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

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Abstract

This BAP guideline replaces the original version published in 2010, and contains updated information and recommendations. A consensus meeting was held in London in October 2017 attended by recognized experts and advocates in the field. They 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, 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 circulated to all speakers for comments, which were incorporated into the final document. Although the first author prepared the document for publication, all authors contributed equally to the consensus.

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# 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 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 sleep disordered breathing; NICE guidelines for this are summarised on the NICE website and an updated guideline will be available in 2020; a comprehensive toolkit is available at the British Sleep Society website http://www.sleepsociety.org.uk. We also did not consider certain sleep disorders for which sets of guidelines already exist, such as narcolepsy (Billiard *et al*, 2006) and restless legs syndrome (Picchietti et al., 2015). Thus the main scope of this document is to address insomnia, circadian rhythm disorders and the more common parasomnias which are likely to present to primary care physicians and psychiatrists.

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 organisation of its kind worldwide, and publishes the *Journal of Psychopharmacology*. The Association started publishing consensus statements more than two decades ago, and the first BAP guidelines on depression were considered a landmark publication when they appeared in 1993 (Montgomery, 1993). There are now guidelines for the treatment and management of most of the disorders encountered in psychiatry; all guidelines are available to download from the BAP website (http://www.bap.org.uk).

# Method

A consensus meeting was held in London in October 2017 attended by recognized experts and advocates in the field. They 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, 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.

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.

## Table 1: Levels of evidence

**Category of evidence:**

Ia—evidence for meta-analysis of randomised controlled trials

Ib—evidence from at least one randomised controlled trial

IIa—evidence from at lease one controlled study without randomisation

IIb—evidence from at lease 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 or clinical experience of respected authorities, or both

**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.

# Insomnia

## Scope of the guidelines

Our intention is to provide an updated statement to guide clinicians who manage patients in primary or secondary medical care. There have been three sets of guidelines for the treatment of insomnia since the previous BAP consensus (Riemann et al., 2017; Sateia et al., 2017); Qaseem et al 2016. The first concerns adults with insomnia and includes insomnia comorbid with other disorders such as depression; the second addresses primary insomnia without comorbidity; the third covers all adults with chronic insomnia disorder. These were discussed by the expert group and where appropriate some elements were incorporated in the present consensus.

Since the publication of the 2010 BAP guideline there has been an important shift in thinking about the diagnosis and classification of insomnia. The historical perspective that insomnia could be either ‘primary’ or ‘secondary’, is no longer regarded as valid or evidence-based. Rather, the expanding literature has led the American Psychiatric Association, APA (DSM-5) and the American Academy of Sleep Medicine (ICSD-3) to recommend that chronic insomnia disorder (APA) should be considered as a disorder in its own right.

This means that insomnia disorder should be diagnosed whenever insomnia diagnostic criteria are met, irrespective of any concurrent physical disorder or mental disorder; and importantly, also irrespective of any other concurrent sleep disorder. It is anticipated that ICD-11 will reflect the same conclusions when it is presented at the World Health Assembly for adoption by Member States in 2019.

The complex relationship between insomnia and psychiatric disorders has been the subject of much recent research. It is increasingly recognized that sleep plays a central role in the regulation of emotion and emotion processing (Tempesta et al, 2018; Palmer & Alfano, 2017). Therefore, it is not surprising to see a bidirectional relationship between insomnia and mental disorder (Harvey & Buysse, 2017). There is considerable evidence that pre-existing insomnia confers risk for the development of (or relapse into) depression (Baglioni et al, 2011). This makes it all the more important to consider the time-course of how insomnia and other psychiatric symptoms develop and resolve (Sánchez-Ortuño & Edinger, 2012).

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 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. These changes may be more marked in men than women according to a very large study of elderly people living at home in the US (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 apnea, in older adults did not explain changes of sleep parameters with aging and age-sex differences in these relationships.

There is now greater consensus about how long insomnia should have been present before it merits intervention. Chronic insomnia is regarded as established after 3 months of persistent poor sleep. There is also general agreement that when insomnia causes significant personal distress or marked impairment then some form of treatment is appropriate. The cause of insomnia may be known or not, and knowledge of causation is not necessary for a diagnosis.

## Table 2 Insomnia: diagnostic criteria

|  |  |  |  |
| --- | --- | --- | --- |
| International Classification of Sleep Disorders (ICSD3) and (Sateia et al 2017) | AThe patient reports (or the patient’s parent or caregiver reports) marked concern about, or dissatisfaction with, sleep comprising one or more of the following:-difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance in going to bed on the appropriate schedule, difficulty sleeping without the parent or caregiver present. | BOccurs despite adequate opportunity and circumstances for sleep | **C**At least one form of daytime impairment e.g.fatigue; mood disturbance; interpersonal problems; reduced cognitive function; reduced performance; daytime sleepiness; behavioral problems (e.g., hyperactivity, impulsivity, aggression); reduced motivation/initiative; proneness to errors/accidents. |
| International Classification of Diseases ICD-10 (WHO 1993) | 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 DSM5(insomnia disorder) | Unhappiness with the quality or quantity of sleep, which can include trouble falling asleep, staying asleep or waking up early and being unable to get back to sleep. The problem occurs despite ample opportunity to sleep. The difficulty cannot be better explained by other physical, mental or sleep-wake disorders. The problem cannot be attributed to substance use or medication | 3 nights a week for at least 3 months | The sleep disturbance causes significant distress or impairment in functioning, such as within the individual’s working or personal life, behaviorally or emotionally |

## Epidemiology of insomnia

**What is known about prevalence of insomnia**

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

**What is not known:**

* What is the prevalence of distress about sleep
* 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; Leger & Poursain, 2005; Sateia *et al*, 2000), and 6% to 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 can be 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). Two studies have described an increase of insomnia over time: in the UK, insomnia diagnosis increased from 3.1% to 5.8% (National Psychiatric Morbidity Surveys 1993-2007, Calem et al 2012); and in Norway, insomnia diagnosis increased from 11.9% to 15.5% between 2 surveys in 2000 – 2010 (Pallesen et al 2014). Although these estimates vary, the median European prevalence for night-time symptoms of insomnia is 24.8%, for night-time together with daytime symptoms is 12.5%, and for full insomnia diagnosis is 10.1% (Baglioni et al, 2017).

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

## Diagnosis of insomnia

Diagnostic criteria from APA, AASM and WHO are summarized in Table 2. They agree that insomnia is a complaint of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking. In DSM-5 and ICSD-3 this complaint must be present 3 or more nights per week, for at least 3 months, and be associated with impairment to day-time functioning or well-being. In this sense insomnia can be considered a ‘24-hour’ disorder, because a complaint of unsatisfactory sleep without reported functional sequelae would not meet clinical diagnostic criteria.

Like other disorders and conditions classified within DSM-5, insomnia is largely a subjectively determined disorder. Polysomnographic (PSG) and actigraphic studies do indicate that people with insomnia take longer to fall asleep and have sleep that is more fragmented than healthy good sleepers. However, these parameters do not reflect the level of sleep disturbance reported by people with insomnia; nor do they sample daytime experience. Moreover, PSG and actigraphy are not indicated for use in insomnia -except if other sleep disorders are suspected (Sateia et al) - and are seldom in any case available in routine care.

Like depression, anxiety, or pain, there is no objective test for insomnia, and in practice it is evaluated clinically. Diagnosis, therefore, is through appraisal against diagnostic criteria, clinical observations and the use of validated rating scales.

