



British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders

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Abstract

Sleep disorders are common in the general population and even more so in clinical practice, yet are relatively poorly understood by doctors and other health care practitioners. These British Association for Psychopharmacology guidelines are designed to address this problem by providing an accessible up-to-date and evidence-based outline of the major issues, especially those relating to reliable diagnosis and appropriate treatment. A consensus meeting was held in London in May 2009. Those invited to attend included BAP members, representative clinicians with a strong interest in sleep disorders and recognized experts and advocates in the field, including a representative from mainland Europe and the USA. Presenters were asked to provide a review of the literature and identification of the standard of evidence in their area, with an emphasis on meta-analyses, systematic reviews and randomized controlled trials where available, plus updates on current clinical practice. Each presentation was followed by discussion, aimed to reach consensus where the evidence and/or clinical experience was considered adequate or otherwise to flag the area as a direction for future research. A draft of the proceedings was then circulated to all participants for comment. Key subsequent publications were added by the writer and speakers at draft stage. All comments were incorporated as far as possible in the final document, which represents the views of all participants although the authors take final responsibility for the document.

Keywords

Sleep, insomnia, parasomnia, circadian rhythm disorder, consensus, treatment

Introduction

Sleep disorders are common in the general population and even more so in clinical practice, yet are relatively poorly understood by doctors and other health care practitioners. These British Association for Psychopharmacology (BAP) guidelines are designed to address this problem by providing an accessible yet up-to-date and evidence-based outline of the major issues, especially those relating to reliable diagnosis and appropriate treatment. We limited ourselves to discussion of sleep problems that are not regarded as being secondary to respiratory problems (e.g. sleep apnoea – see NICE Guidance TA139), as these fall outside the remit of the BAP. We also did not consider certain neuropsychiatric disorders for which recent sets of guidelines already exist, such as narcolepsy (Billiard et al., 2006) and restless legs (Vignatelli et al., 2006) and also refer interested readers to the British Sleep Society website <http://www.sleeping.org.uk>. Thus the main scope of this document is to cover insomnia, circadian rhythm disorders and the more common parasomnias which are likely to present to psychiatrists or primary care physicians.

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The BAP is an association of psychiatrists, psychopharmacologists and preclinical scientists who are interested in the broad field of drugs and the brain. BAP is the largest national organization of its kind worldwide, and publishes the *Journal of Psychopharmacology*. The Association started publishing consensus statements more than a decade ago, and the first BAP guidelines on depression were considered a landmark publication when they appeared in 1993 (Montgomery, 1993). That document, updated in 2000 and in 2008 (Anderson et al., 2000; Anderson et al., 2008), has become the standard of care in many countries as it is considered an accessible consensus to guide practising psychiatrists. Additional guidelines have covered management of bipolar disorder (Goodwin, 2003; Goodwin, 2009) drug treatments for addiction (Lingford-Hughes et al., 2004), anxiety disorders (Baldwin et al., 2005), old age psychopharmacology (Burns et al., 2006), and attention-deficit hyperactivity disorder (ADHD) (Nutt et al., 2007) all of which use a similar style and process. All guidelines are available via the BAP website (<http://www.bap.org.uk>).

Method

A consensus meeting was held in London on 21–22 May 2009. Those invited to attend included BAP members, representative clinicians with a strong interest in sleep disorders and recognized experts and advocates in the field, including a representative from mainland Europe and the USA. The main age groups and clinical subtypes were specifically covered by individual speakers. Presenters were asked to provide a review of the literature and identification of the standard of evidence in their area, with an emphasis on meta-analyses, systematic reviews and randomized controlled trials (RCTs) where available. Each presentation was followed by discussion, aimed to reach consensus where the evidence and/or clinical experience was considered adequate, or otherwise to flag the area as a direction for future research. A draft which pulled together the presentations and the transcript of the taped proceedings was drawn up by SJW and DJN and circulated to all speakers and other participants for comment. Key subsequent publications were added by the writer and speakers at draft stage. All comments were incorporated as far as possible in the final document, which represents the views of all participants although the authors take final responsibility for the document.

Categories of evidence for causal relationships, observational relationships and strength of recommendations are given in Table 1 and are taken from Shekelle et al., 1999. The strength of recommendation reflects not only the quality of the evidence, but also the importance of the area under study. For example, it is possible to have methodologically sound (category I) evidence about an area of practice that is clinically irrelevant, or has such a small effect that it is of little practical importance and therefore attracts a lower strength of recommendation. However, more commonly, it has been necessary to extrapolate from the available evidence leading to weaker levels of recommendation (B, C or D) based upon category I evidence statements.

The costs of the meeting were partly defrayed by unrestricted educational grants from two pharmaceutical companies (Lundbeck and GSK). Observers from these companies were

invited to attend but did not participate in the summary proceedings or in drafting the guidelines. All attendees completed conflict of interest statements that are held at the BAP office according to BAP policy.

Scope of the guidelines

Our intention is to present a comprehensive statement to guide clinicians, who are managing patients in primary or secondary medical care.

Definition of insomnia

Insomnia is a common disorder whose definition is often not clearly understood. A number of international organizations with interests in sleep disorders have proposed varying definitions of insomnia that share three key elements (see Diagnostic criteria). They all agree insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking. They also agree that insomnia is a disorder that impairs daytime well-being and subjective abilities and functioning, and so can be considered a '24-hour' disorder.

It is important to recognize that insomnia is a subjective disorder, and its diagnosis is through clinical observations rather than via measurements; in this sense, it is a syndrome similar to pain. The cause of insomnia may be known or not, and knowledge of causation is not necessary for a diagnosis. However, in some cases it may be possible to identify and remedy a physical cause for insomnia (see treatment section).

Insomnia often starts with a specific problem, for example a stressful life event such as the loss of a job or change to a more demanding one, or through something that changes sleep patterns such as the birth of a child or starting shift work. In some people this acute insomnia persists into a chronic state. Factors involved in the persistence of insomnia are not fully established, but include anxiety about sleep, maladaptive sleep habits and the possibility of an underlying vulnerability in sleep-regulating mechanisms. Persistence of the precipitating stressor can also contribute. Some cases of insomnia are precipitated by, or are co-morbid with, other psychiatric disorders, especially anxiety and depression, or by physical illness such as cancer or arthritis.

The nature of sleep changes with age. Older age is associated with poorer objectively measured sleep with shorter sleep time, diminished sleep efficiency, and more arousals, and these changes may be more marked in men than in women, according to a very large study of elderly people living at home in the USA (Sleep Heart Health Study, Unruh et al., 2008). In the same study the association of subjective report of poor sleep with older age was stronger in women. The higher prevalence of chronic health conditions, including sleep apnoea, in older adults did not explain changes of sleep parameters with aging and age/sex differences in these relationships.

There is some disagreement about how long insomnia should have been present for before it requires intervention (see treatment section), but there is general agreement that when insomnia causes significant personal distress or marked impairment then some form of treatment is appropriate.

Definition of insomnia: Diagnostic criteria

	A	B	C
International Classification of Sleep Disorders (ICSD) and Research Diagnostic Criteria for Insomnia (RDC) (Edinger et al., 2004)	Difficulty – initiating sleep, – maintaining sleep, – waking up too early or – sleep is chronically non-restorative or poor in quality	Occurs despite adequate opportunity and circumstances for sleep	At least one form of daytime impairment i. Fatigue or malaise ii. Attention, concentration, or memory impairment iii. Social or vocational dysfunction or poor school performance iv. Mood disturbance or irritability v. Daytime sleepiness vi. Motivation, energy, or initiative reduction vii. Proneness for errors or accidents at work or while driving viii. Tension, headaches, or gastrointestinal symptoms in response to sleep loss ix. Concerns or worries about sleep
International Classification of Diseases ICD-10 (1992)	Difficulty – falling asleep, – maintaining sleep or – non-refreshing sleep	3 times a week and for longer than 1 month	Marked personal distress or interference with personal functioning in daily living
Diagnostic and Statistical Manual of Mental Disorders DSM-IV	Predominant complaint – difficulty initiating sleep – difficulty maintaining sleep or – non-restorative sleep	For at least 1 month	Clinically significant distress or impairment in social, occupational, or other important areas of functioning

Table 1. Levels of Evidence

Categories of evidence for causal relationships and treatment

- Ia: evidence from meta-analysis of randomized controlled trials
 Ib: evidence from at least one randomized controlled trial
 IIa: evidence from at least one controlled study without randomization
 IIb: evidence from at least one other type of quasi-experimental study
 III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
 IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

This categorization is most appropriate to questions of causal relationships. Similar taxonomies for other types of research question do not yet exist and the following is proposed.

Proposed categories of evidence for non-causal relationships

- I: evidence from large representative population samples
 II: evidence from small, well-designed, but not necessarily representative samples
 III: evidence from non-representative surveys, case reports
 IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

Recommendations are graded A to D as shown below. We distinguish between the category of evidence and the strength of the associated recommendation. It is possible to have methodologically sound (category I) evidence about an area of practice that is clinically irrelevant or has such a small effect that it is of little practical importance and therefore attracts a lower strength of recommendation. More commonly, a statement of evidence only covers one part of an area in which a recommendation has to be made, or covers it in a way that conflicts with other evidence. Therefore, to produce comprehensive recommendations it is necessary to extrapolate from the available evidence. This may lead to weaker levels of recommendation (B, C or D) based upon category I evidence statements.

Strength of Recommendation

- A directly based on category I evidence
 B directly based on category II evidence or extrapolated recommendation from category I evidence
 C directly based on category III evidence or extrapolated recommendation from category I or II evidence
 D directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Epidemiology of insomnia

What is known about prevalence of insomnia

- Estimates of prevalence of insomnia vary according to the definition used (1a)
- Prevalence of symptoms varies with age, with increase of nocturnal awakenings but decrease in complaints of non-restorative sleep as people get older (1b)
- Prevalence is between 1.5 and 2 times higher in women than in men (1a)
- Insomnia is a long-term disorder; many people have had insomnia for more than 2 years (1b)
- Approximately half of all diagnosed insomnia is related to a psychiatric disorder (1b)

What is not known

- What is the prevalence of distress?
- What is the significance of duration of symptoms on distress?

Studies of prevalence of insomnia in the general population indicate that one-third of adults in Western countries experience difficulty with sleep initiation or maintenance at least once a week (LeBlanc et al., 2009; Léger and Poursain, 2005; Sateia et al., 2000), and 6–15% are thought to meet criteria of insomnia in that they report sleep disturbance as well as significant daytime dysfunction (LeBlanc et al., 2009; Sivertsen et al., 2009). One-year incidence rates have been reported to be 30.7% for insomnia symptoms and 7.4% for insomnia syndrome. These rates decreased to 28.8% and 3.9% for those without a prior lifetime episode of insomnia (LeBlanc et al., 2009). There is much evidence that insomnia is a long-term disorder. In one large UK study, about three-quarters of patients reported symptoms lasting at least a year (Morphy et al., 2007) and in a population-based 3-year longitudinal study 46% of subjects who had insomnia at baseline still had it at the 3-year time point. The course of insomnia was more likely to be persistent in those with more severe insomnia at baseline, and in women and older adults (Morin et al., 2009a).

