INTRODUCTION

Epidemiology of insomnia in adolescents

Insomnia symptoms are prevalent in both adults and children [1-4]. Female sex [4], low socioeconomic status [2], stressful life events [2], and poor general and mental health [5] are commonly identified risk factors. In particular, female sex is a consistent risk factor for insomnia in adult and elderly populations in terms of the higher prevalence, more persistent natural course [6], and more serious health-related repercussions [7]. For example, stronger impacts of insomnia symptoms on pain perception [8], increased cortisol awakening response [9], and resistant hypertension [10] were found in adult females when compared with adult males.

Interestingly, most studies did not find any sex differences in insomnia in children [1,5,6]. Thus, puberty has been postulated as a critical stage for the development of insomnia and the emergence of the sex differences in insomnia [7-10]. Indeed, puberty is accompanied by a series of factors that may contribute to the development of insomnia, such as decreased homeostatic sleep drive and delayed circadian phase leading to a mismatch with social activity [11]. Several studies have explored the timing of sex differences in insomnia [8-10]. Johnson et al. [9] found that the onset of menses was a critical phase with an increased risk of developing insomnia in adolescent girls but pubertal maturation was not associated with increased prevalence of insomnia in adolescent boys. By using a large-scale school-based survey, we found that the prevalence of insomnia symptoms progressively increased from 3.4% to 12.2% in girls (3.6-fold) and from 4.3% to 9.1% in boys (2.1-fold) [12]. There was a significant interaction between sex and puberty in the prevalence of insomnia symptoms (p<0.001) with the emergence of female preponderance at Tanner stage 4 even after controlling for age, family income, and school start time [12].

Taken together, previous studies have almost unanimously sug-
gested that pubertal maturation plays a critical role in the onset of insomnia symptoms and the emergence of sex differences in insomnia. In this regard, this review paper will focus on insomnia in adolescents.

**Epidemiology of depression in adolescents and its relationship with insomnia**

Unipolar depression is one of the most common disorders in adolescents. About 20% of adolescents have a diagnosable mental disorder, with depression being the single most common type [13]. In addition, depression increases in adolescence and occurs at double the rate in females than males, which is similar to the prevalence of insomnia in adolescents [14]. In adolescents with major depression, insomnia is the most common sleep disturbance with a rate of 72.7%. Those adolescents who reported insomnia symptoms were also accompanied with more severe depression [15]. Insomnia is not just a symptom or by-product of depression, but in many cases insomnia contributes to depression onset and/or maintenance, complicates and attenuates the effectiveness of depression treatment. In addition, insomnia is the most common residual symptom in remitted depression [16].

Recently studies also suggest that insomnia is associated with an increased risk of depression in adolescents. Several studies had proven that insomnia is a risk factor for depression and can predict the development of later depression in adolescents [17,18]. It has been argued that insomnia in early adolescence leads to the development of later depression by altering corticolimbic circuitry possibly via the disruptive effect of hyperarousal and insufficient sleep [19], which in turn affect adolescents’ emotional regulation and cognitive functioning. Others have suggested that insomnia in adolescents may reinforce ruminative thinking styles, perpetuating further insomnia symptoms, and that these processes could develop into depression over time [20]. Despite the high incidence of insomnia and the risk factor for the onset and maintenance of depression in adolescents, adolescent insomnia has received less attention in the literature [21].

On the other hand, adolescent insomnia and depression share many common features, both at the symptom level and at the disease level. There is an emerging sex difference in the prevalence of insomnia and depression in adolescents. In part, the sexual dimorphism in the prevalence of insomnia in adolescence could relate to the higher prevalence of depression in females, which also emerges after puberty [12]. Several social and biological changes occur during puberty that are sexually differentiated, such as higher stress level and greater stress reactivity in females [12] and differential changes in sex steroids associated with increased neuroendocrine sensitivity [12], which may increase risk for both depression and insomnia. Our previous study [12] has explored the associations of insomnia symptoms with lifestyle, and emotional and behavioral problems in females and males. While some relationships were common in both boys and girls, interactions with sex were also found. For example, insomnia symptoms were associated with greater consumption of energy drinks and alcohol in boys only where insomnia symptoms were associated with self-reported poorer emotional and behavioral wellbeing in girls only. The American Psychological Association in the 2014 nationwide “Stress in America” survey clearly indicated stress as a major concern in adolescents: perceived stress may have a detrimental effect on health by affecting mood, eating behaviors, and sleep [22].

