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SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

Insomnia as a Precipitating Factor in New Onset Mental Illness: a Systematic Review of Recent Findings

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Abstract
Purpose We aimed to systematically review recent publications (01/2014–03/2017) with longitudinal designs allowing for the assessment of the prospective risk of insomnia on new onset mental illness in key conditions: anxiety, depression, bipolar disorder, posttraumatic stress disorder, substance use disorders, and suicide.
Recent Findings A literature yielded 1859 unique articles meeting search criteria were identified; 16 articles met all selection criteria and reviewed with some studies reporting on more than one mental health outcome. Overall, the review supports the hypothesis that insomnia is a predictor of subsequent mental illness.
Summary The evidence is strongest for an insomnia-depression relationship. The new studies identified and reviewed add to a modest number of publications supporting a prospective role of insomnia in new onset mental illness in three areas: anxiety disorders, bipolar disorder, and suicide. The few selected new studies focused on SUD were mixed, and no studies focused on PTSD were identified that met the selection criteria. Treatment of insomnia may also be a preventive mental health strategy.

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Introduction

Insomnia has a somewhat unique history in the annals of mental health. Unlike many disorders, insomnia was long conceptualized as simply a symptom associated with other, primary mental health disorders [1]. As such, insomnia was seldom a treatment target when it presented with another psychiatric condition. Instead, the general treatment approach was to address the underlying disorder with the assumption that sleep difficulties would resolve as an associated symptom (e.g., treating depression would alleviate insomnia).

Two seminal studies began the slow dismantling of these assumptions by establishing that the presence of insomnia was a prospective risk factor for the development of psychiatric illness [2, 3]. Ford and Kamerow utilized data from the National Institute of Mental Health Epidemiologic Catchment Area study [4] to assess whether the presence of baseline insomnia contributed to a higher incidence of a psychiatric disorder 1 year later [2]. Individuals with baseline insomnia that remitted at 1 year, compared to those with no baseline insomnia, were at higher risk of an incident psychiatric disorder at the 1 year follow-up with an adjusted odds ratio (AOR) of 2.4 and a 95% confidence interval (CI) of 1.2–4.8. Individuals with insomnia present at both time points were at higher risk (AOR = 5.6; CI: 1.1–26.9). Similar findings were observed by Breslau et al. among 979 young adults assessed at baseline and 3 years later [3]. For example, baseline insomnia was associated with increased risk for incident major depression (AOR = 3.95; 2.22–7.00), anxiety disorder (1.97; 1.08–3.60), and drug use disorder (7.18; 2.13–24.37), but not alcohol use disorder (1.72; 0.85–3.52).

Subsequent work has both corroborated and extended these early findings. In one domain, depression, the literature has been large enough to conduct a meta-analysis. Baglioni and colleague's 2011 meta-analysis included 21 longitudinal studies, published between 1980 and 2010 that examined insomnia's relationship with the development of depression [5]. Their analyses revealed that insomnia doubled the odds of developing depression. In addition to this type of work, two other bodies of work have helped to transform the perception of insomnia as a symptom to insomnia as a disorder [6]. One is literature demonstrating that insomnia co-occurring with other psychiatric conditions responds well to insomnia treatments with some gains generalizing to non-sleep symptoms [7–9]. The other is literature underscoring that when insomnia is not treated in the course of treating other psychiatric illness, it can blunt overall treatment response and/or remains a residual problem (e.g., [10, 11]). As segments of the health care field continue to shift toward an appreciation of the importance of treating insomnia, studies testing the hypothesis that insomnia precipitates new onset mental illness can further inform the views of individual clinicians and systems of care.

Contributing to the ongoing re-appreciation of the importance of insomnia in clinical care is, in part, the impetus for the current systematic review. In addition, we wished to determine the extent to which new literature now exists to expand upon Bagloni and colleagues' depression focus [5], allowing for the examination of whether insomnia is a precursor to other mental health disorders. Focusing on studies that were longitudinal in nature, the systematic review that follows aims to synthesize the literature published during the past 3 years (2014–2017). The review covers insomnia's association with new onset mental illness including anxiety, depression, bipolar disorder, posttraumatic stress disorder (PTSD), substance use disorders (SUDs), and suicide.

Method

Adhering to the PRISMA guidelines [12], a systematic review was conducted examining the most recent literature related to insomnia's role as a precipitant to new onset mental illness. PubMed and PsycINFO databases were searched for a period beginning January 1, 2014 and ending March 14, 2017. Boolean search logic was utilized to identify all articles with content inclusive of insomnia with the following search terms: depress*, MDD, suicid*, anxiety, GAD, PTSD, post traumatic stress, posttraumatic stress, acute stress, bipolar, manic depress*, alcohol, AUD, SUD, substance*, using "NOT" to separate keywords in subsequent searches (e.g., insomnia AND anxiety NOT depress*).

