

Benzodiazepines

Positive allosteric modulators at the GABA-A receptor that produce anxiolysis, sedation, muscle relaxation, anticonvulsant activity and amnesia, learned most usefully by duration of action, because that is what decides which agent suits which indication and how much trouble it causes on stopping.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/benzodiazepines>

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Quick revision

One Liner: Benzodiazepines make an existing inhibitory signal larger rather than creating one, which explains both their broad usefulness and the dependence, withdrawal and falls that dominate their modern labelling.

1. Every current benzodiazepine label carries one shared boxed warning covering three hazards: concomitant opioid use, abuse and addiction, and dependence with withdrawal reactions. [1][2][6]
2. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. [1]
3. Abrupt discontinuation or rapid dosage reduction after continued use may precipitate acute withdrawal reactions, which can be life-threatening. [7]
4. They are positive allosteric modulators at the GABA-A receptor and raise how often the chloride channel opens; barbiturates instead lengthen how long each opening lasts. [12]
5. Duration organises the class: midazolam is short acting with a mean elimination half-life of about three hours, while diazepam is long acting through a metabolite whose terminal half-life reaches up to 100 hours. [4][1]
6. Lorazepam, oxazepam and temazepam are cleared by conjugation to inactive glucuronides rather than by cytochrome P450 oxidation to an active metabolite. [2][8][7]
7. Flumazenil competitively blocks the benzodiazepine recognition site, but its boxed warning reports seizures, so it is not a routine reversal agent. [11]
8. Up to 30% of clonazepam responders lose anticonvulsant activity, often within three months of starting it. [6]
9. Older people are at higher risk of falls on these medicines, and pooled observational data put the hip-fracture risk at RR 1.52 during benzodiazepine use. [7][14]
10. Alprazolam is contraindicated alongside strong CYP3A inhibitors such as the azole antifungal agents, with the exception of ritonavir. [5]

Overview

1. Benzodiazepines act on the brain's principal inhibitory system. The diazepam label describes the group as exerting anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnestic effects, most of which are thought to result from facilitation of the action of gamma aminobutyric acid, an inhibitory neurotransmitter in the central nervous system. The alprazolam label is more specific still, attributing the effect to binding at the benzodiazepine site of GABA-A receptors with enhancement of GABA-mediated synaptic inhibition. Those five effects are not separate drugs doing separate things; they are one pharmacological action read out in five different circuits. [1][5]
2. What then distinguishes one member from another is almost entirely kinetics. A drug whose effect has faded within hours suits an endoscopy list; one that lingers for days suits alcohol withdrawal or a seizure disorder, and is a liability in an eighty-year-old. Midazolam has a mean elimination half-life of roughly three hours, alprazolam about 11.2 hours, and clonazepam typically 30 to 40 hours; diazepam is longer still because N-demethylation yields N-desmethyldiazepam, whose terminal half-life runs to 100 hours. Flurazepam shows the same trick in reverse, with a parent half-life of 2.3 hours but a desalkyl metabolite eliminated over 47 to 100 hours that plateaus only after seven to ten days of dosing. [4][5][6][1][10]

3. The regulatory picture has hardened considerably. United States labels across the class now open with a single boxed warning covering opioid co-prescription, abuse and addiction, and dependence and withdrawal, and in January 2026 the MHRA required United Kingdom packaging and leaflets to carry a warning that these medicines may cause addiction, dependence, and withdrawal reactions. Alongside that sits the geriatric problem: labels warn that patients, particularly older ones, are at higher risk of falls, and a meta-analysis of observational studies found a relative risk of hip fracture of 1.52 in benzodiazepine users, rising to 2.40 in newly prescribed users. [1][13][7][14]

Classification and drug examples

Intro: Grouped by duration of action, because half-life and the presence or absence of a long-lived active metabolite predict the indication a drug fits, the accumulation risk in older or hepatically impaired patients, and how difficult withdrawal will be. The antagonist is listed separately since it belongs to the same receptor story.

1. Name: Short-acting agents

1. Note: Cleared quickly enough that the effect is over within a procedure or a shift. Used where a defined, brief period of sedation is wanted and recovery matters.

Name: Midazolam

Route: Intravenous and intramuscular

Note: Described in its label as a short-acting benzodiazepine central nervous system depressant, with an elimination half-life of 1.8 to 6.4 hours and biotransformation mediated by cytochrome P450-3A4. Its boxed warning centres on respiratory depression and respiratory arrest in noncritical care settings. [4] [4]

2. Name: Intermediate-acting agents

2. Note: Half-lives of roughly eight to twenty-four hours with no long-lived active metabolite. This is where most oral anxiolytic and hypnotic prescribing sits.

