

Z-drugs and other hypnotics

The hypnotics that are not benzodiazepines: Z-drugs acting at the benzodiazepine site of the GABA-A receptor, melatonin-receptor agonists working through the circadian system, and orexin-receptor antagonists that remove a wake-promoting signal - grouped by target, because the target predicts the scheduling, the withdrawal behaviour and the characteristic hazard.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/z-drugs-and-hypnotics>

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Quick revision

One Liner: Three unrelated targets share one clinical heading, and only one of the three - the benzodiazepine site of the GABA-A receptor - brings the boxed warning, the scheduling and the withdrawal that define the Z-drugs.

1. Zolpidem is labelled as a GABA-A receptor positive modulator that binds the benzodiazepine site of alpha-1 subunit containing receptors. [1]
2. Zaleplon is described as binding selectively to the brain omega-1 receptor on the alpha subunit of the same chloride channel complex. [3]
3. Eszopiclone's label refuses that certainty and calls its hypnotic mechanism unclear, so the page states the selectivity claim only as far as each label does. [2]
4. Eszopiclone and zolpidem carry a boxed warning about complex sleep behaviours, and both are contraindicated in anyone who has had such an episode on them. [2][1]
5. These are controlled substances, not a safe substitute for a benzodiazepine: zaleplon's abuse potential is labelled as similar to benzodiazepine hypnotics. [3]
6. Zolpidem clearance is lower in women, whose peak and total exposure run about 45% higher than men's at the same dose. [1]
7. The MHRA advises against driving, operating machinery or working at heights until at least eight hours after zolpidem. [9]
8. Ramelteon acts on melatonin MT1 and MT2 receptors, has no appreciable GABA-receptor affinity, and its label states it is not a controlled substance. [4]
9. The orexin antagonists suvorexant, lemborexant and daridorexant are each contraindicated in narcolepsy. [5][6][7]
10. Temazepam sits on the benzodiazepine page and appears here only as the comparator, with its three boxed warnings. [8]
11. The NHS states that GPs now rarely prescribe sleeping pills for insomnia, and that cognitive behavioural therapy is sometimes offered. [12]

Overview

1. The Z-drugs were an attempt to keep the sleep-promoting action of the benzodiazepines and leave the rest of that pharmacology behind. Zolpidem's label describes a GABA-A receptor positive modulator presumed to act through the benzodiazepine site of alpha-1 subunit containing receptors, and zaleplon's describes selective binding to the brain omega-1 receptor situated on the alpha subunit of the GABA-A chloride ion channel receptor complex. Zopiclone and its active enantiomer eszopiclone complete the group; zopiclone is a United Kingdom product rather than a United States one. [1][3][10][2]
2. Two later mechanisms leave the GABA system alone altogether. Ramelteon has high affinity for melatonin MT1 and MT2 receptors with selectivity over MT3, and no appreciable affinity for the GABA receptor complex; melatonin itself is the hormone whose night-time rise helps control how and when a person sleeps. Suvorexant, lemborexant and daridorexant instead antagonise the orexin receptors through which the orexin neuropeptide signalling system sustains

wakefulness. [4][11][5][6][7]

3. One safety issue dominates the class. Complex sleep behaviours - sleep-walking, sleep-driving and other activities carried out while not fully awake - are a hazard of the Z-drugs as a group rather than of any single member, and they have caused serious injury and death. The eszopiclone and zolpidem labels carry this as a boxed warning and bar further use in anyone who has had such an episode. The zaleplon labelling reviewed for this page states the same hazard outside a box while directing that discontinuation be strongly considered in any patient who reports an episode. That difference is one of labelling format between products, and should not be read as evidence that zaleplon carries a lower risk. [2][1][3]

4. None of this makes a Z-drug a benign stand-in for a benzodiazepine. All of them are Schedule IV controlled substances in the United States, the zaleplon label rates its abuse potential as similar to benzodiazepine and benzodiazepine-like hypnotics, and the zolpidem label records dependence rising with dose and duration alongside withdrawal signs after abrupt discontinuation. Against that background the NHS states that GPs now rarely prescribe sleeping pills to treat insomnia, that they can have serious side effects and that dependence can develop. [3][1][12]

Classification and drug examples

Intro: Divided by molecular target. The target is what decides whether an agent is scheduled, whether stopping it produces withdrawal, and which specific hazard has to be counselled for.

1. Name: Z-drugs (benzodiazepine-site GABA-A modulators)

1. Note: Structurally unrelated to the benzodiazepines, yet converging on the same binding site. Their initial letter is the only thing the group name records.

