

Future Directions in the Management of Insomnia

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Research on insomnia has provided a number of important new insights, but fundamental deficits in our understanding remain. In considering priorities for future research, 3 areas warrant immediate attention. First, a causal relationship between insomnia and the adverse outcomes seen in insomnia patients needs to be established. Second, currently available symptomatic therapies need to be optimized. Recent data suggest that some benzodiazepine receptor agonists produce their hypnotic effect without side effects that were presumed to be inherent to sedation. Understanding the neuropharmacology underlying this differential effect would allow substantial improvements in the risk-benefit ratio for these drugs. Finally, the mechanisms of insomnia need to be better understood. Several lines of evidence suggest that physiologic arousal is important to the clinical presentation of primary insomnia. It remains unclear, however, whether this activation is primary or secondary to the insomnia itself. If physiologic hyperarousal causes primary insomnia, it would provide new approaches to the management of this disorder.

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Research on insomnia has provided important new information about the prevalence, pathophysiology, and therapy of this symptom, but progress in these areas has been frustratingly slow, and several important questions remain unanswered. The task of identifying areas in the field of insomnia research that are in need of focused attention is necessarily an editorial one. Others in the field, both clinicians and researchers, could readily identify multiple deficits in our current understanding of insomnia and its optimal management. Indeed, compilation of a list of what is not known about insomnia is, unfortunately, not a hard task. We do not know, for example, the nature of the basic neural mechanisms underlying primary insomnia. Nor do we know the identity of specific neurotransmitters that might be involved, or even whether specific neurotransmitter systems are involved. The genetics of the disorder are also not known. Are individuals genetically predisposed to insomnia? If so, what are the potential mediators of this genetic predisposition? For example, given the important relationship between insomnia and major psychiatric disorders, how does genetic predisposition to insomnia overlap with that to depression?

A therapeutic perspective also yields multiple unanswered questions. For example, what is the site, or sites, of action for benzodiazepine receptor agonists (BzRAs)? Does treatment, whether pharmacologic or behavioral, address underlying mechanisms, or is it entirely symptomatic, or does it depend on the type of insomnia and the individual patient? Does effective treatment also reverse the growing list of identified consequences or correlates of the insomnia complaint, such as impaired memory, psychomotor deficits, and heightened risk for depression?

More troubling than the limits in our current understanding of insomnia is the suggestion that research on these issues is not proceeding as rapidly as it is in other related fields. Recognizing that the complaint of insomnia represents a heterogeneous group of disorders and that this makes simplifying and unifying hypotheses about mechanism and clinical correlates difficult, it nonetheless appears that the study of insomnia lags substantially behind the study of other major sleep disorders such as narcolepsy or sleep apnea. Particularly when one considers the relative prevalence of the major sleep disorders, it would appear that insomnia would benefit from substantially greater attention from the research community.

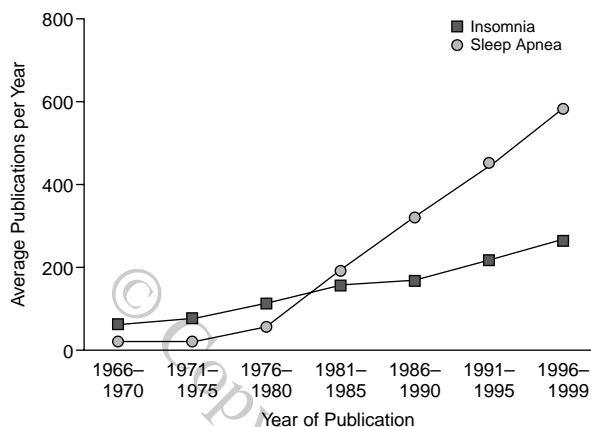
Evidence for this assertion comes from the scientific literature itself. Using MEDLINE, it is possible to track the number of publications in that database for which *insomnia* is listed as a keyword as a function of year of publication. Comparison is made with the number of references citing *sleep apnea* as a keyword. Figure 1 shows the 2 different curves. Sometime in the early 1980s, research on sleep apnea became a more popular enterprise (measured in numbers of publications) than that on insomnia and since that time has continued to grow at a significantly

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Figure 1. Average Number of Publications per Year Listing *Insomnia* or *Sleep Apnea* as Keywords^a



^aData are from MEDLINE database.

greater rate. For the 5-year period ending in 1999, publications about sleep apnea are almost twice as common as those about insomnia, despite a prevalence rate for insomnia that is, conservatively, 10 times that of sleep apnea.