There are a number of ways in which sleep can be assessed. The simplest is by asking the patient about their sleep. *Are they having difficulty getting to sleep and/ or staying asleep? Is this occurring most nights?* *Is this persistent and affecting how they feel during the day?*

An extension of this interview enquiry is to administer a clinical rating scale. The Sleep Condition Indicator is one such scale and has been validated in over 200,000 adults. It also has a short-form version comprising only 2 items (Espie et al, 2014; 2017; 2019; see Appendix).

A further step is to provide the patient with a sleep diary. This allows the assessment of sleep difficulties over time and gauges the potential contribution of poor sleep and lifestyle habits to daytime impairment. Some patients appreciate completing a diary to capture the nature of their sleep problems, including the unpredictability of their sleep from night to night. The SCI and the diary may also be useful to assess treatment-related change.

Finally, it is important to determine if another sleep disorder (see preliminary questions below), or a physical (such as pain, heart or metabolic disease), neurological (such as Parkinson’s disease or cerebrovascular disease) or psychiatric disorder (such as depressive illness, anxiety disorder, or substance use disorder) is present alongside the insomnia. The insomnia problem should be actively treated, but consideration of the interplay between conditions is good clinical practice.

Comorbidity

There is a generally high incidence of sleep disorders in psychiatric conditions. The most widely reported are shown below:

|  |  |
| --- | --- |
| Major depressive disorder | Up to 70% insomniaUp to 15 % hypersomnia |
| PTSD | InsomniaNightmaresNon-REM parasomnia |
| Schizophrenia | Circadian rhythm disorder |
| Dementia | InsomniaCircadian rhythm disorder |
| Substance abuse | Insomnia |
| Parkinson’s disease, Lewy Body dementia | REM Behaviour disorderRestless legs syndrome |

Eliminating other sleep disorder as primary: preliminary questions

• *Are you a very heavy snorer? Does your partner say that you sometimes stop breathing at night?* (**obstructive sleep apnea syndrome** (OSAS))

• *When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?* (**restless legs syndrome** - RLS)

• *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 or unpleasant experiences or behaviours associated with your sleep that trouble you or that are dangerous?* (**parasomnias**)

### Recommendation

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 e.g. parasomnia, restless legs syndrome/periodic limb movement disorder (polysomnography) (A)

## Costs and consequences of insomnia

**What is known about detrimental effects of insomnia:**

* Quality of life is impaired in insomnia (Ia)
* There is an increased risk of subsequent first-episode depression, and of relapse into depression, in those with a pre-existing chronic insomnia (Ib)
* There is an increased risk of type 2 diabetes and hypertension in insomnia with objectively-measured short sleep duration (II)
* ‘Presenteeism’ (lack of productivity at work), 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 insomnia treatments rectify risk markers for emotional, metabolic and cardiovascular disease?

Insomnia is now recognised as reliably associated with mental health disorders including risk of suicide (Baglioni et al, 2012; Pigeon, Bishop & Krueger, 2017), cardiovascular disease (Khan & Amoud, 2017) and type 2 diabetes (Vgontzas et al, 2009; Cappuccio, Strazzullo & Miller, 2010). Increased fatigue, impaired work productivity, reduced quality of life, and relationship dissatisfaction are also common in those with insomnia (Kyle, Morgan & Espie, 2010; Espie et al, 2012; Roth & Ancoli\_Israel, 1999). Indeed, such impaired functioning is an important driver for help-seeking behaviour (Morin et al, 2006).

There is an at least two-fold increased risk of subsequent depression and anxiety disorder in patients with pre-existing insomnia (Baglioni et al, 2012). 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). Poor sleep quality also 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, though not necessarily with low negative emotions (Baglioni *et al*, 2010).

The strong relationship between insomnia and emotional vulnerability has been established for 30 years. The National Institute of Mental Health Epidemiologic Catchment Area interviewed 7954 adults on two occasions a year apart, and 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 depressive episode one year later (Ford & Kamerow, 1989). This increased risk of developing depression has been confirmed in numerous investigations: in a survey of 1200 young adults in Michigan the odds ratio of new depression was 4 times greater in those subjects who had insomnia 3 years earlier (Breslau *et al*, 1996) and of new anxiety disorder the risk was 2 fold greater. In a questionnaire survey of adults in the UK there was a 3-fold increased risk of new depression and a 2-fold risk of new anxiety disorder if subjects had reported 1 sleep problem occurring ‘on most nights’ a year earlier (Morphy *et al*, 2007). In a much longer study in Norway, with 2 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 about 5 times if insomnia was present at both time points. Doctors in a prospective study who had complained of insomnia whilst studying at medical school in the 1950s and 60s 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 (ACTH) 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 3-5 fold 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). In France, Japan and the USA, insomnia patients scored significantly lower on all 8 domains of the SF-36, compared to good sleepers (Leger, 2011).

People with a diagnosis of insomnia also 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 over-aroused, but feel subjectively tired. Objectively, they show poorer performance on psychomotor tasks, particularly those requiring the 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 (Altena *et al*, 2008) reported that people with insomnia perform more poorly on complex cognitive tasks, an effect which normalises following CBT intervention. A recent meta-analysis of 24 studies comparing the daytime cognitive performance of people with insomnia and good sleeper controls found that those with insomnia exhibited performance impairments of small to moderate magnitude in working memory, episodic memory and some aspects of executive functioning (Fortier-Brochu et al, 2012).

The economic burden of insomnia is high, with overall costs thought to exceed $100 billion USD per year in the United States (Wickwire et al., 2016). In Europe, economic costs of insufficient sleep, including disruption from insomnia and other sleep difficulties were modelled across five countries; in the UK costs were estimated at 1.86% of GDP or $50 Billion to the economy (Hafner et al., 2016). Costs result from both direct (prescription costs, appointments and inpatient care) and indirect (lost workplace productivity/presenteeism, absenteeism, and increased risk of traffic and workplace accidents) costs (Daley et al, 2009; Leger et al., 2006). Increased insomnia severity has also been shown to be associated with increased health care utilisation (Wickwire et al., 2016) and people with insomnia have higher health care costs than controls (Wickwire et al, in press). The majority of studies indicate that the cost of treating insomnia is less than the cost of not treating insomnia, and that treatment costs appear to be recouped within 6-12 months (Wickwire et al., 2016; Morgan, Dixon et al., 2004).

### 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 diabetes and cardiovascular disorders (A)**

**Goal of treatment**

* **to lessen suffering**
* **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 psychological treatment of insomnia**

* CBTi is an effective treatment for insomnia when delivered individually or in small group format (Ia)
* CBTi is an effective treatment for insomnia when delivered digitally as a web/ mobile intervention
* CBTi is 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)
* Improvements in sleep following CBTi for chronic insomnia mediate improvements in mental health symptoms, wellbeing and quality of life (1a)

**What is not known:**

* What are the predictors of failure to respond to CBTi?
* Does hypnotic medication enhance the effects of CBTi and, if it does, under what circumstances?

Psychological treatment of insomnia should be considered appropriate for several reasons.

First, insomnia has across diagnostic and classification systems been long regarded as a ‘psychophysiological’ disorder in which mental and behavioural factors play crucial roles as predisposing, precipitating and perpetuating factors (Spielman et al, 1987; Espie 2002; Espie et al, 2006; Riemann et al, 2010; Kalmbach et al, 2018). Core 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. All of these sleep-related behaviours and attitudes contrast with those of the ‘good sleeper’ who seems to sleep without much thought or planned behaviour.