1. Name: Zolpidem

Ambien

1. Route: Oral, including sublingual and extended-release forms

1. Note: Presumed to act at the benzodiazepine site of alpha-1 subunit containing GABA-A receptors, raising the frequency of chloride channel opening. Cleared more slowly in women than in men. [1]

2. Name: Zopiclone

Imovane

2. Route: Oral

2. Note: A United Kingdom product. The NHS notes it is usually not prescribed beyond four weeks because the body can become used to it, and that a bitter or metallic taste is a common complaint. [10]

3. Name: Zaleplon

Sonata

3. Route: Oral

3. Note: Labelled as binding selectively to the brain omega-1 receptor on the alpha subunit, with a terminal half-life of roughly an hour and metabolism chiefly by aldehyde oxidase. [3]

4. Name: Eszopiclone

1. Lunesta

2. S-zopiclone

4. Route: Oral

4. Note: The active enantiomer of zopiclone. Its label states that the mechanism as a hypnotic is unclear, and an unpleasant taste is its most frequently reported adverse reaction. [2] [1][3]

2. Name: Melatonin-receptor agonists

2. Note: These work through circadian timing rather than by adding inhibitory tone, and the risk profile changes accordingly.

1. Name: Melatonin

Circadin

1. Route: Oral

1. Note: A hormone occurring naturally in the body, rising at night and falling by day. In the United Kingdom it is available on prescription only and used mainly for short-term sleep problems in people aged 55 and over. [11]

2. Name: Ramelteon

Rozerem

2. Route: Oral

2. Note: High affinity for MT1 and MT2 receptors with selectivity over MT3. Its label states that it is not a controlled substance and that ramelteon does not appear to produce physical dependence. [4] [4][11]

3. Name: Orexin-receptor antagonists

3. Note: Wakefulness is blocked at its source instead of sleep being pushed forward, and every member of the group is barred in narcolepsy.

1. Name: Suvorexant

Belsomra

1. Route: Oral

1. Note: The first of the group, with a mean half-life near twelve hours, elimination chiefly by CYP3A, and somnolence reported more often in women than in men. [5]

2. Name: Lemborexant

Dayvigo

2. Route: Oral

2. Note: Licensed for insomnia with difficulty in sleep onset or maintenance. Its label warns of sleep paralysis, hypnagogic and hypnopompic hallucinations and symptoms resembling mild cataplexy. [6]

3. Name: Daridorexant

Quviviq

3. Route: Oral

3. Note: Terminal half-life of approximately eight hours; contraindicated in narcolepsy and in known hypersensitivity to the drug. [7] [5][6][7]

4. Name: Benzodiazepine hypnotics (comparator only)

4. Note: Set out in full on the benzodiazepines page. Temazepam is carried here purely so the comparison has an anchor.

Name: Temazepam

Restoril

Route: Oral

Note: Indicated for short-term treatment of insomnia, generally seven to ten days, and carrying boxed warnings on concomitant opioid use, on abuse, misuse and addiction, and on dependence and withdrawal reactions. [8] [8]

Mechanism of action

Summary: One heading, three targets. The Z-drugs modulate the GABA-A receptor from the benzodiazepine site; the melatonin agonists act at MT1 and MT2 receptors; the orexin antagonists withdraw a wake-promoting input. The labels differ in how firmly they connect binding to hypnosis, and the wording below follows each of them rather than smoothing the differences away.

Target: The benzodiazepine site of GABA-A receptors, melatonin MT1 and MT2 receptors, and orexin receptors

Cidal Static: Sleep-promoting rather than curative

Kill Kinetics: Effect confined to the hours over which drug exposure is measurable

1. Step: 1

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

1. Detail: Zolpidem is presented as a GABA-A receptor positive modulator presumed to exert its therapeutic effect through binding to the benzodiazepine site of alpha-1 subunit containing GABA-A receptors. Zaleplon is described as binding selectively to the brain omega-1 receptor situated on the alpha subunit of the GABA-A chloride ion channel

receptor complex. [1][3]

2. Step: 2

2. Title: More chloride channel opening, less neuronal excitation

2. Detail: Occupancy of that site increases the frequency with which the chloride channel opens, and the consequent inhibition of neuronal excitation is what the zolpidem label offers as the basis of its short-term effect in insomnia. [1]