1. Name: Alprazolam

Xanax

1. Route: Oral

1. Note: Mean plasma elimination half-life approximately 11.2 hours, extensively metabolised by CYP3A4 to two major active metabolites, 4-hydroxyalprazolam and alpha-hydroxyalprazolam. That CYP3A dependence is why strong inhibitors of the enzyme are a contraindication. [5]

2. Name: Lorazepam

Ativan

2. Route: Oral and parenteral

2. Note: Rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide, which is then excreted in the urine and has no demonstrable central nervous system activity in animals. Unconjugated lorazepam has a mean plasma half-life of about 12 hours. [2]

3. Name: Temazepam

Restoril

3. Route: Oral

3. Note: Completely metabolised through conjugation before excretion, with the O-conjugate accounting for 90% of the metabolite recovered and a mean terminal half-life of 8.8 hours. Licensed only for short-term insomnia. [7]

4. Name: Oxazepam

4. Route: Oral

4. Note: Its label records a single major inactive metabolite in man, a glucuronide excreted in the urine, and a mean elimination half-life of approximately 8.2 hours. It is also the active metabolite of several longer-acting members of the class. [8]

5. Name: Estazolam

ProSom

5. Route: Oral

5. Note: A triazolobenzodiazepine hypnotic whose mean elimination half-life estimates range from 10 to 24 hours. Its label warns that because sedative-hypnotics cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls. [9] [5][2]

3. Name: Long-acting agents

3. Note: Either a long parent half-life or an active metabolite that outlives the parent by days. Accumulation on repeated dosing is the defining risk, and the smooth self-taper is the defining benefit.

1. Name: Diazepam

Valium

1. Route: Oral and parenteral

1. Note: N-demethylated by CYP3A4 and CYP2C19 to the active metabolite N-desmethyldiazepam and hydroxylated by CYP3A4 to temazepam, itself an active drug. The terminal elimination half-life of N-desmethyldiazepam is up to 100 hours. [1]

2. Name: Clonazepam

Klonopin

2. Route: Oral

2. Note: Elimination half-life typically 30 to 40 hours, highly metabolised, with less than 2% of unchanged drug appearing in the urine. Licensed for defined seizure syndromes as well as for panic disorder. [6]

3. Name: Flurazepam

Dalmane

3. Route: Oral

3. Note: The parent has a harmonic mean apparent half-life of only 2.3 hours, but the major blood metabolite N1-desalkyl-flurazepam is eliminated over 47 to 100 hours and reaches plateau levels only after seven to ten days of dosing. Staggering and falling have been reported, particularly in geriatric patients. [10] [1][6]

4. Name: The competitive antagonist

4. Note: One agent, included because it defines the receptor site the whole class occupies and because its hazards are examined as often as its use.

Name: Flumazenil

Romazicon

Route: Intravenous

Note: An imidazobenzodiazepine derivative that competitively inhibits activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Its boxed warning reports that its use has been associated with the occurrence of seizures. [11] [11]

Mechanism of action

Summary: Benzodiazepines bind a site on the GABA-A receptor complex that is distinct from the GABA site itself and increase the receptor's response to GABA. Because they modulate rather than open the channel directly, their effect is proportional to inhibitory traffic already present. The examinable contrast is with the barbiturates, which act on the same receptor but change a different property of the channel.

Target: The benzodiazepine recognition site on the GABA-A receptor complex

Cidal Static: Symptom-suppressing rather than disease-modifying

Kill Kinetics: Effect tracks plasma concentration of the parent drug and of any active metabolite

1. Step: 1

1. Title: Binding at the benzodiazepine site of the GABA-A receptor

1. Detail: Alprazolam is described in its label as acting through binding to the benzodiazepine site of gamma-aminobutyric acid-A receptors in the brain and enhancing GABA-mediated synaptic inhibition. The lorazepam injection label puts the same idea differently, stating that lorazepam interacts with the GABA-benzodiazepine receptor complex and that attachment to the specific binding site enhances the affinity of GABA for its receptor site. [5][3]

2. Step: 2

2. Title: Positive allosteric modulation raises the frequency of chloride channel opening

2. Detail: A positive allosteric modulator increases the frequency with which the chloride channel opens when an agonist binds to its own site on the GABA receptor. This is the property that separates the group from the barbiturates, which instead increase the time chloride channels remain open. The frequency-versus-duration distinction is sourced here to a StatPearls review of GABA receptor positive allosteric modulators rather than to any product label, because the labels do not describe channel gating at all. [12]

3. Step: 3

3. Title: Greater chloride influx hyperpolarises the neuron and reduces firing

3. Detail: The increased opening frequency facilitates the GABA-A receptor potential and reduces neuronal firing. Nothing happens without GABA present, since the drug amplifies an existing signal rather than generating one, which is the pharmacological basis for the class being modulators rather than direct agonists. [12]

4. Step: 4

4. Title: One receptor action, five clinical readouts

4. Detail: The diazepam label lists anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnestic effects and attributes most of them to facilitation of GABA. This is why the same molecule can be used for an anxiety disorder, for skeletal muscle spasm and adjunctively in convulsive disorders, and why amnesia turns up as an adverse effect in one setting and a licensed purpose in another. [1][4]