There is a higher incidence of insomnia in women, and the incidence increases in men and women as they get older. The symptom prevalence changes with age, so that people over 65 show more sleep maintenance problems but a decrease in reported daytime problems compared with younger age groups, with little change in prevalence of sleep-onset insomnia.

Diagnosis

Insomnia

Insomnia is a subjective complaint. Patients complain that sleep is inadequate, either by being too short (such as after a long period of trying to get to sleep, or due to early waking), too interrupted or not sufficiently restorative or refreshing. In many patients there is a combination of these factors. As a consequence of the disrupted sleep daytime function is impaired.

There are a number of ways in which sleep can be assessed. The most simple is by asking the patient (and family member or carer if possible) about their sleep, and a sleep diary (see Appendix). This allows the assessment of sleep difficulties over time and gauges the potential contribution of poor sleep and lifestyle habits to daytime impairment. Preliminary questions for eliminating other sleep disorders as primary diagnosis are summarized below.

Eliminating other sleep disorder as primary: preliminary questions – see Appendix for more detailed follow-up questions.

- Are you a very heavy snorer? Does your partner say that you sometimes stop breathing at night? (obstructive sleep apnoea syndrome (OSAS))
- Do your legs often twitch and can't keep still in bed? Do you wake from sleep with jerky leg movements? (restless legs syndrome (RLS), periodic limb movements in sleep (PMLS))
- Do you sometimes fall asleep in the daytime completely without warning? Do you have collapses or extreme muscle weakness triggered by emotion, for instance when you're laughing? (narcolepsy)
- Do you tend to sleep well but just at the 'wrong times'; and are these sleeping and waking times regular? (circadian rhythm sleep disorder; evidence also from sleep diary)
- Do you have unusual behaviours associated with your sleep that trouble you or that are dangerous? (parasomnias – see text)

It is important to determine if another sleep disorder (see preliminary questions above), or a physical (such as pain, heart or lung disease), neurological (such as Parkinson's disease or cerebrovascular disease) or psychiatric disorder (such as depressive illness, anxiety disorder, or substance misuse) is the primary diagnosis. In depression, however, in many cases insomnia should be regarded as a co-morbid condition, rather than as a secondary one. The majority of epidemiological evidence suggests that insomnia typically predates other psychiatric symptoms and may represent an independent risk factor for the development of depression in particular (see below).

Circadian rhythm disorder

Circadian rhythm disorders are sleep disorders where there is a mismatch between circadian rhythms and required sleep-wake cycle. Thus there can be sleeplessness when trying to sleep at a time not signalled by the internal clock, and excessive sleepiness when needing to be awake.

Some circadian disorders (jetlag and shift-work disorder) are due to an individual lifestyle, including work and travel schedules, that conflicts with the internal clock. Others are:

- delayed sleep-phase syndrome (DSPS), where there is difficulty falling asleep before 2–3 a.m. (sometimes later), and on days without work/school/college the preferred wake time is after 10 a.m., resulting in sleep-onset insomnia

and difficulty waking up in the morning on days when an early bedtime for an early start time is necessary.

- free-running sleep disorder, where there is a daily increment of sleep and wake times (getting later each day). This is often associated with insomnia of varying severity and daytime sleepiness.

Parasomnias

Parasomnias are unusual episodes or behaviours occurring during sleep which disturb the patient or others; here we addresses those that cause significant distress and therefore present for treatment. Assessment of parasomnia may be possible with a detailed history from the patient or a witness but, in general, for an adequate diagnosis referral to a specialist sleep centre for polysomnography (PSG) and video recording may be necessary. Violent or unusual night-time attacks may arise from deep non-REM sleep (night terrors and sleepwalking) or from REM sleep (severe recurrent nightmares, REM behaviour disorder), and treatments depend on which disorder is present.

Night terrors (also called sleep terrors) are recurrent episodes of abrupt awakening from deep non-REM sleep, usually in first third of the night, usually with a scream and signs of intense fear and autonomic arousal. The patient is unresponsive to comforting; they may sit up in bed and sometimes engage in automatic behaviour associated with fear and escape. There is usually no detailed recall, and if the patient wakes from a terror (not common), there is confusion and disorientation and only a vague memory of fear. Night terrors are common in children, with about 30–40% having at least one episode, and repeated episodes in about 5%. The peak age for these is at about 2–7 years, with a gradual diminution up to early adolescence (DiMario and Emery, 1987). In some cases night terrors persist into adult life; the prevalence in adults is unknown. Almost all adult patients have had night terrors or sleepwalking as a child (Crisp, 1996). There is a strong genetic component (Nguyen et al., 2008), and night terrors and sleepwalking in the same patient is fairly common.

Sleepwalking alone probably has 15–20% lifetime prevalence. The main symptom is of automatic behaviour at night with the sufferer unresponsive to surroundings and other people. The behaviour is most commonly walking around, but can include other behaviours which are highly familiar to the subject such as dressing, washing, making tea, arranging objects in the house, etc. Some cases of sleepwalking seem related to use of certain drugs, for example alcohol and hypnotics, especially zolpidem and triazolam (Pressman, 2007). It is rare for affected individuals to present for treatment, except if they have injured themselves or a partner, have put themselves into potential danger, or have excessive daytime fatigue because of night-time disturbance. Another reason for presentation is anxiety and disruption of sleep of partner, family or housemates.

Nightmares and REM sleep behaviour disorder (RBD) are disorders arising from REM sleep, and the main difference in presentation from the non-REM episodes is that they are normally recalled by the patient, who wakes from them and is aware of the episode and can describe it. RBD is a disorder, first described in the late 1980s, with violent complex behaviour at night, which is mostly recalled by the patient. There are two sleep abnormalities; lack of atonia during REM sleep,

and increased vividness and/or unpleasant content of dreams. The violent behaviour is described as ‘acting out of dreams’, made possible by the lack of the normal muscle paralysis in REM sleep. Its incidence is unknown (probably <1%), it occurs in older people with a steady rise after 55 years of age, and has a marked male preponderance. It may be idiopathic but much more often is associated with Parkinson’s disease (it is seen in up to 50% of patients with Parkinson’s disease), Lewy body dementia (~70%), and multiple system atrophy (>90%). RBD may be the first manifestation of these disorders, antedating the onset of parkinsonism, cerebellar syndrome, dysautonomia, and dementia by several years (Gagnon et al., 2006).

Figure 1 summarizes the diagnosis algorithm for sleep problems.

Recommendations

- The diagnosis of insomnia is primarily based on patient-derived and family or caregiver complaints, as determined by the clinical interview, ideally with patient diary (A).
- In some circumstances referral to a specialist sleep centre may be necessary for other investigations, for instance:
 - Differential diagnosis of circadian rhythm disorder (actigraphy) (A)
 - Other primary sleep disorder suspected including parasomnia (polysomnography) (A)
 - In the case of treatment failure (D)

Costs and consequences of insomnia

What is known about detrimental effects of insomnia

- Quality of life is impaired in insomnia (I)
- There is an increased risk of subsequent first episode depression, and of relapse into depression, in those with a pre-existing persistent insomnia (I)
- Primary insomnia is associated with poor objective sleep and impaired objectively measured daytime performance (II)
- There is an increased risk of hypertension in insomnia with objectively measured short sleep duration (II)
- Absenteeism, accidents at work and road accidents are increased in insomnia (II)

What is not known

- What are the potential confounding effects of medication and comorbid disorders in reports of increased accidents?
- To what extent do treatments rectify the health risks of insomnia?

Several large studies have demonstrated reduced quality of life, increased functional impairment and increased healthcare costs in insomnia (Chevalier et al., 1999; Léger et al., 2001; Philip et al., 2006; Simon and VonKorff, 1997; Zammit et al., 1999). Impairments in the areas of vitality, energy, emotional and mental health domains have been the most widely reported. One study shows that severe insomnia is independently associated with worsened health-related quality of life to almost the

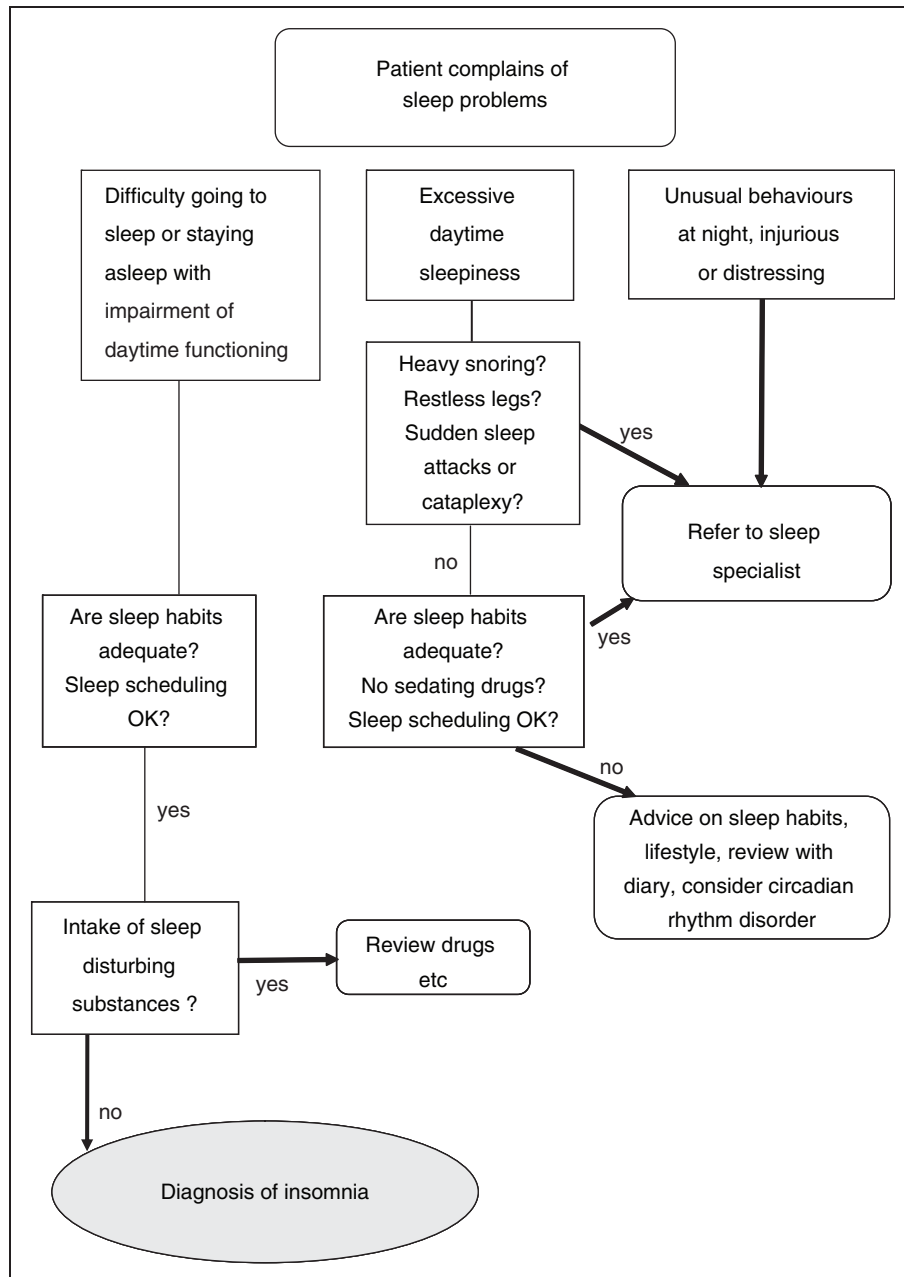


Figure 1. Diagnosis algorithm.

same extent as chronic conditions such as congestive heart failure and major depression (Katz and McHorney, 2002). Studies suggest that the resulting economic burden of insomnia is very high, with the largest proportion of all expenses (76%) attributable to insomnia-related work absences and reduced productivity (Daley et al., 2009). The incidence of road accidents is increased in individuals with insomnia (Léger and Bayon, 2010), but the potential confounding effects of medication and co-morbid medical disorders have not been studied extensively.

