 - 10%	0.1 - 1%	<1%	<1%	Reported	0.5 - 0.9%	4.6%
constipation	8.1 - 26.2%	<1%	2 - 10%	<5%		Reported	>1%	<1%	Reported			Reported		<0.5%
dizziness	1.8 - 29.8%			5 - 12%	1 - 10%	2 - 5%	7%	1 - 10%	6.9%	<1%	1 - 10%	1.5%	4.5%	7.8%
drowsiness	23 - 76.8%	>10%	16 - 25%	26 - 50%	>10%	23 - 84%	42%	>10%	1.5 - 15.9%	1.2 - 10%	>10%	12%	9.1%	14%
dysarthria	10.9 - 23.3%	1 - 10%	2 - 5%	3 - 4%	Reported	1 - 32.1%		Reported	Reported	<2%		Reported		Reported
fatigue	13.9 - 48.6%		3 - 5%	6 - 9%	Reported	56.8%		>10%	Reported			1.9%	4.8%	0.5 - 0.9%
fever	0.1 - 0.9%		10 - 17%	0.1 - 1%			0.1 - 1%							
impaired cognition	7.2 - 28.8%						Reported							
libido decrease	6 - 14.4%	Reported		<3%		18.5%	<0.1%		Reported			Reported		
libido increase	1 - 7.7%	Reported		0.1 - 1%		18.5%			Reported					
memory impairment	5.5 - 33.1%	Reported		2 - 5%	Reported	39.5%	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
menstrual irregularity	10.4%	Reported		0.1 - 1%	Reported	18.4%								Reported
nausea	6 - 22%	1 - 10%		Reported		Reported		1 - 10%	<1%	1.5 - 2.8%	<1%	Reported	<1%	4.6%
respiratory depression		Reported	Reported	Reported	Reported	9%	Reported	Reported	Reported	8 - 23.3%	Reported	Reported	Reported	Reported
urinary incontinence	0.1 - 0.9%	Reported		0.1 - 1%	Reported	17.3%	<0.1%		Reported			Reported		Reported
urinary retention		Reported	Reported	0.1 - 1%	Reported	17.3%	0.1 - 1%							Reported
weight gain	2.7 - 27.2%			0.1 - 1%		23.5%	<0.1%							
weight loss	2.3 - 22.6%			0.1 - 1%		12.3%	<0.1%							
withdrawal	10 - 35%	>10%	Reported	Reported	>10%	Reported	>10%	>10%	Reported	Reported	>10%	Reported	>10%	>10%

Appendix C

Safety Issues Table

Safety Issue	Alprazolam	Chlordiazepoxide Hydrochloride	Clobazam	Clonazepam	Clorazepate Dipotassium	Diazepam	Estazolam	Flurazepam Hydrochloride	Lorazepam	Midazolam Hydrochloride	Oxazepam	Quazepam	Temazepam	Triazolam
REMS														
MedGuide	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes
benzodiazepine hypersensitivity	X			X					X			X		X
benzyl alcohol hypersensitivity									X					
closed-angle glaucoma	X			X	X	X			X	X				
coadministration with other CNS depressants	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW	BBW
epidural administration										X				
hepatic disease				X		X								
hypotension										BBW				
infants						X								
intraarterial administration									X					
intrathecal administration										X				
myasthenia gravis						X								
neonates						X				BBW				
pregnancy							X	X					X	
premature neonates									X					
requires a specialized care setting										BBW				
requires an experienced clinician										BBW				
respiratory depression			BBW							BBW		X		
respiratory insufficiency						X						X		
seizures										BBW				
sleep apnea						X			X			X		

X – Contraindicated
X-BBW – Contraindicated and Black Box Warning
BBW – Black Box Warning, Not Contraindicated
Yes – REMS or MedGuide is available