While the reasons for differential research focus within sleep medicine are doubtless complex, it nonetheless seems fair to suggest that insomnia research would benefit from some increased attention. The intent of this review is to present one perspective on how such growth might be targeted to greatest effect.

CLARIFYING THE GOALS OF INSOMNIA THERAPY

One of the important recent developments in the study of insomnia has been the characterization of adverse outcomes associated with the symptomatic complaint. It is now clear that insomnia is associated with deleterious effects on parameters such as general health¹⁻⁵ and quality of life,⁶ and it is associated with heightened risk for major psychiatric disorders.⁷⁻⁹ Further, for patients with established psychiatric diagnoses, particularly depression, the coexistence of insomnia increases the risk of adverse outcomes such as relapse¹⁰ or suicide.¹¹ A more extensive review of the specific outcomes associated with insomnia is included in this supplement in the article by Benca.¹²

It is important to reiterate, however, that all of the adverse outcomes listed above, as well as others that are associated with insomnia in the literature, are, at this point, only correlates and not proven consequences. The practical corollary of this distinction is that it has not yet been demonstrated that reversal of the insomnia, either as an isolated complaint or as a complication of another primary disorder, results in meaningful mitigation of the various adverse outcomes. This deficit sharply limits the case that can be made for more aggressive clinical attention to the com-

plaint of insomnia, particularly within the primary care setting.¹³ As we contemplate aggressive therapy for the 10% of adults thought to suffer from significant insomnia each year, it will be important to know whether the benefits of therapy are to be assessed relative to symptomatic relief alone, or whether the goal of successful insomnia treatment is to reduce the risk of eventual major depression, reduce utilization of other health care resources, reduce the risk of accident, improve cognitive and psychomotor function, and improve overall quality of life. Knowing whether insomnia is, in fact, a cause of these adverse outcomes would then redefine therapeutic endpoints, thereby guiding future comparative evaluations of therapies. The answers to some of these questions will be necessarily long in coming. Assessments of outcomes will require large study samples evaluated over years of follow-up. One important implication of this argument for the short term is that assessment of the impact of therapy on these other outcomes should be a routine part of ongoing studies.

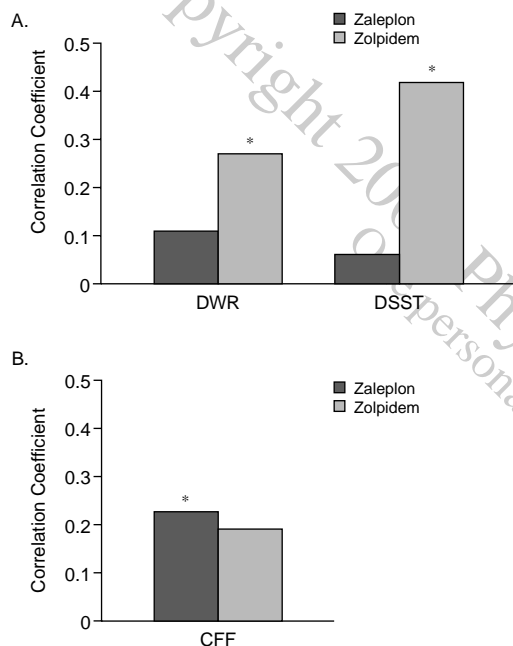
OPTIMIZING CURRENT INSOMNIA THERAPY

Although we cannot yet define the consequences of insomnia nor predict whether successful therapy will address these consequences, it should be emphasized that currently available therapies are effective treatments of the insomnia symptom and the associated objective sleep disturbances. Particularly from the perspective of the patient seeking relief from insomnia, successful reversal of the symptom is not a trivial achievement. Pending definition of additional goals of insomnia therapy, optimizing symptomatic relief while minimizing the risks and adverse consequences of therapy represents an important and realistic short-term research goal.