People with a diagnosis of insomnia have subjective complaints of poor daytime function. When compared with matched controls, they show increased **subjective** sleepiness but decreased **objective** sleepiness, due to the fact that they are

usually overaroused, but feel subjectively tired. Objectively, they show poorer performance on psychomotor tasks, particularly those requiring switching of attention (e.g. frontal/executive tasks) (Edinger et al., 2008), objectively measured time awake after sleep onset (WASO) was the best predictor of impaired daytime performance. Likewise, Altena et al. (2008) have reported that people with insomnia perform more poorly on complex cognitive tasks, an effect which normalizes following cognitive behavioural therapy (CBT) intervention.

There is an increased risk of subsequent depression and anxiety disorder in primary insomnia. Insomnia has been associated with: (1) an increased risk of developing subsequent depression; (2) an increased duration of established depression; and (3)

relapse following treatment for depression (Riemann, 2009). On the other hand, sleep disturbances are widely understood as core symptoms of major depressive disorder rather than associated or co-morbid disorders (Mendlewicz, 2009). Poor sleep quality seems to correlate with high negative and low positive emotions, both in clinical and subclinical samples. Good sleep seems to be associated with high positive emotions, but not necessarily with low negative emotions (Baglioni et al., 2010).

The National Institute of Mental Health Epidemiologic Catchment Area, which interviewed 7954 adults on two occasions a year apart, first highlighted the strong association between sleep disturbance and subsequent depression. It was found that 14% of those with insomnia at the first interview had developed new major depression 1 year later (Ford and Kamerow, 1989). This increased risk of developing depression has been confirmed in other investigations: in a survey of 1200 young adults in Michigan the odds ratio of new depression was four times greater in those subjects who had insomnia 3 years earlier (Breslau et al., 1996), and of new anxiety disorder the risk was twofold greater. In a questionnaire survey of adults in the UK there was a threefold increased risk of new depression and a twofold risk of new anxiety disorder if subjects had reported one sleep problem occurring 'on most nights' a year earlier (Morphy et al., 2007). In a much longer study in Norway with two surveys 10 years apart (Neckelmann et al., 2007), the risk of having an anxiety disorder diagnosis at the second time point increased by about one and a half times if insomnia had been present at the first time point, and by about five times if insomnia was present at both time points, indicating the higher risk of long-standing insomnia. Doctors in a prospective study who had complained of insomnia during medical school in the 1950s and 1960s were twice as likely to have developed depression at follow-up in the 1990s (Chang et al., 1997).

Insomnia is associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis with increased adrenocorticotrophin and cortisol in most studies (Varkevisser et al., 2005; Vgontzas et al., 1998; Vgontzas et al., 2001). When the complaint of insomnia is accompanied by short duration of sleep measured objectively, there is a three to fivefold increased overall risk of hypertension, which is comparable to that seen with other common sleep disorders, such as sleep-disordered breathing (Vgontzas et al., 2009).

Recommendation

- It is important to treat insomnia because the condition causes decreased quality of life, is associated with impaired functioning in many areas, and leads to increased risk of depression, anxiety and possibly cardiovascular disorders (A).
- Goal of treatment:
 - to less suffering and
 - improve daytime function
- Type of treatment:
 - Patient-guided
 - By particular pattern of problem, i.e. sleep onset insomnia, maintenance
 - By choice of treatments with an evidence base

Psychological treatment of insomnia

What is known about CBT for insomnia - CBTi

- CBT is an effective treatment for insomnia delivered either individually or in small group format (Ia)
- CBT has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. Moreover, there are indications that the beneficial effects of CBT may last well beyond the termination of active treatment (Ia)

What is not known

- Are long-term effects of a short-term course of hypnotics better or worse than after CBT?
- Long-term effects of CBT versus optimized (e.g. intermittent) use of hypnotics in the long term

Psychological treatment of insomnia should be considered appropriate for two reasons. First, insomnia is a 'psychophysiological' disorder, in which mental and behavioural factors play predisposing, precipitating and perpetuating roles. Essential features of insomnia are heightened arousal and learned sleep-preventing associations. Arousal can reflect a general cognitive hypervigilance and many patients describe 'racing thoughts' as a problem when they are trying to sleep. A cycle develops in which the more one strives to sleep, the more agitated one becomes, and the less able one is to fall asleep. CBT for insomnia (CBTi) employs a package of interventions designed to encourage poor sleepers to think and behave like good sleepers. The therapy is manualized, and health professionals can be trained to administer it either individually or in a group setting. Therapies are multimodal, embodying techniques such as sleep restriction and stimulus control as well as cognitive restructuring. CBT then is a treatment modality, just as is sleep pharmacotherapy. The latter comprises a range of licensed medications, and the former a range of proven psychotherapeutic methods.

There have been many investigations of CBT in insomnia but it is challenging to design a randomized controlled trial as the therapy cannot be blinded, and contact with professionals is difficult to match with the comparator group. However, in 85 clinical trials involving a total of 4194 participants (including 12 trials in insomnia associated with medical/psychiatric disorders) 70% of patients who completed the course achieved sustained improvement on sleep and daytime reports, reflecting moderate-to-large effect sizes over waiting list (Irwin et al., 2006; Morin et al., 2006). Based on this and other extensive published evidence, including nine systematic reviews or meta-analyses, the National Institutes of Health Consensus and State of the Science Statement (NIH, 2005) concluded that a CBT package containing cognitive and behavioural methods is "as effective as prescription medications are for short-term treatment of chronic insomnia. Moreover, there are indications that the beneficial effects of CBT, in contrast to those produced by medications, may last well beyond the termination of active treatment".

In the majority of studies, CBT employs a package of the previously mentioned techniques which are designed to

encourage poor sleepers to think and behave like good sleepers. The therapy is usually performed from a manual, and health professionals can be trained to administer it either individually or in a group setting. Therapy is multimodal, embodying techniques such as sleep restriction and stimulus control as well as cognitive restructuring. Sleep restriction and stimulus control do not prolong sleep time but result in a shortening of total sleep time during the acute treatment period, because patients reduce the amount of time spent in bed by delaying bedtime or leaving the bedroom when they wake during the sleep period. This means that improvements in sleep continuity and quality parameters, rather than total sleep time, have generally been the significant outcome measures in these studies.

There have been several comparative studies of CBT versus pharmacotherapy. A recent meta-analysis (Riemann and Perlis, 2009) concludes that during the treatment period they produce comparable improvements; that psychological therapy produces significant beneficial long-term effects; and notes that studies of the long-term effects of short-term pharmacotherapy have not been reported. A recent randomized study of combined therapy (Morin et al., 2009b), in which two groups of patients underwent a 6-week CBT intervention, with one group also taking zolpidem nightly during acute treatment, found an approximately 60% response rate in both groups. After the acute phase, patients in the zolpidem group were re-randomized to extended CBT plus or minus intermittent zolpidem; combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended phase and the 6-month follow-up period. In patients with persistent insomnia, the addition of medication to CBT produces added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT.

Outside of the research environment, for example in clinical practice in the UK, the take-up rate for CBT is not certain – for example, in the Bristol insomnia treatment group, which is only available on a weekday during normal working hours, and involves considerable travel for many patients, only half of the patients referred from a secondary care sleep clinic for chronic insomnias agreed to attend and some dropped out before the end of the course; making treatment more accessible in terms of flexibility of times and locations an urgent goal. Provision of psychological treatments for insomnia in the UK is an issue, as there are few trained therapists and insomnia is not a priority for psychologists in the National Health Service. One approach involving ‘stepped care’ has been suggested (Espie, 2009) where, depending on severity, chronicity and complexity of insomnia, people could be allocated to the various levels, with self-administered CBT (e.g. a book) as the ‘entry level’, manualized, small-group CBT delivered by nurses as the next level, and involvement of more specialized professionals thereafter. This would enable this relatively scarce resource to be applied in a cost-effective way to achieve best clinical care.

Recommendation

- CBT-based treatment packages for chronic insomnia including sleep restriction and stimulus control are effective and therefore should be offered to patients as a first-line treatment (A).
- Increased availability of this therapy is required.

Drug treatments for insomnia

What is known about drug treatments for insomnia

- Z-drugs and short-acting benzodiazepines are efficacious for insomnia (Ia)
- Safety (adverse events and carryover effects) are fewer and less serious with decreasing half-lives (Ib)
- Prolonged release melatonin improves sleep onset latency and quality in patients over 55 (Ib)

What is not known

- Does improvement in insomnia last after treatment is stopped?
- Does treatment reduce risk of subsequent depression?

Underpinning principles – pharmacology

An overview of the way in which various drugs are thought to work, classified according to what is thought to be their primary site of action on sleep, is given in Table 2.

The sleep-wake function reflects a complex balance between arousing and sleep-inducing physiological systems. Current research suggests that arousal and wakefulness are promoted by parallel neurotransmitter systems whose cell bodies are located in brainstem or midbrain centres, with projections to the thalamus and forebrain. These activating neurotransmitters are noradrenaline, serotonin, acetylcholine, dopamine and histamine. In addition the newly discovered orexin system with cell bodies in the hypothalamus promotes wakefulness through regulating arousal ‘pathways’ (and inhibiting sedative ones) (Samuels and Szabadi, 2008; Saper et al., 2005). For all these arousal neurotransmitters sleep can be promoted by blocking their post-synaptic actions, leading to reduced arousal. For example, many over-the-counter (OTC) sleep-promoting agents contain antihistamines, which block the histamine H1 receptor and so decrease arousal. The relatively low efficacy of these compounds may be explained by the fact that they target only one of the parallel arousal systems. The same is true for any drug which blocks one of the other arousal systems; they produce a degree of sedation but are not generally effective hypnotics. However, some agents have specific actions on certain sleep parameters; for instance, drugs which block 5HT₂ receptors (such as ritanserin or eplivanserin) can increase slow-wave sleep (Idzikowski et al., 1988; Landolt et al., 1999) whereas the alpha-1 adrenergic blocker prazosin is useful in post-traumatic stress disorder-related nightmares (Raskind et al., 2007). Trazodone is commonly used to promote sleep and has blocking actions at noradrenaline, 5HT and histamine receptors; this multiple action probably explains why it is widely used, although there are few controlled clinical trials. Other drugs such as sedating antidepressants and antipsychotics probably promote sleep in a similar fashion.

