Pharmacological treatments in insomnia

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Drugs used in insomnia

Licensed for insomnia

- GABA-A positive allosteric modulators
- melatonin (modified release)
- promethazine
- diphenhydramine
- doxepin (USA)

Unlicensed prescribed frequently

- antihistamines (and OTC)
- antidepressants

Sometimes prescribed

drugs for psychosis

Some GABA-A positive allosteric modulators

Drugs acting at the GABA-A benzodiazepine receptor

zopiclone

zolpidem

zaleplon

benzodiazepines eg temazepam, lorazepam

(safe in overdose, as long as no other drug involved)

Drugs acting at the barbiturate/alcohol receptor

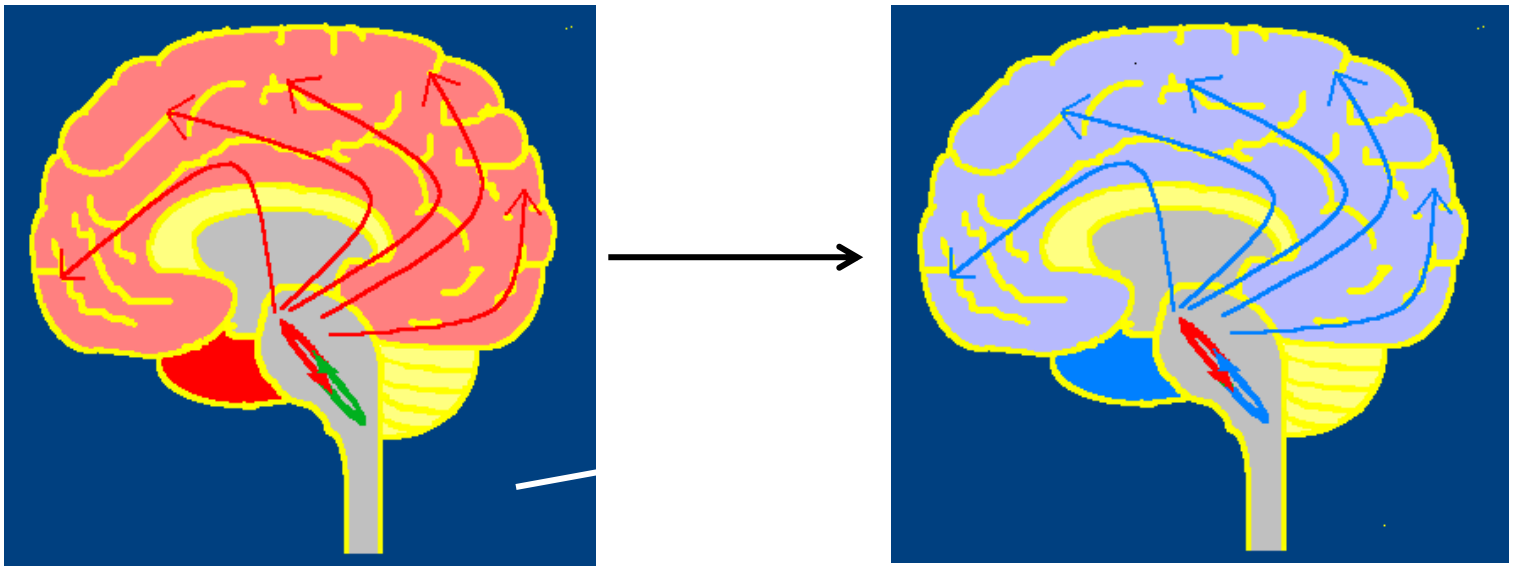
chloral hydrate/chloral betaine

clomethiazole

(dangerous in overdose)

GABA calms the brain

Gamma aminobutyic acid (GABA) is the main inhibitory transmitter in the mammalian central nervous system. It plays the principal role in reducing neuronal excitability and its receptors are prolific throughout the brain, in cortex, limbic system, thalamus and cerebellum



Increase GABA function → sedative
anticonvulsant
anxiolytic
ataxia, memory effects