It is common for adolescents to have and use electronic devices in their bedroom. Specifically in adolescence, the progressive delay in circadian phase results in later bedtimes leaving adolescents more time to perform various activities until late at night. One recent study from our group has also found that long time smart phone use is associated with the incidences of most sleep disturbances and mental distress, including depressive symptoms while discontinuation of long-time mobile phone use seems to alleviate these problems in youths [23]. Electronic media use at bedtime may affect both sleep and mood via the melatonin-suppression effect of bright screen light [24]. According to the comorbid and bidirectional relationship between insomnia and depression in adolescents, it is hypothesized that treating insomnia can improve depressive symptoms in adolescents with both problems. The hypothesis is based on the following reasons. First, insomnia contributes to increasing depression risk in adolescents. Adolescents who complained insomnia symptoms were more likely to report depression [odds ratio (OR)=22.7] [25] and insomnia significantly predicted future depression (hazard rate=3.8) [26]. It has been found that baseline insomnia symptoms increased the risk of anxiety and depression one year later among 2,787 adolescents in China [27]. Second, insomnia predicts the treatment outcomes of depression in adolescents. In depressed adolescents, low sleep efficiency and difficult falling sleep predicted depression recurrence following treatment [28]. Third, residual insomnia is a major component of partially remitted depression. In the Treatment of Adolescent with Depression Study (TADS), residual insomnia was the most common symptoms among depressed adolescents who had incompletely-recovered but responded to treatment [29]. This suggests that insomnia may be an important therapeutic target for treating and preventing recurrent depression in adolescents. Based on the evidences listed above, it is suggested that effective treating insomnia can improve the prognosis of depression or prevent the onset of depression in adolescents.

**Insomnia and depressive symptoms: shares the common characteristics**

Adolescents’ depression treatments include psychological and pharmacological therapies, but the treatments are inadequacy, even in the TADS, the largest, well controlled clinical trial of adolescents’ depression [30]. Many studies have proven that adolescents and their parents favor psychotherapy over pharmacotherapy [31], and cognitive behavioral therapy for insomnia (CBT-I) appears to be superior to hypnotics in the long run [32]. Meta-analysis has already supported that treating insomnia via CBT-I in both adults and elderly with depression has a positive effect on depressive symptoms [33,34]. To date, the literature has not been sys-
TREAT THE DEPRESSION VIA CBT-I IN ADOLESCENTS

We have conducted a comprehensive search of literature in PubMed, PsycINFO and Cochrane Controlled Register of Trial (CENTRAL). We searched for a combination of CBT-I or cognitive behavioral therapy for insomnia with depressive* and adolescents* in titles and with abstracts of using controlled vocabulary and text words in academic journal publications up to 23rd October, 2018. There are 87, 4 and 28 articles identified through searching PubMed, PsycINFO and CENTRAL respectively based on the theme that CBT-I affects or influences on depressive symptoms in adolescents who experience insomnia symptoms. Only four articles are included in our qualitative analysis and the characteristics of the included studies list in Table 1. The participants of these 4 studies were recruited from the community and/or hospital. Across studies, participants were between the ages of 11 and 20 years old, and most of the participants were female [35-38]. Two studies were randomized controlled trial [35,38]; the other two were pre- and post-treatments design [36,37]. The CBT-I interventions ranged from 4 to 10 sessions, and the core intervention technique consisted of an age-appropriate modification of sleep restriction, stimulus control, sleep-focused cognitive therapy and sleep hygiene education. The sample sizes included into analysis were 41, 40, 16 and 116, respectively. All studies reported significant improvement in both insomnia symptoms and depressive symptoms [35-38]. Two studies reported effect size using Cohen’s d [36,38] and one using OR in depressive symptoms [35]. One study did not list the effect size and used pair wise comparisons to show that Quick Inventory of Depressive Symptoms (QIDS) scores decreased by a mean of 3.7 points from session 1 to session 5 (SE=1.03, df=15.1, p=0.027) [37]. Based on the limited evidences represented above, we modestly suggest that CBT-I have a positive effect on decreasing depressive symptoms in adolescents who experience insomnia symptoms.

THE MECHANISM OF CBT-I EFFECT BEYOND INSOMNIA

The mechanism of CBT-I in treating depression may explain through circadian rhythm, Hypothalamic–pituitary–adrenal axis (HPA), and neural processing.

