Treatment of insomnia

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Abstract

Insomnia has a major impact on health, performance, economic productivity and quality of life. It is important to assess patients with sleep disturbance comprehensively and distinguish insomnia from other conditions, such as excessive daytime sleepiness and parasomnias. Once a diagnosis of insomnia is established, behavioural treatments should be tried initially. Prescription of short-term medication can often restore sleeping patterns to normal before maladaptive behaviours become established, and also reduce anxiety about sleeping, which makes sleep problems worse. Choice of hypnotic drug is discussed; most drugs used to help people sleep increase the function of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. Shorter-acting, safe and selective drugs with this action, such as zolpidem and zopiclone, are available, zolpidem having the shorter half-life and therefore less liability to morning 'hangover' effects. Chronic insomnia has a strong conditioned element with negative expectations and anxiety at bedtimes and is a difficult problem to treat. Effective treatments include those involving psychological intervention such as cognitive–behavioural therapy (CBT), combined with education, sleep hygiene and specific behavioural strategies such as sleep restriction. Regarding stopping medication, brain receptors change in character in response to chronic treatment with benzodiazepines. There can therefore be a rebound of symptoms after stopping hypnotics, including the 'z' drugs (zopiclone and zolpidem), involving a worsening of sleep disturbance for one or two nights. Antidepressants with 5-HT_2-blocking properties, such as mirtazapine, are indicated in the depressed patient with severe insomnia and may occasionally be effective in insomniac patients who are not depressed.

Keywords benzodiazepines; insomnia; sleep; zolpidem; zopiclone

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The accurate diagnosis and effective treatment of insomnia is an important public health issue, because it has a major impact on health, performance, economic productivity and quality of life.[1] Epidemiological studies report insomnia that is chronic or severe enough to merit treatment in up to 20% of the general population.[2,3] There are very few specialized sleep clinics in the UK and most clinicians do not have easy access to the psychological treatments which are needed for long-term improvement; often, the simplest course of action is the prescription of hypnotic drugs. However, the appropriate use of hypnotics requires an accurate diagnosis of the sleep disorder.

Diagnosis of sleep disorders

When a patient presents with a sleep problem, it is important to distinguish insomnia from other common sleeping disturbances. Sleep problems can be classified under the following headings.

Insomnia is difficulty initiating or maintaining sleep, resulting in daytime consequences such as fatigue and poor concentration (though daytime sleepiness is rare in chronic insomnia). Objective sleep recording often shows a long delay before sleep onset, frequent awakenings from sleep and a shortened overall sleep time (see Figure 1), but this is not a universal finding.

Hypersomnia is excessive sleepiness in the daytime and a tendency to fall asleep inappropriately during the day. Most patients with hypersomnia suffer from a breathing-related sleep disorder (e.g. sleep apnoea, see below) and should be referred to respiratory physicians, but more rarely this is due to narcolepsy, when the patient will also have cataplexy (sudden collapses without loss of consciousness).

Parasomnias are unusual happenings during the night, such as sleepwalking, night terrors, nightmares and sleep paralysis. Distinguishing these disorders often requires referral to a specialist centre that can offer polysomnography. Nightmares, even those associated with post-traumatic stress disorder (PTSD), can be treated with cognitive–behavioural therapy (CBT) using imagery rehearsal.[4]

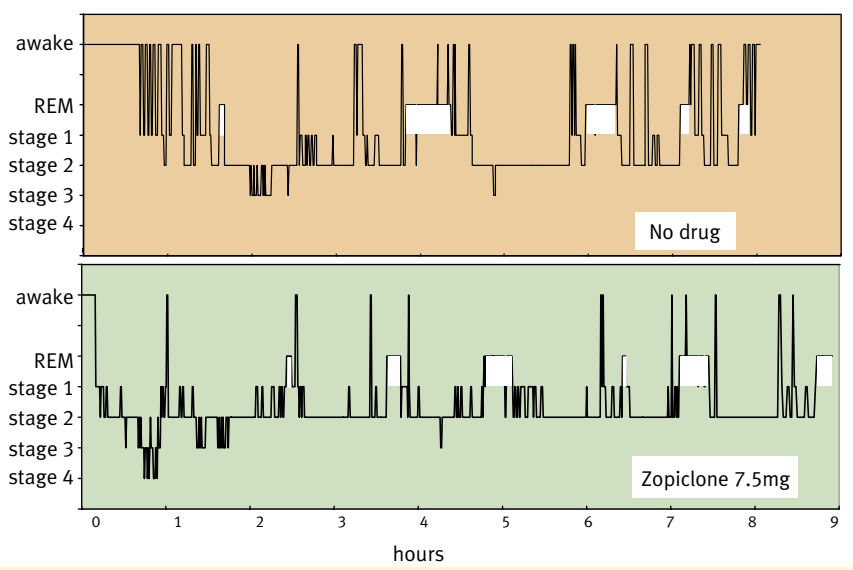
Other sleep disorders, such as restless legs syndrome and circadian rhythm disorder, are best dealt with at a specialist sleep centre or by a clinician with a special interest in these problems.