The promotion of sleep is regulated by a number of other neurotransmitters (see Table 2); primary amongst these is gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. The majority of brain cells are inhibited by GABA, so increasing its function reduces arousal and

Table 2. Neurotransmitters and sleep in humans

Endogenous transmitter	Maintains wakefulness	Promotes sleep	Agents promoting wakefulness	Agents promoting sleep	Agents causing sedation
GABA		✓	antagonists (though not studied in humans)	agonists, positive allosteric modulators e.g. benzodiazepines	agonists, positive allosteric modulators
melatonin		✓		M1 and M2 agonists	
adenosine		✓	antagonist (caffeine)		
noradrenaline	✓		uptake blockers releasers (stimulants)		α1 antagonists
dopamine	✓		stimulants (releasers) and uptake blockers	Possibly agonists (paradoxical effect → sudden sleep attacks)	
serotonin	✓		uptake blockers	5HT2 antagonists, 5HTP	
histamine	✓		H3 antagonist	? H1 antagonists	H1 antagonists
acetylcholine	✓				Muscarinic antagonists
orexin	✓			OR1 and/or 2 antagonists	

produces sleep, and eventually anaesthesia. There are many subsets of GABA neurones distributed throughout the brain but a particular cluster in the hypothalamus (ventrolateral preoptic nucleus) can be considered to be the sleep 'switch' (Saper et al., 2005). These neurones switch off brain arousal systems at the level of the cell bodies and therefore promote sleep. GABA receptors in the cortex can also promote sedation and sleep by inhibiting the target neurones of the arousal system.

The inhibitory effects of GABA are mediated through the GABA_A receptor, which is a complex of proteins with binding sites for a number of sleep-promoting drugs, in particular benzodiazepines, so-called Z-drugs and barbiturates, all of which enhance the effects of GABA's actions at the GABA_A receptor. There are a number of subtypes of this receptor which are relevant for sleep, not only because of their different location in the brain but also because of the fact that some hypnotic drugs are selective for a particular subtype. The alpha-1 subtype is highly expressed in the cortex and probably mediates the sedative and hypnotic effects of many drugs that act at the benzodiazepine site; zolpidem and zaleplon target this subtype preferentially (Sanna et al., 2002). The alpha-3 subtype predominates in the reticular nucleus of the thalamus, which plays an important role in regulating sleep. This subtype is particularly targeted by eszopiclone (Jia et al., 2009). Traditional benzodiazepine hypnotics act on four subtypes – alpha 1, 2, 3 and 5 – which may explain some differences between them and the Z-drugs.

The other main sleep-promoting neurotransmitter is adenosine. Brain levels of this rise during the day and are thought to lead to sleepiness, which increases the longer the time since the last sleep. The arousing and sleep-impairing effects of caffeine (Landolt et al., 2004) are thought to be due to blockade of adenosine-A2 receptors, so attenuating this natural process (Porkka-Heiskanen et al., 2002). Caffeine is a useful translational model for insomnia as its effects in rodents are very similar to those in humans and could be used to screen potential new treatments (Paterson et al., 2007).

Melatonin is a natural hormone that is produced in the pineal gland and which has an important role in regulating

circadian rhythms (Cajochen et al., 2003; Dijk and von Schantz, 2005). The circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus drives melatonin synthesis and secretion from the pineal gland. Once melatonin appears in the plasma it enters the brain and binds to melatonin receptors in the hypothalamus, forming a feedback loop. The SCN contains melatonin 1 and melatonin 2 receptors, and much research is ongoing about their role in sleep/wake regulation and circadian rhythms. Melatonin has both phase-shifting effects (changing the timing of the biological clock), and direct sleep-facilitating effects. Administering exogenous melatonin or analogues such as ramelteon (licensed in the USA) can promote sleep onset. A slow-release formulation of melatonin has been licensed on the basis of improved sleep continuity and daytime well-being in people aged over 55 years with insomnia. Melatonin production is reported to decline with age and to be lower in middle-aged and elderly patients with insomnia than in good sleepers (Attenburrow et al., 1996; Dowling et al., 2008; Haimov, 2001; Léger et al., 2004).

Underpinning principles – pharmacokinetics

The principles of the ideal hypnotic have been discussed for decades and are outlined in Figure 2. All licensed hypnotics improve one or more aspects of subjective sleep and some also improve daytime functioning (see below – but note this treatment outcome has only been seen as being important in recent years, so many drugs have not been evaluated in this parameter).

Kinetic aspects are important both in terms of how quickly the drug enters the brain and how long its effects last (see Tables 3 and 4). The faster the hypnotic enters the brain, the sooner sleep is induced. Some agents used as hypnotics have not been active in this aspect of sleep because of poor kinetic properties: for example, temazepam tablets have a poorer bioavailability and slower absorption (and thus a longer presence in the body) than the previous gel formulations. Drugs that enter the brain very quickly, though effective, may need to be taken in the bedroom or even in bed to prevent people falling asleep before they are in bed (see zolpidem

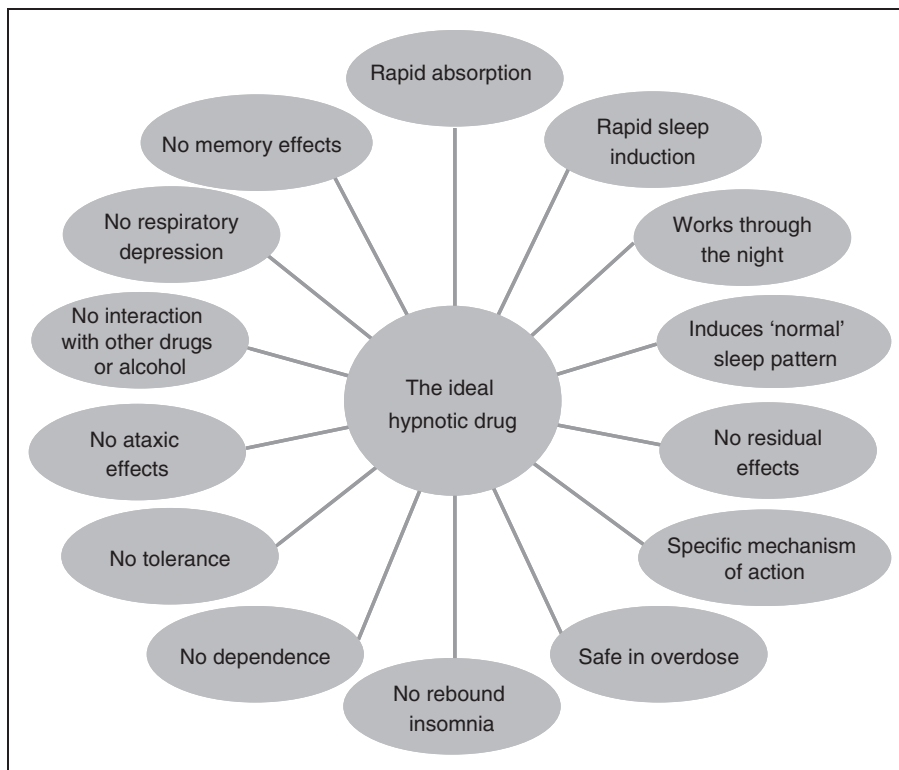


Figure 2. The ideal hypnotic drug.

Table 3. Pharmacokinetic data for benzodiazepine receptor-acting hypnotics

	Availability (%)	Plasma bound (%)	Time to T_{max} (h)	T_{half} (h)
Nitrazepam	78 ^a	87 ^a (85 ^b)	1.6 ^b , 1–5 ^l , 0.5–0.83 ^x	26 ^a , 24 ^b , 20–40 ^l , 28–35 ^o , 15–38 ^p , 25–35 ^x
Flurazepam		96 ^a	0.5–1.5 ^l , 0.5–1 ^y , 0.5–1 ^x	* 76 ^a , 40–100 ^l , 40–103 ^o , 47–100(2.3) ^y , 47–100 ^x
Loprazolam	90 ^q	85 ^q	2 ^q , 2 ^r , 0.5 ^x	7–8 ⁿ , 15 ^o , 6–12 ^p , 12 ^q , 12 ^r , 4.6–11.4 ^x
Lorametazepam	80 ^t , 70–80 ^u	92 ^b	2 ^b	10 ^b , 10 ^o , 10–12 ^p , 10 ^t , 7.9–11.4 ^x
Temazepam	91 ^a	98 ^a , 96 ^b	1.1 ^b , 2–3 ^l , 0.75–1 ^x	11 ^a , 9.1 ^b , 5–20 ^l , 12 ^o , 8–15 ^p , 2–25 ^x
Zaleplon	30 ^d , 30 ⁱ	60 ^b	1.4 ^b , 1 ^f , 0.9–1.5 ^g , 1 ^h , 0.8 ⁱ , 0.25–0.5 ^x	1 ^b , 1 ^f , 0.9–1.1 ^g , 1 ^h , 1 ⁱ , 1 ^x
Zolpidem	70 ^d , 70 ^l , 70 ^m	92 ^b , 90 ^l , 92 ^m	1.7–2 ^h , 0.75–2.6 ^m , 0.5 ^x	2.0–2.2 ^h , 1.5–3.2 ^m , 1.5–4.5 ^x
Zopiclone	70 ^d , 75 ^j , 80 ^l	80 ^b , 45 ^j , 45–80 ^l	1.5 ^c , 0.25–0.5 ^x	5.6 ^c , 4–5 ^j , 5 ^l , 3.5–6.5 ^x
Eszopiclone		52–59 ^e	1.5 ^c , 1 ^e , 1–1.5 ^w	3.8 ^c , 6 ^e , 6 ^k , 6.9–7.3 ^w

Data from ^aBenet et al., 1996; ^bNutt, 2005a; ^cNajib, 2006; ^dDrover, 2004; ^eMelton et al., 2005; ^fPatat et al., 2001; ^gBeer et al., 1994; ^hGreenblatt et al., 1998; ⁱRosen et al., 1999; ^jGaillot et al., 1982; ^kFernandez et al., 1993; ^lChouinard et al., 1999; ^mSalva and Costa, 1995; ⁿClark et al., 1988; ^oJochemsen and Breimer, 1986; ^pAshton, 1994; ^qwww.fda.gov/medwatch/safety/2006/Nov_PIs/Ativan_PI.pdf; ^rGreenblatt et al., 1976; ^sHumpel et al., 1982; ^tDe Vanna et al., 2007; ^uwww.fda.gov/cder/foi/label/2001/16721s74lbl.pdf; ^vBrunello et al., 2008; ^wWagner and Wagner, 2000.