5. Step: 5

5. Title: Competitive antagonism at the same recognition site

5. Detail: Flumazenil, an imidazobenzodiazepine derivative, antagonises the actions of benzodiazepines on the central nervous system by competitively inhibiting activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. That competition is what makes reversal possible, and also what makes abrupt reversal dangerous in someone whose nervous system has adapted to chronic occupancy of that site. [11]

Major clinical uses

1. Drug: Alprazolam

1. Organism: Not applicable

1. Indication: Acute treatment of generalised anxiety disorder, and panic disorder with or without agoraphobia, in adults

1. Line: short-term

1. Note: The label frames the anxiety indication as acute treatment rather than maintenance, which matches the class-wide push away from open-ended prescribing. [5]

2. Drug: Clonazepam

2. Organism: Not applicable

2. Indication: Lennox-Gastaut syndrome, akinetic and myoclonic seizures, and panic disorder

2. Line: alone or adjunctive

2. Note: Its label describes it as useful alone or as an adjunct in Lennox-Gastaut syndrome, and separately indicates it for panic disorder with or without agoraphobia. Efficacy in seizures is not durable in everyone, and abrupt withdrawal in long-term high-dose therapy can precipitate seizures. [6]

3. Drug: Lorazepam injection

3. Organism: Not applicable

3. Indication: Status epilepticus, and preanaesthetic medication

3. Line: first line for the acute seizure

3. Note: The label names respiratory depression as the most important risk in this setting, directs that airway patency be assured and respiration monitored closely, and requires equipment to maintain a patent airway to be immediately available before intravenous administration. [3]

4. Drug: Midazolam

4. Organism: Not applicable

4. Indication: Sedation, anxiolysis and amnesia before or during diagnostic, therapeutic or endoscopic procedures; induction of general anaesthesia; sedation of ventilated patients

4. Line: standard for procedural sedation

4. Note: The amnestic component is part of the point rather than a side effect. Its boxed warning requires immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag, valve and mask ventilation and intubation, with personnel trained in their use and skilled in airway management. [4]

5. Drug: Diazepam

5. Organism: Not applicable

5. Indication: Anxiety disorders, acute alcohol withdrawal, skeletal muscle spasm, and convulsive disorders adjunctively

5. Line: established

5. Note: Its label states that oral diazepam may be used adjunctively in convulsive disorders although it has not proved useful as the sole therapy, and that in acute alcohol withdrawal it may help symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. [1]

6. Drug: Temazepam

6. Organism: Not applicable

6. Indication: Short-term treatment of insomnia

6. Line: short-term hypnotic

6. Note: Licensed for the short-term treatment of insomnia, generally seven to ten days, an unusually explicit duration limit written into the indication itself. [7]

7. Drug: Oxazepam

7. Organism: Not applicable

7. Indication: Anxiety disorders, and anxiety and tremulousness associated with alcohol withdrawal

7. Line: established

7. Note: The label reports that alcoholics with acute tremulousness, inebriation, or with anxiety associated with alcohol withdrawal are responsive to therapy, and describes it as particularly useful for anxiety, tension, agitation and irritability in older patients. [8]

8. Drug: Estazolam

8. Organism: Not applicable

8. Indication: Short-term management of insomnia with difficulty falling asleep, frequent nocturnal awakenings or early morning awakening

8. Line: short-term hypnotic

8. Note: One of the few hypnotic labels in this class to describe the specific sleep complaints it addresses rather than insomnia in general. [9]

9. Drug: Flumazenil

9. Organism: Not applicable

9. Indication: Reversal of sedation after general anaesthesia or conscious sedation, and management of benzodiazepine overdose

9. Line: selective, not routine

9. Note: A licensed indication is not the same as a default action. The seizure risk in its boxed warning, and the requirement to watch for resedation for up to 120 minutes afterwards, are why supportive care rather than reversal is the usual approach in an undifferentiated overdose. [11]