**Regularizing circadian rhythm**

Circadian rhythm is the basis of all physiological processes including mood and brain function regulation. There is growing evidence that emotions are closely linked to circadian rhythm disorders [39]. Proposed mechanism of action of CBT-I comes from the “phase-shift” model of depression. This theory posits that depres-

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**Table 1. Studies investigating CBT-I in depressive adolescents with insomnia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Age, y</th>
<th>Gender (F, %)</th>
<th>Randomization</th>
<th>Intervention technique (comparison group)</th>
<th>Group size, n</th>
<th>Effect size: depression symptoms-scale or questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke et al. [35]</td>
<td>Hospital and community</td>
<td>12–20</td>
<td>63</td>
<td>Yes</td>
<td>CBT-I/4 sessions (SH+CBT-D)</td>
<td>Intervention=21</td>
<td>OR: 0.98 (0.87, 1.11), CDRS-R</td>
</tr>
<tr>
<td>Conroy et al. [36]</td>
<td>Hospital</td>
<td>11–18</td>
<td>75</td>
<td>No</td>
<td>CBT-I 4 sessions</td>
<td>40</td>
<td>Cohen's d: 0.30 (0.04, 0.55), PROMIS</td>
</tr>
<tr>
<td>Palermo et al. [37]</td>
<td>Hospital and community</td>
<td>About 12–19</td>
<td>75</td>
<td>No</td>
<td>CBT-I 5 sessions</td>
<td>16</td>
<td>F=5.3, p=0.011, QIDS</td>
</tr>
<tr>
<td>de Bruin et al. [38]</td>
<td>Community</td>
<td>12–19</td>
<td>87</td>
<td>Yes</td>
<td>CBT-I 7 sessions/waitlist</td>
<td></td>
<td>Cohen's d: YSR IT-CBTI=1.07, YSR GT-CBTI=1.09</td>
</tr>
</tbody>
</table>

By increasing slow wave sleep, the therapeutic effect of the behavior sleep continuity disturbances and slow wave sleep deficits [50,51]. Neurobiological correlates such as sleep EEG profiles with regards to the neural systems level [49]. Depression and insomnia share circuits involved in sleep regulation interact in bidirectional ways. Individuals shows that circuits involved in emotion regulation and the high level of CAR can predict the onset and recurrence of depressive episode [46,47]. Recently, we found that patients with insomnia also have hypercortisol arousal upon awakening [48]. In addition, it is also found that the cortisol and corticotrophin-releasing hormone levels of patients with primary insomnia were significantly higher than those of normal controls [42]. These results suggest that HPA axis dysfunction, including high cortisol arousal response, may be a common pathway of cause-and-effect relationship between insomnia disorder and major depression. In this regard, the mechanisms that CBT-I improves depressive symptoms seems to be via normalizing HPA axis activity in adolescents with both problems. However, further studies, which directly examine this assumption, are definitely needed.

Regularizing neural processing
Convergent evidences from neuroimaging research with healthy individuals shows that circuits involved in emotion regulation and circuits involved in sleep regulation interact in bidirectional ways at the neural systems level [49]. Depression and insomnia share neurobiological correlates such as sleep EEG profiles with regards to sleep continuity disturbances and slow wave sleep deficits [50,51]. By increasing slow wave sleep, the therapeutic effect of the behavioral components of CBT-I (sleep restriction and stimulus control) appears to result in an increase in homeostatic sleep drive [50]. At the behavioral level, one of the components of behavioral interventions, sleep restriction, may lead to increased time awake during the day to participate in planned pleasurable activities and improvement of depression through behavioral activation [51]. Therefore, CBT-I may regularize the central neural processing to improve sleep quality and decrease depressive symptoms.

Reducing inflammation
Another possible mechanism is related to inflammatory bio-

markers. Sleep disturbance is associated with increased levels of inflammatory markers such as interleukin-1 beta and interleukin-6 in individuals with depression [52]. Treatment of insomnia using behavioral interventions leads to reductions in inflammatory markers [53].

**USING CBT-I TO TREAT DEPRESSION OR PREVENT DEPRESSION EPISODE IN ADOLESCENTS**

According to the comorbid and bidirectional relationship in depressive adolescents who experiences insomnia symptoms, and the possible mechanism of CBT-I treating insomnia to decrease depressive symptoms, we recommend that using CBT-I to treat the depressive adolescents who experience insomnia for the insufficient treatment on depression right now. This recommendation is in accordance with DSM-5 guidelines [54] in which treating insomnia is considered as a target for intervention itself.

Additional research should also attempt to elucidate the mechanism of action by which treating insomnia disorder leads to improvement in depression outcomes. This could include measuring inflammatory bio-markers, actigraphy, and measures of neurophysiology such as slow wave activity during sleep. This translational research could help further advance our understanding of the diseases themselves and focus on personalized approaches to treatment.

**CONCLUSION**
In summary, the current state of evidences suggest that in those with both insomnia disorder and, major depressive disorder, in addition to addressing depression, the treatment of insomnia should be an essential component in the overall treatment plan in order to maximize the likelihood of optimal clinical outcomes.

**Conflicts of Interest**
The authors have no potential conflicts of interest to disclose.

**Author Contributions**

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