*Metabolized to desalkylflurazepam (Chouinard et al., 1999).

Table 4. Pharmacokinetic data for other hypnotics

	Availability (%)	Plasma bound (%)	Time to T_{max} (h)	T_{half} (h)
Chloral hydrate (NB $t_{1/2}$ is so short, values are for the primary active metabolite trichloroethanol)	NK	35 ^p , 35 ^q	0.76–0.98 ^o , 2 ^p , 8.2 ^q	9.3–10.2 ^o , 9.3–10.9 ^p
Triclofos sodium	NK	35 ^q	8.2 ^q	NK
Clomethiazole	25–42 ^s	63 ^s	0.92 ^r	3.6–5 ^s
Promethazine hydrochloride	12.3–40 ^t , 25 ^u	NK	4.39 ^u	18.6 ^u
Sodium oxybate	25 ^v	<1 ^v	0.6–0.9 ^w , 0.5–2 ^y	0.57–0.73 ^w , 0.5–1 ^y
Trazodone	75 ^a , 60–80 ^b	93 ^a , 89–95 ^b	1–2 ^b , 1–2 ^c	6.5 ^a , 6–13 ^b , 7–15 ^c
Mirtazapine	50 ^d	85 ^e	0.25–2 ^c , 1.8 ^d , 2 ^e	20–40 ^c , 16.3 ^d , 20–40 ^e
Olanzapine	60 ^g	93 ^g	5 ^c , 6 ^g	30 ^c , 24 ^f , 30 ^g
Quetiapine		83 ^h	1 ^c , 1.5 ^h , 2 ⁱ , 2 ^j	7 ^c , 6 ^h , 5.3 ⁱ , 5.3 ^j
Melatonin	15 ^l	71.5 ^m , 80 ⁿ	0.5–0.88 ^k , 0.87–1 ^l	0.76–0.86 ^k , 1 ^l

Data from ^aBenet et al., 1996; ^bDeVane, 1994; ^cKrystal, 2009; ^dVoortman and Paanakker, 2004; ^eCaraco Mirtazapine PIL, 2/08; ^fTauscher et al., 2002; ^gzyprexa-pi LillyInfo 2009; ^hSeroquel PIL Astrazeneca; ⁱGefvert et al., 1998; ^jDavis et al., 1999; ^kMarkantonis et al., 2008; ^lDeMuro et al., 2000; ^mRizzo et al., 2002; ⁿDi et al., 1998; ^oZimmermann et al., 1998; ^pMerdink et al., 2008; ^qSellers et al., 1978; ^rRätz et al., 1999; ^sJostell et al., 1978; ^tKoytchev et al., 1994; ^uStrenkoski-Nix et al., 2000; ^vAbanades et al., 2006; ^whttp://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000593/WC500057103.pdf
 NK: not known.

summary of product characteristics (SPC)) (see <http://www.medicines.org.uk/emc/medicine/22443/SPC/Zolpidem%20Tartrate%2010%20mg%20Tablets/NHSEvidence>).

The ease of waking and the propensity to daytime carry-over ('hangover') effects are determined by the duration of action – most typically defined by the elimination half-life of the drugs (see Tables 3 and 4) and the dose taken. Drugs with half-lives of more than 6 h tend to leave sufficient residual drug in the brain to cause hangover in the morning. This was particularly the case with the first benzodiazepine hypnotics such as nitrazepam, which was associated with daytime sedation and falls (Trewin et al., 1992). The rationale for developing the Z-drugs was in part to make shorter half-life drugs with minimal carry-over effects (Nutt, 2005b). This was largely achieved, although there is some hangover seen with zopiclone (Staner et al., 2005). The very short half-life of zaleplon means that it can be taken as little as 5 h before the desired time of arising, without the risk of hangover impairment (see SPC and Walsh et al., 2000).

A very short half-life limits a drug's duration of action on sleep, and zaleplon and to some extent zolpidem are not particularly effective at maintaining sleep throughout the night. A controlled release formulation of zolpidem (CR, currently only available in the USA) prolongs its nocturnal actions and enhances sleep continuity, though only by tens of minutes (Greenblatt et al., 2006). Individual factors seem important and some people are more susceptible to carry-over than others, probably due to individual differences either in the rate of drug clearance, which can vary by as much a twofold between subjects, or sensitivity to drug actions.

Tolerance, dependence and withdrawal

Dose escalation above recommended doses in patients with insomnia alone is uncommon, and tolerance to hypnotic drug effects is not a frequent problem in clinical experience; many patients use the same dose of hypnotic for months or years

and still feel it works. However, a temporary worsening of sleep, usually with increased sleep-onset latency, is reported during the withdrawal period for most agents (Hajak et al., 2009; Soldatos et al., 1999; Voshaar et al., 2004). Although there have been no head-to-head studies addressing this question, there is some lower level evidence in humans that subtype selective drugs such as eszopiclone produce less tolerance and rebound (Krystal et al., 2003; Nutt and Stahl, 2009).

Animal and human research demonstrates that brain receptor function changes in response to chronic treatment with benzodiazepine receptor agonists, and this takes time to return to pre-medication levels after cessation of medication. There is evidence from animal studies that chronic administration of benzodiazepines produces adaptive changes in the receptor which attenuate the effects of the endogenous neurotransmitter GABA, and so produce symptoms on withdrawal (Bateson, 2002). It may be possible to develop drugs with a lower propensity to such effects either through targeting specific subtypes of the benzodiazepine receptor, by changing the chemical structure to produce a different interaction at the pharmacophore, or by making partial agonists (Doble et al., 2004).

Considerations of dependence are very much contingent on what happens when treatment is stopped. A psychological dependence is seen in many patients and some are unwilling to stop treatment. If they do stop there can be relapse, where the patient's original symptoms return, or rebound of symptoms, where for one or two nights there is a worsening of sleep disturbance, with longer sleep-onset latency and increased waking during sleep; this is commonly reported by patients and has been documented in some research studies (Hajak et al., 2009; Soldatos et al., 1999). More rarely, there is a longer withdrawal syndrome. All of these can be ameliorated by resuming medication. The withdrawal syndrome is characterized by the emergence of symptoms not previously experienced, such as agitation, headache, dizziness, dysphoria, irritability, fatigue, depersonalization, hypersensitivity to noise and visual stimuli. Physical symptoms which have been described include nausea, vomiting, muscle cramps, sweating,

Table 5. Level Ia evidence of hypnotic efficacy from subjective rating of sleep or objective polysomnographic measures

	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
Benzodiazepines	✓	✓	✓		✓	✓	✓		✓
Z-drugs	✓	✓	✓		✓	✓	✓		✓

Table 6. Effects of individual drugs (significantly different from placebo (Ib)) on sleep parameters

	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	✓	✓	✓	✓	✓	No	✓
zaleplon	✓	✓	No	No	No	No	✓
eszopiclone	✓	✓	✓	✓	✓	✓	✓
ramelteon	✓	✓	✓	(week 1 only)	✓	No	✓
PR melatonin	✓	✓	Not measured	No	Not measured	No	✓

PSG: polysomnography.

*Formulation changed since studies, longer absorption time with current tablet cf gel capsule previous formulation.

weakness, muscle pain or twitching and ataxia. This syndrome typically resolves within a few weeks, but in some patients it persists, and this may be related to personality traits and cognitive factors (Murphy and Tyrer, 1991).

Hypnotic drug treatment

All licensed drugs are efficacious; levels of evidence for short-term use are given in summary in Table 5 (there is as yet no systematic review or meta-analysis evidence for prolonged-release melatonin). The sleep factors which each drug improves are given in Table 6. Thus, for example, in a patient with predominantly sleep-onset insomnia, a shorter-acting drug such as zolpidem or prolonged-release melatonin might be appropriate, and for those with awakenings throughout the night a slightly longer-acting drug such as zopiclone may be preferable.

Most of the licensed drugs enhance GABA function in the brain. As well as promoting sleep these drugs are anxiolytic, anticonvulsant and myorelaxant, and can cause ataxia and memory problems when taken other than just before a period in bed. If their effect in the brain persists after waking up in the morning they are described as having 'hangover' effects, therefore differences in the pharmacokinetics of individual benzodiazepines (or Z-drugs) are of particular importance. Melatonin does not give rise to motor or memory effects. Recent clinical trials have begun to measure daytime outcomes after hypnotic medications, and beneficial effects have been reported for melatonin in over-55s, zolpidem, zopiclone, eszopiclone and lormetazepam. These measures have not been used in studies of other drugs, so their effects on daytime function are not documented.

In systematic reviews of benzodiazepines and Z-drugs, adverse events/side effects are less common and less severe for the Z-drugs zolpidem, zaleplon and eszopiclone

(Buscemi et al., 2007). Controlled studies measuring cognitive and psychomotor function (such as digit-symbol substitution test, and memory) in insomnia patients have only shown next-day deleterious effects consistently after use of flurazepam (very long-acting) or very high doses of other benzodiazepines (Buscemi et al., 2005). Evidence for hypnotic effects on next-day driving in insomnia patients is limited; however, epidemiological studies show that road accidents are increased in people taking benzodiazepines or zopiclone (Barbone et al., 1998; Neutel, 1995). Studies in healthy volunteers show that residual effects of hypnotics increase with their half-life duration (Verster et al., 2006). Effects of insomnia itself on driving have not been studied, but sleep deprivation does impair driving performance (Connor et al., 2002). In a controlled study of patients with insomnia in a driving simulator there was next-day impairment after zopiclone and lormetazepam but not zolpidem, when compared with placebo (Staner et al., 2005). Transient increases in sleep-onset latency and decreases in sleep time have been reported after stopping nearly all hypnotic drugs, except with zaleplon, melatonin and ramelteon: onset and duration is related to half-life, occurring on the first or second nights after stopping with short half-life drugs, and later and more prolonged with longer-acting ones (Hartmann and Cravens, 1973; Voderholzer et al., 2001).

Recommendations

- Factors which clinicians need to take into account when prescribing are efficacy, safety, and duration of action (A).
- Other factors are previous efficacy of the drug or adverse effects, history of substance abuse or dependence (D).

Long-term hypnotic use

What is known about long-term hypnotic treatment

- Insomnia is often long-lasting and is often treated with hypnotics for long periods in clinical practice (Ib)
- These studies suggest that dependence (tolerance/withdrawal) is not inevitable with hypnotic therapy up to 1 year with eszopiclone, zolpidem, ramelteon (Ib)
- There is also evidence that dependence may be more likely with some agents or with polysomnography outcome measures as compared with self-report measures of outcome
- Intermittent dosing may further reduce the risk of tolerance and dependence (Ib)

What is not known

- How can we predict the needed treatment duration?
- How and when should treatment be discontinued?
- Should dosing for longer periods be nightly or intermittent?
- How we detect the abuse-prone individual in the clinic?
- Does hypnotic therapy affect the course of insomnia or associated conditions?

