Sleep disturbance and depression

Depression and insomnia are interlinked disorders, resulting in significant disability and both carry a risk of chronicity. Insomnia is a risk factor for depression and the majority of depressed patients complain of sleep dysfunction, including interrupted sleep, reduced length of sleep and altered sleep architecture.

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Depression is a common mental disorder. In a large European study, 14% of adults reported having a mood disorder at some point in their life[1] and the prevalence is even higher in women and older people. The lifetime risk of major depression has been reported at 6·7% and of dysthymia (a milder more chronic depressive disorder) at 3·6%.[2] A widely quoted prediction is that major depression will become the second largest cause of disability in the world by 2020.[3] The tendency of depression to recur, or to become chronic, presents special therapeutic challenges as patients may require antidepressant medication for prolonged periods. 80% of those who are referred to psychiatrists with depression will experience another episode. There is a median of 4 episodes per lifetime, and 12% of depressed patients will pursue a chronic unremitting course.[4] Elderly depressed people have higher relapse rates than their younger counterparts.[5] 50% of such patients will fail to remit within 2 years.[6]

Depression and sleep

The link between depression and sleep disturbance is well known, so that sleep problems are featured in most operational criteria for the diagnosis of depression, as well as in scales for rating the severity of depressive symptoms. A survey of older depressed patients consulting their GPs with depression revealed that 85% suffered from insomnia.[7]

The risk factors for insomnia overlap with the risk factors for depression. Both late-life depression and insomnia are more common in women, those with a history of alcohol or substance abuse, those who take multiple medications and those who suffer from physical illnesses. Both conditions are also more common in people who have experienced socio-economic stressors, such as bereavement, institutionalisation and other losses.[8] The presence of insomnia is, in itself, a risk factor for developing depression at a later date, whether depression was present or not initially. This finding is particularly noted in elderly people.[9]

Sleep regulation by homeostatic and circadian mechanisms

The sleeping person has reduced motility and muscle activity, and there is partial or complete suspension of voluntary behaviour and consciousness. Several brain centres are involved in a homeostatic process, which maintains the states of wakefulness and sleep.[10] The neuro-chemical control of these nuclei offers a number of potential and, in some cases, actualised drug targets for inducing sleep or promoting arousal eg. the benzodiazepines are hypnotic by virtue of their GABA-agonistic effect and H_1 receptor antagonists also promote sleep.

This homeostatic process is dependent on the amount of time spent awake prior to sleep onset, the level of sleep propensity during the day and the depth of sleep during the previous night. The homeostatic control of sleep dissipates during the night, resulting in reduced pressure to switch from REM (rapid eye movement) to non-REM, and REM prolongation. In normal subjects sleep involves 4–5, 90–110 minute cycles per night. There are 2 phases of sleep: REM and non-REM. 75% of sleep is non-REM. In non-REM sleep there are 4 stages characterised by functional muscle activity, low breathing, and minimal brain activity. Stages one and two involve lighter sleep. Stages three and four, termed slow-wave sleep, are usually concentrated in the first half of the night during which

high amplitude delta brain waves may be recorded on the polysomnograph. This is the deeply restorative period of sleep. In REM sleep, irregular breathing, increased body temperature, heart rate and blood pressure are evident. This is the phase of sleep in which most dreaming occurs and in which the brain wave state is similar to the wakened state. REM cycles tend to be longer in the second half of the night.

The other process regulating sleep and wakefulness is circadian. It is light dependent and functions independently of prior sleep and wakening. In healthy individuals, the desire to sleep is maximum between 3 and 5 am, and is at its lowest at 4pm when it is more difficult to fall asleep. Melatonin, which is synthesised from 5-hydroxytryptamine, is responsible for regulating the circadian sleep-wake cycle[11] in a feedback loop. Melatonin levels are low by day and high during the night.

The circadian influenced melatonin pathway is attracting growing interest. There is a potential to develop better hypnotics that mimic natural sleep, and melatonin is already available for prescription to patients over 55 years with primary insomnia.[12] In addition, altered circadian rhythms are involved in depressive illnesses impacting on both sleep and mood. In patients with seasonal affective disorder (SAD) weight gain, decreased activity and reduced libido emerge when light is reduced during winter.[13] The clear link with light intensity in this disorder may provide more useful information on the relationship between circadian rhythms and mood. Melatonin release signals not only the duration of light in the 24 hour daily cycle but also the change in the light/darkness ratio as the seasons unfold.[14]

Sleep problems in depression

An altered sleep-wake cycle is a core feature of depression and, at the same time, represents a risk factor for the development of depression.[15] Shift workers are more prone to depression and anxiety, due to a phasic shift in circadian rhythm and an alteration in routine affecting the homeostatically controlled sleep-wake cycle.[16] Depressed patients may experience prolonged sleep latency (time taken to fall asleep). Sleep continuity may also be impaired in depression and is the commonest reason for people complaining that their sleep is not refreshing. This involves frequent wakening through the night, prolonged periods awake and/or wakening early in the morning. Because older people have earlier timing of sleep and difficulty maintaining sleep in the latter part of the sleep period, early morning wakening is often the most problematic type of sleep dysfunction in the older depressed person. Depressed patients usually have an increased duration of REM sleep and a reduced duration of non-REM sleep. In the depressed person, and in older people in general, REM onset often occurs earlier than normal in sleep. The sleep disturbance found in depression is more likely to be due to altered circadian rhythms rather than any abnormality in the homeostatic sleep control process. The sleep pattern in depression suggests that circadian rhythms are delayed or there is a phase advance.