The following eligibility criteria were used to select articles: (1) the manuscript was available in the English language, (2) the study utilized human subjects, (3) the study consisted of original research, (4) the manuscript was published in a peer-reviewed outlet, (5) the manuscript reported data on the association between insomnia and the outcome of interest (i.e., new onset of depression, anxiety, PTSD, SUD, bipolar, or suicidality), and (6) the study utilized longitudinal design.

Once studies were identified from the literature search, the review occurred in a three-step process. First, titles and keywords were reviewed to confirm that the publication was focused on insomnia and at least one of the mental health conditions of interest. Second, a review of abstracts was undertaken to confirm that insomnia was an independent variable of interest and that the study design was longitudinal. Third, a full text review was completed to identify articles meeting all selection criteria.

Results

As depicted in Fig. 1, our literature yielded 1859 unique articles after accounting for duplicates. Initial review resulted in the identification of 120 articles that underwent full text review. Among these, 16 articles (see Table 1) were included in the review that met all inclusion criteria including the assessment of insomnia as a precursor to anxiety (n = 5), bipolar disorder (n = 2), depression (n = 11), alcohol/substance use disorders (n = 3), and suicide (n = 2). The sum does not add to 16 as several studies had more than one mental health outcome [13, 14, 15•, 17, 18•].

Insomnia and Anxiety

Insomnia is highly prevalent among patients with a variety of anxiety disorders and is a diagnostic feature of separation anxiety disorder and generalized anxiety disorder (GAD). In early epidemiologic studies, the presence of insomnia was associated with increased risk for the development of a subsequent anxiety disorder 1–3 years later [2, 3].

Five (5) new studies were identified that addressed the role of insomnia in the development of an anxiety disorder [13, 14, 15•, 16, 17]. In a retrospective cohort study of over 30,000 individuals in Taiwan, patients with insomnia alone, compared to those with no insomnia diagnosis and no use of sedative-hypnotic medications, had a significantly higher incidence of an anxiety disorder over a 6-year period (adjusted hazard ratio (AHR) = 2.38 (95% CI 2.21–2.57) [15•]. The AHR was more pronounced among insomnia patients who were also prescribed hypnotic medications (AHR = 6.55: 95% CI 6.06–7.08). In a community sample of older adults (N = 909), baseline insomnia was associated with increased risk for developing incident anxiety symptoms and an incident anxiety disorder 2 years later [16]. Notably, insomnia was one of only two demographic, socioeconomic, and clinical factors associated with incident anxiety. In a sample of Norwegian

