



Sleep disturbance and psychiatric disorders

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Lancet Psychiatry 2020;
7: 628–37

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Signs of mental ill health that cut across psychiatric diagnostic categories at high rates are typically viewed as non-specific occurrences, downgraded in importance and disregarded. However, problems not associated with particular diagnoses should be expected if there is shared causation across mental health conditions. If dynamic networks of interacting symptoms are the reality of mental health presentations, then particularly disruptive and highly connected problems should be especially common. The non-specific occurrence might be highly consequential. One non-specific occurrence that is often overlooked is patients' chronic difficulty in getting good sleep. In this Review, we consider whether disrupted sleep might be a contributory causal factor in the occurrence of major types of mental health disorders. It is argued that insomnia and other mental health conditions not only share common causes but also show a bidirectional relationship, with typically the strongest pathway being disrupted sleep as a causal factor in the occurrence of other psychiatric problems. Treating insomnia lessens other mental health problems. Intervening on sleep at an early stage might be a preventive strategy for the onset of clinical disorders. Our recommendations are that insomnia is assessed routinely in the occurrence of mental health disorders; that sleep disturbance is treated in services as a problem in its own right, yet also recognised as a pathway to reduce other mental health difficulties; and that access to evidence-based treatment for sleep difficulties is expanded in mental health services.

Introduction

"I found I had been lying awake so long that the very dead began to wake too, and to crowd into my thoughts most sorrowfully."

Dickens¹

"Even thus last night, and two nights more I lay, And could not win thee, Sleep! by any stealth: So do not let me wear to-night away: Without Thee what is all the morning's wealth?"

Wordsworth²

"Now human souls are all in love with sleep, in gentle resting, restoration seek."

Labe³

The effects of a bad night's sleep are known to all. Many people are also familiar with the effects of a sequence of disrupted nights. Unoccupied night-time hours can allow worries to take hold and the following day can bring drops in mood, confidence, and sharpness. Life's natural experiments with disrupted sleep, supported by the findings of scientific experiments,^{4,6} lead many people in the general population to conclude that

disrupted sleep provokes worse mental health. This view seems uncontroversial, but it contrasts with how disrupted sleep is typically conceptualised in mental health care. Insomnia symptoms accompanying other mental health conditions have been seen as secondary.⁷ The implication is that insomnia is either a symptom or consequence of other mental health difficulties. The ubiquity of sleep difficulties in patient presentations across diagnoses (ie, its non-specificity) has been taken to imply that it might not explain the occurrence of a particular disorder. Thus, the treatment of sleep difficulties has become an afterthought in patient care. This Review examines the case for a realignment of the importance of sleep in mental health care towards that of the hard-won lessons of lay perception.

The issue might, partly, reflect how current diagnostic systems are used, which train clinicians to spot the specific, leaving non-specific problems to be largely overlooked. If psychiatric diagnostic categories were truly independent and discrete, then such an approach would be appropriate. But high rates of comorbidity, diagnostic instability, and heterogeneity within diagnoses have led many health-care professionals to conclude that the different psychiatric categories are not truly independent. Empirical studies show that the hundreds of different psychiatric diagnoses cluster into far fewer types.^{8,9} Thus, shared causation and symptoms should be apparent across diagnostic categories. Causation for a diagnostic category might best be viewed as complex, comprising both shared and specific causes, with both types of importance in understanding and treatment. From this perspective, non-specific signs will have substantial explanatory power.

An alternative to the standard approach of diagnostic classification is to conceptualise mental health problems as arising from a complex network of interacting psychiatric symptoms.^{10,11} Triggering a symptom can set a whole network of activation in motion, which might vary

Key messages

- Sleep disturbance is ubiquitous in mental health presentations
- Sleep disturbance is likely to be a contributory causal factor in the occurrence of most mental health conditions
- Insomnia in the context of mental health disorders can be successfully treated; when sleep problems are treated, other mental health problems tend to lessen
- Patients are likely to benefit from mental health services incorporating routine assessment and treatment of sleep problems into care pathways
- Mental health professionals might require greater training on disrupted sleep and its treatment

by the individual. This approach puts renewed focus on individual patient experience, which had previously been used to create syndromes linked with diagnoses. This approach also directly tackles the complexity of causation in mental health conditions. Connections (edges) between symptoms (nodes), their strengths, and causal directions within networks can be pictured in probabilistic graphical modelling.^{12,13} Symptoms that might be key to causal cascades can be identified and, hence, become treatment targets. From such a perspective, common mental health symptoms, which are associated with many diagnoses, are potentially influential in networks of psychiatric problems. The importance of disruption to sleep and circadian rhythms across multiple mental health problems is also seen in the Research Domain Criteria framework, with the arousal and regulatory system being one of the six key domains of human functioning likely to affect mental health.¹⁴ In these new conceptualisations of mental health, non-specific problems implicitly have high causal status.

