

Medical Treatments for Nightmares, RLS, CRDs and Insomnia

Dr Hugh Selsick

Insomnia and Behavioural Sleep Medicine Clinic

Royal London Hospital for Integrated Medicine

University College London Hospitals

Nightmares: A Noradrenergic Cycle



Treatment Strategies: Prazosin – Level A

- Alpha 1 antagonist.
- Prazosin is recommended for treatment of PTSD related nightmares in military and civilian patients.
- Average dose of 3mg, although in military populations may be as high as 10-13mg.
- Indicates that noradrenaline is involved in PTSD related nightmares.
- Noradrenaline raised in CSF of PTSD patients and level correlated with severity of PTSD.

Trazodone – Level C

- Has alpha1 antagonist properties.
- Level 4 survey of 74 PTSD patients showed reduction in nightmares in 79% of patients with complete remission in 50%.
- 91% of full responders were on 100mg.
- This is below the antidepressant starter dose.

May also consider – Level C

- Atypical antipsychotics – Olanzapine, risperidone and aripiprazole
- Topiramate – civilians with PTSD. Final dosage 100mg or less in 91% of full responders.
- Gabapentin – mean dose of moderate to marked improvement 1344mg.

My Practice

- Screen for and treat any comorbid sleep disorders.
- Trazodone 1st line – many of these patients have comorbid depression, anxiety and insomnia.
- Trazodone well tolerated and treats multiple symptoms.
- Titration is simple and quick.
- If already on an antihypertensive ask GP if there is any reason not to switch to prazosin – if not then prazosin may be useful.
- Titration is more difficult as GPs not familiar with this indication.

Restless Legs Syndrome

1. Uncomfortable sensation – can be anywhere in the body, but usually the legs.
2. Worse at night.
3. Worse at rest.
4. Temporarily relieved by movement.
 - Easy to localise but hard to describe.
 - Manifests as sleep onset insomnia.

RLS & Depression

- Symptoms of depression are common in RLS (Hornyak, 2010).
- Some data to suggest treating RLS improves depression (Pichiatti, 2005).
- 35% of patients with Restless Legs and Depression report suicidal ideation as a result of their restless legs (Becker, 2006).

Diagnosing RLS

- General physicians correctly diagnose RLS in less than 10% of patients (Hening, 2004).
- It is surprisingly rare for patients to volunteer RLS symptoms. You need to specifically ask about them.
- A single question has been shown to have 100% sensitivity and 96.8% specificity for RLS in a neurology outpatient population (Ferri, 2007):
- “When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?”

But if the Answer is Yes:

- Check it is:
- Worse at night, and
- Worse at rest, and
- Temporarily relieved by movement.
- Ask if it is made worse by:
- Alcohol
- Tiredness
- Inactivity
- Medications (especially antihistamines).

Restless legs is a
clinical diagnosis.
No sleep study is
needed!

Restless Legs Treatment - Iron

- Oral iron supplementation should be offered if the ferritin is below 100mcg/L.
- This is well above the laboratory “normal minimum”.
- Once the ferritin is above 100mcg/L monitor regularly as maintenance doses may be required.
- This is the preferred treatment in pregnancy.
- In cases where patients can't tolerate oral iron or in treatment resistant cases i.v. iron infusions can be effective, though the effect is not immediate.

Treatment - Medications

- The licensed 1st line treatments in the UK are the dopaminergic (anti – Parkinson's) medications. They increase dopamine at night.
- Ropinirole: 250mcg nightly x 2d, then 500mcg nightly x 5d, then 1 mg nightly x 7d, increased by 500mcg each week; max 4 mg per day.
- Pramipexole: 88mcg nightly, doubled every 4 – 7d; max 540mcg.
- Take tablets 1 – 3 hours before onset of symptoms.
- Rotigotine: 1mg/24hr, increased by 1mg/24 each week; max 3mg/24hr.
- Can change patch at any time.

Problems With the 1st Line Treatment

- Nausea and GIT discomfort are the most common side effects in my experience.
- More worrying is compulsive behaviours. These can be subtle so family should be on the lookout.
- Increasing dopamine further runs the risk of creating tolerance.
- It also can cause “augmentation”, a rapid escalation in symptoms, which also start much earlier in the day.
- Risk factors for augmentation: dose of dopaminergic drug, duration of treatment, smoking.