Second, cognitive-behavioural therapy for insomnia (CBTi) directly addresses these cognitive and behavioural factors, particularly those that maintain insomnia. CBT-I employs a package of interventions designed to encourage ‘poor sleepers’ to think and behave like ‘good sleepers’. The therapy is manualised 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.

Third, and most importantly, there is a substantial evidence base for the safety, efficacy and clinical effectiveness of CBT-I. Systematic reviews and meta-analyses have consistently found that CBT-I reduces sleep latency and the duration and frequency of night-time wakenings, as well as increasing sleep efficiency with moderate to large effect sizes. CBT also increases total sleep time, and the benefits of CBT-I are durable at medium to long-term follow up (REFS to be added).

Importantly, side-effects with CBT-I are relatively minimal. Indeed, there is considerable evidence of generalised benefit to mood, wellbeing, and to social and occupational functioning in controlled trials (REFS to be added). Recent insomnia CBT studies have demonstrated a causal relationship between improvements in sleep and improvements in mental health symptoms, wellbeing and QoL (Freeman et al, 2017; Espie et al, 2018)

CBT-I is therefore lastingly effective, and is the recommended treatment of first choice for chronic insomnia in guideline documents (e.g. American College of Physicians: Qaseem et al; European Insomnia Guidelines, Riemann et al). Indeed, CBT-I has for many years been recognised in comparative analyses to be a more efficacious treatment for chronic insomnia than either benzodiazepines drugs (Smith and Perlis ref) or BZRA drugs (add REF).

A longstanding problem for CBT-I is not its effectiveness but its availability. At the time of writing of the 2010 BAP guideline, reference was made to this ongoing challenge and how it hindered real world implementation. CBT is traditionally offered face-to-face and so has been restricted by the number of available therapists to provide treatment. The advent of digital CBT (web and mobile delivery) has changed this landscape.

There are now 4 published meta-analyses of digital CBT which indicate comparable effectiveness to in-person CBT-I and demonstrate the emerging opportunity for patients to access this form of CBT treatment (van Straten & Cuipers, 2009; Cheng & Dizon, 2012; Seyffert et al, 2016; Zachariae et al 2016).

Two dCBT interventions in particular have a considerable evidence base. There are 7 published RCTs of the *SHUT-i* product (with a total sample size n ~ 2,100) (REFS to be added); and there are 8 published RCTs of the fully automated dCBT programme *Sleepio* (total n ~ 6,900) (REFS to be added).

The available evidence base is not just for CBT (in general), but also for discrete dCBT ‘products’ like SHUTi and Sleepio; a situation that more closely aligns with the pharmaceutical literature where specific drugs can be seen as discrete pharmacotherapy products that can be offered as part of a formulary-driven pharmacopeia. It seems likely that the literature on dCBT for insomnia may already be as large, if not larger, than for any established hypnotic drug product.

### 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)**
* **Both face to face CBT-I and digital CBT-I (dCBTi) are efficacious (A)**
* **dCBT-I has the potential to offer patients and clinicians a real choice amongst evidence-based alternatives (CBT or drugs) in routine clinical care (A)**

## Drug treatments for insomnia

**What is known about drug treatments for insomnia:**

GABA-PAMs are efficacious for insomnia (Ia)

Safety concerns (adverse events and carry-over effects) are fewer and less serious in hypnotics with shorter half-lives (Ib)

PR melatonin improves sleep onset latency and quality in patients over 55 (Ib)

Suvorexant is efficacious in insomnia (Ia)

Doxepin in very low dose (3mg and 6mg) is efficacious in insomnia (Ia)

**What is not known:**

Does improvement in insomnia last after treatment is stopped?

Does treatment reduce the risk of subsequent depression?

### Underpinning principles - pharmacology

Most drugs which affect the brain do so by affecting neurotransmitter function in the brain, which they can do by:

• simulating the action of a brain neurotransmitter on the receptor (agonists, partial agonists)

• blocking its action on postsynaptic receptors (antagonists)

• changing receptor sensitivity (allosteric modulators)

• increasing the amount of neurotransmitter present in the synapse, either by increasing the release of it into the synaptic cleft, blocking its transportation out of the cleft, or preventing the action of enzymes which break it down.

Arousal is maintained 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, histamine, and the orexin system with cell bodies in the hypothalamus, which together promote wakefulness through regulating arousal pathways (and inhibiting sedating ones). For all these arousing neurotransmitters, waking can be promoted by increasing their function, and sleep or sedation by decreasing their function in the brain.

The promotion of sleep is regulated by a number of other neurotransmitters; primary amongst these is gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. The majority of brain cells are inhibited by GABA so increasing its function reduces arousal and 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. Benzodiazepines, so-called ‘Z drugs’ and barbiturates all enhance the effects of GABA at the GABAA receptor (positive allosteric modulators (GABA PAMs). 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 drugs for insomnia 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 targets 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 drugs for insomnia act on all four subtypes.

The other main sleep-promoting neurotransmitter is adenosine. Brain levels 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).

Histamine neurons form part of the neurotransmitter network promoting arousal. Histamine levels are high in daytime and low during sleep. Drugs which reduce histamine function (H1 receptor antagonists or antihistamines) reduce arousal. Antihistamine medications which cross the blood-brain barrier, such as promethazine and diphenhydramine, are widely used ‘over-the-counter’ and prescribed to promote sleep. Unfortunately they are not selective for histamine, and their actions at other brain receptors (particularly antagonism at cholinergic, noradrenergic and (promethazine) dopaminergic receptors contribute to the adverse effect profile. The most selective available medication is very low dose doxepin, which at doses from 1-6mg has little or no effect at brain receptors other than H1 receptor antagonism. This drug is approved in USA for insomnia, but is not available in Europe. Esmirtazapine, the S-enantiomer of mirtazapine is also selective for H1 receptors, and is undergoing evaluation (Ruwe 2016, Ivgy-May 2015).

Orexin is a neurotransmitter intimately involved in sleep and waking. When the orexin receptors OR1 and OR2 in the hypothalamus are activated they promote waking, and antagonists for these have been found to promote sleep. Several receptor antagonists have been developed and one, suvorexant, is licensed in the USA for insomnia (Herring et al., 2012). These drugs are not yet available in Europe but several agents are being evaluated in clinical trials.

Melatonin is produced in the pineal gland and has an important role in regulating circadian rhythms (Dijk & von, 2005;Cajochen *et al*, 2003). The circadian ‘pacemaker’ is the suprachiasmatic nucleus (SCN) of the hypothalamus and when active it inhibits melatonin secretion in the pineal gland. Once melatonin appears in the plasma it enters the brain and binds to melatonin receptors in the hypothalamus, inhibiting its action to reduce melatonin and thus promoting melatonin release. Melatonin has both phase-shifting effects, so 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; Leger *et al*, 2004). Beta-adrenergic receptor blockers and NSAIDs both inhibit melatonin secretion.

### Underpinning principles – pharmacokinetics

The principles of the ideal drug for insomnia have been discussed for decades and are outlined in fig 2. All licensed drugs for insomnia improve one or more aspects of subjective sleep, and some also improve daytime functioning (see below – but note that many drugs have not been evaluated on this parameter).

Kinetic aspects are important both in terms of how quickly the drug enters the brain and how long its effects last (for comparison of drugs see tables 3, 4 in (Wilson et al 2010)). The faster the drug enters the brain, the sooner sleep is induced. Some agents used for insomnia 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 fast, 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 SPC).