This Review focuses on the non-specific problem of sleep disruption. Such disruption is a highly plausible candidate contributor to many mental health problems. Sleep is not a passive state and obtaining sufficient sleep has been shown to be important for both physical and mental wellbeing. Over cycles of approximately 90 min, sleep alternates between rapid eye movement (REM) and non-REM states. In adults, REM sleep comprises about a quarter of a total night's sleep, becoming more common in later sleep cycles; whereas, non-REM has three substages corresponding to depth of sleep. Sleep is the result of a combination of factors, including time spent awake (homeostatic load), time of day (circadian rhythm), and amount of arousal. These interacting processes are regulated by multiple neuronal regions, systems, and neurotransmitters across the brain.¹⁵ Sleep is likely to serve many functions, such as supporting memory consolidation,¹⁶ helping to process emotions,¹⁷ and restoration (including perhaps flushing out waste products from the brain).¹⁸

Many of the effects of sleep loss are likely to increase susceptibility to mental health conditions, such as increased state anxiety and depression,⁴ decreased positive mood,¹⁹ poor emotion regulation,²⁰ negative perception of neutral stimuli,²¹ increased perception of pain,⁵ poor response inhibition,²² working memory impairment,⁶ and poor problem solving.²³ Sleep restriction also brings physiological effects, including alterations in endocrine and immune function.^{24,25} It should be noted, however, that conditions such as insomnia are not simply disorders of sleep loss, but typically include additional elements such as fragmented sleep, poor quality of sleep, and negative psychological reactions. Environmental risk factors for mental health disorders, such as trauma, also disturb sleep.²⁶ Sleep disturbance without other mental health symptoms is an exception in clinical presentations.²⁷ A meta-analysis of polysomnographic studies showed that sleep alterations

were present in most mental health conditions.²⁸ Leading sleep and circadian researchers have argued the case for the fundamental influence of sleep on mental health.^{4,29,30} The main noticeable shift has been the removal of the distinction between primary and secondary insomnia from diagnostic systems over the past decade.³¹

In this Review, we consider the potential importance of disrupted sleep in mental health problems. If sleep difficulties are not simply a secondary issue, and instead play a contributory role in the multifactorial causation of major types of mental health disorders, then sleep problems should be apparent before the onset of other disorders, common in clinical presentations, and most importantly, when successfully treated, should result in reductions of other mental health difficulties. We principally consider insomnia because it is the most common and most studied sleep condition, and we note the influence of relatively common parasomnias (eg, nightmares) and circadian rhythm disturbances. Our focus is on sleep disturbance as a common contributory cause of mental health conditions. First, this means that rarer conditions, such as sleep apnoea, are not addressed, even though they are clearly clinically important when present. Second, we prioritise the discussion of longitudinal, experimental, and interventionist-causal studies, all of which enable stronger causal conclusions. Treatment studies, when suitably designed, are increasingly recognised to have the potential to be especially informative about causation. This effect exists because, similar to an experiment, there is direct manipulation of a putative causal factor and assessment of the resultant consequences.³² The addition of mediation analysis can further substantiate the causal claims made from treatment studies.³³ The three conditions that have been most researched for their association with sleep are considered in this Review: schizophrenia, depression, and post-traumatic stress disorder.

Schizophrenia

A re-examination of the role of sleep in schizophrenia has principally come from two converging lines of enquiry. First, clinical experience with patients with persecutory delusions in the context of non-affective psychosis led to the observations that sleep problems are frequent, that psychological treatment can reduce these difficulties, and that improved sleep brings reductions in delusions.^{34,35} These clinical observations prompted the hypothesis that sleep disruption is a factor in psychotic experiences. Second, researchers in circadian neurobiology highlighted the fact that considerable disruption in the sleep-wake cycle is common in patients with schizophrenia.^{36,37} As such, it was proposed that circadian misalignment and schizophrenia share common causes. Additionally, patient accounts are now being recorded, with reports of problems getting to sleep, staying asleep, having too

much sleep, experiencing nightmares, and having erratic sleep patterns.³⁸ However, a survey of mental health professionals found that very few of them formally assessed sleep problems in this patient group.³⁹