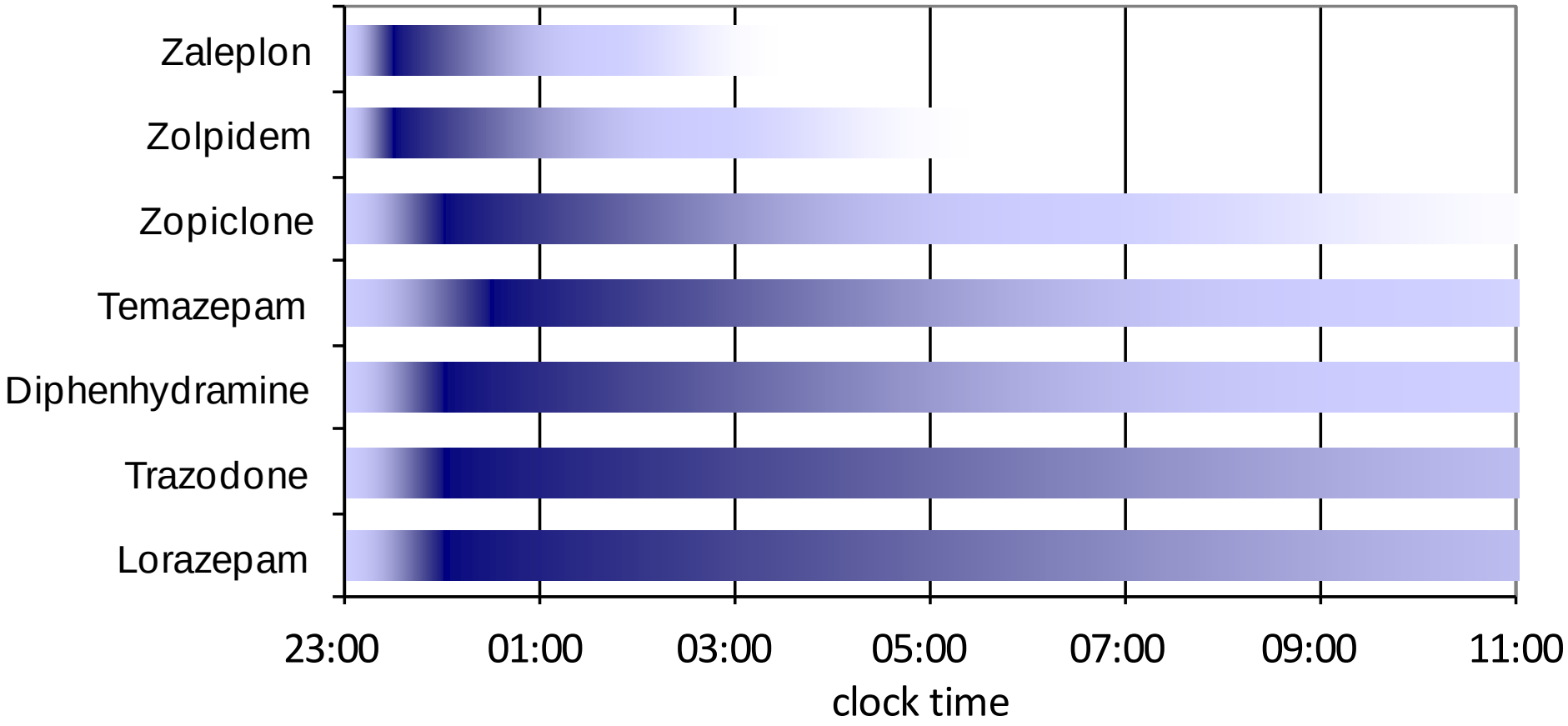
Effects of GABA-A positive allosteric modulators

- These drugs enhance the effect of GABA, the main inhibitory neurotransmitter in the brain
- They all produce sedation, sleep promotion, ataxia, muscle relaxation, effects on memory, anticonvulsant effects
- Therefore for insomnia the duration of action of the drug is important – these effects are unwanted during the day

Effects of these GABA-ergic drugs on sleep EEG/PSG

- Appearance of regular low-amplitude beta activity
- Increase in spindles
- Decrease in delta power, therefore decrease in stage N3 (evident at higher doses)

How long do the effects last?