The ease of waking and the propensity to daytime carry-over (‘hangover’) effects are determined by the duration of action – with GABA-PAMs this is typically defined by the elimination half-life of the drugs (see table 3 & 4 in in (Wilson et al 2010)) and the dose taken. Drugs with half-lives of more than 6 hours tend to leave sufficient residual drug in the brain to cause hangover effects in the morning. This was particularly the case with the first benzodiazepine drugs for insomnia such as nitrazepam, which was associated with daytime sedation and falls (Trewin *et al*, 1992). The rationale for developing zopiclone, zolpidem and zaleplon was to make shorter half-life drugs with minimal carry-over effects (Nutt, 2005b). This was largely achieved, although some hangover effects are seen with zopiclone (Staner *et al*, 2005).

A very short half-life limits a drug’s duration of action on sleep, and zolpidem is less effective at maintaining sleep throughout the night than drugs with a longer half-life. A controlled release formulation of zolpidem (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 effect than others, probably due to individual differences either in the rate of drug clearance, which can vary by as much a two-fold between subjects, or sensitivity to drug actions. In particular, women tend to have higher blood concentrations of zolpidem, and greater impairment of driving ability, the following morning than do men (Farkas et al 2013). The FDA responded to this finding by requiring manufacturers to recommend gender-specific labelling with dosing for women being half that of men.

### Tolerance, dependence and withdrawal

Dose escalation above recommended doses in patients with insomnia alone appears uncommon, and tolerance to the effects of GABA PAM drugs for insomnia is not a frequently encountered problem in clinical experience. Many patients use the same dose 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 GABAergic agents (Hajak *et al*, 2009; Soldatos *et al*, 1999; Voshaar *et al*, 2004). Although there have been no head-to-head studies of 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 & 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) 2003). It may be possible to develop drugs with a lower propensity to such effects: through targeting specific subtypes of the benzodiazepine receptorby changing the chemical structure to produce a different interaction at the pharmacophore; or by making partial agonists (Doble *et al*, 2004).

Considerations of dependence on GABA PAMs are contingent on what happens when treatment is stopped. A psychological dependence is seen in many patients and some are reluctant 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 (Soldatos *et al*, 1999;Hajak *et al*, 2009). 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 reported, 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, weakness, muscle pain or twitching and ataxia. This syndrome usually resolves within a few weeks, but persists in some patients, and this persistence may be related to personality traits and cognitive factors (Murphy & Tyrer, 1991).

### Pharmacological treatment of insomnia

All licensed drugs licensed for insomnia are efficacious (I). As explained above, some may improve sleep earlier in the night, as they enter the brain more quickly, and thus reduce sleep onset latency. Duration of action depends to a great extent on half-life and for instance in a patient with predominantly sleep-onset insomnia, a shorter acting drug such as zolpidem or 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 drugs approved for insomnia 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. Differences in the pharmacokinetics of individual benzodiazepines (or ‘Z drugs’) are particularly important. Melatonin does not give rise to motor or memory effects. Recent clinical trials have measured daytime outcomes after drugs for insomnia, and beneficial effects have been reported for melatonin in over-55s, and for 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 GABA PAMs, adverse events/side effects are less common and less severe for the Z-drugs zolpidem 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 drugs for insomnia increase with their half-life duration (Verster *et al*, 2006). Effects of insomnia itself on driving have not been studied extensively, though 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).

Very low doses of doxepin, (1,2 or 6mg when doxepin acts only as a histamine antagonist) improve sleep in adult (18-65 years) and elderly (65 years and older) insomnia patients (Yeong et al 2015). It has a preferential effect on reducing awakenings in the latter half of the night (Krystal et al 2010) and does not appear to give rise to residual daytime effects (Krystal et al 2011). Suvorexant, an antagonist at orexin OR1 and OR2 receptors, improves sleep in adult and elderly insomnia patients. It increases subjective total sleep time and decreases subjective wake time in the middle and end of the night and subjective time to sleep onset; a few healthy volunteers had impairment of driving ability 9 hours after higher doses of suvorexant (Vermeeren et al 2015). Neither of these drugs is currently available in Europe.

#### 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)**

Fig 3 here

#### Long-term use of sleeping medications

**What is known about long-term treatment:**

* Insomnia is often long-lasting and is often treated with hypnotics for long periods in clinical practice (Ib)
* Studies suggest that dependence (tolerance/withdrawal) is not inevitable with hypnotic therapy up to 1 year with eszopiclone, zolpidem, ramelteon (Ib)
* Intermittent dosing may 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 sleeping 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 US, 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 their use should be limited to periods of 2-3 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 & Uhlenhuth, 1992; Ishigooka *et al*, 1999; Mellinger *et al*, 1985; Ohayon *et al*, 1999).

The reasons for longer term use are complicated and difficult to research but are probably similar to those which affect understanding of longer term benzodiazepine treatment in patients with anxiety disorders. We do not know the proportions of longer term users that 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 (Morin *et al*, 2005a;Belanger *et al*, 2005), 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.

Placebo-controlled trials of treatment for durations longer than 3 weeks that can more definitely assess safety and efficacy, and determine whether dependence phenomena occur have been undertaken. Trials of nightly dosing for up to 12 months duration suggest that tolerance and withdrawal do not generally occur with some hypnotics: zolpidem (1 study of 12 months and one of 8 months duration) eszopiclone (2 studies of 6-months duration); ramelteon (a 6- month study with outcome assessed with polysomnography (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)Roehrs 2011,. Others 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 up to one year with the agents studied (zolpidem, eszopiclone, and ramelteon) suggest that discontinuation symptoms are generally mild and infrequent (Randall 2012; 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 when 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 six 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. The longer-term safety and efficacy of many other commonly used hypnotics remains uncertain.

A number of 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 addresses concerns that once started hypnotic therapy could be unending. Concomitant CBT during tapered discontinuation is helpful (Parr et al 2009, Morin *et al*, 2006). Another unresolved issue is whether to implement nightly or intermittent dosing of hypnotics for a given patient. It is clear that the medication works on the nights it is taken but poor sleep occurs when it is not. 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. In addition, some have argued that intermittent dosing may reinforce psychological dependence on the drug.

#### Recommendation

**Use as clinically indicated (A)**

**In general, hypnotic discontinuation should be based on slowly tapering off medication (A)**

**CBTi during taper improves outcome (A)**

### Using drugs for depression to treat insomnia

**What is known about the use of drugs for depression to treat insomnia**

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

**What is not known:**

* Duration of effect (particularly as they are often prescribed for long periods)
* How their effects compare with approved medications for insomnia

Tricyclic and some other classes of antidepressants have long been used for insomnia. There is no good evidence for this and little for other antidepressants (see Everitt et al), whereas the selective serotonin reuptake inhibitors (SSRI) as a class generally disrupt sleep early in the course of treatment (Mayers & Baldwin, 2005). The alerting effect of SSRIs can sometimes be offset by co-administration of sedating drugs for depression such as trazodone, probably because they block 5-HT2 receptors that are being overstimulated by an increase in 5-HT (Kaynak *et al*, 2004); alpha-1 adrenergic antagonism may also contribute. Other 5-HT2 antagonist drugs for depression 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, have been used for decades to treat insomnia. This is particularly common practice in primary care in the UK, where amitriptyline 10 or 25mg 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 5-HT2 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 demonstrate an effect of doxepin in insomnia at sub-antidepressant dose (25mg) (Hajak *et al*, 2001;Hajak *et al*, 2001) for 4 weeks, with rebound insomnia.