A Better (Unlicensed) 1st Line - $\alpha 2\delta$ Ligands

- Gabapentin and Pregabalin do not cause compulsive behaviours or augmentation.
- Gabapentin: start at 300mg nightly, increase by 300mg a week up to 1200mg nightly if needed.
- But if the dose exceeds 600mg it can be better to split the dose as absorption of higher doses is poor.
- E.g.: for a dose of 900mg, take 300mg 3hr before symptom onset and 600mg an hour before symptom onset.
- Pregabalin: start at 25 – 50mg nightly and increase by 25 – 50mg weekly up to 300mg if needed.

3rd Line - Opiates

- Oxycodone with naloxone (Targinact) licensed as second line if dopaminergic drugs fail.
- As I would use gabapentin or pregabalin as 1st line and dopaminergics as 2nd line, this demotes Targinact to 3rd line.
- (Occasionally one may combine $\alpha 2\delta$ ligands with dopaminergics)
- Start 5/2.5 mg every 12 hours, adjusted weekly according to response, usual dose 10/5 mg every 12 hours; maximum 60/30 mg per day.
- However, I tend to start with night time doses only.
- In severe cases specialists may consider stronger opiates e.g. methadone.

Circadian Rhythm Disorders

- The only evidence based medication is melatonin.
- As most of these patients are young they will likely be prescribing outside the licence.
- But it is a very safe and well tolerated medication.
- The most common disorder is delayed sleep wake phase disorder.
- Treatment is with low dose melatonin (0.5 – 2mg) taken 4 – 6hr earlier than the time of sleep onset the night before.

Neurotransmitters & Hormones of Sleep Wake Regulation

Reduce activity of:

- Glutamate
- Noradrenaline
- Serotonin
- Acetylcholine
- Histamine
- Dopamine
- Orexin/hypocretin

Enhance activity of:

- GABA
- Adenosine
- Melatonin

	Action	Promoters	Inhibitors
GABA	Sedation	BZD's & Z Drugs	Flumazenil; Clarithromycin
Melatonin	Sedation	Melatonin & Agomelatine	B-Blockers; NSAIDs
Adenosine	Sedation		Caffeine
NA	Activation	Venlafaxine	Prazosin; Trazodone
Serotonin	Activation	SSRI's	Trazodone
Dopamine	Activation	Amphetamines	Antipsychotics
Histamine	Activation	Pitolisant	Antihistamines, TCAs, atypical antipsychotics, mirtazapine
Ach	Activation	Cholinesterase inhibitors; nicotine	TCAs; sedating antihistamines
Orexin	Activation		Daridorexant