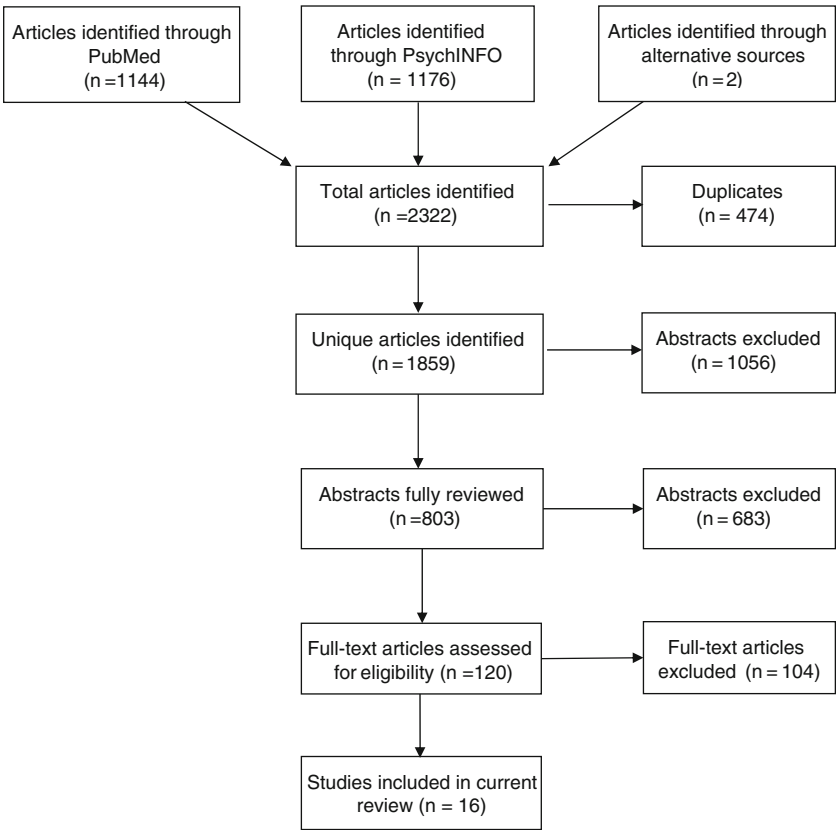

Fig. 1 Study selection flow diagram

shift-workers (N = 799) assessed in waves 2 years apart, a bidirectional relationship was observed wherein anxiety was associated with subsequent insomnia and insomnia was associated with subsequent anxiety [17]. In two smaller studies, focused on adolescents, baseline insomnia did not predict subsequent obsessive compulsive disorder (OCD) or social phobia 6 months later [13], but persistent childhood insomnia was associated with anxiety at 18 years of age in a separate study [14]. In sum, these new studies offer continued support for the contribution of insomnia in the development of anxiety disorders.

Some possibilities exist to explain an insomnia-anxiety relationship. For instance, hyperarousal has long been considered an etiologic factor in the development of insomnia [29, 30] and may represent a shared pathway by which both insomnia and anxiety conditions may develop. It is conceivable that when insomnia develops, first, it creates the conditions for anxiety-vulnerable individuals to develop a full anxiety disorder. In a classic study using caffeine, Bonnet and Arand induced objective and subjective insomnia in a sample of good sleepers who reported a number of symptoms associated with hyperarousal and psychological distress including increased anxiety [31]. This study suggests that acute insomnia leads to the manifestation of acute anxiety symptoms. The mechanisms for the contribution of insomnia to the development of a specific phobia or to OCD are somewhat more speculative. Nonetheless, the chronic experience of insomnia not only contributes to hyperarousal but to impaired emotion regulation [32, 33]. Together, or in concert, this could expose vulnerabilities for those at risk for developing these specific anxiety disorders. GAD presents a more interesting case study. Here, one can envision that insomnia leads to excessive worry about not only sleep and the consequences of poor sleep but to more generalized worry that meets diagnostic criteria for GAD. Indirect evidence for a prospective insomnia-anxiety relationship can be gleaned from clinical trials. For instance, a meta-analysis of cognitive-behavior therapy for insomnia (CBT-i) trials found a moderate effect of the intervention on concomitant anxiety (d = 0.41; 95% CI [0.32–0.49]) among 72 trials reviewed [34]. One small, but novel, trial randomized participants with co-occurring GAD and insomnia to receive GAD followed by insomnia treatment, or vice-versa [35]. In this trial, although superior benefits in both anxiety and sleep were achieved by initiating treatment for GAD first, insomnia treatment did improve worry symptoms. Overall, further work is needed to ascertain how insomnia confers added risk in the development of anxiety disorders.

Insomnia and Bipolar Disorder

Sleep disturbance is common among patients with bipolar disorder both during and between episodes [36] and often

