Sleep disturbance and psychiatric disorders: the non-specific as essential in understanding and treating mental ill health.

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ABSTRACT

Signs of mental ill health that cut across psychiatric diagnostic categories at high rates are typically viewed as non-specific phenomena, downgraded in significance and disregarded. However problems not tied to particular diagnoses should be expected if there is shared aetiology across mental health conditions. If dynamic interacting symptom networks are the reality of mental health presentations then particularly disruptive and highly connected problems should be especially common. The non-specific may be highly consequential. One non-specific phenomenon that is often overlooked is patients' chronic difficulty in getting good sleep. In this review we consider whether disrupted sleep may be a contributory causal factor in the occurrence of major types of mental health disorders. It is argued that there is shared aetiology between insomnia and other mental health conditions, but also a bi-directional 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 may be a preventative strategy for the onset of clinical disorders. Our recommendations are that: insomnia is assessed routinely in the occurrence of mental health disorders; 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.

Search strategy and selection criteria

Three literature searches – on sleep in schizophrenia, depression, and PTSD - were conducted in PubMed to identify studies published in the past five years. The psychosis search was carried out on the 5th August 2019 using the terms: ((sleep OR insomnia OR dream* OR nightmare*) AND (Delus* OR Hallucinat* OR Psychosis OR *Schizophren* OR Schizotyp*)). The depression search was carried out on the 30th August 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])))))). The PTSD search was carried out on the 13th September 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])))))). The results of the literature searches and descriptions of the 518 studies are provided in the supplementary materials.

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." Dickens (1)

"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?"
Wordsworth (2)

"Now human souls are all in love with sleep,
in gentle resting, restoration seek." Labé (3)

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; the following day can bring drops in mood, confidence, and sharpness. Life's natural experiments – supported by the findings of scientific experiments (4, 5, 6) – lead many people in the general population to conclude that disrupted sleep provokes worse mental health. At first blush this seems an uncontroversial view, but it is at odds 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 – its non-specificity – has been taken to imply that it could 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 lay perception.

It may, partly, be a case of not seeing the wood for the trees. Diagnostic categories train clinicians to spot the specific, leaving non-specific problems to fall by the wayside. If psychiatric diagnostic categories were truly independent and discrete then such an approach would be appropriate. But

high rates of co-morbidity, diagnostic instability, and heterogeneity within diagnoses have led many to conclude that the different psychiatric categories are not truly independent. Empirical studies show that the hundreds of different psychiatric diagnoses cluster into a much smaller number of types (8, 9). Thus, shared causation - and symptoms - should be apparent across diagnostic categories. Causation for a diagnostic category may 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 current approach to 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 in train a whole network of activation, which may vary by the individual. This approach puts renewed focus on individual patient experience, which previously had simply been used to create syndromes linked with diagnoses. It also tackles head on 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 may be key to causal cascades can be identified, and hence become treatment targets. From such a perspective, common mental health symptoms - 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 (RDoC) framework, with the arousal/regulatory system 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 carry higher causal status.

This review focuses on the non-specific problem of sleep disruption. It 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 approximately 90 minute cycles, sleep alternates between rapid eye movement (REM) and non-REM (NREM) states. In adults REM sleep comprises about a quarter of a total night's sleep, becoming more common in later sleep cycles, while NREM has three sub-stages corresponding to depth of sleep. Sleep is the result of a combination of factors: time spent awake (homeostatic load); time of day (circadian rhythm); and level 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 toxins (18).

Many of the effects of sleep loss are likely to raise vulnerability to mental health conditions: increased state anxiety and depression (4); decreased positive mood (19); poorer emotion regulation (20); negative perception of neutral stimuli (21); increased perception of pain (5); poorer response inhibition (22); working memory impairment (6); and poorer problem-solving (23). Sleep restriction also brings physiologic 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 the exception in clinical presentations (27). A meta-analysis of polysomnographic studies showed sleep alterations are 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 recent removal from diagnostic systems of the distinction between primary and secondary insomnia (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 multi-factorial 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 will principally consider insomnia, since it is the most common and studied sleep condition. We will note the influence of relatively common parasomnias (such as nightmares) and circadian rhythm disturbances. Our focus is on sleep disturbance as a common contributory cause of mental health conditions. This means, first, that rarer conditions, such as sleep apnea, will not be considered, even though clearly they are clinically important when present. And, secondly, we will prioritise the discussion of longitudinal, experimental, and interventionist-causal studies, which enable stronger causal conclusions. It is increasingly recognised that treatment studies, when suitably designed, have the potential to be especially informative about causation, since, 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 substantiate further the causal

claims made from treatment studies (33). The three conditions in which the most work on sleep has been conducted will be considered: schizophrenia, depression, and PTSD.