The question of long-term hypnotic treatment is one of the more controversial areas in psychopharmacology. It has long been stated that hypnotic medication should not be used long term for the treatment of insomnia. This was the consensus view of the panel of a 1983 National Institute of Health (NIH, 1983) Consensus Conference on the medication treatment of insomnia, which became a guideline for clinical practice in the USA, and later the UK Committee on Safety of Medicines and the Royal College of Psychiatrists both recommended only short-term use. While it was appreciated that benzodiazepine hypnotic agents had a favourable risk–benefit ratio and were first-line agents for insomnia management, all these reports expressed concerns about the risks of physical dependence and recommended that their use should be limited to periods of 2–3 weeks. This view was not based on data demonstrating an unfavourable transition in the risk–benefit ratio after 2–3 weeks of treatment, but appears to have been because no substantive placebo-controlled trials of hypnotics had been carried out for longer than a few weeks. Despite the recommendation for treatment with hypnotic drugs being only 2–4 weeks, many millions of patients worldwide remain on long-term treatment (Balter and Uhlenhuth, 1992; Ishigooka et al., 1999; Ohayon et al., 1999; Mellinger et al., 1985).

The reasons for long-term use are complicated and difficult to research, but are probably similar to those which affect understanding of long-term benzodiazepine treatment in anxiety disorders. We do not know the proportions of long-term users who have continuing insomnia requiring daily drug treatment, or who do not need the drug at all, or who are afraid to try discontinuing because of fear or experience of rebound insomnia. In one study where people were successful in discontinuing benzodiazepine hypnotics, a follow-up after 2 years revealed approximately 40% had resumed regular use (Belanger et al., 2005; Morin et al., 2005a), which suggests

some people have enduring problems with sleep which benefit from treatment. Insomnia may have some similarities with depression, in that both represent long-term disorders in which maintenance treatment may be needed in many patients (Jindal et al., 2004). A related issue is whether early intervention at the onset of insomnia might reduce the likelihood of it persisting. There is very little evidence available on this, and it must be seen as a research priority.

Placebo-controlled trials of hypnotic treatment for durations longer than 3 weeks that can more definitely assess safety and efficacy, and determine whether dependence phenomena occur, have been undertaken only recently. Trials of nightly dosing for up to 6 months' duration suggest that tolerance and withdrawal do not generally occur with some hypnotics: eszopiclone (two studies of 6 months' duration); ramelteon (a 6-month study with outcome assessed with PSG but not self report); and temazepam (a 2-month study) (Bastien et al., 2003; Krystal et al., 2003; Mayer et al., 2009; Morin et al., 1999; Walsh et al., 2007). Other agents have not been studied for longer durations. The available evidence does not suggest there is an unfavourable risk/benefit transition at 3–4 weeks for any agent.

Open-label studies of nightly dosing for periods of up to 1 year with the agents studied (zaleplon, eszopiclone, and ramelteon) suggest that discontinuation symptoms are mild and infrequent (Ancoli-Israel et al., 2005; Richardson et al., 2009). Intermittent, non-nightly dosing is also an important consideration with respect to long-term hypnotic treatment. Many individuals do not have nightly insomnia, and treatment only on the nights when drug is needed can decrease the risks and costs of therapy and reduce psychological dependence/treatment withdrawal anxiety. There is evidence from a placebo-controlled trial for sustained efficacy and safety for 6 months of 'as needed' treatment (subjects being required to take at least three doses per week) with controlled release zolpidem 12.5 mg (Krystal et al., 2008).

In conclusion, insomnia is often long-lasting and often treated with hypnotics for long periods in clinical practice. Controlled trials of longer-term use are being undertaken and these suggest dependence (tolerance/withdrawal) is not inevitable with hypnotic therapy up to 1 year, and is not characteristic of the several agents studied. Dependence may be more likely with some agents or with PSG outcome measures as compared with self-reported measures of outcome. The longer-term safety and efficacy of many other commonly used hypnotics remain uncertain.

A number of other critical issues remain unresolved. We currently lack the means to determine who should receive longer-term treatment and to predict the required treatment duration. Lacking the means to determine the optimal duration of therapy, a rational approach is to carry out periodic trials of tapering and discontinuing medication to determine if continued therapy is indicated (Krystal, 2009). As such, the duration of treatment is decided by a series of risk/benefit decisions based on trial discontinuations. This approach provides an 'exit strategy' and thereby addresses concerns that, once started, hypnotic therapy could be unending. Concomitant CBT during tapered discontinuation may be helpful (Morin et al., 2006). Another unresolved issue is whether to implement nightly or intermittent dosing of hypnotics for a given patient. In many instances this is a practical

decision based on whether the patient can predict, when they go to bed, whether they will have sleep difficulty.

Recommendations

- Use as clinically indicated (A).
- To stop medication, try intermittent use at first if it makes sense, then try to stop at regular intervals, say every 3–6 months depending on ongoing life circumstances and with patient's consent (D).
- CBT during taper improves outcome (A).

Antidepressants

What is known about the use of antidepressants to treat insomnia

- There is limited evidence for efficacy of doxepin, trimipramine, trazodone, paroxetine in insomnia (Ib)
- Antidepressants may affect a wide range of brain receptors and have longer-lasting carry-over effects than traditional hypnotic drugs – antidepressants are associated with increased risks of road accidents especially early in treatment in depression (Ib)

What is not known

- Is the effect of antidepressants on insomnia lasting (particularly as they are often prescribed for long periods)?
- Are they more efficacious than traditional hypnotics?
- Do they improve mood or reduce the risk of emergent depression in patients?

Tricyclic and some other classes of antidepressants have long been used for insomnia, whereas the selective serotonin reuptake inhibitors (SSRI) as a class generally disrupt sleep early in a course of treatment (Mayers and Baldwin, 2005). The alerting effect of SSRIs can be offset by co-administration of sedating antidepressants such as trazodone, probably because they block 5HT₂ receptors that are being overstimulated by an increase in 5HT (Kaynak et al., 2004). Other 5HT₂ antagonist antidepressants such as nefazodone (now discontinued) (Hicks et al., 2002) and mirtazapine (Winokur et al., 2003) have been shown to reduce insomnia in depression, especially early in treatment.

Low doses (sub-therapeutic for depression) of sedating tricyclics, particularly amitriptyline, dosulepin and doxepin, have been used for decades to treat insomnia. This is particularly common practice in primary care in the UK, where amitriptyline 10 or 25 mg is also used for long periods in many patients with chronic illness, particularly those with pain syndromes. At this dose amitriptyline is probably acting mostly as a histamine H₁ receptor antagonist, although a degree of 5HT₂ and cholinergic muscarinic antagonism may also contribute. There are no controlled studies of hypnotic efficacy of low-dose amitriptyline in insomnia, and tricyclics are more likely to be lethal than licensed hypnotics in overdose (Nutt, 2005a). Controlled trials have demonstrated an effect of doxepin in insomnia at low dose (25 mg) for 4 weeks with rebound insomnia (Hajak et al., 2001), and very low 'microdose' studies using 1, 2 or 6 mg for two nights in adult (Roth et al., 2007) and elderly insomnia patients

(Scharf et al., 2008) have shown sleep improvement; at this dose the antihistamine action is paramount.

Trazodone is an antagonist at 5HT_{1a}, 5HT₂ and α ₁ adrenergic receptors as well as a weak 5HT reuptake inhibitor, and is the second most prescribed medication for insomnia in the US. It has a perceived absence of risk, is cheap, and there are no restrictions on use duration, but 25–30% patients experience difficulty tolerating trazodone and dropout rates tend to be higher than for benzodiazepine or Z-drugs. Although there have been 18 trazodone studies measuring sleep outcomes, only two were in primary insomnia, and only one was a controlled study (Walsh et al., 1998). This study used 50 mg trazodone versus placebo, and found a significant effect on sleep maintenance parameters at week 1 but not week 2, and a high incidence of daytime somnolence. Trimipramine is a tricyclic antidepressant which blocks α -1 adrenergic, histamine H₁, dopamine D₂, serotonin 5HT₂ and cholinergic receptors (Gross et al., 1991; Richelson, 1994). There is one controlled trial (Riemann et al., 2002) in insomnia at doses of 50–200 mg for 4 weeks which found a significant improvement in sleep efficiency as measured by PSG, paralleled by subjective improvements. Side effects were described as marginal. Paroxetine, an SSRI, was studied in patients with insomnia aged over 55 years, at a median dose of 20 mg for 6 weeks (Reynolds et al., 2006), there being a 50% response rate (placebo 38%) with subjective sleep quality and daytime well-being improved. This seemingly paradoxical action of paroxetine to improve sleep is probably related to its good efficacy in many anxiety disorders, where it seems to reduce recurrent thinking and ruminations.

Taking SSRIs, venlafaxine, mianserin or mirtazapine increases the risk of restless legs syndrome (RLS) and periodic limb movements in sleep (PMLS) (Hoque and Chesson, 2010), and SSRIs are known to induce or exacerbate sleep bruxism (Wilson and Argyropoulos, 2005).

Recommendations

- Use drugs according to a knowledge of pharmacology (A).
- Consider antidepressants when there is coexistent mood disorder but then use at therapeutic doses (A).
- Beware toxicity of tricyclic antidepressants in overdose even when low unit doses prescribed (A).

Antipsychotics

What is known about use of antipsychotics for treatment of insomnia

- Olanzapine and quetiapine improve sleep in healthy volunteers (Ib)
- Quetiapine improves sleep in primary insomnia (IIB)
- Side effects are common because of the pharmacological actions of these drugs (I)

What is not known

- How do they compare with traditional hypnotic drugs?

Atypical antipsychotics have become relatively widely used in the treatment of sleep problems with very little controlled

trial evidence, although a meta-analysis of atypical antipsychotic agents in mania indicates they all produce somnolence (Scherk et al., 2007). Research studies have been carried out in healthy volunteers. Increases in objective actual sleep time and sleep continuity and in subjective sleep quality have been reported with olanzapine (Gimenez et al., 2007; Lindberg et al., 2002; Sharpley et al., 2000), which also improves sleep continuity when added to an SSRI in depression (Sharpley et al., 2005). Quetiapine at 25 mg and 100 mg for two nights in healthy volunteers increased sleep time and efficiency and subjective sleep quality but periodic leg movements were significantly increased after 100 mg (Cohrs et al., 2004). A single small open study of quetiapine (a 25 mg dose in most patients) for 6 weeks in primary insomnia (Wiegand et al., 2008) showed improvements in total sleep time and sleep efficiency, with transient adverse effects of morning hangover and dry mouth.

Side effects of these antipsychotics are well documented and include weight gain, metabolic syndrome, extrapyramidal symptoms and risk of tardive dyskinesia. There are some case reports of abuse of quetiapine in inpatients and prisoners (reviewed in Sansone and Sansone, 2010).

Recommendation

- 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 (D).