Table 1 Summary of studies reviewed organized by diagnostic category

First author (year)	Number	Population	Prospective period	Insomnia measure	Psychiatric measure	Statisitical approach	Findings
Anxiety							
Alvaro (2017) [13]	255	High school students, South Australia	6 months	ISI	RCADS	Hierarchical regression models	OCD and social phobia predicted subsequent insomnia; insomnia did not predict subsequent OCD or social phobia
Armstrong (2014) [14]	395	Community children, USA	9 years	CSHQ	HBQ	MANOVA	Persistence of insomnia through age 9 was associated with anxiety at age 18
Chung (2015) [15•]	30,670	Adult patients, Taiwan	6 years	ICD-9 code	ICD-9 psychiatric disorders	Adjusted Cox proportional hazards regression models	Insomnia with and without hypnotics was associated with anxiety disorder
Kang (2016) [16]	909	Elderly community adults, Korea	2 years	4 items to diagnose insomnia	GMS-B3, AGECAT	Multivariate logistic regression including demographic, socio-economic, and clinical factors	Insomnia predicted presence of anxiety symptoms and incidence of anxiety
Vedaa (2016) [17]	799	Shift-working nurses, Norway	2 years	BIS	HADS (depression and anxiety), AUDIT-C	Structural equation modeling	There was a bidirectional relationship wherein anxiety was associated with subsequent insomnia and insomnia was associated with subsequent anxiety
Bipolar Disorder							
Chung (2015) [15•]	30,670	Adult patients, Taiwan	6 years	ICD-9 code	ICD-9 psychiatric disorders	Adjusted Cox proportional hazards regression models	Insomnia with and without hypnotics was associated with bipolar disorder
Ritter (2015) [18•]	1943	Adolescents and young adults, Germany	10 years	SCL-90-R sleep items (3)	DIA-X/M-CIDI; SCL-90-R	Adjusted logistic regression models	Sleep disturbance and insomnia severity each associated with incident bipolar disorder
Depression							
Alvaro (2017) [13]	255	High school students, South Australia	6 months	ISI	RCADS	Hierarchical regression models	Bidirectional relationship: baseline depression predicted subsequent insomnia; baseline insomnia predicted subsequent insomnia
Armstrong (2014) [14]	395	Community children, USA	9 years	CSHQ	HBQ	MANOVA	Persistence of insomnia through age 9 was not associated with depression at age 18
Chung (2015) [15•]	30,670	Adult patients, Taiwan	6 years	ICD-9 code	ICD-9 psychiatric disorders	Adjusted Cox proportional hazards regression models	Insomnia with and without hypnotics was associated with depression
Dorheim (2014) [19]	2088	Prenatal females at a university hospital, Norway	8 weeks postpar-tum	BIS	EPDS	Univariate and multivariate linear regression	Mixed findings; higher prenatal insomnia scores in those with postpartum depression, but insomnia was associated with postpartum depression in univariate analyses only
Drake (2014) [20]	2316	Community adults, USA	1 year	4 items based on DSM-IV criteria	QIDS	Logistic regression and mediation analyses	Insomnia predicted depression and mediated the relationship between stress reactivity and depression
Ellis (2014) [21]	54	Adults with and without insomnia, UK	3 months	5 items based on DSM-5 criteria	HADS-depression	ANOVAS for mean scores; raw counts for incident depression	Inconclusive findings; insomnia was associated with higher mean depression scores, but sample was too small to calculate risk for incident depression
Fernandez-Mendoza (2015) [22]	1137	Community adults, USA	7.5 years	Insomnia measure with 1-year duration of insomnia	Checklist of mental health conditions under current treatment	Multivariate logistic regressions	Insomnia increased risk of incident depression in unadjusted and adjusted models

Table 1 (continued)

First author (year)	Number	Population	Prospective period	Insomnia measure	Psychiatric measure	Statisitical approach	Findings
Hayley (2015) [23]	1076	Community early adolescents, Norway	7 time points across 10 years	Single item of difficulty initiating sleep	7 depression items (summed)	Structural equation modeling; multiple time points	Depression consistently predicted subsequent difficulty initiating sleep across time points; difficulty initiating sleep predicted subsequent depression at 3 of 6 time points
Hom (2016) [24•]	2596	Army recruiters and recruiter candidates, USA	18 months	Abbreviated ISI (5 items)	Presence of a major depressive episode in the electronic medical record	Binomial regression analyses	Insomnia severity predicted major depressive episodes
Ritter (2015) [18•]	1943	Adolescents and young adults, Germany	10 years	SCL-90-R sleep items (3)	DIA-X/M-CIDI; SCL-90-R	Adjusted logistic regression models	Sleep disturbance and insomnia severity were each associated with incident major depressive disorder
Vedaa (2016) [17]	799	Shift-working nurses, Norway	2 years	BIS	HADS (depression and anxiety) AUDIT-C	Structural equation modeling	Insomnia did not predict depression
PTSD							
None identified							
Substance Use Disorders							
Chung (2015) [15•]	30,670	Adult patients, Taiwan	6 years	ICD-9 code	ICD-9 psychiatric disorders	Adjusted Cox proportional hazards regression models	Insomnia with and without hypnotics was associated with substance use disorder
Hasler (2014) [25]	349	Both clinical and community adolescents, USA	1, 3 & 5 years	HPC-Insomnia Scale	SCID	Mixed-effects models with covariates	Baseline insomnia predicted 1-year alcohol use disorder; baseline sleep variability predicted 3- and 5-year alcohol use disorder
Wong (2015) [26]	6504	Community adolescents, USA	1 year and 5 years	1 item on trouble initiating or maintaining sleep	Items related to substance use disorder-related symptoms	Adjusted logistic regression models	Mixed findings: Insomnia predicted 1-year interpersonal problems and illicit drug use, but not other substance use disorder symptoms, and predicted 5-year interpersonal problems, driving while drunk, drug related problems, and illicit drug use
Suicide							
Allan (2017) [27]	252	Current or former military service members, USA	1 year	ISI	C-SSRS PHQ-9	Structural equation modeling	Insomnia predicted suicidal behaviors; insomnia was indirectly associated with suicidal ideation via depression mediation
Bernert [28•]	420	Older community adults, USA	10 years	5 items supporting DSM-IV criteria	Death certificate	Hierarchical logistic regression	Insomnia predicted suicide