3. Step: 3

3. Title: How far the labels actually go on subtype selectivity

3. Detail: Not as far as most revision notes do. Zolpidem's label names the alpha-1 subunit and zaleplon's names the omega-1 receptor, but eszopiclone's states that its mechanism as a hypnotic is unclear and that the effect could be related to interaction with GABA-receptor complexes at binding domains close to or allosterically coupled to benzodiazepine receptors. Subtype selectivity is the stated rationale for a more purely hypnotic profile; it is not, in these labels, a settled clinical fact. [2][1][3]

4. Step: 4

4. Title: Agonism at melatonin MT1 and MT2 receptors

4. Detail: Ramelteon binds MT1 and MT2 receptors with high affinity and relative selectivity over MT3. Its label attributes the sleep-promoting property to those two receptors, which endogenous melatonin acts upon and which are thought to be involved in maintaining the circadian rhythm underlying the normal sleep-wake cycle. [4]

5. Step: 5

5. Title: Antagonism of orexin receptors

5. Detail: Orexin neuropeptide signalling plays a role in wakefulness, and the suvorexant label presumes that its action in insomnia comes from antagonism at orexin receptors. The lemborexant and daridorexant labels state the same presumed mechanism, which is why the whole group behaves differently from a GABAergic sedative. [5][6][7]

Major clinical uses

1. Drug: Zolpidem

1. Organism: Not applicable

1. Indication: Short-term treatment of insomnia

1. Line: widely used

1. Note: Its label frames the therapeutic effect explicitly as short-term treatment of insomnia, and the MHRA has advised on the drowsiness and reduced driving ability that can follow the next day. [1][9]

2. Drug: Zopiclone

2. Organism: Not applicable

2. Indication: Sleeping problems that affect everyday life

2. Line: United Kingdom practice

2. Note: The NHS describes treatment lasting from a few days to a few weeks, usually not more than four weeks, because the body can become used to the drug. [10]

3. Drug: Zaleplon

3. Organism: Not applicable

3. Indication: Insomnia, where the very short duration of action is the point

3. Line: selected use

3. Note: A terminal half-life of about one hour distinguishes it within the group; the label still cautions against hazardous activities requiring alertness on the day following ingestion. [3]

4. Drug: Eszopiclone

4. Organism: Not applicable

4. Indication: Insomnia

4. Line: widely used

4. Note: Its label reports no development of tolerance to any parameter of sleep measurement over six months, which

is a narrower statement than an absence of dependence. [2]

5. Drug: Ramelteon

5. Organism: Not applicable

5. Indication: Insomnia characterised by difficulty with sleep onset

5. Line: non-scheduled alternative

5. Note: The indication is narrower than for the Z-drugs, being confined to trouble falling asleep rather than to sleep maintenance. [4]

6. Drug: Suvorexant

6. Organism: Not applicable

6. Indication: Insomnia characterised by difficulties with sleep onset and/or sleep maintenance

6. Line: alternative mechanism

6. Note: Covers both halves of the insomnia complaint, which the melatonin agonist indication does not. [5]

7. Drug: Melatonin

7. Organism: Not applicable

7. Indication: Short-term sleep problems, chiefly in people aged 55 and over

7. Line: United Kingdom prescription-only

7. Note: The NHS records use for up to about thirteen weeks in most cases, with specialists sometimes prescribing for longer-term sleep problems in some children and adults. [11]

8. Drug: Temazepam

8. Organism: Not applicable

8. Indication: Short-term treatment of insomnia, generally seven to ten days

8. Line: comparator

8. Note: The explicit duration limit in a benzodiazepine hypnotic indication is a useful contrast with the looser wording used for several Z-drugs. [8]

Pharmacokinetics

1. Drug: Zolpidem

1. Route: Oral

1. Absorption: Food lowers peak and total exposure and delays the time to peak

1. Csf Penetration: Not applicable

1. Metabolism: Hepatic, principally by CYP3A4, to inactive metabolites

1. Elimination: Metabolites removed mainly by renal excretion

1. Half Life: Mean about 2.6 hours

1. Dose Adjust: Exposure rises sharply in hepatic impairment and in people over seventy, and clearance is lower in women than in men [1]

2. Drug: Zaleplon

2. Route: Oral

2. Absorption: Rapid and near-complete, but absolute bioavailability is around 30% because of presystemic metabolism; a heavy meal delays the peak

2. Csf Penetration: Not applicable

2. Metabolism: Primarily by aldehyde oxidase, and to a lesser extent by CYP3A4

2. Elimination: Around 70% recovered in urine within 48 hours, almost entirely as metabolites and their glucuronides

2. Half Life: Approximately 1 hour

2. Dose Adjust: Clearance falls by 70% in compensated and 87% in decompensated cirrhosis; the label does not recommend use in severe hepatic impairment [3]

