

# Insomnia Risks and Costs: Health, Safety, and Quality of Life

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**I**nsomnia is a disorder of inadequate sleep (poor quantity or quality) that can result in impairment of daytime function or in emotional distress.<sup>1,2</sup> There are several types of insomnia, which are not mutually exclusive and include difficulty initiating sleep (sleep-onset insomnia), frequent or long nighttime awakenings (sleep-maintenance insomnia), and waking up too early without being able to return to sleep (also sleep-maintenance insomnia).<sup>1</sup> The type of insomnia can vary over time in any individual and is classified based on its duration.<sup>3</sup> Acute insomnia lasts 1 to 3 nights, short-term insomnia lasts 3 nights to 1 month, and chronic insomnia lasts longer than 1 month.<sup>4</sup> Acute insomnia is often caused by emotional or physical discomfort and, if left untreated, may develop into chronic insomnia.<sup>5</sup>

Insomnia can exist as a primary disorder or as comorbid with another condition.<sup>6</sup> Primary insomnia is commonly caused by life changes, including extended periods of stress or emotional upset.<sup>5</sup> Comorbid insomnia (sometimes referred to as secondary insomnia) is the most common type of insomnia, afflicting more than 8 of 10 people with insomnia.<sup>5,7</sup> The identification and diagnosis of insomnia are challenged by difficulty and ambiguity because of the variation in the ways insomnia can manifest in an individual, the potential overlap and changes in insomnia symptoms, and the possible disruption of sleep due to lifestyle or environmental factors unassociated with insomnia. Also, there is a discrepancy between subjective reporting and objective measuring of sleep, further complicating insomnia diagnosis and assessment. Generally, insomniacs tend to underestimate their ability to sleep.<sup>8</sup>

Determining the true prevalence of insomnia is further complicated due to patient underreporting and differences in operational definitions.<sup>1,9-11</sup> In the United States, general population surveys consistently find that approximately one-third of adults report having sleep problems.<sup>12-15</sup> Within this group, sleep-maintenance insomnia is reported more commonly than sleep-onset insomnia, as demonstrated by an international survey in which 73% of patients with insomnia reported problems with sleep maintenance, 61% reported difficulties falling asleep, and 48% reported poor sleep quality.<sup>16</sup> In the 2009 Sleep in America Poll conducted by the National Sleep Foundation, 64% of individuals surveyed had complaints of frequent insomnia, with only 15% being formally diagnosed.<sup>15</sup> In this poll, insomnia with nighttime awakenings and with waking up feeling unrefreshed

The effect of insomnia on next-day functioning, health, safety, and quality of life results in a substantial societal burden and economic cost. The annual direct cost of insomnia has been estimated in the billions of US dollars and is attributed to the association of insomnia with the increased risk of certain psychiatric and medical comorbidities that result in increased healthcare service utilization. It is well known that psychiatric conditions, anxiety and depression in particular, are comorbid with insomnia. However, emerging data have shown links with several common and costly medical conditions such as heart disease and diabetes. Furthermore, studies show that patients who have insomnia have more emergency department and physician visits, laboratory tests, and prescription drug use than those who do not have insomnia, increasing direct and indirect consumption of healthcare resources. Insomnia also has been shown to negatively affect daytime functioning, including workplace productivity, as well as workplace and public safety. These daytime effects of insomnia are translated into indirect costs that are reportedly higher than the direct costs of this disorder. These observations have significant implications for managed care organizations and healthcare providers. Improvements in diagnosing and treating insomnia can significantly reduce the healthcare cost of insomnia and its comorbid disorders, while providing additional economic benefits from improved daytime functioning and from increased productivity.

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### Take-Away Points

This review describes the evidence associated with the direct and indirect economic costs of insomnia, as well as available and emerging therapeutic strategies.