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; 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 significant disruption in the sleep-wake cycle is prevalent in patients with schizophrenia (36, 37). As such, it was proposed that circadian misalignment and schizophrenia share aetiology. Patient accounts have also begun to be documented, with reports of problems getting to sleep, staying asleep, too much sleep, nightmares, and erratic sleep patterns (38). However, a survey of mental health professionals found that very few formally assessed sleep problems in this patient group (39).

Sleep problems and psychotic experiences are clearly associated. For instance, in a study of over a quarter of a million people who took part in the World Health Organization's World Health Survey, 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 5,000 adolescent twin pairs (41), insomnia had moderate correlations with paranoia, hallucinations, and cognitive disorganisation, but much lower correlations with negative symptoms and no association with grandiosity. Further, the twin study indicated that the genetic and environmental influences on insomnia overlapped with those for paranoia, hallucinations, and cognitive disorganisation. Consistent with these findings, a molecular genetic study found that polygenic risk for schizophrenia is associated with shorter sleep duration and nightmares (42). Longitudinal studies, including the use of experience sampling methodology, find that poor sleep predicts later levels of paranoia and hallucinations (43, 44, 45, 46). Three-quarters of patients report that sleep disturbance occurs before the onset of persecutory delusions

(47). The linking factor repeatedly found between sleep disturbance and psychotic experiences has been negative affect (34, 48, 41, 49; 45; 46), although this does not necessarily entirely explain the association.

As would logically follow from these studies, rates of sleep disorder are high in patients with schizophrenia. In a self-report assessment study with 1800 patients with non-affective psychosis, insomnia was present in half (50). Higher levels of insomnia were found for patients with current paranoia and/or hallucinations. Using a diagnostic sleep interview with 60 patients with first episode psychosis, it was found that 80% of 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 both predict a poorer prognosis for patients at ultra high risk of psychosis (52, 53). Actigraphy studies confirm lower levels of sleep efficiency and greater sleep fragmentation in patients with schizophrenia compared with non-clinical controls (54), although we would note that it can be difficult to establish sleep using actigraphy when activity levels are generally low and sedentary behaviours common. Polysomnography studies show both lower sleep time and a range of disturbances in sleep architecture, though results have been inconsistent and difficult to interpret (55, 56).

Two studies shine particular light on what happens if levels of sleep are altered. The most important to date is the OASIS trial (57). 3,755 students with insomnia were randomised to either receive an on-line sleep intervention or not. 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, albeit small (effect sizes=0.2), were observed in paranoia and hallucinations. 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. It was not, however, a study with patients with psychosis. The conclusion from the OASIS trial is further supported by a study that tested a reverse manipulation, reducing sleep to 4 hours of sleep 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.

Recent evidence shows that, although sleep problems are complex and often severe in patients with psychosis, sleep can be improved using suitably adapted cognitive-behavioural approaches. The intervention focuses on stabilising rhythms (including setting an appropriate sleep window), learning to associate bed with sleep, and improving daytime activity levels (58, 59). There is encouraging case study and pilot randomised controlled trial data showing 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 provides evidence that nightmares in patients with psychosis can be successfully treated using imagery rehearsal therapy (effect size=1.1) (64). These trials, albeit insufficiently powered to be definitive, indicate that progress in other mental health outcomes (e.g. psychotic experiences, psychological well-being) follows in the wake of 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. Indeed, there are numerous empirical studies showing high levels of sleep disturbance in patients diagnosed with depression. For example, in a US epidemiological study with three and a half thousand people with a major depressive episode, 92% reported significant sleep complaints, 85% had insomnia, 48% hypersomnia, and 30% had insomnia and hypersomnia (66). Polysomnographic abnormalities such as disturbance of sleep continuity and of REM sleep have been found in depression (67, 68), and polysomnography findings in major depression with insomnia are comparable to those found in primary insomnia (69). In small experimental studies with non-clinical individuals, depriving, restricting, or fragmenting sleep leads to increases in depressive mood (4). Classical twin studies indicate that insomnia and depression overlap in their genetic and environmental aetiological influences (70, 71). Adversity and stress have plausibly been linked to the co-occurrence of insomnia and depression (72). Other shared mechanisms hypothesised to link sleep disruption and depression are neurotransmitter imbalance (e.g. enhanced cholinergic or diminished aminergic

