INSOMNIA, THE MOST COMMON SLEEP COMPLAINT THAT AFFECTS THE LIVES OF MILLIONS, HAS BEEN LEFT “BEHIND” IN TERMS OF RESEARCH FOCUS OVER the last 10-15 years. The National Institutes of Health State of the Science Conference Statement is a major step towards recognizing that gap. The following points are offered in the spirit of contributing to a dialogue that is at its very beginning, and I appreciate the opportunity that was made possible by the Editor of SLEEP. One of the proposals included in the Statement is the use of the term “comorbid insomnia” in lieu of terms such as “secondary” or “primary” insomnia. This proposal is based on the recognition that chronic insomnia is usually comorbid with psychiatric and physical conditions and that currently there is limited understanding of the nature of their association or direction of causality. The term “comorbid” suggests the presence of 1 or more disorders (or diseases) in addition to a primary disease or disorder. It does not imply either causality or association. The strong association of insomnia with psychiatric conditions appears to be the single most important association and the most consistent finding across almost all studies in the last 30 years. For example, in a multicenter field trial sponsored by NIMH, insomnia was associated with another diagnosable psychiatric condition in 90-93% of the cases depending on the diagnostic system used (DSM-IV vs. International Classification of Diseases (ICD-10)). Also, in a recent study in 1741 men and women of a random general population sample, depression was the single strongest variable, followed by female gender. Physical disorders were also associated with insomnia but to a much lesser degree, eg, odds ratio (OR) for depression of 5.5 vs. OR for colitis of 1.3. Sleep apnea, defined as an OHI ≥ 15, was not associated with insomnia, which is consistent with earlier findings from clinical samples.

Do these data support any causal link between insomnia and psychiatric conditions? Certainly not, as correctly pointed out in the Statement. Despite the clinical evidence that emotional stress and treatment of insomnia should always include a mental health assessment, even in a brief office visit of a busy practitioner. This message is very important, particularly now that many insomniacs are treated by their primary care physicians, and a large number of sleep specialists have no psychiatric background.

The panel expressed a concern that an emphasis on the association of insomnia with psychiatric conditions may promote undertreatment of insomnia. Insomnia as a distinct disorder has been part of the DSM classification system of the American Psychiatric Association and the ICD for almost 20 years, securing and promoting the idea that insomnia must be the focus of independent research and clinical efforts. Also, clinicians have long recognized that insomnia many times is maintained despite the remission of the accompanying depression and that it requires separate therapeutic interventions from depression, including pharmacological, psychobehavioral, and sleep hygiene interventions. Furthermore, there is evidence that a primary complaint of insomnia associated with depression, in terms of its pathophysiology, is different from depression without a primary complaint of insomnia. For example, in chronic insomnia: (a) sleep efficiency measures are the primary variables that are affected whereas in depression, it is both sleep efficiency measures and REM sleep variables; (b) cortisol secretion is related to sleep disturbance indices, eg, total wake time (TWT) and stage 1 sleep, whereas in depression hypercortisolism is related to REM sleep variables; (c) degree of psychological distress correlates with objective sleep disturbances, whereas in depression there is a dissociation between depth of depression and sleep abnormalities; and (d) sleep deprivation does not have a mood-elevating effect in contrast to depression.

Collectively, these observations suggest that insomnia is not simply a by-product of depression and, as the panel noted, the complex association of these two disorders must be the focus of intense research effort. Such research can only benefit by acknowledging the strong association of insomnia and mental health and not by de-emphasizing its importance. To draw an analogy from another prevalent sleep disorder, ie, sleep apnea, research on that disorder can only gain by recognizing the strong and complex association of sleep apnea with obesity.

Another issue that is not dealt with in the Statement is whether insomnia is a nighttime disorder or a disorder present throughout the 24-hour sleep-wake cycle. Daytime impairment, in its various forms, is now considered to be essential in the diagnosis of insomnia. This approach is a departure from the traditional view in sleep medicine that has focused its efforts to improve the quality and quantity of nighttime sleep of insomniacs with pharmacotherapeutic and/or psychobehavioral techniques.

In clinical and psychometric studies of the 1970s, it was reported that insomnia is frequently associated with depression, anxiety, rumination, and inhibition of emotional expression. At about the same time, other studies pointed to the presence of increased physiologic activation, such as increased heart rate, peripheral vasoconstriction, elevated rectal temperature, and increased body movement before and during sleep. These findings led to the formulation of the hypothesis that insomnia is a disorder of emo-
tional and physiologic arousal.

These early studies were strengthened by findings that insomnia is associated with: (a) decreased sleepiness the next day as measured by a multiple sleep latency test (MSLT) in contrast to normal sleepers after sleep loss;10 (b) increased cortical activation as indicated by increased higher frequency (beta and gamma) wave activity and decreased delta wave activity during sleep and while awake;11,12 (c) increased 24-hour metabolic rate compared to controls;13 (d) greater glucose metabolism during sleep and while awake in the prefrontal cortex;14 (e) 24-hour activation of the stress system and, particularly, the hypothalamic-pituitary-adrenal (HPA) axis,5,6 in contrast to the effects of nonstressful total or partial sleep deprivation in young, normal sleepers.15,16 Furthermore, the sleep disturbance experienced by middle age men compared to young healthy men secondary to the administration of the arousal peptide corticotropin-releasing hormone (CRH) supports the role of increased physiologic arousal/decreased sleep homeostatic pressure in the increased prevalence of insomnia in the older vs. young individuals.17 In summary, these consistent data over a 30-year period suggest that insomnia and sleep loss are 2 distinct states and that insomnia is a disorder of physiologic and emotional hyperarousal present throughout the 24-hour sleep-wake cycle. Such a model has obvious therapeutic implications, and it is important that future research, both clinical and basic, is encouraged to examine its validity and clinical usefulness.

The last section of the report is devoted to the evidence on the safety and efficacy of treatments currently used for chronic insomnia. The panel notes that there has been a significant shift in the pattern of prescribed medications to treat chronic insomnia associated with a substantial increase in the off-label use of antidepressants, particularly trazodone. The panel appears to be puzzled by these trends given the lack of studies documenting the sleep efficacy of antidepressants. Further, the panel is concerned about the risk-benefit ratio of antidepressants given that all antidepressants have potentially significant adverse effects. Although not based on “hard” evidence, it appears that the widespread prescription of antidepressants may be related to the following factors: (1) benzodiazepine receptor agonists are recommended only for short-term use (with the exception of the recently released eszopiclone) for a disorder that is chronic and possibly nonremitting; (2) antidepressant use is not associated with tolerance-withdrawal phenomena as is the case with most benzodiazepine agonists; (3) although the old tricyclic antidepressants, eg, amitriptyline, are associated with significant adverse effects, trazodone appears to be safe with minimal side effects in the dose range commonly used for sleep (50-150 mg); and (4) sedative antidepressants, alone or in combination with the newer antidepressants, eg, SSRIs, appear to have a normalizing effect on measures, ie, cortisol18, which may have an ameliorating effect on mood and other daytime symptoms experienced by chronic insomnia. The panel called on the pharmaceutical industry to “support comparisons of its medications, not only with placebo, but also with other effective treatments, including cognitive behavioral therapy (CBT).” Given the widespread use of antidepressants, and the absence of studies on their hypnotic effectiveness, such a call should also include antidepressants, eg, trazodone, as a primary comparison group. Such information is important to the public, to the practicing physician, and potentially useful to understand further the pathophysiology of chronic insomnia.

REFERENCES