Trazodone is an agonist at 5-HT1A receptors, an antagonist at 5-HT2 and α1 adrenergic receptors and a weak 5-HT reuptake inhibitor: it is the second most prescribed medication for insomnia in the USA. It has a perceived absence of risk and is cheap, but 25-30% patients experience difficulty tolerating trazodone and dropout rates tend to be higher than for benzodiazepine hypnotics or Z-drugs. Although there have been 18 trazodone studies measuring sleep outcomes, only 2 were in primary insomnia, and only 1 was a controlled study (Walsh *et al*, 1998). This study used 50mg trazodone v 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 drug for depression which blocks α-1 adrenergic, histamine H1, dopamine D2, serotonin 5-HT2 and cholinergic receptors (Richelson, 1994;Gross *et al*, 1991). There is one controlled trial (Riemann *et al*, 2002) in insomnia at doses of 50-200mg for 4 weeks which found a significant improvement in sleep efficiency as measured by polysomnography, 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 20mg for 6 weeks (Reynolds, III *et al*, 2006), there being a 50% response rate (placebo 38%) with subjective sleep quality and daytime well-being improved. This seeming 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 and periodic limb movements of sleep (Hoque & Chesson, Jr., 2010) and SSRIs can induce or exacerbate sleep bruxism (Wilson & Argyropoulos, 2005).

### Recommendations

**Use drugs according to a knowledge of pharmacology (A)**

**Consider drugs for depression when there is co-existent mood disorder (A)**

**Beware toxicity of TCAs in overdose even when low unit doses prescribed (A)**

### Drugs for psychosis for treatment of insomnia

**What is known about use of drugs for psychosisin treatment of insomnia**

* Dopamine serotonin antagonists particularly olanzapine and quetiapine improve sleep in healthy volunteers (Ib)
* Quetiapine, ziprasidone and lurasidone improve sleep in models of transient insomnia (Ib)
* When used on label, clozapine, olanzapine, quetiapine, risperidone and ziprasidone improve sleep continuity in schizophrenia, unipolar and bipolar disorder (I)
* Minor improvements in sleep in primary insomnia are seen after quetiapine (IIb)
* Side effects are common because of the broad pharmacological actions of these drugs (I)

**What is not known**

How drugs for psychosis compare with approved drugs for insomnia

Dopamine-serotonin antagonists particularly quetiapine and olanzapine, have become widely used in the treatment of sleep problems with very little controlled trial evidence. For example, prescriptions of quetiapine for sleep disturbances increased by 300% in Canada between 2005-2012 (Pringsheim and Gardner 2014) and a cross-sectional study conducted using the US National Health and Nutrition Examination Survey data from 1999–2010 found that quetiapine was the fourth most common drug prescribed for insomnia (11%) (Bertisch et. al. 2014).

Some polysomnographic sleep studies in healthy volunteers have shown changes in sleep architecture. These include increases in slow wave sleep and decreases in REM sleep with ziprasidone and olanzapine (Cohrs et.al. 2005, Cohrs et al., 2004; Sharpley et al., 2000). Some positive changes in measures of sleep maintenance have been shown with clozapine, quetiapine, olanzapine and risperidone (Gimenez et al., 2007; Lindberg et al., 2002; Sharpley et al., 2000; Staner et.al. 2002). Subjective sleep was improved by risperidone, olanzapine and quetiapine.

In models of transient insomnia such as acoustic stress and phase advance in healthy volunteers, quetiapine, ziprasidone and lurasidone have shown improvements in sleep initiation and maintenance (Karsten et.al 2017; Cohrs et al 2004, 2005; Krystal and Zammit 2016) .

In patients with schizophrenia (see Monti et al 2017) clozapine increased total sleep time (Kluge et.al. 2014); olanzapine increased slow wave sleep and improved sleep continuity measures (Salin-Pascual etal 1999; 2004; Muller et al 2004; Kluge et al. 2014; Gao et Al. 2013; Monti e.al. 2017). Quetiapine administration has generated mixed results in patients with schizophrenia, with Loebel et.al. (2014) finding increases in daytime sleepiness after 6 weeks quetiapine XR 600mg compared with placebo, whereas Keshavan et.al. (2007) found reduced sleep continuity compared with drug naïve patients.

In bipolar patients (see Monti 2016) 6 months add-on clozapine treatment increased total sleep time compared with baseline (Armitage et.al 2004). Risperidone and olanzapine both improved sleep continuity when added to an SSRI in depression (Sharpley et al., 2003; 2005; Lazowski et.al.2014). Furthermore Moreno et.al. (2007) found that olanzapine improved sleep continuity in patients with bipolar disorder during a manic episode. Using actigraphy, Todder et al. (2006) and Kim et al. (2014) showed that adjunctive or monotherapy quetiapine improved sleep continuity in patients with unipolar or bipolar disorder. A PSG study with ziprasidone augmentation in bipolar patients with an acute depressive episode improved sleep induction, sleep continuity and sleep architecture (Baskaran et.al. 2013). Overall, these results indicate a potential beneficial effect on sleep of dopamine -erotonin antagonists in patients prescribed them for a labelled indication.

In patients with insomnia, a small open study of quetiapine (25mg in most patients) for 6 weeks (Wiegand et al., 2008) showed improvements in sleep, with transient adverse eﬀects of morning hangover and dry mouth. A double-blind, placebo- controlled study which investigated the efficacy of quetiapine (25mg) in primary insomnia (Tassniyom et. al. 2010) had a small sample size (13) and subjective improvements in sleep were not significant.

Side eﬀects 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 (Sansone and Sansone, 2010). A review of quetiapine for use in insomnia (Anderson and Vande Griend 2014), concluded that its benefit in the treatment of insomnia has not been proven to outweigh potential risks, even in patients with a comorbid labelled indication for quetiapine. An American Academy of Sleep Medicine Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults (2017) also concluded that quetiapine was not indicated for use in insomnia (Sateia et.al 2017).

**Recommendation**

**Side effects are common because of the pharmacological actions of drugs for psychosis and there are a few reports of abuse.**

**Together these indicate no indication for use as first line treatment (D)**

### Antihistamines (H1 antagonists)

Antihistamines are sedating and are sold as ‘over the counter’ (OTC) sleeping medications. There is only limited evidence that these older non-selective antihistamines work, although some modest benefits have been reported after two 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 & Oswald, 1986;Alford *et al*, 1992) but the latter is not available over-the-counter, and both have quite long durations of action so are likely to cause hangover effects.

Antihistamines are sometimes 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. These drugs have anticholinergic side effects, making them dangerous in overdose.

The selective antihistamine (low-dose) doxepin 1-6mg has been shown to be effective in insomnia in adults and the elderly, with few residual effects, and is approved in the USA but not in Europe. It has been shown to particularly reduce awakenings in the latter part of the night. Another selective agent, low-dose esmirtazapine, is currently undergoing evaluation.

### Recommendations

**The selective antihistamine doxepin (very low dose) is effective in insomnia (A)**

**Non-selective histamine antagonists have a limited role in psychiatric and primary care practice for the management of insomnia (D).**

Here Fig 3 Algorithm for treatment of insomnia

# Circadian rhythm disorders

Daily rhythms of sleeping and waking are controlled by a variety of brain mechanisms, the most prominent of these being the circadian process (the ‘body clock’ signalling time for sleep) and the homeostatic process (a build-up of sleep pressure during the hours of wakefulness). These two processes work together to consolidate sleep and wakefulness (Diik 2005)

Circadian rhythm is a roughly 24-hour cycle in the physiological processes of living beings. It is internally generated, although it can be modulated by external cues (*zeitgebers*) such as sunlight, and feeding and drinking, and in humans by daily routines of work, exercise etc. Circadian rhythms are controlled by a brain pacemaker in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which has a direct input from the retina signalling light levels. Most body systems, not only sleeping and waking, are to some degree modulated by input from this circadian pacemaker.