Evidence for efficacy

Both benzodiazepines and Z drugs significantly improve sleep in chronic insomnia (> 4 weeks' duration) Level 1a

	Sleep onset latency		Total sleep time		Sleep efficiency		Wake time after sleep onset		Sleep quality
	Self-rated	PSG	Self-rated	PSG	Self-rated	PSG	Self-rated	PSG	Self-rated
Bdz	□	□	□		□	□	□		□
Z drugs	□	□	□		□	□	□		□

Melatonin

- Endogenous hormone secreted nightly in the pineal gland
- The 'hormone of darkness'
- Exogenous melatonin brings sleep forward, ie when given in late evening reduces sleep latency
- Does not prolong sleep or reduce night-time awakenings
- Has no motor, memory or known hangover effects

Marketed as a POM as circadin, for the indication insomnia in adults aged >55 y, in whom it improves subjective sleep quality

(Clinical trials conducted only in this age group)

Individual drugs (efficacy) Level 1b

Significantly different from placebo	Sleep onset latency		Total sleep time		Wake time after sleep onset		Sleep quality
	Self-rated	**PSG**	**Self-rated**	**PSG**	**Self-rated**	**PSG**	**Self-rated**
temazepam	?	?	☐	☐	☐	☐	☐
lormetazepam	☐	☐	☐	☐	☐	☐	☐
zopiclone	☐	☐	☐	☐	☐	☐	☐
zolpidem	☐	☐	☐	☐	☐		☐
zaleplon	☐	☐		☐			☐
eszopiclone	☐	☐	☐	☐	☐	☐	☐
PR melatonin	☐						☐

Promethazine

Is a drug used in schizophrenia in many countries. Has antihistamine (ie H1 receptor antagonist) effects

and

Is an antagonist at cholinergic (muscarinic)*, dopamine**, serotonin receptors

* Side effects therefore dry mouth, constipation, tachycardia. Delirium in overdose

** Risk of extrapyramidal symptoms, and (rare) TD

Diphenhydramine

Used in many over-the counter preparations

Antihistamine, has potent anticholinergic effects (see above) and in overdose can affect potassium channels leading to cardiac arrythmia

Histamine and sleep

- Histamine is one of the key wakefulness-maintaining neurotransmitters in the arousal system

- Histamine neurones in the hypothalamus fire prolifically in active waking, much less in quiet waking, and hardly at all during sleep

- Therefore antihistamines are unlikely exert their effect in sleep itself, but require activation of the histamine system to have their effect.

- They may promote quiet waking at the time of desired sleep and may also have effects to decrease short awakenings during sleep

Doxepin

- Doxepin is a drug with a tricyclic structure, used in depression.