Important advances have been made in nonpharmacologic therapy for insomnia. Objective, controlled evaluations have established that, for receptive patients, this approach provides symptomatic relief and objective improvement of sleep that is equivalent in magnitude and greater in duration than that achieved with pharmacologic therapy.¹⁴ Assuming that all patients with insomnia would benefit from a behavioral approach, the limit on a broader application of this mode of therapy is access. The numbers of patients who might benefit from effective insomnia behavioral therapy greatly exceeds the resources available within the increasingly constrained medical environment. Pharmacologic therapy, despite its limitations, offers the only realistic method for treating the large numbers of patients with significant insomnia. If evidence develops to support a causal link between insomnia and depression or other adverse outcomes, the need for safe, effective, and widely applicable therapy will be amplified. Clearly, an important priority has to be the optimization of pharmacologic therapy so as to minimize the risk associated with a much broader application.

Table 1. Evolution of Benzodiazepine Receptor Agonist Hypnotics

Agent	Recommended Dose, mg	Half-Life, h
Flurazepam	15–30	47–100
Quazepam	7.5–15	47–100
Estazolam	0.5–2	10–24
Temazepam	7.5–30	5.5–18.4
Triazolam	0.125–0.25	1.5–5.5
Zolpidem	5–10	1.4–4.5
Zaleplon	5–10	1.0

Figure 2. Correlation Coefficients Between Measured Drug Concentration of Zaleplon or Zolpidem and 2 Measures of Functional Performance (A) and a Physiologic Measure of Central Nervous System Sedation (B)^a

^aData from Danjou et al.¹⁹ Abbreviations: CFF = critical flicker fusion, DSST = digit symbol substitution test, DWR = delayed word recall.
* $p < .05$ vs. no correlation (0).

The drug class of choice for the treatment of insomnia is the BzRAs.¹⁵ Within this drug class, the trend over the 20 years since their initial introduction as hypnotics has been toward shorter and shorter half-lives (Table 1). Reducing the half-life of sedation reduces the risk of carry-over, and with it, sedation-related side effects during the day.¹⁶ This safety concern has driven the progressive decrease in half-life from initial values greater than 50 hours (flurazepam) to current medications with half-lives just over 1 hour (zaleplon).¹⁷

Implicit in the effort to improve the safety of these medications by shortening their half-life is the belief that the adverse effects are an inherent function of their sedative property, i.e., that impairment of memory and psychomotor function is inseparable from the sedative effect

for which the drug is being used. Recent experience with zaleplon has necessitated reconsideration of this assumption. Studies examining performance effects of BzRAs 1.25 hours after administration (at or near peak plasma concentration) demonstrate that zaleplon is uniquely without impairment of memory and psychomotor function at doses that produce reductions of sleep latency equivalent to those of other BzRA hypnotics.¹⁸ Further, a quantitative comparison of impairment and plasma concentration demonstrates that the significant positive correlation between concentration and functional impairment seen with other BzRAs (e.g., zolpidem) is absent with zaleplon (Figure 2A), while a measure of sedation (critical flicker fusion) shows a significant dependence on zaleplon concentration (Figure 2B).¹⁹

A neuropharmacologic basis for the differential effects of zaleplon on performance and sedation is unknown. It has been suggested that the markedly lower affinity of zaleplon for the benzodiazepine receptor may account for its lower risk of impairment. While low receptor affinity is one of the most distinctive features of this compound relative to other nonbenzodiazepine BzRAs, it is difficult to understand how this property would differentially limit performance impairment without affecting hypnotic efficacy. Whatever the basis, further exploitation of this pharmacologic specificity may provide a mechanism for substantial improvements in the safety profile of hypnotic therapy.