AGECAT Automatic Geriatric Examination for Computer-Assisted Taxonomy, *ASHS* Adolescent Sleep Hygiene Scale, *ASWS* Adolescent Sleep-Wake Scale, *AUDIT-C* Alcohol Use Disorders Identification Test-Consumption, *BDI* Beck Depression Inventory, *BIS* Bergen Insomnia Scale, *C-SSRS* Columbia-Suicide Severity Rating Scale, *CPSS-I* Child PTSD Symptom Scale-Interview, *CSHQ* Children's Sleep Habits Questionnaire, *DIA-X/M-CIDI* Munich-Composite International Diagnostic Interview, *DSI-SS* Depressive Symptom Inventory-Suicidality Subscale, *EPDS* Edinburgh Postnatal Depression Scale, *GAD-7* Generalized Anxiety Disorder 7-Item Scale, *GMS-B3* Geriatric Mental State Schedule, *HADS* Hospital Anxiety and Depression Scale, *HAM-D* Hamilton Rating Scale for Depression, *HBQ* MacArthur Health and Behavior Questionnaire, *HPC* Health Problems Checklist, *IES* Impact of Event Scale, *ISI* Insomnia Severity Index, *PHQ-9* Patient Health Questionnaire-Depression, *PSF* Psychiatric Symptom Frequency Scale, *QIDS* Quick Inventory of Depressive Symptomatology, *SCID* Structured Clinical Interview for Depression, *SCL-90-R* Symptom Check List 90 Revised, *RCADS* Revised Child Anxiety and Depression Scale

consists of symptoms of insomnia [37]. There is also some evidence that short sleep times are prospectively associated with both manic and depressive symptoms in patients with bipolar disorder [38]. Both clinical and experimental data support sleep disturbance (typically in the form of insomnia-like sleep disturbance, but at times in the form of hypersomnolence) as a prodrome for relapse in bipolar disorder [39]. In general, insomnia or diminished sleep needs are generally considered to be precursors to (and symptoms of) manic episodes as well as contributors to bipolar disorder. This relationship, however, is based on a relatively small literature and is complicated by the prevalence of hypersomnia in some bipolar patients during depressive episodes.

In the current review, only two new studies were identified that addressed the role of insomnia in the development of bipolar disorder [15•, 18•]. In the Taiwanese retrospective cohort study of Chung et al., insomnia alone, compared to no insomnia diagnosis and no hypnotic medications, was associated with a significantly higher incidence of an anxiety disorder over a 6-year period (AHR = 2.14; [1.48–2.88]) [15•]. As with anxiety disorders as the outcome, the hazard ratio for bipolar disorder was more pronounced among insomnia patients who were also prescribed hypnotics (AHR = 14.69; [11.11–19.43]). In a separate 10-year longitudinal study of adolescents and adults aged 14–24 in Munich, Germany, baseline insomnia predicted incident bipolar disorder (AOR = 1.41; [1.11–1.79]) [18•]. In adjusted models using single sleep items instead of a summed insomnia variable, trouble falling asleep and early morning awakening were each individually predictive of bipolar disorder, whereas restless/disturbed sleep was not.

These two epidemiologic studies are a significant addition to the literature, supporting the role of insomnia in the subsequent development of bipolar disorder. Indirect support for this relationship is also available from what may be the only controlled clinical trial of insomnia treatment in bipolar patients [40]. In this small clinical trial (N = 58), CBT-i adapted for bipolar disorder was associated with lower relapse rates to manic and depressive episodes compared to psychoeducation over a 6-month follow-up period. Finally, besides there being a genetic vulnerability for bipolar disorder, which becomes exposed and activated by insomnia, the most often-mentioned mechanistic candidates for how insomnia may be causally related to bipolar disorder are via alterations in circadian rhythms and alterations in emotion regulation [18•, 32, 33].

Insomnia and Depression

As noted in the introduction, the prospective relationship of insomnia to the development of depression was the focus of a large meta-analysis published in 2011, which found insomnia to significantly increase the risk of a new depressive episode [5]. Eleven new studies that addressed the role of insomnia in the development of depression, published during our search window, were identified [13, 14, 15•, 17, 18•, 19–23, 24•]. Of four studies among children or adolescents, two supported a relationship of insomnia to subsequent depression [13, 18•], one found no such association [14], and the fourth found mixed support across eight waves of data collection over a 10-year period [23].