3. Drug: Eszopiclone

3. Route: Oral

3. Absorption: A high-fat meal leaves total exposure unchanged but lowers the peak and delays it by about an hour
 3. Csf Penetration: Not applicable
 3. Metabolism: Extensive oxidation and demethylation involving CYP3A4 and CYP2E1
 3. Elimination: Urinary, mostly as metabolites, with under a tenth of the dose appearing unchanged
 3. Half Life: Approximately 6 hours
 3. Dose Adjust: Exposure doubles in severe hepatic impairment and rises by around two-fifths in those aged 65 and over, and the label caps the dose in both groups [2]
 4. Drug: Ramelteon
 4. Route: Oral
 4. Absorption: At least 84% absorbed, yet absolute oral bioavailability is only 1.8% because first-pass metabolism is extensive
 4. Csf Penetration: Not applicable
 4. Metabolism: Hepatic, with CYP1A2 the major isozyme and minor contributions from the CYP2C subfamily and CYP3A4
 4. Elimination: About 84% of radioactivity recovered in urine and roughly 4% in faeces
 4. Half Life: On average about 1 to 2.6 hours
 4. Dose Adjust: Not recommended in severe hepatic impairment and to be used with caution in moderate impairment [4]
 5. Drug: Suvorexant
 5. Route: Oral
 5. Absorption: Median time to peak of 2 hours when fasted; a high-fat meal delays the peak by roughly an hour and a half without altering exposure
 5. Csf Penetration: Not applicable
 5. Metabolism: Mainly by CYP3A with a minor contribution from CYP2C19
 5. Elimination: Chiefly faecal, with about two-thirds of a radiolabelled dose in faeces and around a quarter in urine
 5. Half Life: Mean approximately 12 hours
 5. Dose Adjust: Exposure runs higher in women and higher again in obese women; strong CYP3A inducers substantially reduce it [5]
- No dose regimens appear on this page. Choosing a hypnotic, deciding whether one is warranted at all, setting its duration and stopping it are matters for the treating clinician working from a current prescribing reference, because they turn on age, sex, hepatic function, comorbidity, occupation and everything else the patient is taking.

Adverse effects

1. Effect: Next-morning psychomotor impairment
1. Detail: Both the zolpidem and eszopiclone labels state that the risk of next-day psychomotor impairment, including impaired driving, rises when the drug is taken with less than a full night of sleep remaining. The MHRA advises against driving, operating machinery or working at heights until at least eight hours have passed after zolpidem. [1][2][9]
2. Effect: Unpleasant taste
2. Detail: Unpleasant taste was the most commonly reported adverse reaction to eszopiclone and increased with dose. The NHS lists a bitter or metallic taste among the common effects of zopiclone, which is unsurprising given that eszopiclone is its active enantiomer. [2][10]
3. Effect: Daytime drowsiness and feeling dazed
3. Detail: The NHS lists feeling tired, sleepy, dazed or less alert the next day among the common effects of zopiclone, together with dry mouth, and advises against driving, cycling or using machinery for twelve hours after a dose. [10]
4. Effect: Daytime somnolence with orexin antagonists
4. Detail: Suvorexant is described as a central nervous system depressant that can impair daytime wakefulness even when used as prescribed, and at the higher doses studied somnolence was reported in 8% of women against 3% of

men. [5]

5. Effect: Abnormal thinking and behavioural change

5. Detail: Abnormal thinking and behaviour changes have been reported in patients treated with sedative-hypnotics including zolpidem, and this sits alongside, rather than inside, the boxed warning. [1]

1. Effect: Complex sleep behaviours

1. Detail: Sleep-walking, sleep-driving, preparing and eating food, making telephone calls or having sex while not fully awake, usually with no memory of the episode. Some of these events may result in serious injuries, including death. Postmarketing reports describe them occurring with eszopiclone alone at recommended dosages, with or without alcohol or other central nervous system depressants, and after a first or any subsequent dose.

1. Action: The labels direct that the medicine be discontinued immediately after any such episode and that it not be used again in that patient; the assessment and any change of treatment rest with the treating clinician. [2][1][3]

2. Effect: Respiratory depression with opioids

2. Detail: Concomitant use of zolpidem with opioids may increase the risk of respiratory depression, and the temazepam boxed warning states that combining a benzodiazepine with an opioid may produce profound sedation, respiratory depression, coma and death.