- The direct and indirect costs of insomnia are highlighted to impress on the reader a need for improvements in the management of insomnia.
- Links between common costly medical conditions and insomnia are made, demonstrating the importance of improving the diagnosis and treatment of not only insomnia but also its comorbidities.
- The benefits and drawbacks of current and future treatments are discussed to help healthcare providers make informed treatment decisions for their patients.

characterized the most prevalent symptoms (46% and 45%, respectively).<sup>15</sup>

Certain populations have a higher likelihood for developing insomnia.<sup>7</sup> Risk factors include female sex,<sup>17</sup> increasing age,<sup>18,19</sup> employment status,<sup>20,21</sup> shift work,<sup>21</sup> and a family history of insomnia.<sup>22,23</sup> Among women, insomnia seems to be more prevalent in the perimenopausal years, and a gradual increase in insomnia is seen in early-to-late perimenopause transition.<sup>24,25</sup> Although older age is associated with an increased risk of insomnia, reports of insomnia or trouble sleeping have been found to peak in middle age (range, 45-54 years), to decrease slightly during older age (range, 65-84 years), and to increase again at very old age (≥85 years), suggesting that the relationship between insomnia or trouble sleeping and age may not be linear.<sup>26</sup> Greater risk of chronic insomnia exists in shift workers, another group at high risk of insomnia, possibly due to the misalignment of their circadian sleep-wake patterns and sleep-wake schedules.<sup>21</sup>

This review will focus on the health and societal effects of insomnia as they relate to its economic cost burden. This issue is relevant to managed care organizations and healthcare providers because insomnia contributes to increased direct and indirect consumption of healthcare resources. Improvements in diagnosing and treating insomnia can relieve its cost burden by significantly reducing the associated direct and indirect healthcare costs.

## SLEEP ARCHITECTURE AND CHANGES OCCURRING IN INSOMNIA

Normal sleep consists of 2 alternating states, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.<sup>27</sup> The NREM-REM cycle, beginning with NREM, generally occurs 3 to 7 times per night and normally lasts 90 to 120 minutes each time.<sup>28</sup> The NREM sleep is composed of 4 stages (NREM1 through NREM4). Stage 1 is viewed as shallow or light sleep, having the lowest arousal threshold, and stage 2 is the transition from light sleep to deep sleep as the heart rate slows and body temperature decreases. Stages 3 and 4 are defined by high-voltage slow-wave activity, with stage

4 having a predominance of these waveforms.<sup>29</sup> Such high-voltage slow-wave activity is characteristic of slow-wave sleep (SWS) or deep sleep. These latter deep sleep stages have the highest arousal threshold and are believed to be required for physical restoration, while REM sleep is required for cognitive restoration.<sup>30,31</sup>

There are several determinants of a good night's sleep, and these can be measured in different ways. Sleep efficiency is the ratio of time spent asleep (total sleep time) to the time spent in bed. A decrease in sleep efficiency typically reflects a decrease in total sleep time, which subsequently affects next-day alertness and performance.<sup>8</sup> Sleep quality refers to the restorative and undisturbed quality of sleep. The depth of NREM sleep, the amount of REM sleep, and sleep continuity are major determinants of sleep quality.<sup>8</sup> Refreshing sleep (ie, sleep that makes one feel refreshed the next day) requires sufficient total sleep time and sleep that is in synchrony with the sleep-wake circadian rhythm.<sup>32</sup> Ultimately, good sleep manifests as an ability to function well the next day.

The sleep pattern of individuals with chronic insomnia demonstrates a marked deficiency in the SWS stage.<sup>33,34</sup> Electroencephalographic data show that insomniacs have fewer waves that are characteristic of deep sleep and more higher-frequency lower-amplitude waves that are typical of wakefulness, REM sleep, and NREM1 and NREM2 light sleep.<sup>29,31,35</sup>

## EFFECT OF INSOMNIA ON HEALTH, SAFETY, AND QUALITY OF LIFE

Insomnia has a negative association with health and quality of life (QoL) if left untreated. In a study<sup>36</sup> that surveyed severe insomniacs, mild insomniacs, and good sleepers, insomniacs were reported to have a lower self-reported overall health status and higher bodily pain, both of which contribute to reduced QoL. Successful treatment of insomnia is expected to enhance QoL. However, treatment efficacy investigations in insomnia generally have a narrow range of outcome measures that tend to focus on short-term improvements and include mostly quantitative measurements of sleep improvements, with measures of QoL (if included) as secondary evaluations.<sup>37</sup> A placebo-controlled study<sup>37</sup> that included measurement of QoL demonstrated that long-term treatment of insomnia with eszopiclone enhanced QoL.