Among the studies conducted with adult samples, four supported a relationship between insomnia and subsequent depression [15•, 20, 22, 24•], while one of the studies did not [17], and two had mixed or inconclusive findings [19, 21]. In one study with mixed findings, 2088 women had insomnia and depression in week 32 of pregnancy and week 8 postpartum [19]. Prenatal insomnia was associated with postpartum depression in univariate but not adjusted analyses. In addition, women with new onset postpartum depression had higher prenatal levels of insomnia severity than those women with no pre- or postpartum depression. Similarly, in a small sample (N = 54) comparing good sleepers to those with acute insomnia at a baseline evaluation, mean depression scores 3 months later were higher ($p < .05$) among those with insomnia, but the sample was too small to test for the significance of five incident cases of depression in the acute insomnia group compared to one such case in the good sleeper group [21].

Among studies with more consistently positive findings, the Chung et al. retrospective cohort study reported that incident depression disorder was associated with baseline insomnia both with (AHR = 11.86; [10.58–13.29]) and without (2.74; [2.41–3.12]) hypnotic medications [15•]. In one study of 1137 participants with no baseline depression, insomnia was associated with incident depression over an average of 7.5 years (AOR = 1.85; [1.06–3.23]) [22] and insomnia severity was the only baseline predictor of major depressive episodes over an 18-month period in another study [24•]. In a unique study that assessed stress reactivity at baseline, insomnia 1 year later, and depression an additional year later, insomnia was associated with an increased risk for depression (OR = 3.17; $p < .01$) and mediated the relationship between stress reactivity and depression [20].

Overall, then, these studies provide support for the prospective contribution of insomnia in the development of depression, further solidifying a relatively large literature base that predated the current review. Indirect evidence for this prospective relationship is also available from clinical trials in depressed samples. For example, CBT-i significantly reduced depressive symptoms in a large randomized trial (N = 1149) up to 6 months following treatment [41] and to enhanced depression remission rates of antidepressant treatment (61 compared to 33% with antidepressant alone) [42].

As detailed more explicitly elsewhere, a parallel process model of insomnia and depression proposes that alterations in the neurobiologic and cognitive-behavioral domains interact in the pathogenesis of co-occurring insomnia and

depression [43]. In the neurobiologic domain, for instance, insomnia and depression are each characterized by similar changes in stress hormone secretion and elevated levels of inflammatory cytokines, which are each implicated in the etiology and exacerbation of depressive symptoms [44–47]. From a cognitive-behavioral perspective, emotional and cognitive consequences of insomnia may lead to a sense of loss of control that contribute to and activate other depressive schema such as hopelessness. In addition, the capacity to cope with or manage normal life stressors may be weakened as a result of chronic insomnia, which may amplify the negative or depressogenic valence of these life events [43].

Insomnia and PTSD

Sleep disturbance in general has long been recognized as a "hallmark" feature of PTSD [48]. Insomnia is especially pronounced among individuals with PTSD. Prospective data that speak to the role of insomnia in the development of PTSD support such a relationship but is somewhat limited [49]. We actually found no new prospective studies meeting our selection criteria.

There are two new studies, however, which do support an association between the presence of insomnia and the maintenance of PTSD [50, 51]. In addition, as reviewed by others, there are indications that treating insomnia in the context of PTSD can ameliorate non-sleep PTSD symptoms [49, 52]. In fact, a meta-analysis comprised of 11 clinical trials investigating the delivery of cognitive-behavioral sleep interventions in participants with PTSD revealed a moderate effect size for reductions in PTSD severity ($d = 0.58$) [53].

Overall, however, there remains the need for studies to assess whether the presence of insomnia increases the risk for the development of PTSD among individuals exposed to traumatic experiences. Some potential mechanisms for this to occur have been nicely reviewed by Germain [52]. Our view is that there is far more evidence for the role of insomnia to perpetuate and maintain PTSD than there is for insomnia to be a causal factor in the development of PTSD. This, of course, is an important empirical question to be tested

Insomnia and SUD

As in other mental health conditions reviewed, sleep disturbance often in the form of insomnia is highly prevalent among individuals with alcohol use disorder (AUD) and SUD [54]. Sleep problems in early childhood have previously been shown to prospectively predict substance-related problems in adolescence [55] with similar prospective observations among young adults [3]. Three new studies were identified that addressed the role of insomnia in the development of substance use disorders [15•, 25, 26].