Sleep problems and psychotic experiences are clearly associated. For instance, in a study of over 250 000 people who took part in a world health survey by WHO, the presence of sleep problems was associated with a doubling of the odds of reporting a delusional idea or hallucinatory experience.⁴⁰ The type of psychotic experience matters. In a classical twin study design with 5000 adolescent twin pairs,⁴¹ insomnia had moderate correlations with paranoia, hallucinations, and cognitive disorganisation, but low correlations with negative symptoms and no association with grandiosity. Furthermore, the twin study indicated that the genetic and environmental influences on insomnia overlapped with those influences on paranoia, hallucinations, and cognitive disorganisation. Consistent with these findings, a molecular genetic study found that a polygenic risk for schizophrenia was associated with a short sleep duration and nightmares.⁴² Longitudinal studies, including the use of experience sampling methods, found that poor sleep predicted subsequent occurrences of paranoia and hallucinations.^{43–46} Three-quarters of patients with schizophrenia have reported that sleep disturbance occurs before the onset of persecutory delusions.⁴⁷ Negative affect has been repeatedly found as the linking factor between sleep disturbance and psychotic experiences;^{34,41,45,46,48,49} although, this affect does not necessarily explain the association entirely.

As would logically follow from these studies, rates of sleep disorder are high in patients with schizophrenia. In a study of self-report assessment with 1800 patients with non-affective psychosis, insomnia was recorded in half (906 patients).⁵⁰ High rates of insomnia were found for patients with current paranoia, hallucinations, or both. By use of a diagnostic sleep interview with 60 patients with first episode psychosis, it was found that 48 (80%) patients reported at least one sleep disorder (most commonly insomnia and nightmares) and that, on average, these patients had three sleep disorders.⁵¹ Sleep difficulties and circadian disruption predict a poor prognosis for patients at ultra high risk of psychosis.^{52,53} Actigraphy studies showed lower amounts of sleep efficiency and greater sleep fragmentation in patients with schizophrenia than in non-clinical controls;⁵⁴ however, it should be noted that it can be difficult to establish sleep with actigraphy when frequency of activity is generally low and sedentary behaviours are common. Polysomnography studies have shown lower sleep time and a range of disturbances in sleep architecture in patients with schizophrenia compared with controls; nevertheless, results have been inconsistent and difficult to interpret.^{55,56}

Two studies provide insight into what happens if the amount of sleep is altered. The most important study to

date is the OASIS trial.⁵⁷ 3755 students with insomnia were randomly assigned to receive either an online sleep intervention or no intervention. The sleep intervention led to a large reduction in insomnia (effect size 1.1). Most importantly, although the sleep intervention contained no techniques to alter psychotic experiences, improvements were observed in paranoia and hallucinations, albeit small (effect size 0.2). Changes in insomnia mediated the changes in the psychotic experiences, with little evidence for reverse causation. This interventionist-causal study indicates that insomnia is a contributory causal factor in the occurrence of delusions and hallucinations. The study did not, however, involve patients with psychosis. The conclusion from the OASIS trial is further supported by a study that tested a reverse manipulation, reducing sleep to 4 h per night for three nights in 68 non-clinical individuals.⁶ It was found that sleep loss led to increases in paranoia (effect size 0.4), hallucinations (effect size 0.9), and cognitive disorganisation (effect size 0.6), but not grandiosity. Changes in negative affect and related processes, but not working memory impairment, mediated the effects of sleep loss on the psychotic experiences.

Evidence from the past 5 years shows that, although sleep problems are complex and often severe in patients with psychosis, sleep can be improved by use of cognitive behavioural approaches that are suitably adapted. The intervention focuses on stabilising rhythms (including setting an appropriate sleep window), learning to associate bed with sleep, and improving daytime frequency of activity.^{58,59} Encouraging data from case studies and pilot randomised controlled trials show large improvements in sleep for patients at ultra high risk of psychosis (effect size 1.7),^{60,61} patients admitted to psychiatric wards (effect size 0.9),⁶² and patients with persistent delusions and hallucinations (effect size 1.9).⁶³ A pilot randomised controlled trial also provided evidence that nightmares in patients with psychosis can be successfully treated with imagery rehearsal therapy (effect size 1.1).⁶⁴ These trials, albeit insufficiently powered to be definitive, indicate that progress in other mental health outcomes (eg, psychotic experiences or psychological wellbeing) follows after sleep improvement. An area worthy of further research is the link between poor sleep, nightmares, and suicidal ideation.^{64,65}