Pharmacokinetics

1. Drug: Midazolam

1. Route: Intravenous and intramuscular

1. Absorption: Parenteral

1. Csf Penetration: Not applicable
1. Metabolism: Biotransformation mediated by cytochrome P450-3A4
1. Elimination: Hepatic; 60% to 70% of biotransformation products is 1-hydroxy-midazolam
1. Half Life: 1.8 to 6.4 hours, mean approximately 3 hours
1. Dose Adjust: Short duration is the reason it suits a discrete procedure; CYP3A4 dependence makes it vulnerable to enzyme inhibition [4]
2. Drug: Alprazolam
2. Route: Oral
2. Absorption: Peak plasma concentration 1 to 2 hours after a dose
2. Csf Penetration: Not applicable
2. Metabolism: Extensively metabolised, primarily by CYP3A4
2. Elimination: Hepatic, to 4-hydroxyalprazolam and alpha-hydroxyalprazolam
2. Half Life: Approximately 11.2 hours, range 6.3 to 26.9 hours
2. Dose Adjust: Contraindicated with strong CYP3A inhibitors other than ritonavir; reduction is directed in geriatric patients [5]
3. Drug: Lorazepam
3. Route: Oral and parenteral
3. Absorption: Oral
3. Csf Penetration: Not applicable
3. Metabolism: Rapid conjugation at the 3-hydroxy group to lorazepam glucuronide
3. Elimination: Urinary excretion of the glucuronide, which has no demonstrable central nervous system activity in animals
3. Half Life: About 12 hours for unconjugated drug, about 18 hours for the glucuronide
3. Dose Adjust: Age does not appear to have a significant effect on lorazepam kinetics, but lower doses may be sufficient in severe hepatic insufficiency [2]
4. Drug: Oxazepam
4. Route: Oral
4. Absorption: Peak plasma levels at about 3 hours
4. Csf Penetration: Not applicable
4. Metabolism: Glucuronide conjugation
4. Elimination: A single major inactive metabolite, a glucuronide excreted in the urine
4. Half Life: Mean elimination half-life approximately 8.2 hours
4. Dose Adjust: Cautious dosing at the lower end of the range is directed for older patients [8]
5. Drug: Temazepam
5. Route: Oral
5. Absorption: Oral
5. Csf Penetration: Not applicable
5. Metabolism: Completely metabolised through conjugation before excretion
5. Elimination: 80% to 90% of the dose appears in the urine, the major metabolite being the O-conjugate
5. Half Life: Terminal half-life 3.5 to 18.4 hours, mean 8.8 hours
5. Dose Adjust: Licensed duration is itself limited, generally to seven to ten days [7]
6. Drug: Estazolam
6. Route: Oral
6. Absorption: Oral
6. Csf Penetration: Not applicable
6. Metabolism: Hepatic
6. Elimination: Hepatic

6. Half Life: Mean elimination half-life estimates from 10 to 24 hours
6. Dose Adjust: Older patients are identified in the label as being at higher risk of falls [9]
7. Drug: Diazepam
7. Route: Oral and parenteral
7. Absorption: Oral
7. Csf Penetration: Not applicable
7. Metabolism: N-demethylation by CYP3A4 and CYP2C19; hydroxylation by CYP3A4
7. Elimination: Hepatic, to the active metabolites N-desmethyldiazepam and temazepam
7. Half Life: Terminal elimination half-life of N-desmethyldiazepam up to 100 hours
7. Dose Adjust: Smallest effective amount is directed in elderly and debilitated patients to preclude ataxia or oversedation [1]
8. Drug: Clonazepam
8. Route: Oral
8. Absorption: Oral
8. Csf Penetration: Not applicable
8. Metabolism: Highly metabolised
8. Elimination: Less than 2% appears in urine as unchanged clonazepam
8. Half Life: Typically 30 to 40 hours
8. Dose Adjust: The long half-life smooths withdrawal but means several days pass before a change reaches steady state [6]
9. Drug: Flurazepam
9. Route: Oral
9. Absorption: Oral
9. Csf Penetration: Not applicable
9. Metabolism: Converted to N1-desalkyl-flurazepam, the major metabolite in blood
9. Elimination: Renal and hepatic
9. Half Life: Parent 2.3 hours; N1-desalkyl-flurazepam 47 to 100 hours
9. Dose Adjust: Metabolite plateau is reached only after seven to ten days, at 5 to 6 times the levels seen on day one [10]
1. No dose regimens appear on this page. Choosing an agent, deciding how long it should continue and planning any taper belong to the treating clinician working from a current prescribing reference and the individual patient's circumstances.
2. The single most useful kinetic split in the class is between agents cleared by conjugation alone and those requiring cytochrome oxidation first. Lorazepam, oxazepam and temazepam sit in the first group, each producing an inactive conjugate; diazepam, alprazolam and midazolam sit in the second, and their exposure moves when CYP3A activity does. [2][8][7][1][5][4]
3. A short parent half-life does not guarantee a short effect. Flurazepam is the standing counterexample, since the drug itself is gone within hours while its desalkyl metabolite accumulates for over a week. [10]

Adverse effects

1. Effect: Sedation and unsteadiness
 1. Detail: The lorazepam label reports that the incidence of sedation and unsteadiness was observed to increase with age, and directs that patients receiving it be warned not to operate dangerous machinery or motor vehicles. Flurazepam's label adds oversedation, dizziness, confusion and ataxia as effects that increase substantially in elderly and debilitated patients. [2][10]
2. Effect: Anterograde amnesia
 2. Detail: The diazepam label states that anterograde amnesia may occur at therapeutic dosages, with the risk increasing

at higher dosages. Memory impairment, confusion and disorientation also appear among reported reactions to lorazepam. [1][2]

3. Effect: Paradoxical and psychiatric reactions

3. Detail: Psychiatric and paradoxical reactions are known to occur with benzodiazepines, and the lorazepam label notes these may be more likely in children and in the elderly. Excitation or agitation on a sedative is therefore not evidence that the diagnosis was wrong. [1][2]

1. Effect: Profound sedation and respiratory depression with opioids

1. Detail: This is the first arm of the class boxed warning. Combining the two drug groups can suppress ventilation to the point of coma and death, and the labels reserve concomitant prescribing for patients in whom alternative treatment options are inadequate.