2. Action: Reserved for patients in whom alternative options are inadequate, at the shortest duration, with close observation by the prescribing team. [1][8]

3. Effect: Dependence and withdrawal

3. Detail: Use of zolpidem may lead to physical or psychological dependence, with risk increasing with dose and duration, and withdrawal signs including tremor, convulsions and delirium have followed abrupt discontinuation of sedative-hypnotics. The NHS states that addiction to zopiclone is possible and warns that stopping it suddenly can cause agitation or anxiety.

3. Action: Stopping is a planned, supervised process rather than an abrupt one, decided by the treating clinician. [1][10]

4. Effect: Sleep paralysis, hallucinations and cataplexy-like symptoms

4. Detail: Orexin antagonists can produce an inability to move or speak for up to several minutes during sleep-wake transitions, vivid and disturbing hypnagogic or hypnopompic perceptions, and symptoms resembling mild cataplexy. These follow directly from what blocking an orexin signal does.

4. Action: Reported episodes warrant clinical reassessment of whether the drug should continue. [5][6]

5. Effect: Anaphylaxis and angioedema

5. Detail: Observed hypersensitivity reactions to zolpidem have included anaphylaxis and angioedema, and the ramelteon label states that a patient who develops angioedema on treatment should not be rechallenged.

5. Action: A previous reaction makes the drug unusable in that patient. [1][4]

6. Effect: Precipitation of hepatic encephalopathy

6. Detail: The zolpidem label carries a specific warning on precipitating hepatic encephalopathy, which matters because exposure is already several times higher in hepatically compromised patients.

6. Action: Hepatic function forms part of the pre-treatment assessment made by the clinician. [1]

1. Drug: Zolpidem

1. Effect: Sex difference in exposure. Women clear zolpidem more slowly than men, and peak and total exposure are roughly 45% higher at the same dose; the label states that higher morning blood levels increase the risk of next-day impairment in some patients, and sets a lower recommended initial dose for women for that reason. [1]

2. Drug: Eszopiclone

2. Effect: Dose-related unpleasant taste, reported by a third of adults at the higher strength studied against 3% on placebo. [2]

3. Drug: Ramelteon

3. Effect: Effects on reproductive hormones, with decreased testosterone and increased prolactin levels reported in adults. [4]

4. Drug: Suvorexant

4. Effect: Higher exposure in women and higher still in obese women, matching the greater frequency of somnolence seen in female participants. [5]
5. Drug: Zaleplon
5. Effect: Mild rebound insomnia has been described, while no development of tolerance to zaleplon was observed in the studies the label cites. [3]
6. Drug: Temazepam
6. Effect: Use late in pregnancy can produce sedation in the neonate, meaning respiratory depression, lethargy and hypotonia, or neonatal withdrawal symptoms. [8]

Contraindications, precautions and interactions

1. The eszopiclone and zolpidem labels bar further use in a patient who has already experienced a complex sleep behaviour on them. The zaleplon labelling reviewed here directs discontinuation after such an episode rather than listing it under contraindications, so the practical position across the group is the same even where the labelling differs. [2][1][3]
2. Known hypersensitivity to the agent concerned; for zolpidem the observed reactions include anaphylaxis and angioedema, and daridorexant is contraindicated in anyone with a history of hypersensitivity to it. [1][7]
3. Narcolepsy bars the whole orexin-antagonist group: suvorexant, lemborexant and daridorexant each carry that contraindication. [5][6][7]
4. Ramelteon should not be used in combination with fluvoxamine, and a patient who develops angioedema on ramelteon should not be rechallenged. [4]
1. Hepatic impairment changes exposure across the class: zolpidem peak and total exposure are several-fold higher in hepatically compromised patients, eszopiclone exposure doubles in severe impairment, zaleplon clearance falls steeply in cirrhosis, and ramelteon is not recommended in severe hepatic impairment. [1][2][3][4]
2. Age matters. In subjects over seventy, zolpidem peak concentration, half-life and total exposure all rose substantially against younger adults, and eszopiclone exposure was around two-fifths greater in those aged 65 and over. [1][2]
3. An inadequate sleep opportunity is itself a risk factor, because next-day impairment is more likely when the drug is taken with less than a full night of sleep remaining. [1][2]
4. The zolpidem label carries separate warnings on the need to evaluate for comorbid diagnoses, on use in patients with depression and on respiratory depression, so insomnia that has not been worked up is a reason for caution rather than for a prescription. [1]
5. Duration is part of the safety profile: zopiclone is usually not prescribed beyond four weeks, temazepam's indication is limited to short-term treatment generally lasting seven to ten days, and NHS melatonin use is usually up to about thirteen weeks. [10][8][11]
1. With: Alcohol
1. Effect: Zaleplon should not be taken with alcohol; patients are advised not to combine alcohol with suvorexant or with ramelteon because the effects are additive; and the NHS warns that alcohol with zopiclone can cause breathing problems and make waking very difficult. [3][5][4][10]
2. With: Opioids
2. Effect: Co-administration raises the risk of respiratory depression with zolpidem, and the benzodiazepine comparator temazepam carries an explicit boxed warning about profound sedation, respiratory depression, coma and death. [1][8]
3. With: Other central nervous system depressants
3. Effect: Additive depression occurs with benzodiazepines, tricyclic antidepressants and similar agents; the zaleplon label notes that dose adjustment may be necessary for exactly this reason. [2][3]
4. With: CYP3A inhibitors and inducers
4. Effect: Suvorexant is eliminated mainly by CYP3A, and strong inducers such as rifampicin substantially decreased its exposure; zolpidem and eszopiclone are also CYP3A4 substrates. [5][1][2]
5. With: Fluvoxamine and other CYP1A2 inhibitors