The potential negative effect that insomnia may have on health is further evidenced by its association with the increased risk of certain psychiatric and medical comorbidities, including anxiety and depression,<sup>1,38</sup> obesity or weight

gain,<sup>39</sup> obstructive sleep apnea hypopnea syndrome,<sup>40</sup> and alcoholism<sup>41</sup> (Figure). In addition, certain medical conditions are associated with an increased risk of insomnia.<sup>42</sup> These include chronic pain, high blood pressure, gastrointestinal problems, urinary problems, osteoarthritis, hip impairment, fibromyalgia, peptic ulcer disease, and breathing problems (Figure).<sup>43-46</sup> For example, more than 50% of patients with chronic obstructive pulmonary disease complain of difficulties initiating or maintaining sleep,<sup>47</sup> and 50% of adults with diabetes are reported to have insomnia.<sup>48</sup> Shorter sleep time is associated with impaired glucose regulation and with increased risk of diabetes.<sup>49</sup> However, the cause-effect relationship of insomnia with psychiatric and medical comorbidities is unclear.<sup>46,50-52</sup> Some evidence suggests a reciprocal cause-effect relationship between insomnia and psychiatric disorders such as depression, anxiety, and alcohol or drug abuse.<sup>53</sup> Moreover, combined treatment of insomnia and depression or anxiety can augment the efficacy of antidepressants or anti-anxiolytics.<sup>54,55</sup>

Insomnia can affect daytime functioning by impairing one's ability to perform common tasks. In the 2009 Sleep in America Poll, 40% of adults reported that daytime sleepiness interfered significantly with their daily activities.<sup>15</sup> These daytime impairments are due to the negative effects of insomnia on memory, the ability to concentrate and focus, psychomotor function, and alertness. Such functional impairments can result in decreased productivity at home and at work.<sup>56</sup>

Decreased safety in the workplace is another consequence of daytime functional impairments resulting from insomnia. Workers with sleep disorder symptoms have a higher occupational injury rate than those without sleep problems.<sup>57</sup> In a Swedish study,<sup>58</sup> trouble sleeping was significantly associated with increased risk of fatal occupational accidents. Impaired performance due to reduced or inefficient sleep creates public safety risks when individuals with excessive daytime sleepiness are involved in potentially dangerous daily activities such as driving.<sup>59</sup>

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## ECONOMIC COSTS OF INSOMNIA

It is difficult to determine exactly the direct cost of insomnia because there are varying degrees of overlapping expenditures with other medical conditions, and some cost attributed to insomnia may be due to other coexisting conditions.<sup>60</sup> Nevertheless, patients with insomnia have been shown to have 60% higher mean total healthcare costs than those without insomnia.<sup>61</sup> Patients with insomnia have more emergency department and physician visits, laboratory tests, and prescription drug use than those without insomnia, and patients with severe insomnia use more healthcare resources

than their counterparts with less severe insomnia or those without insomnia.<sup>62</sup> Other issues that contribute to the difficulty in assessing costs include differing definitions of insomnia and the fact that not all patients experiencing sleep problems may label or report themselves as insomniacs.

