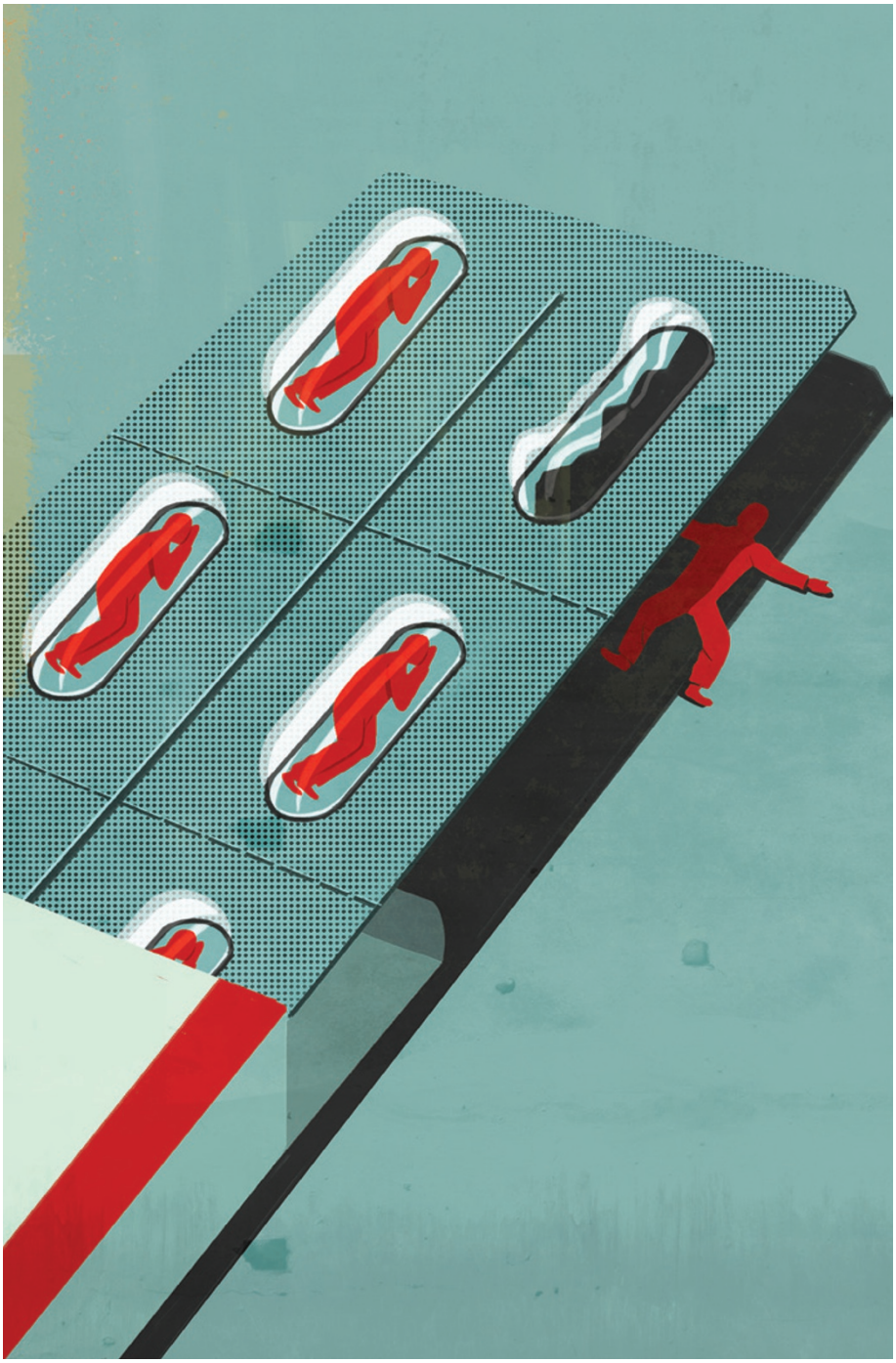

EMILIANO PONZI

INSOMNIA

Chasing the dream

A combination of drugs and cognitive behavioural therapy may finally put an end to the misery of sleepless nights.

BY JAMES MITCHELL CROW

How's your bedroom hygiene? If a sleep therapist asks you this, they aren't interested in your vacuuming habits or laundry routine. What concerns them is another form of detritus that tends to accumulate around our beds: the television across the room, the latest tension-building thriller just downloaded onto your e-reader, and the smartphone chirping the arrival of every new e-mail.

Practising sleep hygiene — cleaning gadgets, and anything else that promotes worry or alertness, out of the bedroom — is a proven technique that could help the huge numbers of people who routinely struggle to sleep.