5. Effect: CYP1A2 is the major isozyme metabolising ramelteon, and co-administration with fluvoxamine increased ramelteon exposure roughly 190-fold, which is why the combination is barred and weaker CYP1A2 inhibitors call for caution. [4]

Comparison tables

Title: What separates these agents in practice

Caption: Target, control status and duration of exposure account for most of the practical difference. Selection belongs to the treating clinician working from a current prescribing reference.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: mechanism

2. Label: Target

3. Key: control

3. Label: Control status

4. Key: half_life

4. Label: Half-life

5. Key: signature

5. Label: Signature issue

1. Drug: Zolpidem

1. Mechanism: Benzodiazepine site, alpha-1 subunit containing GABA-A receptors

1. Control: Schedule IV

1. Half Life: Mean about 2.6 hours

1. Signature: Boxed warning for complex sleep behaviours; slower clearance in women [1]

2. Drug: Zaleplon

2. Mechanism: Brain omega-1 receptor on the alpha subunit of the GABA-A complex

2. Control: Schedule IV

2. Half Life: About 1 hour

2. Signature: Shortest exposure of the group; abuse potential labelled as similar to benzodiazepine hypnotics [3]

3. Drug: Eszopiclone

3. Mechanism: GABA-receptor complexes near the benzodiazepine binding domain; mechanism stated as unclear

3. Control: Schedule IV

3. Half Life: About 6 hours

3. Signature: Boxed warning for complex sleep behaviours; dose-related unpleasant taste [2]

4. Drug: Zopiclone

4. Mechanism: Racemate of eszopiclone, used in the United Kingdom

4. Control: Prescription medicine with recognised addiction potential

4. Half Life: Not stated on the NHS medicines page

4. Signature: Bitter or metallic taste; twelve hours advised before driving [10]

5. Drug: Ramelteon

5. Mechanism: Melatonin MT1 and MT2 receptor agonist

5. Control: Not a controlled substance

5. Half Life: About 1 to 2.6 hours

5. Signature: Fluvoxamine barred; prolactin rise and testosterone fall reported [4]

6. Drug: Suvorexant

6. Mechanism: Orexin receptor antagonist

6. Control: Schedule IV

- 6. Half Life: About 12 hours
- 6. Signature: Contraindicated in narcolepsy; sleep paralysis and cataplexy-like symptoms [5]
- 7. Drug: Temazepam
- 7. Mechanism: Benzodiazepine acting at GABA-A receptor sites
- 7. Control: Schedule IV
- 7. Half Life: Terminal half-life 3.5 to 18.4 hours, mean 8.8
- 7. Signature: Three boxed warnings, covering opioids, addiction, and dependence with withdrawal [8]