### Direct Costs of Insomnia

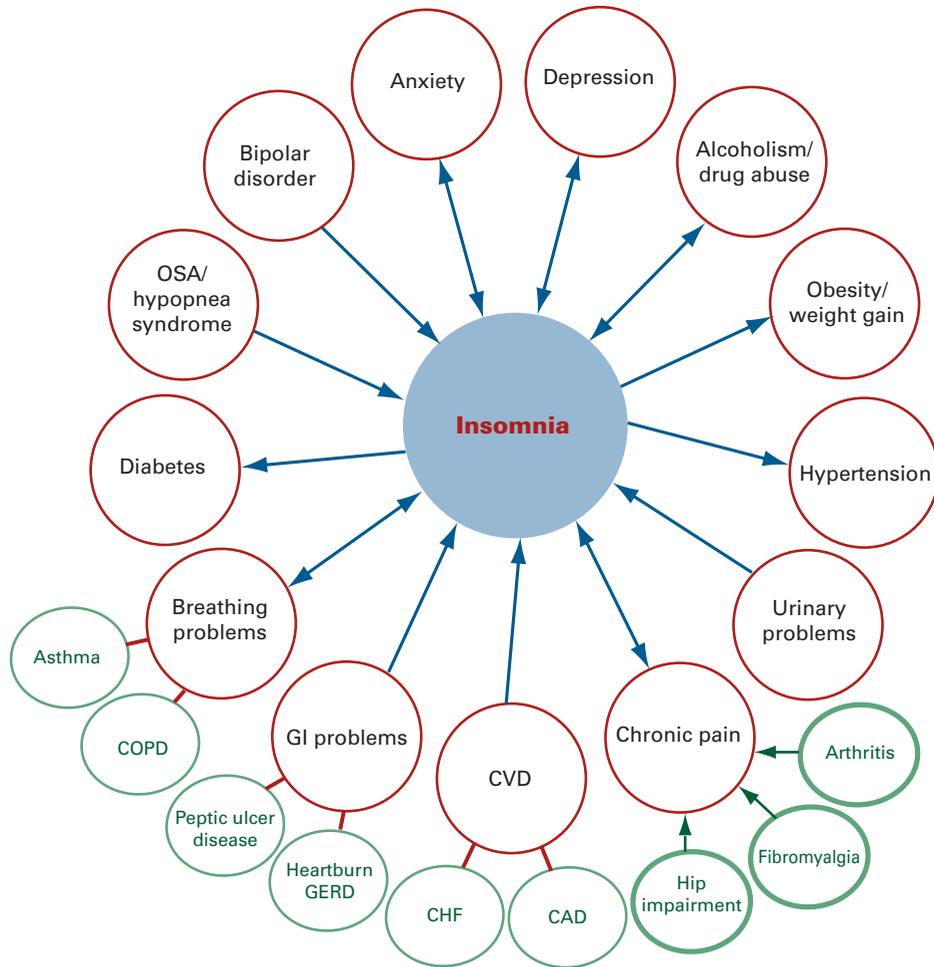
Based on direct healthcare costs, insomnia is considered a significant economic burden for patients. The direct annual costs of insomnia treatment in the United States were estimated in 1990 to be \$15.9 billion<sup>63</sup> and in 1995 to be \$13.9 billion.<sup>56</sup> Another study<sup>64</sup> examining the direct annual cost of insomnia in the United States for 1995 estimated the cost at \$1.79 billion. Disparity between estimates is likely due to inflation, differences in the measuring methods used, and varying attributions of nursing home costs.<sup>56,65,66</sup> Based on direct healthcare costs, insomnia is considered a significant economic burden for younger and older patients. A recent retrospective observational study<sup>61</sup> conducted using medical claims for inpatient, outpatient, pharmacy, and emergency department services found the direct costs of insomnia treatment to be \$924 per patient per 6 months for those aged 18 to 64 years and \$1143 per patient per 6 months for those aged 65 years or older (2003 US dollar pricing).

### Indirect Costs of Insomnia

It is generally accepted that the indirect costs of insomnia are higher than the direct costs.<sup>64,67</sup> Based on a review of the literature, the combined direct and indirect estimated total costs for insomnia are likely to be at least \$92 to \$107 billion (1994 US dollars) annually, with indirect costs (including medical comorbidities, increased hospitalization, insomnia-related alcohol abuse, reduced workplace productivity, and motor vehicle crashes and other accidents) accounting for \$77 to \$92 billion.<sup>66</sup> These data suggest a cost benefit to the treatment of insomnia.