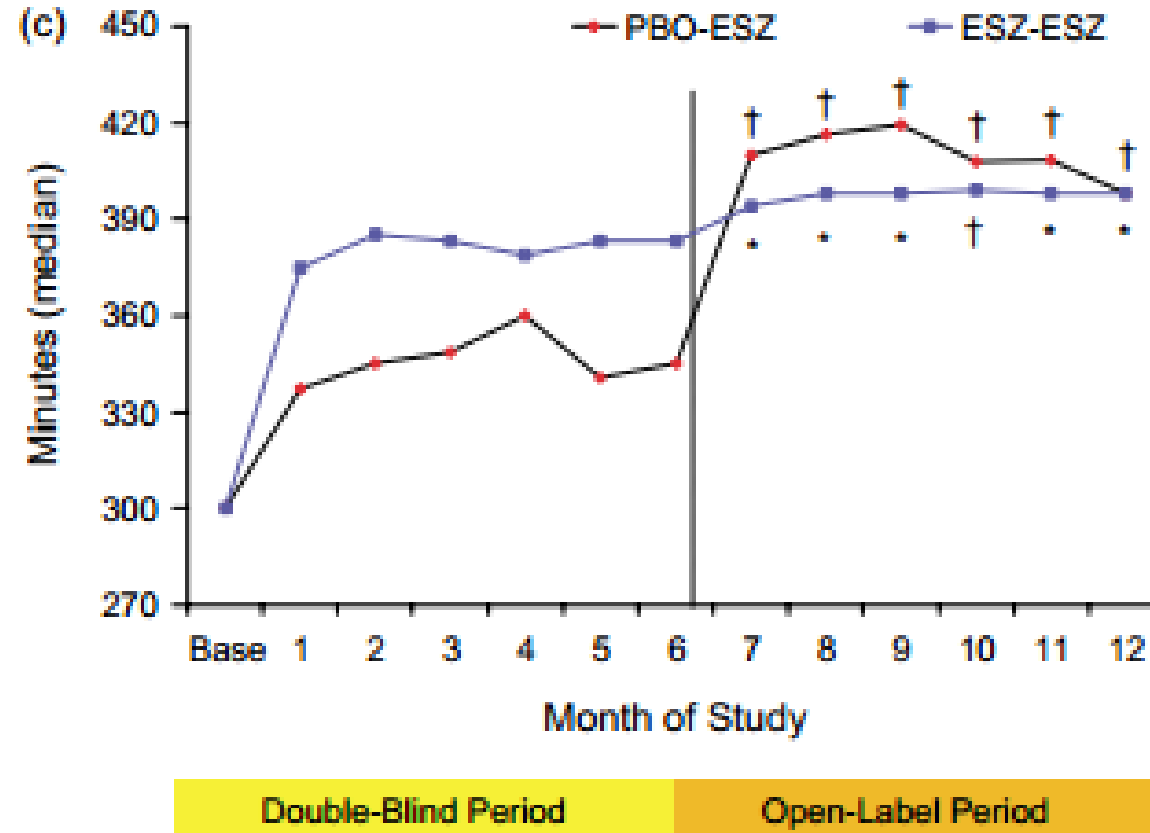
Benzos and Z Drugs

	Tmax (hours)	T _{1/2} (hours)	Hangover
Zopiclone	0.5-2	5-6	Yes
Zolpidem	1.7-2.5	1.5-2.5	Probably not
Temazepam	1-3	8-20	Maybe
Clonazepam	1-2	35-40	Yes

Do They Work?

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	(✓)*	(✓)*	✓	✓	✓	✓	✓
Zopiclone	✓	✓	✓	✓	✓	✓	✓
Zolpidem	✓	✓	✓	✓	✓	No	✓

Do they work in the long term?



Roth, 2005

Do They Work When You Stop Taking Them?

- Once the medication is discontinued the effect is lost (Riemann, 2008).
- Therefore a “short course of hypnotics just to reset the sleep cycle” doesn’t work.
- When the doctor discontinues the medication the patient will experience a recurrence of symptoms and will ask for more.
- This is often mistaken for addiction.

Melatonin for Insomnia

- Reduces sleep onset latency and improves subjective sleep quality.
- Short acting so not great for sleep maintenance.
- Licensed for over 55's & kids with ADHD/ASD, Smith Magenis.
- No consensus on optimal dose – studies have used 0.1mg-300mg.
- However, very little benefit in increasing above 6mg.
- Generally safe and well tolerated.