neurotransmissions), abnormalities in brain activation (e.g. emotion regulation areas), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and inflammation (73). But are sleep disturbances in depression more than just a symptom? Many consider this to be the case, leading to calls for sleep treatment to be given a higher priority in the treatment of depression (74, 75, 76).

Part of the spur for these calls has been evidence from longitudinal studies that insomnia is associated with a raised risk of subsequent depression (74). A meta-analysis of 34 cohort studies involving over a hundred and fifty thousand participants found that the presence of insomnia doubled the relative risk for the development of depression (77). A meta-analysis of ten studies, which used a more stringent definition of insomnia, found that insomnia increased the odds almost threefold for the later development of depression (78). A notable replicated finding is that insomnia also raises the 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, indicating perhaps that insomnia is not simply a symptom. For example, a study of several thousand inpatients found that over half of patients who at discharge were in remission for depression still had significant sleep impairment, although an even higher percentage of patients (over 80%) who still had depression also had sleep problems (81).

Much stronger causal inferences can be made from studies that treat sleep disturbance. 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 six thousand 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 larger (effect size=0.81). Consistent with these results, a recent trial randomised 1711 people with insomnia (recruited online) to either CBT for insomnia delivered digitally or sleep hygiene education (83). Compared to sleep education, the CBT intervention saw a large improvement in sleep and a small to moderate reduction in depression (effect size=0.38) that persisted post-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 small in size to draw firm conclusions. In a 16 week trial, 150 patients with major depressive disorder and insomnia who were not receiving treatment were all given depression pharmacotherapy and randomised to receive in addition either CBT for insomnia (seven sessions) or a credible control therapy (sleep education and desensitization to stimuli associated with hyperarousal) (85). 44% of patients receiving CBT for insomnia attained remission in depression, compared with 36% in the control arm, but this difference was not statistically significant. Depression scores improved in both groups but there was little evidence of group differences, whereas sleep did improve to a greater extent with CBT. 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 the other main trial, 107 patients with major depression and insomnia were randomised to either antidepressant and CBT for insomnia (four sessions), CBT for insomnia and pill placebo, or anti-depressant and sleep hygiene (86). Improvement in depression was comparable across all three groups, but again the trial was underpowered to detect differences between recovering groups. What is perhaps most interesting in this trial is that antidepressants and CBT for insomnia (with pill placebo) had similar effects on depression, although the trial design makes it difficult to disentangle 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 randomised to receive digital CBT 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 CBT for insomnia that include a depression outcome indicate that evidence-based treatments for insomnia also lead to reductions in depression. This is consistent with sleep disturbance being a contributory causal factor in the occurrence of depression. Against that, it could be argued that improvements in mood simply arise from relief at sleeping better rather than a reduction in the core depression. That is, mood would surely be expected to improve to some extent with better sleep, but one cannot necessarily infer that insomnia was a causal factor in the depression. This poses an interesting challenge for interventionist-causal trials. However, the effect sizes of insomnia treatment on depression in some instances are not that dissimilar to

treatments targeted at depression itself. This suggests that the changes are not trivial and is 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: total sleep deprivation ('wake therapy'). The clinical observation behind this work 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 for the efficacy of wake therapy in recovery rates for depression (88). The largest randomised controlled trial to date included 67 in-patients with moderate to severe depression, with half the participants randomised to receive three wake therapy nights over a week together with nine weeks of light therapy and sleep time stabilisation (89). The trial's drop-out rate was high. Compared to the control group, there was inconsistent evidence for a slight reduction in depression with wake therapy in the first week but even this was not maintained in subsequent weeks. The control group tended to spend less time in hospital. Our view is that the current evidence indicates the need to encourage regular, non-fragmented, and standard-length sleep in patients with depression. The evidence is clear that cognitive behavioural approaches are a successful way to achieve this (90), even on psychiatric wards (62).