1. Action: Where both are genuinely needed, close observation for sedation and respiratory depression is directed; the decision and any adjustment rest with the treating clinician. [1][2]

2. Effect: Abuse, misuse and addiction

2. Detail: The second arm of the boxed warning states that the use of benzodiazepines exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death, and adds that abuse and misuse commonly involve concomitant use of other medications, alcohol, and/or illicit substances, associated with an increased frequency of serious adverse outcomes.

2. Action: Risk of abuse, misuse and addiction is assessed before and during treatment by the prescriber. [1]

3. Effect: Physical dependence and life-threatening withdrawal

3. Detail: The third arm of the boxed warning states that continued use may lead to clinically significant physical dependence, with the risks rising with longer treatment duration and higher daily dose. Reported acute withdrawal features include abnormal involuntary movements, anxiety, depersonalisation, derealisation, hyperacusis, panic attacks, photophobia and tremor, and some users develop a protracted syndrome lasting weeks to more than twelve months.

3. Action: A gradual, patient-specific taper is directed rather than abrupt cessation; the taper plan belongs to the treating clinician. [1][2][6]

4. Effect: Falls and hip fracture in older people

4. Detail: Hypnotic labels warn that because these medicines cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls. A systematic review and meta-analysis found a relative risk of hip fracture of 1.52, 95% CI 1.37 to 1.68, in benzodiazepine users, and 2.40, 95% CI 1.88 to 3.05, in short-term or newly prescribed users.

4. Action: The elevated risk concentrates around initiation, which is the point at which a prescriber weighs it most carefully. [7][9][14]

5. Effect: Respiratory depression and arrest with intravenous midazolam

5. Detail: Its boxed warning records association with respiratory depression and respiratory arrest, especially when the drug is used for sedation in noncritical care settings, and requires trained personnel and airway equipment to be available.

5. Action: Continuous monitoring of respiratory and cardiac function during procedural sedation is the point of the warning. [4]

6. Effect: Complex sleep behaviours

6. Detail: The temazepam label reports complex behaviours such as sleep-driving, defined as driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event.

6. Action: Such an episode is treated as a reason to reconsider the hypnotic rather than to adjust the timing of the dose. [7]

7. Effect: Seizures precipitated by flumazenil

7. Detail: Its boxed warning states that use of flumazenil has been associated with the occurrence of seizures, most frequent in patients who have been on benzodiazepines for long-term sedation or in overdose cases showing signs of

serious cyclic antidepressant overdose. Withdrawal seizures can follow even where dependence was established over a relatively few days of high-dose sedation in intensive care.

7. Action: The label directs that prescribers individualise dosage and be prepared to manage seizures, and that patients be monitored for re-sedation for an appropriate period of up to 120 minutes. [11]

1. Drug: Clonazepam

1. Effect: Loss of anticonvulsant activity in up to 30% of patients who initially responded, often within three months of starting treatment. [6]

2. Drug: Diazepam

2. Effect: Accumulation of the active metabolite N-desmethyldiazepam, whose terminal half-life of up to 100 hours prolongs sedation well beyond the parent drug. [1]

3. Drug: Midazolam

3. Effect: Severe hypotension and seizures have been reported after rapid intravenous injection in neonates, particularly with concomitant fentanyl. [4]

4. Drug: Flurazepam

4. Effect: Staggering and falling reported particularly in geriatric patients, consistent with the week-long accumulation of its desalkyl metabolite. [10]

5. Drug: Alprazolam

5. Effect: Exposure rises sharply when CYP3A is inhibited, which is why azole antifungal agents are a contraindication rather than a caution. [5]

6. Drug: Lorazepam given intravenously

6. Effect: Patients over the age of fifty may have more profound and prolonged sedation with intravenous lorazepam. [3]

Contraindications, precautions and interactions

1. Alprazolam is contraindicated in patients receiving strong inhibitors of CYP3A, such as the azole antifungal agents, with ritonavir the stated exception. [5]

2. Flumazenil is contraindicated in patients who have been given a benzodiazepine for control of a potentially life-threatening condition, for example control of intracranial pressure or status epilepticus. [11]

3. Flumazenil is also contraindicated in patients showing signs of serious cyclic antidepressant overdose, and in known hypersensitivity to flumazenil or to benzodiazepines. [11]

1. In elderly and debilitated patients the diazepam label directs that dosage be limited to the smallest effective amount, specifically to preclude the development of ataxia or oversedation. [1]

2. Severe hepatic insufficiency calls for careful adjustment according to response, and the lorazepam label notes lower doses may be sufficient in such patients even though age itself does not appear to have a significant effect on its kinetics. [2]

3. Abrupt withdrawal of clonazepam in patients on long-term, high-dose therapy may precipitate status epilepticus, so discontinuation in an established seizure patient is a planned process. [6]

4. Midazolam should not be administered by rapid injection in the neonatal population, where severe hypotension and seizures have followed rapid intravenous administration. [4]

5. United Kingdom packaging and patient information now carry a warning that these medicines may cause addiction, dependence, and withdrawal reactions, with clearer definitions and guidance on tapering safely. [13]