MECHANISMS OF PRIMARY INSOMNIA

One of the important limitations on research on the pathophysiology of insomnia is the heterogeneous etiology of the complaint. Insomnia is a symptom of multiple disorders that may share little beyond their capacity to limit the quality or quantity of sleep. Studies of mechanism will require a relatively “pure” sample, and it seems clear that definitions of insomnia that focus entirely on the sleep-related symptom cannot provide a sufficiently homogeneous population. For example, although 2 patients may report difficulty falling asleep, it seems clear that the pathogenesis of insomnia in the patient with delayed sleep phase syndrome is very different from that of the patient with primary insomnia. One immediate goal for research in this area will be to develop a working definition for “primary” insomnia that is applicable to both epidemiologic and laboratory studies and provides for reasonably homogeneous subject samples.

The Corticotropin-Releasing Factor Model of Primary Insomnia

Despite the difficulty with working definitions of primary insomnia, several hypotheses have been advanced regarding its pathogenesis. It has been proposed that an endogenous melatonin²⁰ or an endogenous benzodiazepine receptor ligand²¹ may be deficient in primary insomnia,

although specific evidence for either model has not been developed, and therapeutic trials of melatonin in primary insomnia have been disappointing.^{22,23} Other models, based on known neural systems involved in sleep regulation, have been proposed as well.

Consideration of known clinical features of primary insomnia has led us to develop an alternative model for the pathogenesis of that disorder. We propose that increased activity of corticotropin-releasing factor (CRF) neurons, specifically those innervating norepinephrine neurons of the locus ceruleus (LC), is responsible for primary insomnia. Briefly, this hypothesis derives from several convergent lines of evidence that can be summarized as follows: (1) Primary insomnia has extensive overlap with major depressive disorder (MDD), suggesting commonality in pathophysiology, most likely in a predisposing risk factor; (2) abnormal CRF regulation has been extensively implicated in the pathogenesis of depression; (3) hyperactivity of CRF neurons can account for several clinical features of primary insomnia, including physiologic hyperarousal and both subjective and objective sleep disturbance. In the remainder of this article, we summarize the data in support of this model in more detail.

Overlap Between Primary Insomnia and MDD

Several lines of evidence support the suggestion that primary insomnia and MDD share a common pathogenesis. The most important of these is that primary insomnia and MDD are closely linked disorders. The vast majority of patients with MDD report difficulty sleeping,^{24,25} and the severity of insomnia is linked to the severity of psychiatric disturbance.²⁶ As stated above, persistence of insomnia after initiation of therapy predicts treatment outcome, and coexistence of insomnia in MDD increases the risk of suicide.¹¹ Conversely, there is now convincing epidemiologic support for insomnia as a risk factor for the eventual development of MDD. Several studies have established, both retrospectively²⁴ and prospectively,^{7,9,27} that significant insomnia (lasting 2 or more weeks) increases the risk for eventual MDD. This relationship persists even after controlling for the coexistence of other symptoms of depression.⁹ These studies suggest that primary insomnia may be a prodrome for MDD, anticipating its eventual development by as much as 20 years.⁸ It is thus reasonable to predict that the original genetic and/or environmental conditions that predispose individuals to eventual MDD may initially predispose them to primary insomnia.

CRF Activity Is Abnormal in Depression

A large body of work implicates CRF hyperactivity as an important pathophysiologic mechanism in MDD. Multiple complete reviews of the model and its foundation are available in the literature.^{28,29} Briefly, evidence of CRF hyperactivity in MDD includes (1) abnormal hypothalamic-

pituitary-adrenal (HPA) physiology in patients with depression, e.g., dexamethasone nonsuppression³⁰; (2) elevated cerebrospinal fluid (CSF) levels of CRF in depressed patients³¹; (3) decreased CRF receptors in brains of suicide victims³²; and (4) the ability of CRF in animal models to mimic behavioral signs of MDD²⁸ (see below).

Overt markers of HPA hyperactivity, such as plasma and urine cortisol measures,³³ and CSF levels of CRF³⁴ return to normal after successful therapy of MDD, behaving more like state markers than trait markers.²⁸ By contrast, provocative measures of HPA function, specifically the augmented response to exogenous CRF after dexamethasone suppression, are abnormal in individuals at high risk for depression but with no current evidence of the disease.³⁵ This finding suggests that this measure of CRF hyperactivity is a manifestation of the underlying tendency to depression rather than its overt expression, i.e., a trait marker rather than a state marker.