High-yield exam pearls

- 1. Pearl: The boxed warning on eszopiclone and zolpidem names sleep-walking, sleep-driving and other activities performed while not fully awake, and the labels contraindicate re-use after any such event.
- 1. Why: Examiners test the consequence rather than the wording: the correct answer is permanent discontinuation, not a lower dose. [2][1]
- 2. Pearl: Alpha-1 or omega-1 selectivity is what zolpidem and zaleplon labels claim, while the eszopiclone label declines to claim a mechanism at all.
- 2. Why: It is the cleanest example on this page of a class where the textbook story runs ahead of the regulatory text. [1][3][2]
- 3. Pearl: Ramelteon is not a controlled substance and does not appear to produce physical dependence, whereas every Z-drug here is Schedule IV.
- 3. Why: Control status is the fastest way to separate the melatonin agonists from the rest in a single-best-answer question. [4][3]
- 4. Pearl: Narcolepsy is the shared contraindication for orexin antagonists, and the suvorexant label links this to loss of orexin neurons reported in people with narcolepsy.
- 4. Why: The mechanism and the contraindication are the same fact seen from two directions, which makes it examinable in either. [5][6][7]
- 5. Pearl: Zolpidem exposure is around 45% greater in women than in men at the same dose because clearance is lower, and the label recommends a lower initial dose in women.
- 5. Why: It is one of very few sex-specific dosing statements in any drug label, and it is asked about often. [1]
- 6. Pearl: Zaleplon's half-life of roughly an hour sits against suvorexant's twelve, which explains why one is used for trouble falling asleep and the other spans the night.
- 6. Why: Half-life predicts both the useful effect and the next-morning hangover better than potency does. [3][5]
- 7. Pearl: Fluvoxamine raised ramelteon exposure by roughly 190-fold, and the combination is therefore prohibited.
- 7. Why: The size of the interaction makes it memorable, and CYP1A2 inhibition is the mechanism behind it. [4]

Common exam traps

- 1. Trap: Treating the Z-drugs as non-addictive because they are not benzodiazepines.
- 1. Correction: They are Schedule IV controlled substances; zaleplon's abuse potential is described as similar to benzodiazepine and benzodiazepine-like hypnotics, and zolpidem dependence rises with dose and duration with withdrawal signs after abrupt stopping. [3][1]
- 2. Trap: Assuming a non-benzodiazepine hypnotic cannot act on the benzodiazepine receptor.
- 2. Correction: That is precisely where zolpidem acts, at the benzodiazepine site of GABA-A receptors containing the alpha-1 subunit; the chemical class differs, the binding site does not. [1]
- 3. Trap: Believing complex sleep behaviours only happen when a hypnotic is combined with alcohol.
- 3. Correction: Postmarketing reports describe them with eszopiclone alone at recommended dosages, with or without concomitant alcohol or other depressants, and the zaleplon label states that sleep-driving may occur with zaleplon alone at therapeutic doses. [2][3]
- 4. Trap: Assuming a very short half-life removes any next-morning risk.

4. Correction: Zaleplon's label still cautions against hazardous activities requiring complete mental alertness on the day following ingestion, and the MHRA sets an eight-hour interval before driving after zolpidem. [3][9]
5. Trap: Calling melatonin a harmless supplement in a United Kingdom examination answer.
5. Correction: The NHS describes melatonin as available on prescription only, used mainly for short-term sleep problems in people aged 55 and over, with specialist prescribing for longer-term problems in some children and adults. [11]
6. Trap: Filing the orexin antagonists with the sedatives as just another way of dampening the brain.
6. Correction: They remove a wake-promoting signal rather than adding inhibition, which is why the group is contraindicated in narcolepsy and why sleep paralysis and cataplexy-like symptoms appear in their warnings. [5][6]

Self-test questions

1. Question: A man taking a Z-drug for insomnia is found by his family to have driven to a shop overnight with no memory of it. What does the labelling direct?
 1. Continue at the same dose and review in a month
 2. Discontinue the medicine immediately and do not use it again in this patient
 3. Halve the dose and add a melatonin agonist
 4. Switch to the extended-release form of the same drug
1. Explanation: The boxed warning covers exactly this event, and the labels both direct immediate discontinuation and contraindicate further use in a patient who has experienced a complex sleep behaviour. [1][2]
2. Question: Which statement most accurately reflects what the labels say about how the Z-drugs work?
 1. All three labels state a proven selective action at alpha-1 subunit receptors
 2. Zolpidem and zaleplon name a specific site, while the eszopiclone label calls its hypnotic mechanism unclear
 3. They act as direct GABA-A channel openers independent of the benzodiazepine site
 4. They inhibit orexin signalling in the hypothalamus
2. Explanation: Zolpidem's label names the benzodiazepine site of alpha-1 subunit containing receptors and zaleplon's names the brain omega-1 receptor, but eszopiclone's states only that the effect could be related to interaction with GABA-receptor complexes near the benzodiazepine binding domains. [1][3][2]
3. Question: Which hypnotic on this page is stated by its label not to be a controlled substance?
 1. Zolpidem
 2. Eszopiclone
 3. Ramelteon
 4. Suvorexant
3. Explanation: The ramelteon label states that it is not a controlled substance and that it does not appear to produce physical dependence, whereas zolpidem, eszopiclone and suvorexant are all Schedule IV. [4][5]
4. Question: A woman with narcolepsy asks about a newer insomnia medicine she has read about. Which class is contraindicated for her?
 1. Melatonin-receptor agonists
 2. Orexin-receptor antagonists
 3. Benzodiazepine hypnotics
 4. Antihistamine sedatives
4. Explanation: Suvorexant, lemborexant and daridorexant are each contraindicated in narcolepsy, which follows from the loss of orexin signalling that characterises the disorder. [5][6][7]
5. Question: Why does the zolpidem label recommend a lower initial dose in women than in men?
 1. Women report more taste disturbance
 2. Zolpidem clearance is lower in women, giving roughly 45% higher peak and total exposure
 3. Women absorb the drug more rapidly from the gut
 4. The drug is more protein-bound in women