1. With: Opioid analgesics

1. Effect: The class boxed warning covers this pairing, and the labels direct that dosages and durations be limited to the minimum required with follow-up for signs and symptoms of respiratory depression and sedation. [2][1]

2. With: Alcohol and other central nervous system depressants

2. Effect: Abuse and misuse commonly involve concurrent use of other medicines, alcohol or illicit substances, and that combination is associated with an increased frequency of serious adverse outcomes. [1]

3. With: Strong CYP3A inhibitors

3. Effect: A contraindication for alprazolam, and a mechanistic concern for midazolam and diazepam, whose biotransformation also depends on CYP3A4. [5][4][1]
4. With: Valproate and probenecid
4. Effect: Both raise lorazepam concentrations and reduce its clearance, an effect the label attributes to inhibition of glucuronidation, and it directs that the lorazepam dosage be reduced by approximately half when either is co-administered. [2]
5. With: Flumazenil in a benzodiazepine-dependent patient
5. Effect: Known to precipitate withdrawal seizures even where dependence was established over relatively few days of high-dose sedation, with patients having experienced seizures before regaining consciousness. [11]

Comparison tables

1. Title: Duration of action and the job it fits
1. Caption: Half-life and the fate of any active metabolite decide the clinical niche. Selection of an agent belongs to the treating clinician working from a current prescribing reference.
1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: group
2. Label: Duration group
3. Key: clearance
3. Label: Clearance route
4. Key: role
4. Label: Where it fits
1. Drug: Midazolam
1. Group: Short acting, mean about 3 hours
1. Clearance: CYP3A4 to 1-hydroxy-midazolam
1. Role: Procedural sedation, anxiolysis and amnesia; induction of anaesthesia [4]
2. Drug: Alprazolam
2. Group: Intermediate, about 11.2 hours
2. Clearance: CYP3A4 to hydroxylated metabolites
2. Role: Acute generalised anxiety disorder and panic disorder [5]
3. Drug: Lorazepam
3. Group: Intermediate, about 12 hours
3. Clearance: Direct glucuronidation to an inactive conjugate
3. Role: Anxiety orally; status epilepticus and preanaesthetic use parenterally [2][3]
4. Drug: Oxazepam
4. Group: Intermediate, about 8.2 hours
4. Clearance: Single major inactive glucuronide
4. Role: Anxiety, including tremulousness and anxiety in alcohol withdrawal [8]
5. Drug: Temazepam
5. Group: Intermediate, mean 8.8 hours
5. Clearance: Complete conjugation, mainly the O-conjugate
5. Role: Short-term insomnia, generally seven to ten days [7]
6. Drug: Estazolam
6. Group: Intermediate, 10 to 24 hours
6. Clearance: Hepatic
6. Role: Short-term management of insomnia [9]

- 7. Drug: Diazepam
- 7. Group: Long acting through metabolite, up to 100 hours
- 7. Clearance: CYP3A4 and CYP2C19 to active metabolites
- 7. Role: Anxiety, alcohol withdrawal, muscle spasm, adjunct in convulsive disorders [1]
- 8. Drug: Clonazepam
- 8. Group: Long acting, 30 to 40 hours
- 8. Clearance: Extensive hepatic metabolism
- 8. Role: Lennox-Gastaut, akinetic and myoclonic seizures; panic disorder [6]
- 9. Drug: Flurazepam
- 9. Group: Long acting through metabolite, 47 to 100 hours
- 9. Clearance: Conversion to N1-desalkyl-flurazepam
- 9. Role: Insomnia, with accumulation over the first week of dosing [10]
- 10. Drug: Flumazenil
- 10. Group: Antagonist, monitored for resedation up to 120 minutes
- 10. Clearance: Hepatic
- 10. Role: Selective reversal, constrained by a boxed warning for seizures [11]
- 2. Title: The GABA-A channel: frequency against duration
- 2. Caption: Two drug groups, one receptor, two different channel properties. This is the contrast examiners return to most often in this area.
- 1. Key: group
- 1. Label: Drug group
- 1. Is Row Header: true
- 2. Key: site
- 2. Label: Action at the receptor
- 3. Key: channel
- 3. Label: Effect on the chloride channel
- 1. Group: Benzodiazepines
- 1. Site: Positive allosteric modulation at the benzodiazepine site
- 1. Channel: Increase the frequency of chloride channel opening [12]
- 2. Group: Barbiturates
- 2. Site: Positive allosteric modulation at a separate site
- 2. Channel: Increase the time the chloride channel remains open [12]

High-yield exam pearls

- 1. Pearl: Benzodiazepines increase how often the GABA-A chloride channel opens; barbiturates increase how long it stays open once opened.
- 1. Why: It is the single most frequently examined discrimination in sedative pharmacology, and the wording of the question usually turns on the words frequency and duration. [12]
- 2. Pearl: Lorazepam, oxazepam and temazepam are handled by conjugation to an inactive glucuronide rather than by cytochrome oxidation to an active metabolite.
- 2. Why: It is the reason these three are the agents taught as least dependent on hepatic oxidative capacity, and the reason they leave no long-lived active product behind. [2][8][7]
- 3. Pearl: Diazepam's long action comes from N-desmethyldiazepam, whose terminal elimination half-life reaches up to 100 hours, not from the parent molecule.
- 3. Why: Questions about accumulation, about the drug of choice in alcohol withdrawal, and about hazards in older patients all reduce to this metabolite. [1]
- 4. Pearl: The flumazenil boxed warning names two settings where seizures are most frequent: long-term

benzodiazepine sedation, and overdose with signs of serious cyclic antidepressant poisoning.