While physical health problems such as congestive cardiac failure, chronic obstructive pulmonary disease, hip problems and prostatic disease are all associated with insomnia, major depression is at least twice as likely to cause insomnia.[17] Depression is also associated with severe daytime sleepiness,[18] increasing the risk of accidents in the home, on the road and in the working environment, with older people at higher risk.

Treatment for depression and its impact on sleep

Antidepressants should only be prescribed for at least moderately severe depression according to NICE. This approximates to a Hamilton Depression Rating Scale (HDRS) score of >17. Antidepressants may also be used in sub-threshold depression that has persisted for 2 years or more.[19] NICE asserts that there is little to choose between antidepressants in terms of efficacy and suggests the first choice should be a generically available selective serotonin reuptake inhibitors, citalopram or fluoxetine. These antidepressants may not be suitable for all depressed patients, especially if they are sensitive to particular side effects or have special needs due to comorbid illnesses. In addition, antidepressant treatment may have to address disabling symptoms in the depression such as sleep disturbance. These caveats, together with the fact that many do not respond even after receiving two consecutive antidepressants,[20] means that a wider choice of antidepressant has to be available to meet the needs of depressed patients.

Tolerability issues are especially important in treating depression as it is recommended that patients should be

taking their antidepressants for at least 6 months after full remission and for at least a year if they are at higher risk of relapse (eg. elderly people).[19]. Those who have experienced more than five episodes of depression in their lifetime, two or more episodes in the last few years and elderly depressed patients with comorbid medical illness should remain on antidepressants for at least 2 years, possibly even indefinitely, to reduce the risk of relapse.

Most antidepressants, when administered to depressed patients, suppress the REM phase of sleep and increase the latency to REM onset. As a result less time is spent in REM sleep and there is a longer duration of slow-wave sleep. An exception is the tricyclic antidepressant, trimipramine, which neither suppresses REM nor increases REM onset latency.[21] While bupropion, an antidepressant more commonly used in the US, does not suppress REM it may not increase REM onset latency,[22] as is the case with trazodone.[23] Antidepressants that have 5HT2c antagonistic properties, such as trazodone and mirtazapine, improve sleep continuity.[24]

The level of day-time sedation following antidepressant administration is an important limiting factor in treatment for many patients. If it is excessive it may impair cognition and, as with insomnia, result in falls in elderly people. Sedation is also undesirable in car drivers and depressed people who are working or hoping to return to work when in remission. This factor is especially important where it is planned to prescribe antidepressants in the longer term. By way of contrast, a degree of day-time sedation may be useful for depressed patients who have chronic pain, or are recuperating from serious illness or traumatic injuries. Of the tricyclics, amitriptyline and dosulepin are the most sedative. Most SSRIs are non-sedative but fluvoxamine possesses a modest sedative effect. Other sedative choices are the noradrenalin serotonin specific antagonist (NaSSA) mirtazapine and trazodone.

REM rebound on antidepressant withdrawal is a potential problem for all patients when antidepressants, which suppress REM, are discontinued resulting in dream laden and often unrefreshing sleep. The absence of this phenomenon is a claimed benefit for the prescription of melatonin as an hypnotic.[12]

Since circadian rhythms are disrupted in depression, it seems logical to treat depression and SAD using therapies that modify the availability of light and sleep to the depressed person. Total sleep deprivation induces rapid resolution of depression in 40–60% of patients, but unfortunately the effect is short-lived.[25] The recovery may be sustained by adding in antidepressant drugs, lithium, shifting of sleep time or light therapy. Bright light therapy seems to be effective in SAD, and to a lesser extent in non-seasonal depression, although many studies of this therapy are methodologically flawed.[26] A common strategy to deal with insomnia in depression is to add a benzodiazepine hypnotic such as temazepam or one of the newer, so-called Z drugs-zopiclone, zolpidem and zaleplon. The problem with this approach is that the benzodiazepines are dependency forming, and have abuse potential, while the need to add a second drug to the antidepressant regime increases the risk of pharmacokinetic and pharmacodynamic interactions, resulting in over sedation.

A novel and more fundamental approach to the treatment of depression involves influencing circadian rhythms thereby treating depression and its associated sleep dysfunction simultaneously. Agomelatine, which has demonstrated efficacy against placebo and other antidepressants in short-term randomised controlled trials,[27-29] has a unique pharmacological profile geared towards this end. It is a melatonin 1 and 2 (MT1 and MT2) receptor agonist and a serotonergic, 5-HT2c, antagonist. Agomelatine is an effective antidepressant, especially in patients with more severe depressive illnesses.[30] It also improves sleep quality, continuity and efficiency, normalises sleep architecture and restores slow-wave sleep in early cycles without suppressing REM.

Conclusion

Depression and insomnia are inter-linked disorders, resulting in significant disability and both carry a risk of chronicity. Insomnia is a risk factor for depression and the majority of depressed patients complain of sleep dysfunction, including interrupted sleep, reduced length of sleep and altered sleep architecture. Sleep is regulated by both a homeostatic mechanism dependent on the time spent awake prior to sleep onset, and a neural pathway influenced by the circadian cycle of light and darkness. Conventional antidepressants mostly suppress REM sleep and delay its onset. They do not restore normal sleep functioning.

Dr H Livingston and Dr M Livingston have acted as consultants to Servier

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