One in three adults find it difficult to fall asleep, or stay asleep, at least one night a week[1]. Around half of those sleep so badly they have problems functioning during the day. "Insomnia must not be taken lightly, it is a very prevalent and significant public health problem," says Charles Morin, a clinical psychologist specializing in insomnia at Laval University in Quebec, Canada. "It carries a very significant burden for the individual — such as increasing the risk of depression and the risk of accidents — and has direct and indirect costs for society, including decreased work productivity."

But treatment options are limited: although insomnia is a long-term condition, sleeping pills are typically recommended for people with significant distress or marked daytime impairment, but only for short-term treatment. One promising alternative is psychotherapy, which includes teaching sleep hygiene, but the sheer number of people experiencing insomnia makes cognitive behavioural therapy impractical as a first-line therapy for the masses.

LITTLE HELPERS

People have been taking substances to induce sleep throughout recorded history. The ancient Egyptians and Greeks used extracts of the opium poppy and the hemp plant[1]. In the second half of the nineteenth century, synthetic drugs such as chloral hydrate and bromide salts, which calm the brain by inhibiting neurons from firing, supplanted these herbal extracts.

Successive waves of sleep-inducing, or hypnotic, drugs have since reached the clinic, each safer and more effective than the last. The first barbiturate — barbitone, or barbital — hit the market in 1904 after its power to send dogs to sleep was discovered. The 1960s brought the benzodiazepines, such as diazepam (Valium) and temazepam. Today's hypnotics of choice, known as 'non-benzodiazepines', reached the clinic in the 1990s, with zolpidem, zopiclone and zaleplon — a group known as the Z-drugs — being most commonly prescribed.

All these hypnotic drugs work in basically the same way: they interact with γ-aminobutyric acid (GABA) receptors in the brain. GABA is the brain's main inhibitory neurotransmitter, calming brain cell activity, which explains why barbiturates and benzodiazepines have also been used as anti-anxiety treatments and

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sedatives. In particular, one group of GABA-producing neurons in the hypothalamus forms a key part of the central switch that triggers the change from wake to sleep.

There are two families of GABA receptor: $GABA_A$ and $GABA_B$. Hypnotic drugs bind to the $GABA_A$ receptor, enhancing the action of the GABA neurotransmitter. Because GABA suppresses a multitude of central nervous system functions, enhancing its activity can cause a cascade of side effects. Barbiturates have a notoriously narrow range of safe dosage — taking just a little too much can fatally suppress the brain centres that control heart rate and breathing. Even at lower, non-lethal doses, they can produce amnesia, sometimes causing patients to forget they had taken them and then to take more — a perilous cycle that can easily lead to an overdose[2]. Habitual users can also become physically addicted, experiencing severe withdrawal symptoms when they try to quit the drug.

Benzodiazepines are more potent hypnotics than barbiturates, and are also much less likely to lead to overdose. But some risk of physical or physiological dependence remains, and the drugs are associated with a 'hangover' — a residual drowsiness as the drugs slowly wear off. "A lot of people take sleeping pills because they are afraid their poor sleep is going to impair them the next day," says Daniel Kripke, who studies sleep disorders at the Scripps Clinic in San Diego, California. "But in the vast majority of studies of insomnia, sleeping pills make daytime performance worse, not better."

The Z-drugs have less of a hangover effect than benzodiazepines, thanks to their shorter half-life in the body, so their effects are less likely to be felt the next morning. Comparative studies show that these non-benzodiazepines also generally induce sleep a few minutes faster than benzodiazepines, and they significantly reduce the occurrence of next-day drowsiness[3].

Even Z-drugs can make activities such as driving more dangerous the next morning, however. In one study, more than half of trial participants given zopiclone were worse at driving 8.5 hours later than someone with a blood alcohol content of 0.05%, the legal limit for driving in many countries[4]. A lack of long-term clinical trials and the increased potential for patients to become dependent on sleeping tablets mean that these drugs are still generally recommended only for short-term use[2].

Epidemiological studies suggest there is good reason to be cautious. According to one recent report co-authored by Kripke, patients taking hypnotics such as zolpidem and temazepam were over four times more likely to die during the 2.5-year study period than hypnotic-free control patients[5]. The researchers estimate that sleeping medication played a role in half-a-million deaths in the United States in 2010.

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For more on targeting GABA to influence sleep:
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HOW SLEEPING PILLS WORK
Several classes of drug share the same mechanism, but others increasingly target different molecular pathways.