The innate frequency of the circadian clock in humans is slightly longer than 24 hours, and synchronisation with the external 24-hour physical environment and day- to-day activities requires daily adjustments to the internal clock. The light-dark cycle is the strongest synchronizing agent for the circadian system. In humans, light exposure in the evening produces delays, and in the early morning produces advances. The SCN also receives internal signals from the pineal gland, via the nocturnal release of melatonin. Endogenous melatonin release begins to increase 2-3 hours before sleep onset, and peaks in the middle of the night. Exogenous melatonin given during the early morning delays the timing of circadian rhythms, and given during the early evening induces advances in this timing, which contrasts with the effects of light.

There are differences within humans in their preference for sleep times (chronotype). Some people preferring to rise early and are at their best in the morning (‘morningness’, or ‘larks’) and those who rise later and are at their peak later in the day (‘eveningness’, or ‘owls) These preferences be determined in part by genetics. Children are early chronotypes and become progressively later (delaying) as they grow older, reaching a maximum in their ‘lateness’ at around the age of 20. After 20, they become earlier again (advancing) with increasing age. Young women reach their maximum in lateness earlier than men; men continue to delay their sleep until around the age of 21 and remain later chronotypes for most of their adulthood (Roenneburg 2004). This gender difference disappears at around the age of 50 years, which coincides with the average age of menopause.

Circadian rhythm sleep-wake disorders (CRSWDs) occur when there is an alteration of the endogenous circadian system or a misalignment between the endogenous circadian rhythm and the sleep-wake schedule required by the physical environment or social or work timetable. This results in insomnia when they are needing to sleep, and sleepiness when alertness is required, causing significant distress and impairment of function.

There are six CRSWDs defined in ICSD:-

The most common is Jet Lag Disorder, in which the circadian clock has a temporary misalignment after transition across time zones. Symptoms of insomnia, daytime sleepiness and physical discomfort normally disappear once there is exposure to *zeitgebers* in the new environment, within a length of time proportional to the number of time zones crossed. Thus after an eastbound trip from the USA west coast the circadian clock might take 8 or so days to settle into the UK routine. This condition tends not to present to health professionals for treatment, although it is likely to have some destabilizing impact on conditions such as bipolar disorder.

Delayed Sleep Wake Phase Disorder (DSWPD) affects 2-8% of the population and is greatest in young adults. There is usually difficulty falling asleep before 2–3 a.m. (sometimes later), and on days without work/school/college the preferred wake time is after 10am, 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. There is a high incidence of comorbidity with psychiatric disorder in those with DSWPD with up to 60% of people having a diagnosis of depression, substance abuse, or anxiety (Redid et al 2012; Abe et al 2011)

Advanced Sleep Wake Phase Disorder (ASWPD) is much rarer, with reports of an average sleep onset from 6 to 9 pm and wake time of 2 to 5 am. However, if allowed to sleep during their preferred times, the sleep quality and duration are normal for age. Prevalence is around 1%, but this may be a low estimate as the lifestyle disruption may be less of a problem with earlier timings. There sometimes a hereditary component to advanced sleep wake phase disorder, and mutations of clock genes have been identified in familial cohorts.

In Irregular Sleep Wake Rhythm Disorder (ISWRD) there is no clear main sleep period, but sleep and wake periods distributed irregularly through the 24 period with at least 3 sleep bouts. There is thought to be a disruption of either the central pacemaker, or of perception of environmental cues, and this disorder is most common among young people with neurodevelopmental disorders and adults with neurodegenerative disorders and occasionally with traumatic brain injury.

Non 24-hour Sleep Wake Rhythm Disorder occurs when individuals are unable to entrain to the 24-hour day but follow their endogenous circadian period, which is usually slightly longer than 24 hours. Their sleep-wake routine moves progressively later each day, and sleep complaints may consist of insomnia, excessive daytime sleepiness, or both. A large proportion of people with this disorder are visually impaired, and without light perception, so the resetting of endogenous rhythms from the retino-hypothalamic pathway is not possible.

Shift work disorder is characterised by excessive sleepiness during work and insomnia when trying to sleep between shifts. . There are many shift work schedules; they may be permanent, rotating or irregular, so the presentation of SWSD is variable. It is not known why some people adapt adequately to changing work period timing, and others do not.

## Diagnosis of circadian rhythm disorders

Assessment of these disorders involves interview, sleep diaries (from parents/carers if necessary) and actigraphy for 14 days. In the case of DSWPD and ASWPD it is recommended to give the morningness-eveningness questionnaire (Horne and Ostberg 1976.

## Treating circadian rhythm disorders

**What is known:**

* Melatonin is effective in jet lag disorder (1a), delayed sleep phase syndrome (Ib) and non 24hr sleep rhythm disorder (IIa)
* Light therapy is effective in delayed sleep phase syndrome (III)

**What is not known**:

* What are the best efficacy measures – subjective or objective?
* Is there a need to distinguish between adults and adolescents in DSPD 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 DSPD?

Current understanding of circadian rhythms and sleep physiology provides a strong theoretical basis for the use of melatonin in some, but not all 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 solid evidence to support the use of melatonin in jet lag (Spiegelhalder 2017) but (immediate release) melatonin has to be taken near desired bedtime otherwise there may undesired daytime sleepiness. An evidence-based strategy for minimising jetlag which includes strategic scheduling of sleep combined with melatonin is given by Sack (Sack, 2010).

In delayed sleep wake phase disorder**,** there is both a theoretical and an empirical basis for use of melatonin, which is effective in practice, shown in 2 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 non-24 hour sleep rhythm 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 & Arendt, 2007; Skene *et al*, 1999).

There is no evidence of the 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 (Sack *et al*, 2007b).

Bright light therapy has been used effectively in delayed sleep phase syndrome (Shirani & St Louis, 2009). Exposure to bright light of 2500 lux for 2 hours in the early morning, combined with light restriction after 16:00 (dark goggles) is an effective treatment for delayed sleep phase syndrome and a light mask offering exposure to gradually increasing light intensity through closed eyelids over the last 4 hours of habitual sleep time has been shown to be effective in these patients.

In the elderly patient with dementia with an irregular sleep wake disorder there is a little evidence to support the use of bright light therapy in combination with behavioural interventions, but the use of melatonin is discouraged (Auger et al 2015).

### Recommendations

**Clinical assessment is essential in delayed sleep wake phase disorder, non-24 hour sleep rhythm disorder [A]**

**Melatonin may be useful in delayed sleep wake phase disorder, non-24 hour sleep rhythm disorder in non-sighted individuals and jet lag disorder [B]**

**Other approaches such as behavioural regimes and scheduled light exposure (in sighted individuals) can also be used [B/C]**

**Because of the necessity for careful timing of interventions, patients with these disorders need to be treated in specialised sleep disorders centres (D)**

# Parasomnias

Parasomnias are unusual episodes or behaviors occurring during sleep which disturb the patient or others and this document addresses those that cause significant distress and therefore present for treatment. Violent or unusual night-time attacks may arise from deep non-REM sleep (night terrors and sleepwalking) or from REM sleep (sleep paralysis, 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 night, usually with a scream and signs of intense fear and autonomic arousal, and 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 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 (Stallman & Kohler 2016). In some cases they 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. Some cases of sleepwalking seem related to use of certain drugs e.g. alcohol and hypnotics, especially zolpidem and triazolam, opiates (possibly related to sleep-disordered breathing) (Pressman et al 2007), or other sleep disorders such as sleep apnoea. 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.