Assessing insomnia

The first step in characterizing insomnia is to take a careful history, in particular to exclude depression as a cause of the sleeping problem: over 90% of patients with major depression have difficulty initiating or maintaining sleep. A sleep diary will reveal much about the patient's sleep habits (Table 1) and the variability of the problem. If, for example, the patient is reporting good sleep but not at the desired time, then the diagnosis is a circadian rhythm disorder such as delayed sleep-phase syndrome.

Treatment

The causes of short-term insomnia are shown in Table 2. An important first step is to try to ameliorate the cause if possible.



Hypnograms of an insomniac patient with no treatment (top graph) and after zopiclone 7.5 mg. As can be seen from the untreated hypnogram, it took the patient about an hour to establish sleep, and there are many awakenings thereafter. Sleep efficiency, defined as per cent time asleep of time in bed, was 79% before and 96% after zopiclone.

Figure 1

Good sleep habits should then be initiated and compliance monitored with a diary. If the problem persists, a standard hypnotic drug may be tried for a short period. Once a patient has been sleeping badly for a short time, thoughts and behaviours that are negatively associated with sleep tend to become established. The most common of these are the tendency to associate being in bed with not sleeping, together with a vicious circle at bedtime when thoughts about the consequences of not falling asleep cause worry and physiological arousal, which in turn inhibit falling asleep. Prescription of short-term medication can often restore sleeping patterns to normal before these maladaptive behaviours become established, and also reduce anxiety about sleeping, which makes sleep problems worse.

Choice of hypnotic drug

Most drugs used to help people sleep increase the function of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. This increased transmission has sedative, anticonvulsant and anti-anxiety effects. Benzodiazepines and the non-benzodiazepine 'z' drugs (zopiclone, zolpidem and zaleplon) are safe and effective hypnotics[5–7] that have their effects at a site on the GABA receptor and modulate the inhibitory effects of GABA neurons. An appropriate choice would be one of these drugs whose absorption and elimination characteristics suit the patient's problem: that is, a fast-acting and short-lasting drug for someone whose only problem is falling asleep, or a slower-acting and longer-lasting agent for someone who has problems with sleep interruptions later in the night (see Figure 2 and Table 3). An important consideration is the 'hangover' effect of hypnotic drugs in the daytime, which can affect the performance of skilled tasks such as driving. Any drug with a half-life greater than 2–3 hours may potentially give rise to these problems. Care should be taken in prescribing these hypnotics to patients with comorbid sleep-related breathing disorders such as obstructive sleep apnoea syndrome, which is exacerbated by benzodiazepines.

Objective measures of sleep show that these hypnotics decrease the time to sleep onset and reduce waking during the night. The

Good sleep habits

- Schedule enough time for sleep
- Stick to a regular routine of bedtimes and rise times
- Get some daylight in the morning
- Take some exercise every day, preferably not late at night
- Don't nap in the daytime
- Wind down towards bedtime
- Deal with problems early in the evening – no worrying in bed

Table 1

Factors leading to insomnia

Psychological

Increased arousal due to:
- stress or worry
- bereavement
- being 'on call'
- noise
- children

Pharmacological

Prescribed drugs, e.g.:
- β-blockers
- antidepressants
- steroids

Non-prescribed drugs, e.g.:
- alcohol
- caffeine
- stimulants
- withdrawal

Physical
- Pain
- Pregnancy
- Illness, especially cardiorespiratory
- Urinary problems