Class	Action	Examples
Barbiturates Benzodiazepines Non-benzodiazepines ('Z-drugs')	Increase effect of γ-aminobutyric acid (GABA) by binding to the GABAA receptor (see diagram). The ventrolateral preoptic nucleus (VLPO) in the hypothalamus uses GABA to inhibit wakefulness; more GABA means more sleep	Phenobarbital. Chlordiazepoxide, diazepam, temazepam. Zolpidem, zopiclone, eszopiclone.
Antihistamines	Block histamine in the ascending arousal system	Diphenhydramine, hydroxyzine.
Antidepressants	Inhibit serotonin and histamine receptors	Trazodone, nefazodone.
Adrenergic agonists	Hamper noradrenaline-releasing neurons, block part of the ascending arousal system, and allow the VLPO system to activate	Dexmedetomidine.
Melatonin agonists	Increase the activation of melatonin receptors, a circadian cue that primes the body for sleep via VLPO activation	Melatonin, ramelteon.
Orexin receptor antagonists	Block orexin neurons, inhibiting their wake-promoting signal	Suvorexant, SB-649,868 (both unapproved).

The precise risk of sleeping pills is still not yet known, however. "There is a clear correlation between mortality and the use of hypnotics," says Jian-Sheng Lin, a sleep researcher at Lyon Neuroscience Research Centre in France who is looking for new hypnotic drugs. "However, the causality remains to be demonstrated."

BOUND TO WORK

One route to making sleeping pills safer that looked promising for a while was to make them more selective. $GABA_A$ receptors can be subdivided into several structurally distinct subtypes. Benzodiazepines activate them relatively unselectively, binding to four of the six subtypes (those containing the α1, α2, α3 or α5 subunits). More recent sleeping drugs are less scattershot: zolpidem preferentially binds to receptors containing α1, for example, and another non-benzodiazepine, eszopiclone, has a slight selectivity for those containing α2 and α3.

Researchers are trying to figure out what each subtype does. Genetic neuropharmacologist Uwe Rudolph at McLean Hospital in Belmont, Massachusetts, uses molecular genetics to test whether benzodiazepine's various effects — anxiety relief, sedation and sleep induction — are exerted through specific receptor subtypes. Rudolph's team introduced genetic mutations to disable each subtype in mice, one at a time, and tested benzodiazepine's effects.

When they gave diazepam to mice with a mutated α1 subunit, the drug's sedative properties were lost: it no longer calmed muscle activity when the mice were given a convulsant. When the team mutated the α2 subunit, diazepam lost its anxiety-reducing effects, suggesting that the anti-anxiety effect of the drug operates through this receptor subtype. All the evidence seemed to be falling into place.

The surprises started when Rudolph and colleagues used electroencephalography (EEG) to monitor sleep in mutant mice given diazepam by measuring characteristic shifts in brain activity. "Our prediction was, as α1 is responsible for sedation, then it might be responsible for the sleep-inducing action of diazepam," Rudolph says. "This was not really the case." Instead, mice with a mutated α1 subunit slept just as soundly as wild-type (unmutated) mice when given diazepam.

The EEG readouts of the α2 knockout mouse were just as confusing. This time, there were significant differences between the wild-type mouse and the mutant, suggesting that diazepam's sleep-inducing effects are mediated by receptors containing the α2 subunit[6].

The mixed messages thrown up by the mouse studies have failed to signpost a clear path for improved hypnotic drugs targeting particular $GABA_A$ receptors, says Rudolph. "Part of the problem," he says, "is that existing hypnotics have only weak preferences for GABA subtypes." Drugs with complete subtype selectivity could have clarified the picture — but no such compounds are known, and without stronger evidence that subtype selectivity would improve on today's Z-drugs, drug developers aren't rushing to make them. In the absence of such compounds, the development of new GABA-targeting sleeping pills has stalled.

In the meantime, promising alternative targets have emerged, and the next generation of sleeping pills may sidestep GABA receptors entirely (see 'How sleeping pills work').

One well-travelled path involves histamine blockers, such as doxepin, which has been used for decades as an antidepressant in doses of up to 150 milligrams. "It turns out that lower doses — 3 mg or 6 mg — have some benefit for sleep, and probably very little side effect," Kripke says.

Doxepin generally targets a receptor known as H1, which is found throughout the body. But Lin and his colleagues at Lyon are concentrating instead on the H3 receptor, which is found at high densities in the hypothalamus, where the sleep–wake switch lies[7]. "We use H3-receptor antagonist to treat excessive daytime sleepiness disorders such as narcolepsy, but we think that an H3-receptor agonist could be very useful for insomnia," Lin says. Animal studies

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A HISTORY OF SLEEP RESEARCH

The past century has seen a growing research effort to probe – and control – the sleeping brain.