In a study of adolescents that included those with and without a past or current AUD, for those with no baseline AUD ($N = 349$), insomnia predicted AUD symptoms 1 year later [25]. This association did remain significant at 3- and 5-year follow-ups. Instead, at these latter time points, baseline sleep variability was prospectively associated with AUD symptoms. Interestingly, unlike insomnia and sleep variability, baseline depression was not a predictor at any time point in adjusted models. Another longitudinal study assessed adolescents ($N = 6504$) at baseline and at 1- and 6-year follow-ups [26]. Baseline trouble falling or staying asleep predicted only 1 year interpersonal problems and illicit drug use, but not other SUD symptoms such as binge drinking, driving while drunk, or drug-related problems in fully adjusted models. Trouble sleeping at the 1-year follow-up predicted interpersonal problems, driving while drunk, drug-related problems, and illicit drug use at the 6-year follow-up. In addition to these mixed findings, lower total sleep time, which was also included in the models, also predicted SUD symptoms. It is unknown, of course, whether a variable that more robustly captured the presence or severity of insomnia disorder would have strengthened or weakened findings. In contrast, the Chung et al. study, which used medical record diagnostic coding as variables, reported that incident substance-related disorder was associated with baseline insomnia with (AHR = 4.12; [3.45–4.93]) and without (1.91; [1.61–2.26]) hypnotic medications over a 6-year follow-up period (15).

The addition of these new studies provides modest support for the role of insomnia in the development of new onset AUD/SUDs. Overall, the evidence does not overwhelmingly support this association. This is another area where more data is needed to ascertain the prospective risk for AUD/SUDs posed by insomnia. While not the focus of this review, the same can be said for the literature as it relates to whether insomnia increases the risk for relapse following AUD/SUD treatment where a relatively small body of both prior and newer work support the presence of this relationship (see, for example, [56, 57]).

Most proposed insomnia-SUD mechanistic pathways are in the direction of substance effects on sleep, although some have proposed that the frequent use of alcohol, marijuana, or sedating medications as sleep aids can lead to the development of SUDs [58, 59]. Other possible mechanisms are related to how chronic sleep loss that occurs with insomnia disorder may alter executive function in ways that promote risk-taking, increase impulsivity, and/or reduce inhibition, all of which could contribute to the development of SUDs. Finally, in the absence of further evidence, it is also quite feasible that although some shared pathway(s) between insomnia and SUDs may exist, the relationship is bidirectional and not necessarily causal.

Insomnia and Suicide

There are now two meta-analyses that support a relationship between sleep disturbance and suicidal outcomes including suicidal ideation, non-fatal suicide attempts, and suicide [60,

61]. In the 2012 meta-analysis, although the majority of studies identified were cross-sectional and/or focused on suicidal ideation as the outcome, several prospective studies supported the relationship between insomnia and suicide attempts and suicide [61]. The second meta-analysis focused exclusively on studies of comorbid insomnia with similar results [60]. In addition, several sleep-suicide reviews have been published since these meta-analyses [62–64], which identified a few additional studies supporting a sleep-suicide link. Among them was a large psychological autopsy of suicide decedents ($N = 388$) compared to a control cohort ($N = 416$) that found insomnia to be an independent risk factor for suicide [65].

We, however, identified only two new published studies fully meeting our selection criteria [27, 28•]. A study of 252 past and current military service members who endorsed recent suicidal ideation or a lifetime suicide attempt and were reassessed 12 months later [27]. Here, insomnia, and not depression, was directly predictive of suicidal behaviors at the 12-month follow-up, whereas insomnia's relationship to suicidal ideation was mediated by cognitive/affective depression. In a longitudinal case-control cohort study, 20 suicide decedents were identified at a 10-year follow-up and matched to 400 control subjects from a large population-based community sample [28•]. Baseline insomnia (termed sleep quality in the publication but based on five items consistent with insomnia disorder) was associated with increased risk for suicide while controlling for depressive symptoms (AOR = 1.30; [1.04–1.63]).

Although, these two new studies (and others identified in recent reviews that did not fully meet our inclusion criteria) do not sizably expand the insomnia-suicide literature, they do continue to support a prospective association between insomnia and the development of suicidal thoughts and behaviors. Studies such as these that control for depressive symptoms or mood disorder diagnoses actually strengthen the literature as a good deal of early work linking sleep and suicide did not control for depression.