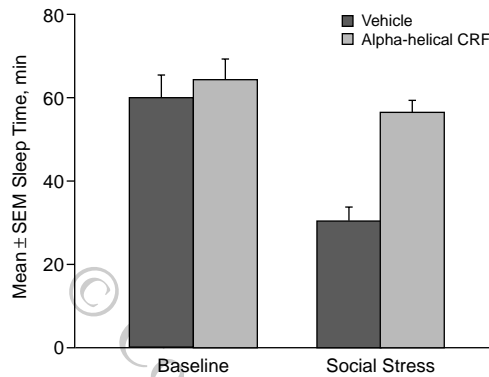
Abnormal CRF Regulation Could Account for Primary Insomnia

Among the features that distinguish patients with primary insomnia from those with insomnia secondary to another disorder is hyperarousal.³⁶ The most direct manifestation of this feature is prolonged sleep latency during the day, despite fragmentation and foreshortening of nocturnal sleep.^{36,37} Assessments of other measures suggest that the prolongation of sleep latency is part of a broader physiologic arousal in patients with primary insomnia, an important component of which is augmented activity of the sympathetic nervous system (SNS). Patients with chronic insomnia show elevated levels of circulating catecholamines,³⁸ increased basal metabolic rates,³⁹ increased body temperature,⁴⁰ and altered heart rate variability^{37,41} and pupillometry patterns,⁴² consistent with SNS activation. On the basis of these findings, some authors have speculated that activation of the SNS may be a primary component in the pathophysiology of primary insomnia.³⁹

Interestingly, SNS activation may be particularly important in the perception of inadequate sleep among patients with insomnia. Patients with primary insomnia routinely overestimate the severity of sleep pathology relative to objective measures,⁴³ and in extreme cases, subjectively perceived insomnia occurs in the absence of any objective signs of sleep disruption ("sleep state misperception").⁴⁴ These patients also show evidence of SNS activation, with measured metabolic rates intermediate between those of normal subjects and those of subjects with objective signs of insomnia.⁴⁵ This suggests that the SNS activation, in particular, may contribute to the perception of poor sleep.

Some evidence also suggests that other systems regulated by CRF are abnormal in primary insomnia, just as in MDD. Specifically, preliminary data indicate that the HPA axis is overactive in insomnia. Patients with primary insomnia show elevated levels of urinary free cortisol, and

Figure 3. Effects of a Corticotropin-Releasing Factor (CRF) Antagonist (alpha-helical CRF) on Stress-Attenuated Sleep^a



^aData from Matsumoto et al.⁶³ Under basal conditions, alpha-helical CRF, relative to placebo (vehicle), had no effect on ethanol-induced sleep time at baseline (left), while attenuation of sleep following stress exposure was reversed with pretreatment with antagonist (right).

the extent of the elevation is proportional to the amount of wakefulness during the night.³⁸ Beyond this evidence, the recognized relationship between stress and insomnia suggests that, at least during the precipitating episode, activation of stress hormonal systems and sleep disruption are likely to overlap. It remains unclear whether HPA activation is limited to this acute period or correlates with the insomnia disorder in a more fundamental and sustained way.

Most importantly, CRF could explain the sleep disruption that is the sine qua non of primary insomnia. Data from animal studies demonstrate that CRF has a number of behavioral effects that collectively can be thought of as consistent with the neuroendocrine function of CRF, in that they are manifestations of an integrated “stress response.”⁴⁶ For example, instillation of CRF into the third ventricle and/or specific brain regions of rats produces increased motor activity and agitation in a familiar environment,⁴⁷ but decreased exploratory activity in a novel environment.⁴⁸ Intracerebroventricular CRF also exaggerates the response to acoustic startle⁴⁹ and produces heightened anxiety responses in social interaction tests.⁵⁰ Centrally acting CRF antagonists block the behavioral responses to stress.^{51,52} These behavioral responses to CRF do not require an intact HPA axis and can occur after hypophysectomy.^{53,54} Microinjection studies suggest that many of the behavioral effects of CRF localize to the LC,⁵⁵ as do many of the effects of CRF on autonomic function and SNS activity described above.⁵⁶ Evidence that CRF acts as a neurotransmitter in the LC also comes from anatomical localization of CRF-positive fibers to the LC⁵⁷ and evidence that CRF directly increases LC neuronal firing.⁵⁸ It has been suggested that the LC serves as the site at which behavioral and autonomic effects of CRF are integrated.⁵⁹