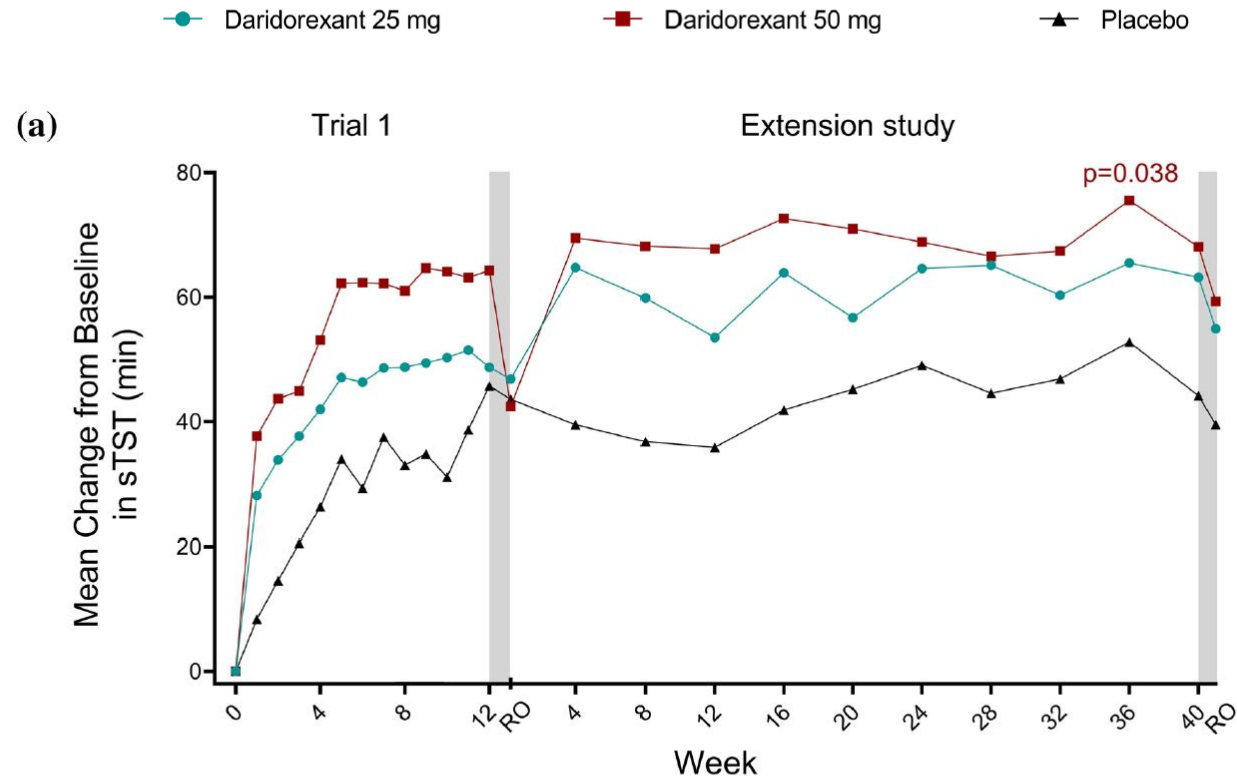
Antihistamines

- Can be useful for sleep maintenance insomnia or early morning waking.
- Over the counter antihistamines act on multiple receptors and tend to have significant anticholinergic effects.
- Promethazine prescribing has increased dramatically in the last few years. Promethazine is the most anticholinergic antihistamine.
- In the USA very low dose (3-6mg) Doxepin is licensed as a hypnotic. At this dose it is a remarkably pure antihistamine.
- In practice, low dose mirtazapine may be the best alternative.

Daridorexant

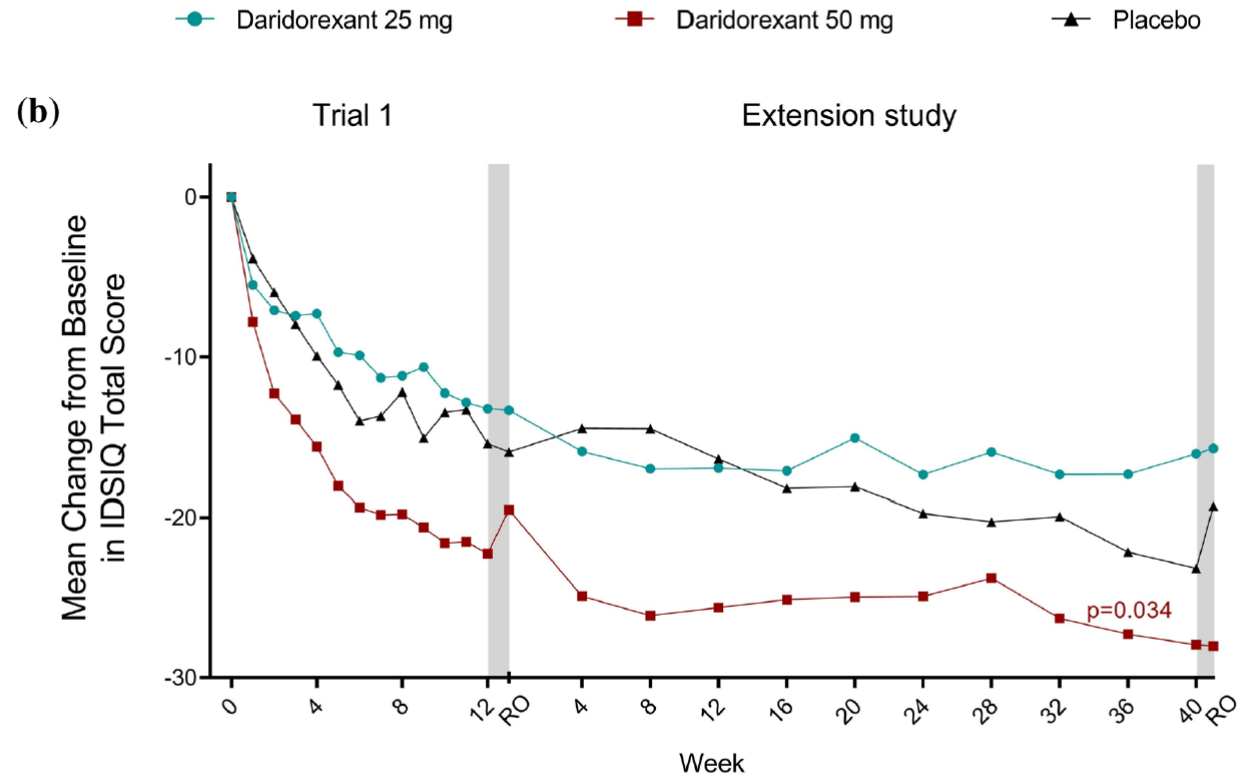
- Dual orexin receptor antagonist.
- Guidance from NICE is as follows:
 - 1.1 Daridorexant is recommended for treating insomnia in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected, only if:
 - cognitive behavioural therapy for insomnia (CBTi) has been tried but not worked, or
 - CBTi is not available or is unsuitable.
 - 1.2 The length of treatment should be as short as possible. Treatment with daridorexant should be assessed within 3 months of starting and should be stopped in people whose long-term insomnia has not responded adequately. If treatment is continued, assess whether it is still working at regular intervals.