Indirect costs of insomnia result primarily from its daytime effects. As such, the effect of insomnia on daily functioning is key to understanding its effect on cost burden, particularly indirect costs. Individuals with severe insomnia miss work twice as often and have a higher rate of work accidents and errors, as well as lower self-rated job performance scores, compared with those without insomnia.<sup>68,69</sup> One retrospective analysis used the Human Capital Management Services Research Reference Database to compare the annual costs of insomnia between employees who have insomnia and those who do not have insomnia.<sup>70</sup> The annual incremental costs, including medical and drug costs, sick leave, short-term disability, long-term disability, and workers' compensation, were significantly higher for employees who have insomnia.<sup>70</sup> In another study,<sup>71</sup>

■ **Figure.** Psychiatric and Medical Conditions Associated With Insomnia



Arrows indicate the direction of cause—effect between insomnia and comorbidities, where known. CAD indicates coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal; OSA, obstructive sleep apnea.

the effect of insomnia on work productivity was found to result in a high cost to employers. It must be noted that cost estimates as they relate to work productivity are likely to be low because of the difficulty in accurately determining the economic burden of insomnia in the workplace.

A recent study<sup>72</sup> conducted in the Canadian province of Quebec found that the indirect costs of untreated insomnia are much greater than the direct costs of treating it: For individuals meeting all diagnostic criteria for insomnia, the annual per-person insomnia-related costs averaged CaD \$5010 (US \$4388), with indirect costs (including costs associated with work absenteeism and productivity and motor vehicle crashes and other accidents) accounting for CaD \$4717 (US \$4131) and direct costs (including costs associated with healthcare visits, transportation to healthcare appointments, and alcohol and prescription medication to promote sleep) accounting for CaD \$293 (US \$257). Costs attributed to loss

of work productivity and absenteeism were estimated using Statistics Canada Labour Force Survey data on mean salaries according to age group and sex. This study cited lost hours of work productivity, an estimated 27.6 days of work lost per person, as the highest cost of insomnia, accounting for 76% of all insomnia costs.<sup>72</sup> The highest direct cost of treating insomnia was attributed to the use of alcohol as a sleep aid, accounting for 5% of all insomnia costs.<sup>72</sup> It should be noted that these findings are in the context of Quebec's centralized healthcare system, which keeps medical costs low and relies on a self-report method.

## BENEFITS AND DRAWBACKS OF TREATMENTS FOR INSOMNIA

In a predictive analysis that used clinical literature and medical claims data, treatment of insomnia was associated

with significant net savings in healthcare cost per patient per year ( $\leq \$2362$  [2007 US dollars] per patient per year for zolpidem tartrate extended-release treatment using total sleep time as the modeled efficacy measure).<sup>73</sup> However, this study was limited to a national healthcare database, and the results may not be generalized to reflect all types of healthcare structures. Furthermore, information on long-term savings or trends was not obtained. In another model that used patient-level data from a 6-month clinical trial, assessment of the cost-effectiveness of eszopiclone for chronic primary insomnia demonstrated a net gain in quality-adjusted life-years (QALYs), with a cost-effectiveness of approximately \$5000 per QALY gained, including indirect costs.<sup>74</sup> However, these values may not translate to real-world cost-effectiveness, as patients receiving protocol-driven care in this trial had a low rate of physician visits and were healthier than the general population with insomnia, thereby reducing healthcare utilization.<sup>74</sup>

There are further economic benefits of treating insomnia that should be considered in the context of any associated comorbidity of the individual patient. In many cases, effective treatment of insomnia may reduce the indirect costs of treating comorbidities. In other cases, effective treatment of comorbidities may improve the insomnia symptoms and thereby reduce the economic burden.