Among the behavioral effects of CRF, the most relevant to this discussion is the potentiation of wakefulness. Cen-

tral CRF has been shown to decrease sleep in rats, particularly after exposure to stress. Antagonists of CRF block the stress-induced reduction in spontaneous sleep⁶⁰ and sleep in response to pentobarbital,⁶¹ interleukin-1,⁶² or ethanol⁶³ (Figure 3). Circadian rhythmicity in CRF secretion under nonstressed conditions may play a role in the normal sleep-wake expression,⁶⁴ although not all studies agree on a role for CRF in nonstressed wakefulness.⁶⁵ In humans, some studies using peripherally administered CRF have also shown sleep disruption,⁶⁶ although others have seen no effect.⁶⁷ These studies are difficult to interpret given the uncertainty regarding the locus of action for peripherally administered CRF and the potentially confounding effect of the endogenous glucocorticoid response.

As with other behavioral effects of CRF, the potentiation of wakefulness also appears to be mediated by the LC and norepinephrine. The attenuation of pentobarbital-induced sleep by CRF can be reversed with β -blockade⁶⁸ and other pharmacologic inhibitors of norepinephrine neurotransmission.⁶⁹

Implications of the CRF Model of Primary Insomnia

In summary, we hypothesize that CRF hyperactivity, arising either through a genetic predisposition or possibly as a consequence of early stress experiences,^{70–72} results in an exaggerated CRF response to stress. Subsequent repeated exposure to stress results in amplification of the abnormal response through autodestruction of inhibitory centers in the hippocampus.⁷³ We hypothesize that this process results in marked difficulty sleeping when stressed, exaggerated and protracted sleep disturbances following stress, and, eventually, primary insomnia. CRF hyperactivity produces both the sleep disturbance and the physiologic hyperarousal characteristic of that disorder. Interestingly, emerging data from animal models demonstrate that recurrent stress can produce some of the changes in serotonin neurotransmission that characterize depression,^{74,75} providing a potential mechanism linking CRF hyperactivity and MDD, as well as a possible pathophysiologic foundation for the epidemiologic link between primary insomnia and MDD.

SUMMARY AND CONCLUSIONS

While research on insomnia has made important recent progress, important and fundamental questions about this symptom and its optimal therapy remain unanswered. The exercise of identifying research priorities in this area is necessarily an editorial one for which each researcher and clinician is likely to have differing solutions. From our perspective, 3 important areas should be at the top of the priority list. We believe that the primary goal should be to establish whether the known correlates of insomnia are, in fact, consequences of that disorder and whether treatment of the insomnia can attenuate adverse outcomes. Resolu-

tion of this issue will have broad implications for the development of future therapies and for the optimization of currently available ones. Although it may take years to answer this question definitively, the time to begin these studies is now.

Second, we suggest that data emerging from clinical evaluations of new benzodiazepine receptor agonists, most notably zaleplon, compel a reconsideration of the idea that adverse effects of these drugs are inseparable from their desired hypnotic effect. Confirmation of these results and characterization of the neuropharmacology underlying these differential effects would have immediate impact on the optimization of currently available pharmacologic therapy.

Finally, future work on insomnia therapy requires a better understanding of the mechanisms involved. We propose a model for the pathogenesis of primary insomnia in which hyperactivity of CRF neurons produces sleep disruption and physiologic hyperarousal and predisposes patients with this disorder to eventual MDD. This model, if validated, would have important implications for future therapies of both insomnia and depression.

Drug names: estazolam (ProSom and others), pentobarbital (Nembutal and others), temazepam (Restoril and others), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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