Daridorexant: Total Sleep Time



Daridorexant 25 mg	132	132	131	127	128	103	107	106	97	98	95	88	90	85	68	76
Daridorexant 50 mg	137	136	136	133	135	115	113	105	99	97	97	94	90	87	73	85
Placebo	57	57	57	53	56	51	48	47	40	41	40	37	35	36	26	31

Daridorexant: IDSIQ Total Score



Daridorexant 25 mg	132	132	132	128	128	105	106	106	98	98	96	90	89	85	70	74
Daridorexant 50 mg	137	136	136	134	132	115	113	107	101	97	97	93	89	87	73	84
Placebo	57	57	57	53	56	51	48	48	39	41	39	36	35	35	26	32

Daridorexant in Practice

- Safety data is very encouraging.
- No increased risk of falls.
- Reduces sleep onset latency but not likely to be as effective as z drugs/benzos.
- Good for sleep maintenance.
- Effect may be cumulative.
- It has NICE approval for longer term prescribing than other hypnotics.

Antidepressants

- Sedative antidepressants are widely used in insomnia, often below the antidepressant dose. Very little of this prescribing is evidence based.
- There is some evidence for trimipramine, doxepin, trazodone, mirtazapine (Krystal 2010) and paroxetine (Wilson, 2019).
- Long half lives can lead to increased daytime sedation, particularly early in treatment. Beware of anticholinergic effects with TCAs.
- TCAs probably more toxic in O.D. than hypnotics.

Driving

- Impaired driving performance the morning after taking zopiclone, flunitrazepam, nitrazepam, lormetazepam, oxazepam, loprazolam and flurazepam, TCAs.
- No impairment after zolpidem (despite FDA caution) and melatonin CR.
- But caution advisable nevertheless (Verster, 2013).
- Rule of thumb: Avoid driving for 13hr after zopiclone, 9hr after zolpidem or daridorexant.

Hypnotics in the Elderly and Falls

Roth (2011) in Principles and Practice of Sleep Medicine concludes:

- There is evidence that hypnotics, antidepressants and anticonvulsants are associated with an increased risk of falls in the elderly.
- There is also evidence that insomnia itself increases the risk of falls.
- Some data suggests that it is the insomnia rather than the hypnotic that raises the risk and that hypnotics are less risky than antidepressants.

Stopping Hypnotics

- Most studies use 25% reduction every 1-2 weeks.
- If you are removing a treatment, ensure you have another treatment to replace it. Discontinuation is more successful if combined with CBT for Insomnia.
- Warn patients about rebound insomnia.



Before Prescribing

- Be sure it is insomnia! Could it be restless legs, a circadian rhythm disorder or OSA?
- Pluck the low hanging behavioural fruit.
- Try to avoid polypharmacy – are they on a medication where you could choose a sedating alternative?
- Be aware of any comorbid medical conditions, substances and medications.
- Be clear on what time of night they have a problem.

Insomnia prescribing: My Practice

- Initial insomnia: zolpidem at bedtime; melatonin, mirtazapine, trazodone 1-2 hour before bed .
- Mid insomnia: sedating antidepressant, zopiclone, daridorexant, at bedtime.
- Terminal insomnia: zopiclone, daridorexant or sedating antidepressant at bedtime.
- But if prescribing long term then antidepressants/daridorexant may cause less anxiety in HCPs and patients.
- If daytime sedation is undesirable avoid long acting drugs (always ask about driving).
- Don't rely solely on medication – combine with behavioural approach.

Questions?

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