Nonpharmacologic treatments of insomnia primarily include behavioral and cognitive techniques that modify the precipitating and perpetuating factors that contribute to insomnia.<sup>75</sup> Pharmacologic treatments for insomnia include self-prescribed treatments such as over-the-counter sleep aids, alcohol, and “natural” treatments (eg, valerian, chamomile, and St John’s wort), as well as prescription agents.<sup>76-78</sup> Although widely used, over-the-counter sleep aids such as those containing antihistamines (diphenhydramine or hydroxyzine), have negative adverse-effect profiles that include cognitive impairment and next-day sedation.<sup>75</sup> Prescription agents most commonly used in the management of insomnia include benzodiazepines, nonbenzodiazepine hypnotics, and Ramelteon, as well as some antidepressants, particularly those that target the serotonergic system.<sup>14,75,77,79-82</sup>

Benzodiazepines (eg, estazolam, flurazepam hydrochloride, quazepam, temazepam, and triazolam) function as modulators of  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) receptors and have been the first-line pharmacologic treatment option in the short-term management of insomnia.<sup>75</sup> Benzodiazepines are known for their efficiency in reducing the time to sleep onset (sleep latency) and the number of nighttime awakenings, thereby increasing total sleep time.<sup>75</sup> However, safety and tolerability concerns should be considered for their long-term use; for example, benzodiazepines can result in next-day “hangover” symptoms, including a negative effect on memory and recall

and next-day sleepiness.<sup>75</sup> Such adverse effects are likely attributed to the lack of differentiation of benzodiazepines between different GABA<sub>A</sub> receptors, some of which are located in areas of the brain involved in cognitive, memory, and psychomotor functions.<sup>83</sup> Additional adverse effects of benzodiazepine use include addiction and tolerance to their sleep-promoting effects.<sup>84,85</sup>

Nonbenzodiazepine hypnotics (eg, zolpidem tartrate [sanofi-aventis, Bridgewater, NJ], zolpidem tartrate extended-release [sanofi-aventis], zaleplon [King Pharmaceuticals, Bristol, TN], and eszopiclone [Sepracor, Marlborough, MA]) produce the same hypnotic effects as benzodiazepines, while offering more favorable safety and tolerability profiles.<sup>83</sup> These drugs exhibit greater selectivity for GABA<sub>A</sub> receptor subtypes located in areas of the brain involved in sleep-wakefulness and sedation.<sup>75,83</sup> As a result, they reduce the risk of next-day sedative (hangover) effects and do not exhibit the same propensity for tolerance and addictive properties as traditional benzodiazepines.<sup>83</sup> Nevertheless, evidence for the addictive properties of nonbenzodiazepines exists, requiring these drugs to be scheduled.<sup>76,82,86,87</sup>

Ramelteon, a melatonin receptor agonist that is not scheduled, is indicated for the treatment of sleep-onset insomnia. It may have promise in the treatment of circadian disruptions such as those exhibited by shiftworkers and jet-lagged travelers.<sup>88,89</sup>

Although there is limited evidence for their efficacy in specifically treating insomnia, antidepressants such as amitriptyline hydrochloride, doxepin hydrochloride, trazodone hydrochloride, and mirtazapine have been prescribed off-label for the treatment of insomnia due to their sedative effects. Trazodone and mirtazapine elicit their sedative effects by acting as serotonergic serotonin receptor antagonists, with the former also having antihistaminergic properties.<sup>90</sup> All of these drugs are associated with several adverse effects, including dizziness and psychomotor impairment.<sup>81,91-94</sup> Furthermore, few studies have specifically examined the efficacy and safety of these antidepressants in the treatment of insomnia, and clinical trials that have examined the effect of antidepressants on insomnia have focused specifically on depression-associated insomnia.<sup>94,95</sup>

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## FUTURE DEVELOPMENTS IN INSOMNIA TREATMENTS

There is an evolving conceptual framework that views insomnia as a chronic disorder. Within this framework, therapeutic considerations would include the different types of insomnia and the potential need for their long-term treatment. The association of insomnia with increased risk of