Psychiatric
- Depression
- Anxiety
- Substance abuse

Table 2

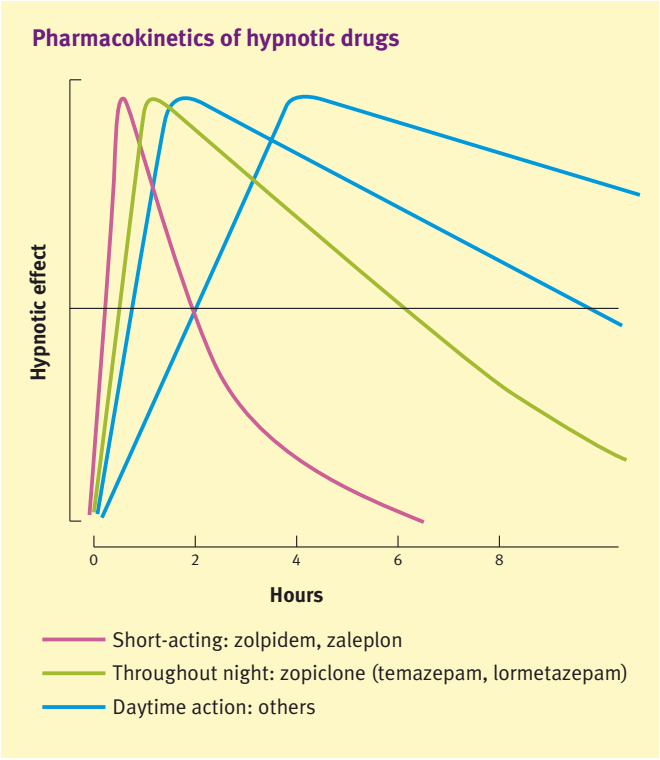


Figure 2

subjective effects of improved sleep are usually greater than the objective changes, probably because of the anxiolytic properties of these drugs (selectivity between anxiolytic and sedative effect is low). Other changes in sleep architecture are dependent on duration of action, with the very short-acting compounds having the least effect. Most commonly, very light (stage 1) sleep is decreased and stage 2 sleep is increased. Higher doses of longer-acting drugs partially suppress slow-wave sleep.

Other drugs that act on the $GABA_A$–benzodiazepine receptor are chloral hydrate, clomethiazole and barbiturates, which also enhance GABA function. However, at high doses they have the additional capacity directly to open the membrane chloride channel; this may lead to potentially lethal respiratory depression and explains their low therapeutic ratio. These drugs also have a propensity for misuse and are thus very much second-line treatments.

Non-prescribed medications in insomnia: most proprietary (over-the-counter) sleep remedies contain antihistamines. Both promethazine and hydroxyzine reduce sleep-onset latency and awakenings during the night after a single dose, but there have been no studies showing enduring action, and neither of these antihistamines is available over the counter. Trimeprazine is sometimes used as a hypnotic in children. There are no controlled studies showing improvements in sleep after other antihistamines. Most antihistamine sedatives have a relatively long action and may cause daytime sedation; many also have unwanted effects at other receptors in the brain, such as dopamine receptors.

Melatonin, the hormone produced by the pineal gland during darkness, has been investigated for insomnia, but it appears to be ineffective in adults.[8,9] The impressive nature of the diurnal rhythm in melatonin secretion has stimulated interest in its use therapeutically to reset circadian rhythm to prevent jet-lag after long-haul flights, and for blind or partially sighted people who cannot use daylight to synchronize their natural rhythm. There is controversy about dose and timing of treatment, however, and in most countries – as in the UK – pharmaceutical preparations are not generally available.

Herbal preparations are widely used by patients. Randomized clinical trials have shown some effect of valerian in

Benzodiazepines and other hypnotic drugs

	Usual dose (mg)	Rapid onset	Elimination half-life (hrs)	Daytime (hangover) effects	Works selectively to enhance GABA	Safety
Zopiclone	7.5	+	3.5–6	?Yes	✓	✓
Zolpidem	10	++	1.5–3	No	✓	✓
Zaleplon[a]	10	++	1–2	No	✓	✓
Temazepam	20		5–12	?Yes	✓	✓
Loprazolam	1		5–13	?Yes	✓	✓
Lormetazepam	1	+	8–10	?Yes	✓	✓
Nitrazepam	5–10	+	20–48	Yes	✓	✓
Lorazepam	0.5–1	+	10–20	Yes	✓	✓
Diazepam	5–10	+	20–60	Yes	✓	✓
Oxazepam	15–30		5–20	Yes	✓	✓
Alprazolam	0.5	+	9–20	Yes	✓	✓
Clonazepam	0.5–1	+	18–50	Yes	✓	✓
Chloral hydrate/betaine	0.7–1	+	8–12	?Yes	✗	✗
Chlormethiazole	192	+	4–8	?Yes	✗	✗
Barbiturates	Varies	+	Varies	Yes	✗	✗
Promethazine	25		7–14	?Yes	✗	✗/✓