Depression

The standard psychiatric position is that insomnia and hypersomnia are symptoms of depression. Perhaps all that can be assumed at a conceptual level from this diagnostic standpoint is that sleep disturbance is common in depression. There are numerous empirical studies showing high frequencies of sleep disturbance in patients diagnosed with depression. For example, in an US epidemiological study with 3573 people with a major depressive episode, 3299 (92%) reported at least one type of sleep complaint, 2809 (85%) had insomnia, 1566 (48%) had hypersomnia, and 1079 (30%) had both insomnia

and hypersomnia.⁶⁶ Polysomnographic abnormalities, such as disturbance of sleep continuity and REM sleep, have been found in depression,^{67,68} and polysomnography findings in major depression with insomnia are similar to those found in primary insomnia.⁶⁹ In small experimental studies with non-clinical individuals, depriving, restricting, or fragmenting sleep led to increases in depressive mood.⁴ Classical twin studies indicated that insomnia and depression overlapped in their genetic and environmental causal influences.^{70,71} Adversity and stress have been plausibly linked to the co-occurrence of insomnia and depression.⁷² Other shared mechanisms hypothesised to link sleep disruption and depression are neurotransmitter imbalance (eg, enhanced cholinergic or diminished aminergic neurotransmissions), abnormalities in brain activation (eg, emotion regulation areas), dysregulation of the hypothalamic–pituitary–adrenal axis, and inflammation.⁷³ But are sleep disturbances in depression more than just a symptom? Many health-care professionals consider this theory to be the case, leading to calls for sleep treatment to be given a high priority in the treatment of depression.^{74–76}

Part of the reason for these calls has been evidence from longitudinal studies that insomnia is associated with an increased risk of subsequent depression.⁷⁴ A meta-analysis of 34 cohort studies involving over 150 000 participants found that the presence of insomnia doubled the relative risk of developing depression.⁷⁷ A meta-analysis of ten studies, which used a stringent definition of insomnia, found that insomnia was associated with almost three times greater odds of later development of depression.⁷⁸ A notable replicated finding is that insomnia was also associated with an increased risk of suicidal ideation and attempts.^{79,80} Whether sleep disruption has differential effects by types of depressive symptom (as has been found for psychotic symptoms) has not yet been systematically examined. Patient studies show a degree of dissociation between sleep problems and depression, perhaps indicating that insomnia is not simply a symptom. For example, a study of 5481 inpatients found that over half (1691) of 3108 patients who were in remission for depression at discharge still had considerable sleep impairment.⁸¹ Nevertheless, an even higher proportion (1987 patients [84%]) of 2373 patients who still had depression also had sleep problems.⁸¹

Much stronger causal inferences can be made from studies that treat sleep disturbance than from those investigating associations between insomnia and depression only. A meta-analysis examined the effects on depression of psychological interventions (mostly cognitive behavioural therapy) to improve sleep.⁸² The analysis included 49 studies covering approximately 6000 participants and featuring randomised controlled designs and an outcome measure for depression. The participants did not necessarily have a diagnosed mental health disorder. Psychological intervention for sleep led to a moderate reduction in symptoms of depression (effect

size 0·45). In the seven studies with participants who had insomnia in the context of mental health disorders, the reduction in depression was large (effect size 0·81). Consistent with these results, a 2019 trial randomly assigned 1711 people with insomnia (recruited online) to either cognitive behavioural therapy for insomnia, which was delivered digitally, or sleep hygiene education.⁸³ Compared with sleep education, the cognitive behavioural therapy intervention showed a large improvement in sleep and a small to moderate reduction in depression (effect size 0·38) that persisted after the intervention. Treating insomnia can also reduce the likelihood of depression occurring over at least the next year.⁸⁴