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1929
Hans Berger records electrical activity of the sleeping brain

1940s
Robert Moore identifies the suprachiasmatic nucleus

1953
Nathaniel Kleitman and Eugene Aserinsky at the University of Chicago, Illinois, describe the rapid eye movement (REM) stage of sleep and propose a correlation with dreaming

1960
Librium, the first benzodiazepine, is launched

1970s
Benzodiazepines begin to replace barbiturates as insomnia treatments

1972
Suprachiasmatic nucleus pinpointed as site of our biologic clock

1977
Frédéric Bremer hypothesizes how the ascending arousal system and VLPO work together as a 'flip flop' switch

1984
Serge Daan proposes that sleep is regulated by circadian and homeostatic processes

1993
US National Institutes of Health (NIH) establishes National Center on Sleep Disorders Research

2001
Louis Ptáček discovers first human gene involved in circadian rhythms

2012
Merck & Co. submits orexin-antagonist suvorexant for US Food and Drug Administration approval

confirm that stimulating the receptor increases sleep. "As a drug target, it is in the proof of concept stage, but we have candidate agonists in development," he adds.

Drug companies also have other targets in their sights. In the late 1990s, several research groups found that narcolepsy can be caused by insufficient amounts of a neurotransmitter called orexin, or by a shortage of orexin-detecting neurons. Since then, several candidate orexin-receptor antagonists have been discovered that mimic the effect of narcolepsy and trigger sleep. Furthest along the development pipeline is suvorexant, for which pharmaceutical company Merck recently filed for approval from the US Food and Drug Administration after it completed clinical trials. The results suggest that suvorexant might be safer than existing sleep medications. Merck recently compared a suvorexant-related compound called DORA-22 with diazepam, zolpidem and eszopiclone in rats and monkeys. DORA-22 was the only drug to promote sleep at doses that did not impair the animals' cognition or memory[8].

MIND OVER MATTER

While drug developers continue to work on a new generation of more effective sleeping pills, Kripke and others think the best solution is already at hand — and has nothing to do with drugs. Cognitive behavioural therapy (CBT) is a form of psychotherapy that aims to remove the dysfunctional thoughts and behaviours that underlie a variety of conditions, from depression to eating disorders.

Learning good sleep hygiene is key to the behavioural component of CBT. Patients must remove from their bedrooms any gadgets and other items that might promote worry or alertness. They are taught to go to bed only when sleepy, and to get out of bed if they find themselves wide-awake for a spell during the night. On the cognitive side, therapists teach relaxation techniques and aim to help patients work through worries that keep them awake. The aim is to break the cycle of being unable to sleep and becoming frustrated.

Numerous studies have found that CBT is a more effective long-term solution for insomnia than sleeping pills. A recent meta-analysis showed that at the end of a course of treatment, benzodiazepines and Z-drugs were approximately as effective as CBT — but that patients taking these drugs who also were given CBT maintained these gains in improved sleep, or even reported further improvements, in the months and years afterwards. No such effects have ever been shown for benzodiazepines or Z-drugs, according to this analysis[9]. Kripke says that compared with hypnotic medication, CBT is "safer, in the long run less expensive, and just plain works better".

But CBT is not a quick fix. A typical six-session course with a therapist is far more time consuming and expensive than simply writing out a prescription for a sleeping pill. "The difficulty with CBT has been getting it out there on a scalable basis," says Colin Espie, a neuroscientist who specializes in sleep research at the University of Oxford, UK. "There are 15 million prescriptions for sleeping pills written annually in the UK, whereas only a few hundred people get access to CBT."

Espie is among a growing group of researchers hoping to make CBT available to the masses by delivering it via the Internet. Alongside online business developer Peter Hames, Espie recently developed a web-based CBT programme called Sleepio. Advice delivered by an animated virtual therapist is tailored to the individual patient — in a section helping patients learn to slow a racing mind, for example, more than two million different response combinations are possible, Espie says. His tests show that web-based CBT is more effective than a placebo — and about as effective as CBT delivered in person by a therapist[10]. The team is investigating how to integrate online CBT with clinical care, for example by developing a portal that allows doctors to monitor their patients' progress. A similar service is already in place in the United Kingdom for web-based CBT to treat depression.

This is a promising start towards helping CBT become a mainstream insomnia treatment, but nobody is arguing that research to develop safer and more effective sleeping pills should stop. It's about being able to offer patients the choice, says Espie — some people will embrace the challenge of working through a CBT programme and making the lifestyle changes needed for long-term benefits, whereas others will simply prefer to pop a pill. Meanwhile, Morin's research shows that CBT and sleeping pills don't have to be mutually exclusive: patients given a short course of zolpidem at the start of their therapy had slightly better long-term improvement than those using CBT alone[11].

So, after countless years of suffering, relief from sleepless nights and daytime sleepiness may soon be within reach, thanks to new drugs being developed and the spread of CBT. Just make sure you leave your smartphone at the bedroom door. ■

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