Finally, the mechanistic pathways by which insomnia confers risk for subsequent suicide are far from established, though several possibilities exist [66–68]. Our own contention is that insomnia and a suicide trajectory may have both a number of shared pathways and some direct insomnia-suicide pathways. In this regard, we suggest that such linkages include those that have been proposed to undergird the insomnia-depression relationship [43]. We proffer simply that neurobiologic and cognitive-behavioral sequelae of insomnia contribute to additional vulnerability for suicide. There is some indication, for instance, that the psychobiologic dysregulation that occurs in insomnia [69] may distinguish suicide attempters from other depressed patients [70, 71]. In addition, as suggested with respect to insomnia and the development of depression, direct consequences of insomnia may diminish coping capacity giving rise to increased disinhibition and poor reasoning that creates vulnerability for suicidal thoughts and behaviors. Impulsivity and emotional dysregulation have also been proposed as one pathway from insomnia to suicide by others [72]. At perhaps the most direct level, being awake at night for extended periods increases the time available to contemplate suicide when others are not awake and when changing distressing thoughts is difficult [73]. These propositions highlight how the addition of insomnia to a co-occurring condition and/or to significant life stressors can further predispose individuals to thoughts of suicide and diminish their capacity to refrain from suicidal behaviors.

Conclusion

In the current systematic review of recently published longitudinal studies, 16 studies were identified that addressed whether insomnia was prospectively associated with a subsequent new onset mental illness. As some studies had more than one mental illness outcome, 23 separate analyses between insomnia and a mental health condition were reviewed. Overall, 15 of 23 comparisons supported a prospective relationship of insomnia to new onset psychiatric illness, two did not support the relationship, and six had mixed results. In sum, recent findings indicate that insomnia is a prospective risk factor for psychiatric illness. The evidence continues to be strongest with respect to the development of depression with accumulating evidence for the a role of insomnia in the development of anxiety disorders, bipolar disorder, and suicide. The limited data with respect to SUDs was mixed, and there were no identified studies with PTSD as an outcome. In general, the small number of studies conducted in child or adolescent samples were more mixed and less robust than findings from studies conducted in adult samples.

If insomnia heralds the onset of mental illness, one must next ask what the potential mechanisms underlying the relationship may be. We have reviewed putative pathways for individual conditions, although it is also useful to think of broad diagnostic-neutral pathways that may exist. Indeed, Harvey has previously proposed taking a transdiagnostic approach to the contribution of sleep disturbance to psychiatric conditions that focused on shared neurobiological substrates [33]. In addition to these, several other pathways exist through which insomnia may precipitate the onset of mental illness. First, at the most basic level, the general psychosocial distress associated with insomnia may serve as the stressor that foments pre-existing vulnerabilities for illness in accord with the diathesis stress model [74]. Second, insomnia has been associated with impaired executive functioning [75] which theoretically contributes to a reduced ability to utilize effective coping strategies and filter negative cognitions. Third, insomnia, and sleep disturbances in general, often result in excessive daytime fatigue and sleepiness, which in turn may decrease

one's engagement in pleasurable activities, social relationships, and associated coping strategies [76]. Fourth, insomnia shares some neurobiological underpinnings with disorders to which it may be a precursor. Last, some cases of insomnia may be prodromal in nature, with impending dysfunction first appearing in the form of sleep disturbance [77].

There are a number of limitations of this review. It focused only on recent additions to the literature and was not a meta-analysis. We did not rate the quality of the studies. We also did not limit the studies by sample size or by the length of the longitudinal period, leaving these study characteristics free to vary. We also chose to accept a liberal definition of insomnia, which means that the samples in some studies may not have met current diagnostic definitions of insomnia disorder. On the other hand, one shortcoming of the study was that we were conservative in focusing only on new onset mental illness, thus precluding a review of how insomnia may contribute to recurrence or relapse in psychiatric conditions. It is also worth noting that the review did not focus on sleep disturbance more broadly or other sleep disorders (e.g., nightmares, obstructive sleep apnea), which are also associated with the onset of some psychiatric conditions.

The clinical implications of this review are not unlike pronouncements that have been made by many others, but bear repeating. The assessment of sleep in general, and insomnia in particular, should be an integral part of a comprehensive assessment and screening strategy by mental health and primary care providers. Identification of insomnia should be followed quickly with direct treatment according to most recently available practice guidelines (i.e., CBT for insomnia as the first-line treatment, with pharmacotherapy as a second-line treatment following a shared decision-making process [78]). Finally, given that insomnia can be a prospective risk factor in the development of mental illness, treatment of insomnia should be considered as both treatment of a serious condition and as preventive mental health care.

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Compliance with Ethical Standards

Conflict of Interest Wilfred R. Pigeon reports personal fees from Merck.

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