Sleep paralysis, nightmares and REM sleep behaviour disorder (RBD) are disorders arising from REM sleep. Sleep paralysis and nightmares are recalled by the patient. REM behaviour episodes are sometimes recalled but more often only apparent to the bed partner.

Sleep paralysis is a brief state of involuntary immobility usually occurring on waking from a night’s sleep or a nap (more rarely at sleep onset). It is often accompanied by dream imagery, sometimes of a frightening kind, and sometimes a feeling of chest tightness. It is attributed to waking abruptly from a REM sleep episode with the REM atonia persisting briefly. It appears to be more common in those with narcolepsy, and in those with irregular sleep-wake routine and after drinking alcohol.

RBD is a disorder first described in the late 1980s with violent complex behaviour at night. There are 2 sleep abnormalities: lack of atonia during REM sleep (which can be quantified using video-polysomnography), and increased vividness and/or nasty 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 causes injury to self or bed partner in up to 70% of patients. Its incidence is estimated at 0.5% to 1% of those over 55), occurs in older people with a steady rise after 55 and has a male preponderance in older patients. It is now well recognised as the most robust prodromal, non-motor symptom of a subsequent neurodegeneration, typically an alpha synucleinopathy. Several cohorts under long term follow up have shown that 50% at 5 years and 91% at 15 years will have developed another neurodegenerative problem. It is often associated with Parkinson’s disease (it is seen in up to 50% of PD pts), Lewy body dementia (~70%), multiple system atrophy (>90%). RBD often precedes other symptoms of neurodegeneration by several years (Iranzo et al 2014).

## Diagnosis of parasomnias

Assessment of parasomnia may be possible with a detailed history from patient or witness, but in general for adequate diagnosis, referral to a specialist sleep centre for polysomnography and video recording may be necessary. Two successive nights of polysomnography are desirable, and in the case of suspected non-REM parasomnia these should comprise a sleep-restricted (5 hours) night and a recovery night: this maximises deep slow wave sleep on the second night and thus increases the chance of capturing an event.

## 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 (Harris & Grunstein, 2009). Priorities are to minimise possible trigger factors such as noise, 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 3mg per night has been reported to be effective (case series, n=69) (Schenck & Mahowald, 1996). Smaller case series have reported good effects of paroxetine (Wilson et al, 1997) and imipramine (Cooper, 1987) (both effective immediately) and there are several case series of hypnotherapy in sleepwalkers (Becker PM 2015). A randomised controlled study of 3 weeks’ treatment with 5-hydroxytryptophan 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, 2001; Hansen et al 2013). There is good evidence of beneficial effects of the alpha-1 adrenergic blocker prazosin in reducing nightmares related to PTSD in both military and civilian settings and in the paediatric population (Nadorff et al, 2014; Keeshin et al 2017). 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 drugs for depression.

For REM sleep behaviour disorder, all data on treatment comes from retrospective case notes review and for melatonin, a single, small crossover randomised trial. There are no prospective or controlled studies of clonazepam for REM behaviour disorder, but large case series suggest a good effect when used at doses between 1- 4mg (Boeve et al, 2004; Aurora et al, 2010) in reducing number of episodes and injury during them. Dose-limiting side effects are common in those with dementia, disorders of gait or balance, or concomitant OSAS (Anderson& Schneerson 2009). Beneficial effects for have been reported for melatonin 3-12 mg but with fewer adverse events. A single, small RCT has shown benefit for melatonin including in quantitative measure of REM atonia (Kunz and Mahlberg 2010). 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).

# Special populations

## Sleep disorders in women: effects of menopause and pregnancy

### Menopause

Insomnia increases as women approach and pass through the menopause (Kuh *et al*, 1997; Owens & Matthews, 1998; Bixler *et al*, 2009). Post-menopausal women have a longer sleep latency and decreased slow wave sleep. This is due to a variety of reasons – climacteric symptoms e.g. hot flushes due to hormonal changes and psychiatric disorders are most often cited. Hormone therapy appears to protect women from these changes (Bixlet et al. 2009).

CBTi has been shown to be effective in insomnia in this group, with long lasting benefits up to 6 months post treatment (McCurry et al 2016). There are modest benefits from some but not all studies of pharmacotherapy with SSRI and SNRI drugs including escitalopram, citalopram and venlafaxine although short duration of follow up limits the conclusions that can be drawn from the studies (Ensrdu et al 2012; Davaro-Tahna et al 2015).

Post menopause, there is also a rise in the incidence of sleep disordered breathing (Young et al. 2003) (Bixler *et al*, 2001). Post-menopausal women with sleep disordered breathing are more likely to complain of depression and insomnia than men with a similar degree of OSAS (Shepertycky *et al*, 2005).

### Recommendations

**1. 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 to men (D)**

**2. The use of hormone therapy should involve informed individualised treatment of symptoms, looking at risks and benefits in light of recent studies (A)**

**3. Follow recommendations for insomnia in other sections (A)**

### Pregnancy

Many women report 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 troublesome. By the third trimester, sleep is more disturbed with complaints again of urinary frequency, backache in addition to cramps, itch and unpleasant dreams. Most women fall asleep fairly easily but wake more frequently (Sedoy et al 2017).

If a 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 & Schwab, 2004). However, non-selective histamine antagonists such as diphenhydramine can exacerbate restless legs syndrome and have anticholinergic actions. Zolpidem may be preferable as it is short acting and does not have anticholinergic side effects. The hypnotics temazepam and zopiclone have not been associated with any increase in congenital malformations (Ban et al 2014).

Restless legs syndrome is common in pregnancy, with a prevalence between 15-25%, peaking in the third trimester with improvement in the last 2 weeks and often resolving post partum. It is sometimes associated with anaemia (Hubner et al 2013; Neau et al 2010). Iron replacement is safe and may be effective based on small case series, with carbidopa/levodopa or clonazepam only recommended in severe and refractory cases (Picchietti et al 2015).

Snoring and sleep disordered breathing, especially in obese subjects, is increasingly recognised, is associated with worse foetal outcomes and affects up to 8% of women by the third trimester. (O’Brien et al 2014).

### Recommendations

* **Good sleep hygiene and lifestyle (D)**
* **Manage general pregnancy associated complaints e.g. decrease fluid intake, pillow support. (D)**
* **The effects of CBT-I in pregnancy have only been assessed in one small open label study, but this approach seems sensible (B).**
* **Recognise restless leg syndrome by careful history and investigations if necessary.**
	+ **Dopamine agonists are contraindicated (FDA category C or greater)**
	+ **Iron supplementation has been shown to be effective in restless legs syndrome. Supplementation is suggested even if levels are not low. (D)**
	+ **Keep caffeine low as it can exacerbate RLS (D)**
	+ **Mild-moderate exercise in the early evening, stretching, massage.(D)**
* **If patient suffers from intractable insomnia and a pharmacological agent is required, zolpidem or zopiclone should be used short term after discussion on potential risks and benefits (D)**

## Treatment of insomnia in older adults

**What is known about treatment of insomnia in older adults**

* Cognitive-Behavioral Therapy for Insomnia (CBT-I) is effective in older adults and is associated with minimal side effects (Ia)
* Eszopiclone, suvorexant and doxepin improve global and sleep outcomes (Ib)
* Prolonged release melatonin given for 3 weeks improves sleep onset latency and sleep quality in patients over 55 (Ib)
* Drugs with sedative effects increase the risk of falls in older adults (III)
* Benzodiazepine hypnotics have an unfavourable risk/benefit ratio (B)
* Insomnia increases the risk of falls and fractures in nursing homes independently of medication (III)

**What is not known?**

**Is there an effective treatment for sleeplessness in older adults with dementia?**

Insomnia in elderly patients often responds well to CBTi (see psychological treatment section above). Meta-analyses comparing CBT outcomes in older adults (55 years plus), have reported moderate to large effect sizes, whether or not insomnia is comorbid with other disorders (Alessi and Vitiello, 2015).