4. Why: Both are exactly the situations in which a candidate is tempted to give it, which is why the question is set that way. [11]

5. Pearl: Clonazepam tolerance is quantified in its own label: up to 30% of initial responders lose anticonvulsant activity, often within three months.

5. Why: A named percentage attached to a named drug is the kind of detail single-best-answer papers use to separate recall from recognition. [6]

6. Pearl: Alprazolam is the class member whose label carries an outright contraindication with strong CYP3A inhibitors rather than a dose caution.

6. Why: It converts an interaction that most candidates would classify as a caution into an absolute bar, which is the trap the question relies on. [5]

7. Pearl: Flurazepam separates parent half-life from clinical duration: the drug is gone in hours, the desalkyl metabolite persists for 47 to 100 hours.

7. Why: It is the clearest demonstration that half-life of the marketed molecule can be irrelevant to how long a patient stays sedated. [10]

Common exam traps

1. Trap: Saying benzodiazepines prolong chloride channel opening.

1. Correction: That is the barbiturate effect. Benzodiazepines raise the frequency of opening; barbiturates increase the time the channel remains open. [12]

2. Trap: Calling flumazenil the standard antidote to be given in any suspected benzodiazepine overdose.

2. Correction: Its boxed warning links it to seizures, it is contraindicated where a benzodiazepine is controlling a life-threatening condition or where serious cyclic antidepressant overdose is suspected, and resedation must be watched for afterwards. [11]

3. Trap: Treating benzodiazepine withdrawal as merely unpleasant rather than dangerous.

3. Correction: The class boxed warning records that acute withdrawal reactions after continued use can be life-threatening, and the clonazepam label notes abrupt withdrawal on long-term high-dose therapy may precipitate status epilepticus. [6][7]

4. Trap: Assuming a short elimination half-life means a short-lived clinical effect.

4. Correction: Flurazepam's parent half-life is 2.3 hours while its major metabolite persists for 47 to 100 hours and plateaus only after seven to ten days of dosing. [10]

5. Trap: Describing these drugs as GABA-A agonists.

5. Correction: They are modulators. A positive allosteric modulator increases opening frequency when an agonist binds to its own site, so the effect requires GABA to be present rather than substituting for it. [12]

6. Trap: Reading the geriatric risk as sedation alone.

6. Correction: Labels warn specifically that older patients are at higher risk of falls, and pooled observational data attach a raised hip-fracture risk to benzodiazepine use, greatest around initiation. [7][14]

Self-test questions

1. Question: How does a benzodiazepine differ from a barbiturate in its effect on the GABA-A chloride channel?

1. It increases the frequency of channel opening, while a barbiturate increases the time the channel stays open

2. It increases the time the channel stays open, while a barbiturate increases the frequency of opening

3. It blocks the channel pore, while a barbiturate opens it directly

4. Both increase the frequency of opening, but the benzodiazepine acts at the GABA site itself

1. Explanation: A positive allosteric modulator raises the frequency with which the chloride channel opens when an agonist binds its own site, and this is the benzodiazepine action; barbiturates instead increase the time chloride channels remain open. [12]

2. Question: Which three of the agents below are cleared principally by conjugation to an inactive glucuronide rather than by oxidative metabolism to an active product?

1. Lorazepam, oxazepam and temazepam
2. Diazepam, alprazolam and midazolam
3. Clonazepam, flurazepam and diazepam
4. Midazolam, estazolam and clonazepam

2. Explanation: Lorazepam is rapidly conjugated at its 3-hydroxy group into a glucuronide with no demonstrable central nervous system activity, oxazepam has a single major inactive glucuronide metabolite, and temazepam is completely metabolised through conjugation with the O-conjugate predominating. [2][8][7]

3. Question: A patient on long-term benzodiazepine therapy for sedation in intensive care is unresponsive. Why is flumazenil not a routine first move?