Antihistamines

Antihistamines are sedating and are sold as over-the-counter (OTC) sleeping medications. There is limited evidence that OTC antihistamines work, although recently some modest benefits have been reported after 2 weeks' dosing with diphenhydramine in mild insomnia (Morin et al., 2005b). More profound acute effects on sleep have been reported for both promethazine and hydroxyzine in healthy volunteers (Adam and Oswald, 1986; Alford et al., 1992), but the latter is not available as an OTC hypnotic, and both have a long duration of action so are likely to cause hangover. Triprolidine is used in many other European countries and may be better as it has a shorter half-life; however, there are no placebo-controlled studies.

Antihistamines are commonly used in alleviation of insomnia in drug and alcohol withdrawal where traditional hypnotics are less suitable due to the risk of cross-dependence, although there are no controlled trials in this setting.

Recommendations

- Antihistamines have a limited role in psychiatric and primary care practice for the management of insomnia (D).
- The algorithm for the treatment of insomnia is summarized in Figure 3.

Special populations

Sleep in women: effects of menopause

Insomnia increases as women approach and pass through the menopause (Bixler et al., 2009; Kuh et al., 1997; Owens and

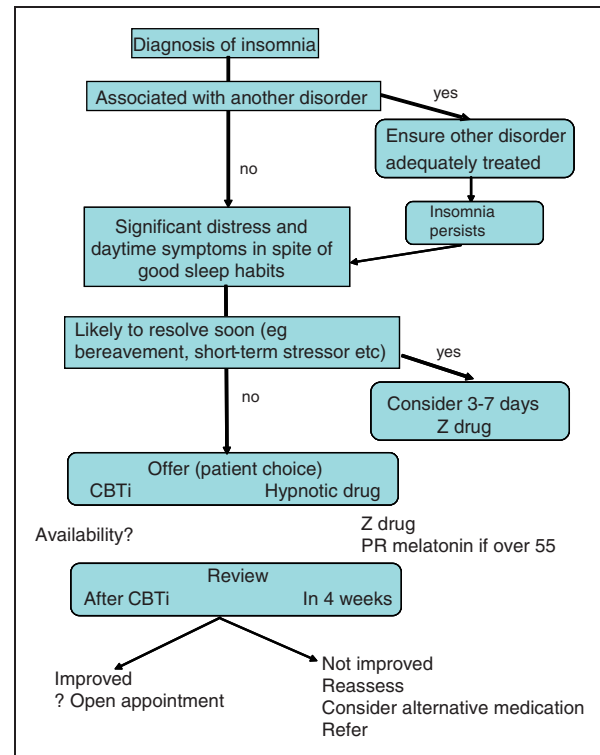


Figure 3. Treatment algorithm.

Matthews, 1998). This is due to a variety of reasons: climacteric symptoms such as hot flushes due to hormonal changes, psychiatric disorders and a rise in the incidence of sleep-disordered breathing (Bixler et al., 2001). A recent study looking at gender differences in the clinical presentation of patients diagnosed with obstructive sleep apnoea syndrome (OSAS) showed that at the time of OSAS diagnosis, women were more likely to be treated for depression, to have insomnia and to have hypothyroidism than men with similar degree of OSAS (Sheperdycky et al., 2005). In the Wisconsin cohort of individuals followed over time, there were no significant PSG sleep architectural changes associated with transition to menopause, but there was an increase in obstructive apnoeas (Young et al., 2003). In contrast, a recently published US study of normal sleepers showed that women sleep more deeply than men and that the menopause is associated with longer sleep latency and decreased slow-wave sleep. In addition, hormone therapy appeared to protect women from these unfavourable changes (Bixler et al., 2009).

Recommendations

- Clinicians should appreciate that there is a rise in incidence of sleep-disordered breathing after the menopause and that clinical presentation, often including insomnia, in women is different than in men.
- The use of hormone therapy should involve informed individualized treatment of symptoms, looking at risks and benefits in light of recent studies.
- Follow recommendations for insomnia in other sections.

Sleep in women: effects of pregnancy

Many women complain of poor sleep during pregnancy, with the reasons varying depending on the trimester. In the first trimester, nausea, backache and urinary frequency can cause sleep disturbance. The second trimester tends to be easier but foetal movements and heartburn may be issues. By the third trimester, sleep is more disturbed with complaints again of urinary frequency and backache in addition to cramps, itch and unpleasant dreams. Most women fall asleep easily but wake more frequently (Schweiger, 1972).

If patient suffers from intractable insomnia and a pharmacological agent is required, it is helpful to note that zolpidem and diphenhydramine are in FDA class B (foetal harm possible, but unlikely; no evidence of foetal harm in animal studies); for review see Pien and Schwab, 2004. Zolpidem is preferable as it is short acting and does not have anticholinergic side effects.

RLS is common in pregnancy with a prevalence of 11–26% and is sometimes associated with anaemia (Manconi and Ferini-Strambi, 2004). Snoring and sleep-disordered breathing, especially in obese subjects can also occur and affect sleep quality (Pien and Schwab, 2004).

Recommendations

- Good sleep hygiene and lifestyle (D).
- Manage general pregnancy-associated complaints, e.g. decrease fluid intake, pillow support (D).
- The benefits of CBT in pregnancy have not been published but approach would appear sensible (B).
- Recognize RLS by careful history and investigations if necessary.
 - Dopamine agonists are contraindicated (FDA category C or greater)
 - Iron and folic acid supplementation have been shown to be effective in RLS. Supplementation is suggested even if levels are not low (D)
 - Keep caffeine low as it can exacerbate RLS (D)
 - Mild to moderate exercise in the early evening, stretching, massage (D)
- If patient suffers from intractable insomnia and a pharmacological agent is required, zolpidem is preferable as it is short acting and does not have anticholinergic side effects. Short-term use is recommended after discussion on potential risks and benefits (D).

Treatment of insomnia in the elderly

What is known about treatment of insomnia in the elderly

- Cognitive behavioural therapy is effective in insomnia in the elderly (Ia)
- Short-acting Z-drugs increase the risk of falls in elderly patients (III)
- Prolonged release melatonin given for 3 weeks improves sleep onset latency and sleep quality in patients over 55 (1b)

What is not known?

- What is the long-term efficacy and safety of melatonin?

Insomnia in elderly patients responds well to CBT (see psychological treatment section). Meta-analyses comparing CBT outcomes in middle-aged and older adults (55 years plus) have reported moderate-to-large effect sizes, regardless of age, in sleep-onset latency (SOL) and wake time after sleep onset (Irwin et al., 2006; Montgomery and Dennis, 2003).

A systematic review (Bain, 2006) and meta-analysis (Glass et al., 2005) concluded that benzodiazepine receptor agonist hypnotics had an unfavourable risk/benefit ratio in elderly patients. However, the different methods of collection and categorization of drug-related side effects in the studies included makes them difficult to interpret. Individual randomized controlled studies with short-acting Z-drugs show little evidence of adverse effects, particularly cognitive side effects in the morning. However, if a patient needs to rise within a few hours after taking a benzodiazepine agonist drug there may be undesired effects on motor control. Falls are increased after sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, non-steroidal anti-inflammatory drugs and calcium channel antagonists (Woolcott et al., 2009) and, for example, there is a 2.5-fold increase in the risk of falls in hospital after zolpidem (Rhalimi et al., 2009). However, in nursing homes the situation may be different; in a large study (Avidan et al., 2005) insomnia itself, but not hypnotic use, was associated with an increase in falls and hip fractures. Therefore the development of sleep-promoting drugs without motor side effects has been welcomed. Prolonged-release melatonin has been shown to reduce SOL and increase subjective sleep quality in two large trials in patient over 55 years (Lemoine et al., 2007; Wade et al., 2007); its effects are fairly modest but it has no known motor side effects.

Recommendations

- CBT is effective and should be offered as a first line where available (A).
- When a hypnotic is indicated in patients over 55, prolonged-release melatonin should be tried first (B).
- If a GABA_A hypnotic is used then a shorter half-life will minimize unwanted hangover (A).

Treatment of sleep problems in children

What is known

- Most sleep disorders in childhood respond well to behavioural treatments (I)
- Melatonin reduces long sleep latency (following appropriate behavioural interventions) in children with sleep onset insomnia or delayed sleep phase syndrome and learning difficulties, autism and ADHD (II)
- Antihistamines may have a role in short-term symptomatic treatment (II)

What is not known

- What are the long-term effects of melatonin?

Sleep problems are commonly associated with certain genetic and neuro-developmental problems seen in childhood

including ADHD, autism, learning difficulties and epilepsy. Training and awareness of paediatric sleep disorders is poor, and accurate diagnoses and hence appropriate treatments are often delayed. Evidence from systematic review suggests that most sleep disorders in childhood respond well to behavioural treatments (Mindell et al., 2006). Appropriate sleep hygiene measures and more specific techniques of extinction, or graduated extinction, are all more effective than placebo at improving sleep and reducing the number of weekly night wakes in otherwise healthy children who regularly wake up in the night (Ramchandani et al., 2000). These interventions hold for both typically developing children and children with learning difficulties and sleep problems. These interventions may not change sleep parameters in the child, but instead improve outcomes related to impact on parents and other carers.

The sedative side effects of antihistamines may speed up behavioural programmes over short periods (France et al., 1991) but seem not to work without behavioural interventions; in a placebo-controlled double-blind trial in infants aged 6–27 months the same authors found no significant effect of 15 mg or 30 mg trimeprazine tartrate, and concluded that it is not recommended as a pharmacological treatment for infant sleep disturbance unless as an adjunct to a behavioural therapy program (France et al., 1999). Clinically, the short-term use of an H1 blocker for transient or extreme insomnia can be helpful and is frequently employed. However, tolerance can develop quickly and some children can experience dramatic and paradoxical over-arousal. Nevertheless, the TIRED RCT specifically investigated the use of diphenhydramine in infants aged 6–15 months and found it was no more effective than placebo in reducing night-time awakening (Merenstein et al., 2006).

The evidence supporting use of melatonin to reduce long sleep latency (following appropriate behavioural interventions) in populations of children with idiopathic sleep-onset insomnia (Smits et al., 2003) or DSPS and learning difficulties, autism and ADHD (van der Heijden et al., 2007) is increasingly robust. However, evidence that melatonin can significantly improve sleep fragmentation and total sleep time in this group is only weak. The majority of research in children has employed supraphysiological doses of fast-release melatonin, and although there is little evidence of short-term adverse effects, there are also only limited data on long-term potential adverse effects. Melatonin at doses between 0.5 and 12 mg is commonly used as a sedative agent in children undergoing procedures such as electroencephalography (EEG), as an alternative to sleep deprivation that does not affect the EEG morphology. A melatonin-induced sleep EEG was as useful as a sleep-deprived EEG, but children's behaviour on the day of the melatonin-induced sleep EEG recording was more acceptable to parents (Wassmer et al., 2001).