POST-TRAUMATIC STRESS DISORDER (PTSD)

It could be considered self-evident that there is a fundamental connection between anxiety and sleep. At the heart of anxiety is perceived threat (91), which brings in its wake defensive responses of alertness, preparation for action, and escape. A warning of danger prompts a reaction of hyperarousal. This, obviously, cannot be conducive to sleep. From the opposite direction, the most dominant view of insomnia is that it reflects a failure to dampen high levels of cognitive, somatic, and cortical arousal that are present throughout the day. Insomnia, in other words, is a disorder of hyperarousal (92) and as such provides fertile ground for the development of anxiety. Even during sleep, individuals with insomnia have higher cortical arousal than good sleepers (93). There are tight anatomical connections between arousal/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 sleep-promoting signals (94). These theoretical perspectives on anxiety and insomnia indicate not only a bi-directional relationship but imply a high likelihood of aetiological overlap. Complete overlap in genetic influences has been found for insomnia and generalised anxiety disorder (95). Altogether, rates of sleep problems would be expected to be high in anxiety disorders, and indeed they are. For example, a study of 500 patients with an anxiety disorder who were attending primary care found that three-quarters reported sleep disturbance (96). Sleep problems were most likely in patients with either a diagnosis of generalised anxiety disorder or post-traumatic stress disorder (PTSD). Both these anxiety disorders have sleep disturbance as a symptom.

Two types of sleep dysfunction are considered symptoms of PTSD: trauma-related nightmares are an intrusion-type symptom and insomnia an arousal-type symptom. The rates of each in PTSD are highly likely to vary by the severity, type, and timing of the trauma and the particular population studied (97; 98). In an urban general population survey, 70% of individuals with PTSD had sleep disturbance, with 40% having insomnia and 20% having nightmares (99). In a study of Vietnam veterans with PTSD, 44% had difficulties getting to sleep, 91% had difficulties staying asleep, and 52% had nightmares (100). A meta-analysis of 31 polysomnography studies with around a thousand patients found PTSD to be associated with less sleep, more disrupted sleep, and less deep sleep (101). The meta-analysis did not find significant overall differences in REM sleep between patients and controls, although patients with PTSD under the age of 30 were found to spend a smaller percentage of sleep time in REM sleep compared with controls. REM sleep, the sleep stage most associated with dreaming, has been given particular attention in PTSD because of the occurrence of nightmares (102, 103). At present, the findings in this area are mixed.

Similar to depression, PTSD is a clinical area in which researchers have long highlighted that sleep problems are likely to play a role in disorder onset and hence require specific treatment (103, 104, 94). Experimental studies support this view. For example, in a fear conditioning study, non-clinical individuals learnt different associations of faces to an electric shock and then were either deprived of sleep that night or slept (105). The next day the faces generated greater expectancy of a shock in individuals who were deprived of sleep compared with those who slept. This indicates that sleep disturbance may increase the perceptions of threat that are central to anxiety disorders. A single night of sleep loss in non-clinical adults 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 PTSD, sleep after watching a traumatic film has been shown to reduce the occurrence of later 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 will be more likely to persist (108). This is consistent with evidence from a clinical study of specific phobia in which sleep was found to enhance exposure learning in therapy (109). These studies all point towards good sleep lessening future anxiety responses.