But what about the effects of treating insomnia in patients diagnosed with major depression? Relevant trials are surprisingly too few and too small in size to identify such effects. In a 16-week trial, 150 patients with major depressive disorder and insomnia who were not receiving treatment were all given depression pharmacotherapy, and randomly assigned to receive either cognitive behavioural therapy for insomnia (seven sessions) or a credible control therapy (sleep education and desensitisation to stimuli associated with hyperarousal).⁸⁵ 33 (44%) of 75 patients receiving cognitive behavioural therapy for insomnia attained remission in depression, compared with 27 (36%) of 75 participants in the control group; however, this difference was not significant. Depression scores improved in both groups but little evidence was recorded of group differences; whereas, sleep improved to a greater extent with cognitive behavioural therapy than with the control therapy. The trial was underpowered to detect potential group differences, especially given that the patients were all receiving treatment for the first time and, therefore, on an improving course. In another main trial, 107 patients with major depression and insomnia were randomly assigned to receive either antidepressant and four sessions of cognitive behavioural therapy for insomnia, or four sessions of cognitive behavioural therapy and pill placebo, or antidepressant and four sessions of sleep hygiene.⁸⁶ Improvement in depression was similar across all three groups, but the trial was again underpowered to detect differences between recovering groups. Antidepressants with sleep hygiene and cognitive behavioural therapy for insomnia (with pill placebo) had similar effects on depression; however, the trial design makes it difficult to interpret the effects of particular treatment elements. The results are consistent with a year-long trial, in which 43 patients with major depression and insomnia were randomly assigned to receive digital cognitive behavioural therapy for either insomnia or depression, with both treatments leading to similar reductions in depression.⁸⁷ Much larger trials focused on treating sleep problems in patients with depression are warranted and are a notable missing element in the evidence base.

Taken together, the trials of cognitive behavioural therapy for insomnia that include a depression outcome

indicate that evidence-based treatments for insomnia also lead to reductions in depression. This finding is consistent with sleep disturbance being a contributory causal factor in the occurrence of depression. By contrast, it could be argued that improvements in mood simply arise from relief at improved sleeping, rather than a reduction in the core depression. In other words, mood would surely be expected to improve to some extent with improved sleep; however, it cannot necessarily be inferred that insomnia was a causal factor in the depression. This hypothesis poses an interesting challenge for interventionist-causal trials. Nevertheless, the effect sizes of insomnia treatment on depression in some instances are similar to treatments targeted at depression itself. This finding suggests that the changes are not trivial and are more indicative of a causal role.

It should also be noted that a few small randomised controlled trials have tested the effects of an opposite type of treatment for patients with depression, termed total sleep deprivation (so-called wake therapy). The clinical observation behind this research is that patients' mood is improved during the daytime hours after the restriction. However, depression is also observed to return following the next sleep. The data are sparse, but a review of the randomised controlled trials did not support the efficacy of wake therapy in recovery rates for depression.⁸⁸ The largest randomised controlled trial to date included 64 inpatients with moderate to severe depression, with half (32) of the participants randomly assigned to receive three nights of wake therapy over 1 week, together with 9 weeks of light therapy and sleep time stabilisation.⁸⁹ The trial's dropout rate was high. Compared with the control group, there was inconsistent evidence for a slight reduction in depression with wake therapy in the first week, although this finding was not maintained in subsequent weeks. The control group tended to spend less time in hospital than did patients who had the wake therapy. Evidence indicates the need to encourage regular, non-fragmented sleep of standard length in patients with depression. Data are clear that cognitive behavioural approaches are a successful way to acquire such sleep,⁹⁰ even on psychiatric wards.⁶²

Post-traumatic stress disorder

It could be considered self-evident that a fundamental connection exists between anxiety and sleep. At the heart of anxiety is perceived threat,⁹¹ which leads to defensive responses of alertness, preparation for action, and escape. A warning of danger prompts a reaction of hyperarousal. Evidently, this response cannot be conducive to sleep. From the opposite direction, the most dominant view of insomnia is that it reflects an inability to lessen high amounts of cognitive, somatic, and cortical arousal that are present throughout the day. In other words, insomnia is a disorder of hyperarousal⁹² and, as such, gives rise to the development of anxiety. Even during sleep, individuals with insomnia have higher cortical arousal than have good sleepers.⁹³ There are tight anatomical connections

between arousal and wake centres in the brainstem and the cerebral cortex, which means that anxiety-related information sent to the cerebral cortex can easily elicit arousal, despite signals promoting sleep.⁹⁴ These theoretical perspectives on anxiety and insomnia indicate not only a bidirectional relationship, but also a high likelihood of overlap between their causes. Complete overlap in genetic influences has been found for insomnia and generalised anxiety disorder.⁹⁵ Taken together, rates of sleep problems are expected to be high in anxiety disorders, and they are. For example, a study of 533 patients with an anxiety disorder who were attending primary care found that three-quarters (393 patients) reported sleep disturbance.⁹⁶ Sleep problems were most likely to develop in patients with either a diagnosis of generalised anxiety disorder or post-traumatic stress disorder. Both of these anxiety disorders have sleep disturbance as a symptom.