**Table.** Psychiatric and Medical Comorbidities of Insomnia and Their Associated Direct Medical Costs

Disease	Incidence or Prevalence of Disease	Direct Costs of Disease	Comorbidity With Insomnia
Insomnia	27.1% Of US adults aged >18 y <sup>16</sup>	\$15.9 Billion/y total (1990), <sup>57</sup> \$13.9 billion/y total (1995), <sup>58</sup> \$924 and \$1143 per patient per 6 mo for those aged 16-64 and ≥65 y, respectively (2003) <sup>55</sup>	—
<b>Psychiatric Comorbidities</b>			
Anxiety disorders	12-mo Prevalence of any anxiety disorder among US adults aged ≥18 y is 18.1% <sup>100</sup>	\$2536 PPPY (1998), <sup>101</sup> \$1393 PPPY (1990), <sup>102a</sup> approximately \$11.6 billion/y total (1990) <sup>103</sup>	Anxiety disorders precede insomnia in 73% of cases, <sup>104</sup> risk of anxiety is increased ≥17-fold in patients with insomnia, <sup>105</sup> approximately 25% of insomnia patients have comorbid anxiety disorder <sup>106</sup>
Depression	12-mo Prevalence of MDD among US adults aged ≥18 y is 6.7% <sup>100</sup>	\$3132 PPPY (1998), <sup>101</sup> \$1498 PPPY (1994), <sup>107</sup> \$4246 PPPY, <sup>108</sup> \$7494 PPPY (2004) <sup>109</sup>	Risk of depression is increased approximately 10-fold in patients with insomnia, <sup>105</sup> 40%-60% of patients with insomnia have features of depression, <sup>105</sup> insomnia precedes depression in 69% of patients <sup>104</sup>
Bipolar disorder	12-mo Prevalence among US adults aged ≥18 y is 2.6% <sup>100</sup>	\$7663 PPPY (1997), <sup>110</sup> \$10,402 PPPY (2004) <sup>109</sup>	≤100% Of patients with bipolar disorder experience insomnia <sup>111</sup>
Alcohol abuse and dependence	12-mo Prevalences of alcohol abuse and dependence among US adults aged ≥18 y are 3.1% and 1.3%, respectively <sup>100</sup>	\$175.9 Billion/y total for alcohol abuse (1995) <sup>112b</sup>	Patients with insomnia caused by worry are twice as likely to develop alcohol-related problems, <sup>113</sup> insomnia occurs in 36%-72% of patients with alcoholism <sup>37</sup>
<b>Medical Comorbidities</b>			
Diabetes	1.6 Million new cases of diabetes in the United States in 2007 among people aged >20 y <sup>114</sup>	\$116 Billion/y total (2007) <sup>114</sup> ; \$90 billion/y total <sup>115</sup> ; \$53,000 per person aged >10 y <sup>116</sup> ; \$1700 and \$2100 PPPY for men and women, respectively <sup>117c</sup> ; \$689 PPPY <sup>118</sup> ; \$6631 PPPY (2000-2006) <sup>119</sup>	Shorter sleep time is associated with an increased risk of diabetes, <sup>45</sup> 50% of adults with diabetes have insomnia <sup>44</sup>
Obesity	34% Of US adults aged >20 y are obese (2005-2006) <sup>120</sup>	\$90 Billion/y total <sup>115</sup>	Decreased total sleep time increases the likelihood of obesity, <sup>121</sup> sleep duration <5 h is associated with 3.7-fold and 2.3-fold increased likelihoods of obesity in older men and women, respectively <sup>122</sup>
Hypertension	1 In 3 US adults has hypertension <sup>123</sup>	\$1803 PPPY, <sup>118</sup> \$6226 PPPY (2000-2006) <sup>119</sup>	Sleep restriction is associated with an increased risk of hypertension <sup>124</sup>
COPD	11.2 Million US adults were reported to have COPD in 2002 <sup>125</sup>	\$6300 PPPY (2004), <sup>126</sup> \$5204 PPPY (2004), <sup>127</sup> \$4932 PPPY (2000), <sup>128</sup> \$21.8 billion/y total (2005) <sup>129</sup>	>50% Of patients with COPD have sleep problems, <sup>43</sup> sleep loss may negatively affect pulmonary function in patients with COPD <sup>130</sup>
Asthma	7.3% Of adults and 9.4% of children in the United States have asthma <sup>131</sup>	\$3745 PPPY (2004), <sup>132</sup> \$46740 PPPY (1993) <sup>133</sup>	Sleep-maintenance insomnia and early morning awakening are reported by 44% and 51% of adults with asthma, respectively <sup>134</sup> ; >40% of children with asthma have nighttime awakenings <sup>135</sup> ; nighttime awakening in children with asthma significantly affects school attendance and performance, as well as work attendance by parents <sup>135</sup>
<p>BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; MDD, major depressive disorder; PPPY, per patient per year.</p> <p><sup>a</sup>Includes nonpsychiatric and psychiatric medical costs, mortality costs, and prescription pharmaceutical costs, and excludes indirect workplace costs.</p> <p><sup>b</sup>In addition to footnote a, includes indirect costs.</p> <p><sup>c</sup>Median costs for subjects of white race/ethnicity with diet-controlled type 2 diabetes mellitus, BMI of 30, and no microvascular, neuropathic, or cardiovascular complications. A 10-point increase in BMI, treatment with oral antidiabetic or antihypertensive agents, diabetic kidney disease, cerebrovascular disease, and peripheral vascular disease were each associated with 10% to 30% increases in cost.</p>			