5. Explanation: The label states that women clear zolpidem at a lower rate than men, that peak and total exposure are about 45% higher at the same dose, and that higher morning blood levels increase the risk of next-day impairment in some patients. [1]

6. Question: Which combination is explicitly barred by the ramelteon label?

1. Ramelteon with fluvoxamine
2. Ramelteon with rifampicin
3. Ramelteon with melatonin
4. Ramelteon with a proton pump inhibitor

6. Explanation: CYP1A2 is the major isozyme metabolising ramelteon, and fluvoxamine raised its exposure roughly 190-fold, so the label states that the two should not be used together. [4]

7. Question: Which of these is the correct description of temazepam's place on this page?

1. A Z-drug with a long half-life
2. A melatonin-receptor agonist used in older adults
3. A benzodiazepine hypnotic included only as the comparator, with three boxed warnings
4. An orexin antagonist licensed for sleep maintenance

7. Explanation: Temazepam is a benzodiazepine indicated for short-term treatment of insomnia, generally seven to ten days, and its boxed warnings cover concomitant opioid use, abuse and addiction, and dependence with withdrawal reactions; the class itself is covered on the benzodiazepines page. [8]

Frequently asked questions

1. Question: Are Z-drugs safer than benzodiazepines?

1. Answer: Not in the way the question usually implies. They share the same binding site, the same Schedule IV status in the United States and the same broad problems of dependence, withdrawal and next-morning impairment, and zaleplon's abuse potential is put on a level with benzodiazepine hypnotics. What they do have is the specific boxed warning on complex sleep behaviours, which the benzodiazepine comparator temazepam does not carry. [3][1][8]

2. Question: What exactly is a complex sleep behaviour?

2. Answer: An activity carried out while not fully awake, with no memory of it afterwards. The labels list sleep-walking, sleep-driving, preparing and eating food, making telephone calls and having sex. They have been reported after a first dose as well as after long use, at recommended dosages, and with or without alcohol. [2][1]

3. Question: Why is an orexin antagonist described as a different kind of hypnotic?

3. Answer: Because it does not add inhibition to the brain. Orexin signalling maintains wakefulness, and blocking its receptors removes that drive rather than sedating the cortex. The same fact explains the contraindication in narcolepsy, a disorder marked by loss of orexin neurons, and the appearance of sleep paralysis and cataplexy-like symptoms among the warnings. [5][6]

4. Question: Where do melatonin and ramelteon fit?

4. Answer: Both act at melatonin receptors rather than on inhibitory neurotransmission. Ramelteon binds MT1 and MT2 receptors with selectivity over MT3 and has no appreciable affinity for the GABA receptor complex; melatonin is the endogenous hormone that rises at night, supplied in the United Kingdom on prescription only and mainly for short-term sleep problems in people aged 55 and over. [4][11]

5. Question: Is medication the first step for insomnia?

5. Answer: The NHS states that GPs now rarely prescribe sleeping pills to treat insomnia, that these medicines can have serious side effects and that dependence can develop, and that cognitive behavioural therapy is sometimes offered instead, face to face or through an online self-help programme. Where a hypnotic is used at all, courses are short: zopiclone is usually not prescribed for more than four weeks. [12][10]

6. Question: How long after a hypnotic is driving unsafe?

6. Answer: It depends on the drug and on how much sleep was actually available. The MHRA advises not driving, operating machinery or working at heights until at least eight hours after zolpidem, the NHS gives twelve hours for

zopiclone, and both the zolpidem and eszopiclone labels warn that impairment is likelier when the drug is taken with less than a full night of sleep remaining. [9][10][1][2]

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