Two types of sleep dysfunction are considered to be symptoms of post-traumatic stress disorder. Trauma-related nightmares are an intrusion-type symptom and insomnia is an arousal-type symptom. The prevalence of each in post-traumatic stress disorder is highly likely to vary by the severity, type, and timing of the trauma, and the particular population studied.^{97,98} In a survey of an urban general population, approximately 70% of 34 individuals with post-traumatic stress disorder had sleep disturbance, with 14 (40%) having insomnia and 6 (20%) having nightmares.⁹⁹ In a study of Vietnam veterans with the disorder, 102 (44%) of 233 participants had difficulties getting to sleep, 211 (91%) had difficulties staying asleep, and 122 (52%) had nightmares.¹⁰⁰ A meta-analysis of 31 polysomnography studies with around 1000 patients found that post-traumatic stress disorder was associated with less total sleep time, more disrupted sleep, and less deep sleep, compared with controls.¹⁰¹ The meta-analysis did not find significant overall differences in REM sleep between patients with post-traumatic stress disorder and controls; however, patients aged 30 years and younger were found to spend a smaller proportion of sleep time in REM sleep than did age-matched controls. REM sleep, the sleep stage most associated with dreaming, has been given particular attention in post-traumatic stress disorder because of the occurrence of nightmares.^{102,103} At present, the findings in this area are mixed.

Similar to depression, post-traumatic stress disorder is a clinical area in which researchers have long highlighted that sleep problems are likely to play a role in the onset of the disorder and, hence, require specific treatment.^{94,103,104} Experimental studies support this view. For example, in a fear conditioning study, individuals of the general population learned to associate different faces to an electric shock and were then either deprived of sleep that night or allowed to sleep.¹⁰⁵ The next day, the faces generated greater expectancy of a shock in individuals who were deprived of sleep than in those who slept. This finding indicates that sleep disturbance might increase

the perceptions of threat that are central to anxiety disorders. A single night of sleep loss in adults of the general population results in a neural pattern (hypoactivity within the medial prefrontal cortex and increased amygdala activity) similar to that seen in anxiety disorders.¹⁰⁶ In an analogue study of the symptoms of post-traumatic stress disorder, sleep after watching a traumatic film has been shown to reduce the later occurrence of intrusive memories compared with staying awake.¹⁰⁷ Importantly, there is evidence that sleep deprivation hinders extinction learning about a conditioned fear, which means that fears are more likely to persist.¹⁰⁸ This evidence is consistent with findings from a clinical study of specific phobia, in which sleep was found to enhance exposure learning in therapy.¹⁰⁹ These studies all suggest that good sleep lessens future anxiety responses.

Longitudinal studies show that sleep difficulties before a trauma^{110–112} and in the weeks and months after a trauma^{113,114} are a predictor of the development of post-traumatic stress disorder. This finding is consistent with a meta-analysis of six longitudinal studies that showed that insomnia predicted the development of anxiety disorders.⁷⁸ In a study of over 2000 US service members and veterans with post-traumatic stress disorder, less than 4 h of sleep every night predicted the persistence of the disorder over subsequent years.¹¹⁵ These studies cannot establish causation, but a reciprocal relationship between anxiety and insomnia can be seen in treatment outcome studies. First, cognitive behaviour treatments for anxiety lead to improvements in sleep. A meta-analysis found that psychological therapy for anxiety disorders resulted in moderate reductions in insomnia (effect size 0.5).¹¹⁶ Psychological therapy for post-traumatic stress disorder, especially when techniques focusing on trauma are used, leads to clear improvement in sleep; however, clinically significant insomnia remains for almost half of patients.^{117–119} Second, when standard cognitive behaviour techniques for insomnia, nightmares, or both, are used, symptoms of post-traumatic stress disorder decrease. A meta-analysis of 11 randomised controlled trials of cognitive behavioural therapy focused on sleep, including almost 600 trial participants, showed that symptoms of post-traumatic stress disorder are reduced, although to a lesser extent than the best cognitive behavioural therapy for the disorder (effect size 0.6).¹²⁰ As is typical for cognitive behavioural therapy treatments, individual sessions are more likely to produce large effect sizes for both insomnia and post-traumatic stress disorder than are group approaches.^{121,122} Clinical trials clearly show that intervening on sleep provides another pathway or mechanistic route to treating post-traumatic stress disorder, and this finding is consistent with the view of sleep disturbance as a contributory causal factor. The question has been raised of how best to integrate sleep treatment with treatments for post-traumatic stress disorder,¹²³ and empirical investigation is merited. Sleep

treatment could be delivered before or after the treatment for the comorbid post-traumatic stress disorder, or the two treatments could potentially be interlinked.