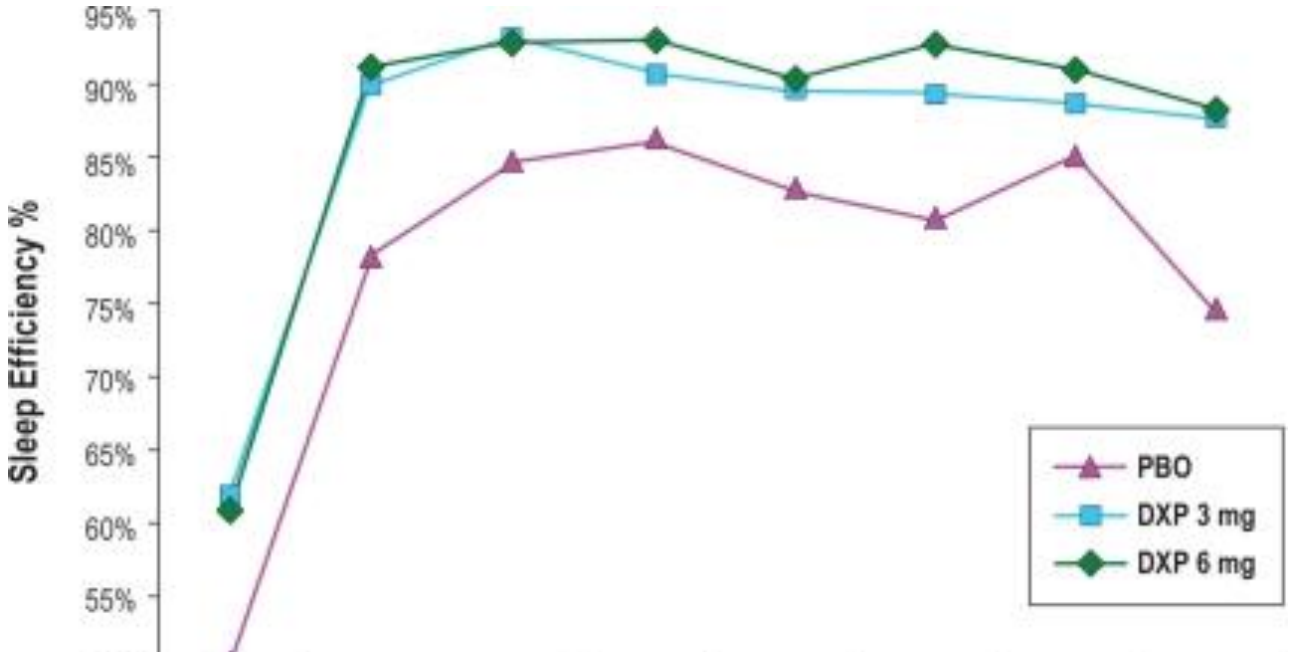
- At antidepressant doses is a noradrenaline and serotonin reuptake inhibitor, and an antagonist at various brain receptors

- Its most potent action is as a histamine H1 antagonist

- Therefore at very low doses will affect histamine receptors but have little effect at transporters or other brain receptors

- Low dose (1-6mg as opposed to antidepressant dose of ~100mg) licensed for insomnia in USA

Effects of doxepin 3 mg and 6 mg across the night: sleep efficiency % by hour



P-value	1	2	3	4	5	6	7	8
3 mg	0.0367	0.0007	0.0001	0.0355	0.0379	0.0033	0.2402	< 0.0001
6 mg	0.0579	< 0.0001	0.0003	0.0010	0.0150	< 0.0001	0.0266	< 0.0001

Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, Roth T. Sleep. 2011

Amitriptyline

- This is another drug with a tricyclic structure, used in depression. It also is a serotonin and noradrenaline reuptake inhibitor, and an antagonist at other brain receptors

- Usually used in low dose, eg 10, 25mg (antidepressant dose ~ 150mg) for insomnia

- At this dose, likely to affect primarily histamine receptors

- No evidence for efficacy in insomnia, but used in pain and reduces pain-related sleep disruption.
- Is cheap and has no restrictions on length of prescribing

NB ALL TRICYCLIC DRUGS LIKE THIS ARE DANGEROUS IN OVERDOSE

Trazodone

- Another antidepressant drug, which is a receptor antagonist at 5-HT2* and alpha-1 adrenergic and partial agonist at 5-HT1A brain receptors. Much less potent at H1 histamine receptors

- Usually used at low end of antidepressant dose (~ 100mg) for insomnia

- Some lower level evidence for efficacy in insomnia

* increases slow wave sleep

Drugs for psychosis sometimes used in insomnia

- Quetiapine occasionally used in low doses, although patients often escalate. Olanzapine used less often