Longitudinal studies show that sleep difficulties prior to a trauma (110, 111, 112) and in the weeks and months after a trauma (113, 114) are a predictor of the development of PTSD. This is consistent with a meta-analysis of six longitudinal studies that showed insomnia predicts the development of anxiety disorders (78). In a study of over two thousand US service members and veterans with PTSD, fewer than four hours sleep a night predicted the persistence of PTSD 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 results in moderate reductions in insomnia (effect size=0.5) (116). Psychological therapy for PTSD, especially when trauma-focussed techniques are used, leads to clear improvement in sleep but clinically significant levels of insomnia remain for almost half of patients (117, 118, 119). Second, when standard cognitive behaviour techniques for insomnia and/or nightmares are used reductions in PTSD symptoms occur. A meta-analysis of 11 randomised controlled trials of sleep focused CBT, including almost 600 trial participants, showed that PTSD symptoms are reduced (though to a lesser extent than the best CBT for PTSD treatments) (effect size=0.6) (120). As is typical for CBT treatments, individual sessions (121, 122) are likely to produce larger effect sizes for both insomnia and PTSD than group approaches. The clinical trials are clear that intervening on sleep provides another pathway or mechanistic route to treating PTSD, and this 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 PTSD treatments (123), and empirical investigation is merited. Sleep treatment could be delivered before or after the treatment for the comorbid PTSD or the two treatments could potentially be interwoven.

DISCUSSION

It is clear that sleep disruption is a common part of the presentations of mental health conditions, often 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, to a degree, overlap in genetic, neurobiological, psychological, and environmental causes. For example, we have seen in this review statistical evidence from classical twin studies of shared genetic and environmental causation (41, 95, 71), descriptions of overlap in the neurobiology of sleep-wake regulatory processes and mental health disorders (30, 73, 76, 94), and that environmental stressors such as trauma can trigger both sleep disturbance and mental health difficulties (26). But the evidence also points strongly towards a bidirectional relationship, with the dominant path being that from sleep difficulties to the occurrence of other mental health disorders. Sleep difficulties may 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 significant cause for optimism: sleep problems are eminently treatable. Evidence-based treatment protocols (124, 125, 126), and especially 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 may also be a route to affect other mental health difficulties. This knowledge could be used to improve mental health services.

In this review it has been seen that 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, the majority of patients with the disorders discussed will be taking one or more psychotropic drugs, especially antipsychotics and antidepressants. Whilst sleep problems are rarely the reason for their prescription, these drugs can have a range of effects on sleep and related phenomena which need to be considered. Many antipsychotics affect sleep and sleep architecture, including when they are used for psychosis (127)

or for mood disorder (128). Generally, antipsychotics are sedative, promoting more rapid sleep onset and increased total sleep duration, and improving sleep continuity. The evidence is best for second generation drugs such as clozapine and olanzapine; effects of quetiapine are less consistent (31). Antipsychotics can also produce substantial somnolence or daytime sedation (129); this needs strong consideration when assessing presentations of this nature, especially as the sedation may contribute to functional impairments and/or be mistaken for negative symptoms. Antidepressants have important but differing effects on sleep and related phenomena (130). A number have clear sleep-promoting properties (e.g. trazodone, mirtazapine) and are sometimes used for this purpose either as sole agents or as adjunctive treatments (131). Conversely, SSRIs and venlafaxine can lead to insomnia and reduced sleep quality, as well as impairing sleep via restless legs and bruxism (132). Finally, some psychotropic medications, notably atypical antipsychotics, are associated with considerable weight gain. This increases risk of obstructive sleep apnoea, which has major effects on sleep and daytime functioning, and which should always be enquired about as part of clinical evaluation. Various antidepressants have been trialled for treatment of obstructive sleep apnoea, but with very limited efficacy and with 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 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). Also required is systematic consideration within services of the effects of medication on the quality of patients' sleep. All these changes will need to be reflected in workforce training. Significant research endeavours must also be undertaken. Definitive trials in clinical populations are needed to establish the effect of sleep interventions on mental health symptoms. It will need to be determined, for each disorder, how best to integrate sleep interventions into standard treatments. Tests are needed of sleep interventions, particularly in adolescent populations, as a preventative measure against the later onset of disorder. The development of even better sleep treatments will be facilitated by basic research on the causes of such problems, how changes in sleep patterns and architecture may 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 casts its shadow over the work covered in this review: Why, despite repeated calls over the decades, is there such slowness in giving greater priority to sleep in mental health research and treatment?

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 then 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 may require greater training on disrupted sleep and its treatment.

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Author contributions

DF was the lead researcher, was responsible for synthesising the evidence, and wrote the paper. DF and BS set-up the systematic literature reviews. BS edited the supplementary materials. PH provided text on the effects of psychiatric medications. AH, PH, BS, & FW all provided comments and feedback on the draft of the paper.

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