Discussion

It is clear that sleep disruption is a common part of the presentation of mental health conditions; often, such disruption is so common that it is included as a symptom of the disorder. The data are primarily based on subjective reports, but the effects of sleep disturbance on objective sleep measures and sleep architecture are apparent too. Too little and too fragmented sleep are the most common difficulties, but problems of too much sleep, shifts in sleep timing, and parasomnias also often occur. Sleep difficulties tend to be an early sign of the emergence of mental health conditions. The associations between sleep difficulties, such as insomnia and other mental health conditions, are likely to reflect overlap in genetic, neurobiological, psychological, and environmental causes, to a degree. For example, statistical evidence exists of shared genetic and environmental causation from classical twin studies,^{41,71,95} overlap in the neurobiology of sleep–wake regulatory processes and mental health disorders,^{30,73,76,94} and how environmental stressors such as trauma can trigger both sleep disturbance and mental health difficulties.²⁶ But the evidence also strongly indicates a bidirectional relationship, with the dominant path being from sleep difficulties to the occurrence of other mental health disorders. Sleep difficulties might lead to the development of mental health disorders due to the elicitation of negative affect, emotional dysregulation, and hyperarousal, with the close association of anxiety and insomnia of particular note. It is also highly likely that the presence of other mental health symptoms leads to a worsening of sleep problems. There is great cause for optimism, given that sleep problems are eminently treatable. Evidence-based treatment protocols,^{124–126} and particularly psychological treatments, lead to large reductions in sleep difficulties. The psychological treatments appear safe, with few side-effects. Sleep can form a treatment target in its own right, but might also be a route to affect other mental health difficulties. This knowledge could be used to improve mental health services.

This Review has discussed how sleep problems are an integral part of psychiatric disorders and can precede them. Hence, sleep problems cannot be solely attributed to the effects or side-effects of medication and should not be dismissed as such. However, most patients with schizophrenia, depression, or post-traumatic stress disorder take one or more psychotropic drugs, especially antipsychotics and antidepressants. Although sleep problems are rarely the reason for their prescription, these drugs can have a range of effects on sleep and related occurrences, which need to be considered. Many antipsychotics affect sleep and sleep architecture, including when they are used for psychosis¹²⁷ or mood disorder.¹²⁸

Search strategy and selection criteria

We did three literature searches on PubMed on sleep in schizophrenia, depression, and post-traumatic stress disorder to identify studies published in the past 5 years from each search date. We searched psychosis on Aug 5, 2019, using the terms: "((sleep OR insomnia OR dream* OR nightmare*) AND (Delus* OR Hallucinat* OR Psychosis OR *Schizophren* OR Schizotyp*))". We searched depression on Aug 30, 2019, using the terms: "((((((((((((((((sleep[Title/Abstract]) OR insomnia[Title/Abstract]) OR dream*[Title/Abstract]) OR nightmare*[Title/Abstract])) AND (depress*[Title/Abstract])) NOT (((((((((((((((Parkinson*[Title/Abstract]) OR Dementia*[Title/Abstract]) OR Alzheimer*[Title/Abstract]) OR cancer[Title/Abstract]) OR oncology[Title/Abstract]) OR tumour[Title/Abstract]) OR tumor[Title/Abstract]) OR carcin*[Title/Abstract]) OR neoplasm[Title/Abstract]) OR postmenopausal[Title/Abstract]) OR stroke[Title/Abstract]) OR epilepsy[Title/Abstract]) OR pain[Title/Abstract]) OR "seasonal affective disorder"[Title/Abstract])))))). We searched post-traumatic stress disorder on Sep 13, 2019, using the terms: "((((((((((((((((sleep[Title/Abstract]) OR insomnia[Title/Abstract]) OR dream*[Title/Abstract]) OR nightmare*[Title/Abstract])) AND ((post-traumatic[Title/Abstract]) OR PTSD[Title/Abstract])) NOT (((((((((((((((Parkinson*[Title/Abstract]) OR Dementia*[Title/Abstract]) OR Alzheimer*[Title/Abstract]) OR cancer[Title/Abstract]) OR oncology[Title/Abstract]) OR tumour[Title/Abstract]) OR tumor[Title/Abstract]) OR carcin*[Title/Abstract]) OR neoplasm[Title/Abstract]) OR postmenopausal[Title/Abstract]) OR stroke[Title/Abstract]) OR epilepsy[Title/Abstract]) OR pain[Title/Abstract]) OR "seasonal affective disorder"[Title/Abstract])))))). We limited our search to articles published in English. The results of the literature searches and descriptions of the 518 studies are provided in the appendix.