A meta-analysis (Glass *et al*, 2005) concluded that benzodiazepine hypnotics had an unfavourable risk/benefit ratio in elderly patients, but the different methods of collection and categorisation of drug-related side effects in the studies included makes them difficult to interpret. Individual randomised 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, drugs for depression or psychosis, benzodiazepines, nonsteroidal anti-inflammatory drugs and calcium channel antagonists (Woolcott et al., 2009) but this study did not specify daytime/night-time use. There is a 2.5-fold risk of falls in hospital after zolpidem (Rhalimi et al., 2009), but 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 sleep onset latency and increase subjective sleep quality in patients over 55 years (Lemoine et al., 2007; Wade et al., 2007) (Wade et al., 2011): its effects are modest but it has no known motor side effects.

The antihistamine drug doxepin (in very low dose 3mg, see above) has been found effective in insomnia in the older patient, in particular decreasing awakenings in the latter half of the night without daytime effects (Lankford et al., 2012; Krystal et al., 2013).

### Recommendation

**CBTi is effective and should be offered as a first line treatment where available (A)**

**When a hypnotic is indicated in patients over 55 years prolonged release melatonin should be tried first (B)**

**If a GABA-A hypnotic is used then a shorter half-life will minimise unwanted hangover effects (A)**

## Sleep problems in children

**What is known**

* Most sleep settling and maintenance problems 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)

**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. Settling and sleep maintenance problems may be exacerbated by a sleep disorder such as obstructive sleep apnea or restless legs syndrome.

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 15mg or 30mg 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 is frequently employed: however, tolerance can develop quickly and some children can experience dramatic and paradoxical over-arousal. The TIRED RCT specifically investigated the use of diphenhydramine in infants aged from 6 to 15 months and found it was no more effective than placebo in reducing night-time awakening (Merenstein *et al*, 2006). It is important to consider the effects of these medications at neurotransmitter systems other than H1 receptors, particularly in relation to side effects due to anticholinergic or dopamine antagonist action.

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 delayed sleep phase syndrome and learning difficulties, autism and ADHD (Rossignol & Frye 2011, van der Heijden *et al*, 2007, Gringras 2017, Maras 2018) is increasingly robust.

There is evidence to support a behavioural intervention both before a trial of melatonin (Gringras P et al 2012) (as many will respond without requiring melatonin), and for continuing a behavioural intervention whilst administering melatonin. The combination of both has been shown to be more effective than either one alone (Cortesi et al 2012).

The most recent randomised controlled study showed a paediatric mini-pill sustained release melatonin at a dose of 2mg -10mg was well-tolerated, efficacious and safe compared to placebo for treatment of insomnia in children with ASD. These studies have resulted in the first licensed sleep medication for insomnia in children with ASD. They showed clinically meaningful improvements in total sleep time (TST), duration of uninterrupted sleep (longest sleep episode) and sleep latency (SL) with corresponding behavioural improvements for the children, and improved quality of life measures in their parents over a two year period. (Gringras P et al 2017, Maras et al 2018)

Melatonin at doses between 0.5 and 12mg is commonly used as a sleep-promoting agent in children undergoing procedures such as EEG, as an alternative to sleep deprivation to induce drowsiness and sleep 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 is licensed for children with ADHD and improves sleep maintenance in some children. The therapeutic window is narrow, both for adverse effects on sleep architecture and tolerability. Tolerance to the sleep-inducing effects develops over time leading to the need for increased doses with concomitant risk of adverse effects.

Chloral hydrate and triclofos are still popular hypnotics for children but have a very long half-life and considerable potential for ‘‘hang-over’’ 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 first in children with disturbed sleep (A)**

**Melatonin improves sleep in children with autistic spectrum disorders (A)**

**Melatonin administration can be used to advance sleep onset to normal values in children with attention deficit hyperactivity disorder who are not on stimulant medication. (B)**

## Sleep disturbance in adults with intellectual disability

There is little clarity in the definition of sleep problems in adults with intellectual disability (Richdale 2013). This is primarily because it is difficult to obtain subjective measures from the patient who may be unable to communicate verbally or even perceive that they are having a problem. Reports of sleep difficulties tend to be from carers as they struggle to cope with issues which only seem to be exacerbated when they, and the person they care for, experience sleep disturbance. There is a compelling need to develop a more accurate, standardised measure of sleep for this population (Meltzer and Mindell 2014), to obtain essential information about prevalence.

Difficulties in assessing sleep disorders include diagnostic overshadowing, where behaviours such as daytime sleepiness, inattention and challenging behaviour are regarded as symptomatic of the intellectual disability as opposed to being indicative of a sleep disorder. In these circumstances therefore, clinicians may fail to consider the possibility of sleep disturbance and thus neglect to undertake more detailed investigations.

The situation is further compounded by the fact that health and behavioural problems can increase as sleep problems develop. For example, the inability to problem solve combined with daytime somnolence exacerbates cognitive processing problems in those already compromised intellectually (Carr et al 2003; Symons et al 2000).

Within this population there are additional high-risk groups including those with co-morbidities such as Down Syndrome where people may present with sleep related breathing disorders, or Smith Magenis Syndrome where melatonin rhythm is inverted.

In general, there are a wide range of precipitating and perpetuating factors to consider including maladaptive coping strategies (Spielman et al 1987), the impact of medication e.g. drugs used in psychosis, depression, epilepsy including side-effects and the impact of polypharmacy on sleep and daytime functioning. For those in institutional or residential living environments the environment itself may contribute to disturbed or inconsistent sleep patterns, as other patients/residents wake others up or staff shift patterns determine wake/sleep times rather the individuals themselves.

### Assessment

Sound clinical assessment should elicit any aetiological or exacerbating factors which can be reversed. This may be best undertaken by direct observation initially. Carers should be supported to keep a structured 24-hour record of sleep pattern and behaviour. Actigraphy or EEG may be useful when a sleep disorder other than insomnia or settling difficulties is suspected, but clinicians should be aware that the recording equipment may not be tolerated by people with more moderate to severe levels of intellectual disability. The possibility of a circadian rhythm disorder should also be excluded in individuals with additional visual impairment.

### Treatment considerations

There is a varying degree of evidence for treatments of sleep difficulties in this heterogeneous population. Systematic review (van de Wouw et al 2012) used SIGN 50 methodology but no statistical analysis in 50 studies using behavioural interventions in adults with intellectual disabilities. They concluded there was some indication of the effectiveness of behavioural interventions. In addition, they reported that in some cases sleep problems were associated with challenging behaviour and medication.

The relatively small number of controlled studies in this area give support to parental/carer education and modifying environmental factors (Montgomery *et al*, 2004). Behavioural regimes such as chronotherapy, bedtime fading, extinction, distancing / desensitisation and sleep-wake scheduling (Wiggs & France, 2000; Gunning & Espie, 2003) may also prove beneficial. The use of light therapy has been described (Short & Carpenter, 1998).

There is little evidence for effectiveness of sleep-promoting drugs, apart from melatonin. A meta-analysis (Braam *et al*, 2009) indicated that melatonin (1-9mg) 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, however long term safety requires 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**

 