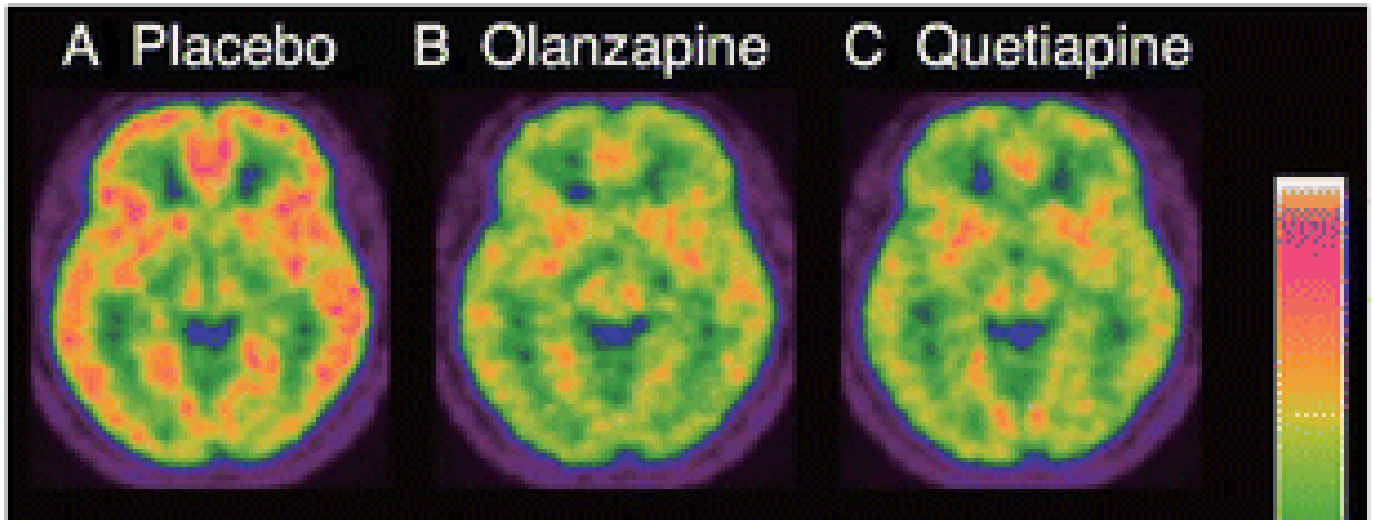
- Both drugs have a wide range of action at brain receptors, including dopamine , serotonin and histamine H1 receptors

- Both improve sleep in healthy volunteers

- Quetiapine improves sleep in primary insomnia

- Side effects are common because of the pharmacological actions of these drugs and there are a few reports of abuse. Together these indicate no indication for use as first line treatment.

H1 receptor occupancy by quetiapine and olanzapine



Representative PET scan of [11C]doxepin in the human brain [11C]Doxepin was densely distributed in the H1R-rich cortical and subcortical regions in the placebo condition (a). In contrast, brains treated with olanzapine (b) and quetiapine (c) showed much lower radioactivity distribution of [11C]doxepin.