Clonidine is an antihypertensive agent with sedative side effects that may improve sleep maintenance in some children. The therapeutic window is narrow, both for adverse effects on sleep architecture and tolerability. Also tolerance to the sleep-inducing effects develops over time, leading to the need for increased doses with concomitant risk of adverse effects. Despite these concerns, it is still widely used in the UK and by as many as a third of clinicians surveyed in the USA (Schnoes et al., 2006).

Chloral hydrate and triclofos are still popular hypnotics for children but have a very long half-life and considerable

potential for 'hangover' effects in children. The half-life of chloral hydrate itself is short (a few minutes), but the half-lives of its active metabolites are longer, being 8–12 h for trichloroethanol and 67 h for trichloroacetic acid. Toxicity is an important concern due to central nervous system depressant action, arrhythmogenic potential and stomach irritation.

Recommendations

- Behavioural strategies should be tried in children with disturbed sleep (A).
- Melatonin administration can be used to advance sleep onset to normal values in children with ADHD who are not on stimulant medication (A).

Treatment of insomnia in children and adults with learning disability

Epidemiological studies show a very high prevalence of sleep disturbance in people with learning disability, with findings ranging from 58–86% in children (Didden and Sigafoos, 2001) and 14–56% in adults (Brylewski and Wiggs, 1999) (this study reported a 15% prevalence of parasomnias). Positive associations have been reported between sleep disturbance and sleep breathing disorders, challenging behaviours, early childhood, severe or profound learning disability, institutional care, autism/ADHD, various genetic syndromes, physical health problems, sensory impairment, epilepsy and caffeine intake (Brylewski and Wiggs, 1999). Many different aspects contribute to aetiology, such as neurodevelopmental causes, sensory impairments, chaotic or institutionalized environments, failure of learning and psychotropic medications, including anticonvulsants.

Clinical assessment should elicit any aetiological or exacerbating factors which can be reversed. Assessment will usually take place by direct observation initially. Carers should be supported to keep a structured 24-h record of sleep pattern and behaviour. Actigraphy or EEG may be useful when a sleep disorder other than insomnia or settling difficulties is suspected. A circadian rhythm disorder should be considered in individuals with visual impairment (see below).

There is a varying degree of evidence for treatments of sleep difficulties in this heterogeneous population. The relatively small number of controlled studies in this area give support to parental/carer education and modifying environmental factors (Montgomery et al., 2004) and behavioural regimes such as chronotherapy, bedtime fading, extinction, distancing/desensitization and sleep-wake scheduling (Gunning and Espie, 2003; Wiggs and France, 2000). The use of light therapy has been described (Short and Carpenter, 1998).

There is very little evidence for effectiveness of sleep-promoting drugs apart from melatonin. A recent meta-analysis (Braam et al., 2009) shows that melatonin (1–9 mg) decreases sleep latency and number of wakes per night, and increases total sleep time in individuals with intellectual disabilities. There were few adverse events in the relatively short-term studies included, and long-term safety needs further research.

Recommendations

- Clinical assessment should describe sleep disturbance and elicit aetiological and exacerbating factors (A).
- Environmental, behavioural and educational approaches should be used first line (A).
- Melatonin is effective in improving sleep (A).
- Treatment should be planned within a capacity/best interests framework.

Treating circadian rhythm disorders

What is known

- Melatonin is effective in jet lag disorder (Ia), delayed sleep phase syndrome (Ib) and free-running disorder (IIa)
- Light therapy is effective in delayed sleep-phase syndrome (III)

What is not known

- What are the best efficacy measures – subjective versus objective?
- Is there a need to distinguish between adults and adolescents in delayed sleep-phase disorder, since sleep times are somewhat delayed in normal adolescence?
- Is there a need to distinguish between sighted and blind individuals?
- Is melatonin or light therapy more effective for delayed sleep-phase disorder?

Current understanding of circadian rhythms and sleep physiology provides a strong theoretical basis for the use of melatonin in some, but not all circadian rhythm disorders (CRDs). Empirical evidence for efficacy is strong in some CRDs, but weak or absent in others. Melatonin agonists may be promising in the treatment of CRDs but there remains a need for RCTs in well-characterized CRD populations.

There is sufficient evidence to support the use of melatonin in jet lag (Herxheimer and Petrie, 2002; Sack et al., 2007b), but melatonin has to be taken near desired bedtime otherwise there may be undesired daytime sleepiness. An evidence-based strategy for minimizing jet lag which includes strategic scheduling of sleep combined with melatonin is given in a recent paper by Sack (2010).

In delayed sleep-phase disorder, there is both a theoretical and an empirical basis for use of melatonin, which is effective in practice, shown in two systematic reviews (Sack et al., 2007a; MacMahon et al., 2005); however, studies in these reviews vary in the physiological and subjective outcomes measured. Direct comparison with other therapies such as timed light exposure, for which there is a little evidence of efficacy (see below), or chronotherapy, for which there are no controlled trials, has not been reported.

In free-running disorder in sighted individuals, case reports ($n = 5$) suggest a positive benefit of melatonin. The evidence in blind people is more compelling, where case reports and two small, single-blind placebo-controlled studies are positive (Sack et al., 2007a; Skene and Arendt, 2007; Skene et al., 1999).

There is no evidence of efficacy of melatonin in irregular sleep-wake rhythm, or in shift work disorder, although there

have been some reports of use in shift workers with varying results (for review see Sack et al., 2007b).

Bright light therapy has been used effectively in DSPS (for review see Shirani and St Louis, 2009). Exposure to bright light of 2500 lux for 2 h in the early morning, combined with light restriction after 16:00 (dark goggles) is an effective treatment for DSPS, and a light mask offering exposure to gradually increasing light intensity through closed eyelids over the last 4 h of habitual sleep time has been shown to be effective in these patients. Despite limited evidence, the American Academy of Sleep Medicine currently considers timed phototherapy as “a rational and effective intervention for DSPT” (Sack et al., 2007a).

Recommendations

- Clinical assessment is essential in DSPS and free-running disorder (A/B).
- Melatonin may be useful in DSPS, free-running disorder and jet lag (A).
- Other approaches such as behavioural regimes and scheduled light exposure (in sighted individuals) can also be used (B/C).

Treatment of parasomnias

There is little high-level evidence for treatments in these disorders. There are no controlled trials of treatment of non-REM parasomnias in adults (see Harris and Grunstein, 2009). Priorities are to minimize possible trigger factors such as frightening films, caffeine, alcohol or meals late at night, and to make sure there is a stable and adequate sleep-wake schedule. It is important to safeguard against harm to the patient, such as by locking windows, bolting doors, or sleeping on the ground floor, and safety of the bed partner or nearby children also requires attention.

Drug treatment decisions should be based on the frequency and severity of events. Clonazepam in doses up to 3 mg per night has been reported to be effective (case series, $n = 69$) (Schenck and Mahowald, 1996). Smaller case series have reported good effects of paroxetine (Wilson et al., 1997) and imipramine (Cooper, 1987) (both effective immediately), and there is a small case series of hypnotherapy in sleepwalkers (Reid et al., 1981). A randomized controlled study of 3 weeks' treatment with 5-hydroxytryptamine in children found evidence of efficacy at 6-month follow-up (Bruni et al., 2004).

For nightmares, psychological treatments are effective and these focus on exposure – writing down dreams – or guided imagery, pleasant images, and ‘changing the ending’ (Burgess et al., 1998; Krakow et al., 1995). There have been a few case series showing beneficial effects of the alpha-1 adrenergic blocker prazosin in reducing nightmares related to post-traumatic stress disorder in both military and civilian settings (Raskind et al., 2007). Nightmares have been reported to be triggered or worsened by many drug treatments, including cholinesterase inhibitors, beta-blockers, SSRIs (especially paroxetine) levodopa, and following withdrawal from antidepressants.

There are no prospective or controlled studies of drug treatment of REM behaviour disorder, but case series suggest

a good effect for clonazepam 1–4 mg (Aurora et al., 2010; Boeve et al., 2004) in reducing the number of episodes and injuries during them, although it should be used with caution in patients with dementia, disorders of gait or balance, or concomitant OSAS. Smaller beneficial effects have been reported for melatonin 3–12 mg (Gagnon et al., 2006). Single case studies and small series have reported beneficial effects of clonidine (Nash et al., 2003), donepezil (Massironi et al., 2003) and sodium oxybate (Kosky et al., 2008).

Drugs which can worsen RBD or provoke its symptoms include SSRIs, venlafaxine, mirtazapine, bisoprolol, and tramadol (Gagnon et al., 2006).

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Conflict of interest

All attendees completed conflict of interest statements that are held at the British Association for Psychopharmacology office according to BAP policy.

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Appendix

Suggested algorithm to screen for sleep disorder other than insomnia.

Ask the lead question, and then proceed with supplementary only if answer is 'yes'.

1. Narcolepsy

a. Do you sometimes fall asleep in the daytime completely without warning?

- b. Is it literally impossible to resist 'sleep attacks' during the day?
- c. Do you have collapses or extreme muscle weakness triggered by extreme emotion?
- d. Do you have visual hallucinations, either just as you fall asleep or when you wake in the morning?
- e. Are you paralysed and unable to move when you wake up from your sleep?

[Possible narcolepsy: 1a = "TRUE" AND (1b OR 1c OR 1d OR 1e = "TRUE")]

2. Sleep breathing disorder

a. Are you a very heavy snorer?

- b. Does your partner say that you sometimes stop breathing?
- c. Do you often wake up gasping for a breath?
- d. Are you often excessively sleepy during the day or fall asleep without wanting to?

[Possible sleep breathing disorder: 2a = "TRUE" AND (2b OR 2c OR 2d = "TRUE")]

3. PLMS/ RLS

a. Do your legs often twitch or jerk or can't keep still in bed?

- b. Is it very difficult to get to sleep because of repeated muscle jerks?
- c. Do you frequently wake from sleep with sudden jerky movements or with a compulsion to move your legs?
- d. Do you simply have to get out of bed and pace around to get rid of these feelings?

[Possible PLMS/ RLS: 3a = "TRUE" AND (3b OR 3c OR 3d = "TRUE")]

4. Circadian Rhythm Sleep Disorder

a. Do you tend to sleep well but just at the "wrong times"?

- b. Can you sleep well enough, but only if you stay up very late?
- c. Are you in a very sound sleep at normal waking time and could sleep on for hours more?
- d. Can you sleep well enough, but only if you go to bed very early?
- e. Do you wake very early, bright and alert and no longer sleepy?

[Possible CRSD: 4a = "TRUE" AND EITHER (4b AND 4c = "TRUE") OR (4d AND 4e = "TRUE")]

5. Parasomnia

a. Do you have unusual behaviours associated with your sleep that trouble you or that are dangerous?

- b. Do you sleepwalk frequently and run the risk of injuring yourself or others?
- c. Do you have frequent night terrors when you are extremely distressed but not properly awake?
- d. Do you act out your dreams and risk injuring yourself or others?
- e. Do you have terrible recurring nightmares?

[Possible parasomnia: 5a = "TRUE" AND EITHER (5b OR 5c OR 5d OR 5e = "TRUE")]

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