[a]Can be taken during the night, until 4 hrs before needing to drive, etc.

Table 3

mild-to-moderate insomnia, and hops, lavender and other herbal compounds show promise in pilot studies that are currently being pursued more fully.

Treatment of long-term insomnia

Chronic insomnia, which has a strong conditioned element with negative expectations and anxiety at bedtimes, is a difficult problem to treat. The treatment of choice is CBT targeted at specific thoughts and behaviours in insomnia. Evidence for a conditioning element is provided by the fact that many patients sleep well in a new environment that is not associated in their experience with poor sleep, such as when on holiday or in hospital.

Patients with long-term insomnia have often been taking hypnotic drugs for long periods and are unwilling to stop, partly because they cannot tolerate the rebound insomnia, however short-lived, which is to be expected even after short-acting drugs.[10] There is little evidence that long-term use of hypnotics causes medical problems, but some studies have shown that waking during the night (as recorded with polysomnography) is decreased by hypnotic drugs but may start to increase again after 4–8 weeks of treatment, suggesting that some tolerance develops. However, dose escalation is rarely necessary. Regarding withdrawal effects, both animal and human research has shown that brain receptors change in character in response to chronic treatment with benzodiazepines, and therefore will take time to return to pre-medication levels after cessation of medication. There can be a rebound of symptoms after stopping hypnotics, involving a worsening of sleep disturbance for one or two nights, with longer sleep-onset latency and increased waking during sleep – this is common.

For patients who wish to stop their hypnotics there are various strategies. One is to encourage intermittent use of short-acting hypnotics, so that the patient knows they will get a good night's sleep two or three times a week with medication. Another is to encourage dose tapering over a short period, with education of the patient about rebound insomnia. Planning the timing of this taper is important, and many patients prefer to use a period of leave from work, or recruit help with family responsibilities for the period during which they expect their sleep to be temporarily worse. Treatments that have been shown to improve symptoms in chronic insomnia are those involving psychological intervention such as CBT. Treatment packages combining this with education, sleep hygiene and specific behavioural strategies such as sleep restriction are effective but not widely available. Once patients have been taught some of these techniques they may find reduction of the hypnotic medication easier.

Despite these efforts there will be some patients who continue to complain that their insomnia responds only to hypnotic drugs. In such cases the patient and clinician together need to weigh up the risks and benefits of remaining on medication, bearing in mind the possible risk of the patient using alcohol (or unprescribed drugs) as an alternative. An antidepressant drug may be tried; the patient should be stabilized on a standard antidepressant dose before withdrawal of the hypnotic is started.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) often cause insomnia early in treatment, but in depressed patients, improvement in mood is almost always accompanied by improvement in subjective sleep; therefore, choice of antidepressant should not usually involve additional consideration of sleep effects. Nevertheless, some patients are more likely to continue with medication if there is a short-term improvement, in which case an antidepressant that promotes sleep (such as mirtazapine) may be preferred. It is thought that this effect of mirtazapine may be due to its action to block serotonin (5-HT_2) receptors; indeed, nefazodone, which also blocks these receptors, has also been shown to be sleep-promoting.[11]

In insomniac patients who are not depressed, antidepressant drugs with 5-HT_2-blocking effects may occasionally be effective. There have also been reports of SSRIs ameliorating long-term insomnia, presumably because of their anxiolytic or anti-obsessional effects.

Insomnia may occur in psychoses such as schizophrenia and mania. In such situations it is advisable to use an anti-psychotic with 5-HT_2-blocking effects because it will help sleep. Occasionally, low doses of these newer antipsychotics are used in non-psychotic patients with intractable insomnia; quetiapine is probably the safest to use as it has the shortest half-life. ◆

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