disease and with potential long-term health problems highlights the importance of using effective treatment modalities. This includes effectively treating the often underappreciated acute health risks associated with short-term insomnia, such as distress, anxiety, and the development of long-term insomnia.<sup>96</sup> Treating short-term insomnia can alleviate acute health risks and has the potential to decrease the development of chronic insomnia.<sup>97</sup> As such, early diagnosis and treatment action may benefit patients with insomnia and may improve individual and societal safety in the long term.<sup>98</sup> Furthermore, studies<sup>73,74,99,100</sup> have shown that treating insomnia can reduce direct healthcare costs for patients, as well as for healthcare plans.

Novel therapies are being developed to specifically treat different types of insomnia such as targeting serotonin receptor subtypes, with the aim of avoiding complicating adverse effects, while promoting SWS.<sup>101</sup> Of particular interest have been the highly homologous 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors. Antagonism of these receptors by the serotonin antagonist ritanserin has been shown to improve deep sleep and sleep quality in poor sleepers.<sup>102-104</sup> Antagonists of 5-HT<sub>2a</sub> such as eplivanserin and pruvanserin are being investigated as therapeutics for sleep-maintenance insomnia.<sup>101</sup>

Other possible promoters of SWS are extrasynaptic GABA agonists such as gaboxadol, an investigated drug that was not approved,<sup>105</sup> that function selectively via the extrasynaptic GABA<sub>A</sub> receptors.<sup>106</sup> Prospective inducers of sleep initiation include orexin receptor antagonists, or orexinergics, which aim to inhibit the wake-promoting effects of endogenous orexins.<sup>107</sup>

## CONCLUSIONS

Extensive data clearly demonstrate that insomnia is a significant clinical problem resulting in major societal costs. Insomnia has been shown to negatively affect workplace productivity and health-related QoL and increase healthcare utilization and costs.

The association of insomnia with increased consumption of healthcare resources has significant implications for managed care organizations and healthcare providers. Effective treatment of insomnia may reduce the indirect costs of treating comorbidities (summarized in the **Table**). Early diagnosis and treatment of insomnia may significantly decrease the US healthcare dollars spent on insomnia, with further benefits from improved daytime functioning and from increased productivity.

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