Sato et al Psychopharmacology October 2015, Volume 232, Issue 19, pp 3497-3505

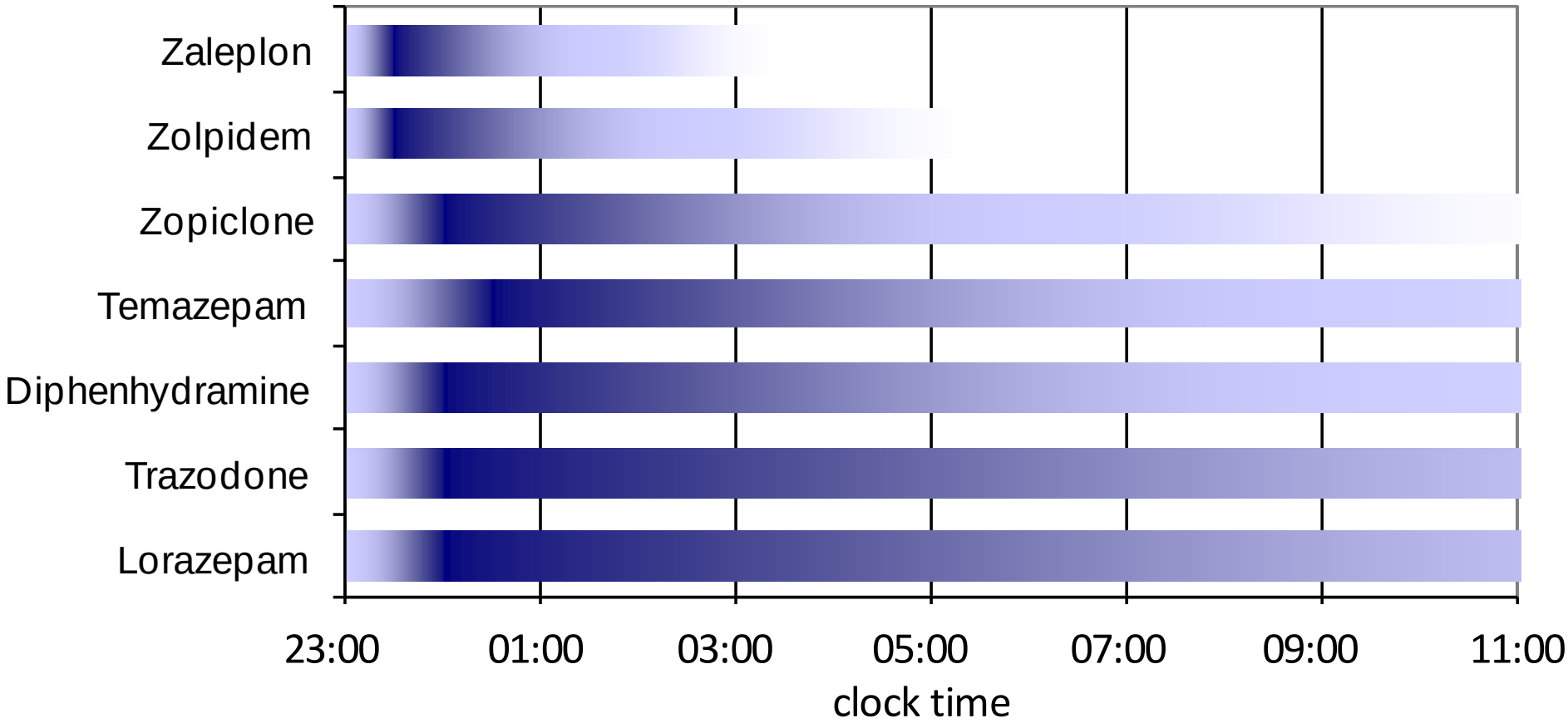
Safety

- Controlled studies measuring cognitive and psychomotor function (eg DSST, memory) *in insomnia patients* have only shown next-day deleterious effects consistently after flurazepam (v long-acting) and very high doses of other benzos

- Next-day driving
  - Epidemiology studies show that road accidents increased with benzos and zopiclone
  - deficits in driving simulator performance benzos and zopiclone
  - no reported effects of zolpidem, zaleplon, PR melatonin

- Rebound insomnia – all except zaleplon, melatonin
  - onset and duration related to half-life

How long do the effects last?



Properties of some drugs mentioned today

	Rapid onset	Elimination half-life (h)	Daytime (hangover) effects	Safety
Zopiclone	+	3.5–6	?Yes	✓
Zolpidem	+ +	1.5–3	No	✓
Temazepam	+	5–12	?Yes	✓
Lormetazepam	+	8–10	?Yes	✓
Lorazepam	+	10–20	Yes	✓
Chloral hydrate/betaine	+	8–12	?Yes	✗
Chlormethiazole	+	4–8	?Yes	✗
Barbiturates	+	varies	Yes	✗
Melatonin (PR)		4	No	✓
Promethazine		9-16	Yes	?
Diphenhydramine		5-11	?Yes	?
Amitriptyline		15	Yes	?
Trazodone		10-12	Yes	✓
Quetiapine		6-12	Yes	?

Licensed for insomnia in UK