See Online for appendix

Generally, antipsychotics are sedative, promoting more rapid sleep onset and increased total sleep duration, and improving sleep continuity. The evidence base is strong for second-generation drugs such as clozapine and olanzapine; whereas, effects of quetiapine are less consistent.³¹ Antipsychotics can also produce substantial somnolence or daytime sedation,¹²⁹ which needs strong consideration when assessing presentations of this nature, especially because sedation might contribute to functional impairments or be mistaken for negative symptoms. Antidepressants have important but differing effects on sleep and related occurrences.¹³⁰ Various antidepressants have clear sleep-promoting properties (eg, trazodone or mirtazapine) and are sometimes used for this purpose either as sole agents or adjunctive treatments.¹³¹ Conversely, selective serotonin reuptake inhibitors and venlafaxine can lead to insomnia and reduced sleep quality, as well as sleep impairment via restless legs and bruxism.¹³² Some psychotropic medications, notably atypical antipsychotics, are associated with considerable weight gain. This effect increases risk of obstructive sleep apnoea, which has major effects on sleep and daytime functioning, and should always be enquired about as part of clinical evaluation. Various antidepressants have been trialled for treatment of obstructive sleep apnoea, but with very minimal efficacy and clinically significant adverse events.¹³³

In clinical services, we recommend routine assessment of sleep problems for patients at initial presentation. When sleep problems are identified, these should be treated at the appropriate time with the

recommended evidence-based treatments. This treatment plan will undoubtedly require an expansion of the provision of treatments, such as cognitive behaviour therapy for insomnia. The necessity for initiatives to implement such sleep treatments at scale is evident.¹³⁴ Systematic consideration of the effects of medication on the quality of patients' sleep is also required within services. All of these changes will need to be reflected in workforce training. Considerable research endeavours should also be done. Definitive trials in clinical populations are needed to establish the effect of sleep interventions on symptoms of mental ill health. How best to integrate sleep interventions into standard treatments will need to be established for each disorder. Tests are needed of sleep interventions as a preventive measure against the late onset of disorders, particularly in adolescent populations. The development of improved sleep treatments will be facilitated by basic research on the causes of such problems, how changes in sleep patterns and architecture might link to particular mental health symptoms, and how sleep interacts with physical health. The effects of sleep disruption across the full range of mental health diagnoses and lifespan will require systematic investigation. A further issue that needs careful consideration is why, despite repeated calls over the past three decades, has there been such delay in giving high priority to sleep in the research and treatment of mental health disorders?

Contributors

DF was the lead researcher and was responsible for synthesising the evidence and writing this Review. DF and BS set up the systematic literature reviews. BS edited the supplementary materials. PJH provided text on the effects of psychiatric medications. AGH, PJH, BS, and FW provided comments and feedback on the draft of the paper.

Declaration of interests

DF reports grants from the Wellcome Trust, National Institute for Health Research, Medical Research Council; and is a founder and director of a University of Oxford spin-out company, Oxford Virtual Reality. BS reports previously receiving personal fees from Big Health (Sleepio). AGH reports grants from the National Institute of Health and book royalties (American Psychological Association, Oxford University Press, Guilford). FW and PJH declare no competing interests.

Acknowledgments

The work was supported by a Wellcome Trust Strategic Award (098461/Z/12/Z) to the Oxford Sleep and Circadian Neuroscience Institute. PJH and DF are grant holders. DF is supported by a National Institute for Health Research (NIHR) Professorship (NIHR-RP-2014-05-003). The work was also supported by the NIHR Oxford Health Biomedical Research Centre (BRC-1215-20005). The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or the Department of Health. We thank Hannah Wilkinson for helping with the literature searches.

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