1. Because its use has been associated with seizures, most frequently after long-term benzodiazepine sedation
2. Because it has no activity at the benzodiazepine recognition site
3. Because its effect lasts longer than that of any benzodiazepine
4. Because it worsens respiratory depression by an additive mechanism

3. Explanation: The flumazenil boxed warning states that its use has been associated with the occurrence of seizures, most frequent in patients on benzodiazepines for long-term sedation or in overdose with signs of serious cyclic antidepressant poisoning, and withdrawal seizures may follow even brief high-dose dependence. [11]

4. Question: Which single metabolite best explains why diazepam is classed as long acting?

1. N-desmethyldiazepam, with a terminal elimination half-life of up to 100 hours
2. Lorazepam glucuronide, which is renally excreted
3. 1-hydroxy-midazolam, formed by CYP3A4
4. The O-conjugate of temazepam

4. Explanation: Diazepam is N-demethylated by CYP3A4 and CYP2C19 to the active metabolite N-desmethyldiazepam, and its label puts the terminal elimination half-life of that metabolite at up to 100 hours. [1]

5. Question: Which statement about the modern benzodiazepine class boxed warning is correct?

1. It covers concomitant opioid use, abuse and addiction, and dependence with withdrawal reactions in one warning
2. It covers only the risk of respiratory depression during procedural sedation
3. It applies only to the long-acting members of the class
4. It warns solely about serious cutaneous reactions

5. Explanation: Current labels for diazepam, lorazepam, clonazepam, temazepam, oxazepam and estazolam all carry the same combined heading covering risks from concomitant use with opioids, abuse, misuse and addiction, and dependence and withdrawal reactions. [1][2][6][9]

6. Question: Which agent's label carries an explicit contraindication with strong CYP3A inhibitors such as the azole antifungals?

1. Alprazolam
2. Oxazepam
3. Temazepam
4. Lorazepam

6. Explanation: Alprazolam is extensively metabolised primarily by CYP3A4, and its label contraindicates use in patients receiving strong inhibitors of CYP3A such as azole antifungal agents, with ritonavir the stated exception. [5]

7. Question: Roughly what proportion of patients who initially respond to clonazepam for seizures lose anticonvulsant activity, and over what period?

1. Up to 30%, often within three months
2. Up to 5%, usually after two years
3. Around 70%, within one week
4. Fewer than 1%, only after ten years

7. Explanation: The clonazepam label states that in some studies up to 30% of patients who initially responded have shown a loss of anticonvulsant activity, often within three months of administration. [6]

8. Question: Which agent is licensed for sedation, anxiolysis and amnesia before or during diagnostic, therapeutic or endoscopic procedures?

1. Midazolam
2. Oxazepam
3. Flurazepam
4. Estazolam

8. Explanation: Midazolam injection is indicated intravenously as an agent for sedation, anxiolysis and amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, and its boxed warning requires trained personnel and airway equipment to be immediately available. [4]

Frequently asked questions

1. Question: Why is duration of action the best way to organise this class?

1. Answer: Because every member does the same thing at the receptor, so the differences that matter clinically are kinetic. A three-hour drug fits an endoscopy and a forty-hour drug does not; a drug with a metabolite lasting several days smooths a taper but piles up in someone whose clearance is reduced. Comparing midazolam at a mean of about three hours with clonazepam at 30 to 40 hours and with diazepam's metabolite at up to 100 hours makes the point in a single line. [4][6][1]

2. Question: What exactly does the opioid part of the boxed warning say?

2. Answer: That putting the two together may produce profound sedation, respiratory depression, coma and death, and that concomitant prescribing should be reserved for patients in whom alternative treatment options are inadequate. Where both are used, the labels direct that dosages and durations be limited to the minimum required and that patients be followed for signs and symptoms of respiratory depression and sedation. [1][2]

3. Question: Is benzodiazepine withdrawal actually dangerous, or just uncomfortable?

3. Answer: The labels treat it as dangerous. The boxed warning records that acute withdrawal reactions following abrupt discontinuation or rapid dose reduction can be life-threatening, and the clonazepam label adds that abrupt withdrawal in long-term high-dose therapy may precipitate status epilepticus. Some people also develop a protracted syndrome with symptoms lasting weeks to more than twelve months. [6][1][7]

4. Question: Why are these medicines treated so cautiously in older people?

4. Answer: Sedation and unsteadiness are reported to increase with age, hypnotic labels state plainly that older patients are at higher risk of falls, and a systematic review and meta-analysis of observational studies found a relative risk of hip fracture of 1.52 among benzodiazepine users, rising to 2.40 in newly prescribed users. Paradoxical reactions are also noted as more likely in the elderly. [2][7][14]

5. Question: How do benzodiazepines compare with the Z-drugs and newer hypnotics?

5. Answer: That comparison is handled on the sibling page for Z-drugs and hypnotics rather than here. One point worth carrying across is that the same hip-fracture meta-analysis found a relative risk of 1.90 for Z-drugs against 1.52 for benzodiazepines, with the authors concluding there is little difference between their respective risks in older people. [14]

6. Question: If flumazenil reverses these drugs, why is benzodiazepine overdose not simply reversed?

6. Answer: Because reversal has its own hazards. Flumazenil competes at the benzodiazepine recognition site, so in a physically dependent patient it can strip that occupancy away and precipitate withdrawal seizures, and it is contraindicated where the benzodiazepine is controlling raised intracranial pressure or status epilepticus, or where serious cyclic antidepressant overdose is suspected. Resedation is also possible once it wears off, so monitoring continues afterwards. [11]

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