

# Excessive daytime sleepiness in adolescents: current treatment strategies

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## ABSTRACT

The complaints of excessive daytime sleepiness are very common among adolescents. In addition, in this particular subpopulation, the presence of excessive daytime sleepiness is associated with negative impact on school performances, interpersonal difficulties (school friends or family), extracurricular activities, health and driving. In adolescents with complaints of excessive daytime sleepiness, it is important to perform a complete clinical assessment including systematic clinical interview, physical examination, sleep diaries, use of specific questionnaires and possible confirmatory tests. In adolescents, the main causes of excessive daytime sleepiness are sleep deprivation, inadequate sleep hygiene, insomnia disorders, circadian rhythm disorders, chronic somatic pathologies, psychiatric disorders, movement disorders related to sleep, respiratory disorders related to sleep, parasomnias, hypersomnia disorders and use of drugs or medications. Given the multiple aetiologies of excessive daytime sleepiness in adolescents, the implementation of targeted therapeutic strategies is essential in order to allow optimal management of this symptom and better prevention of its negative consequences. The aim of this review is therefore to provide health care professionals caring for adolescents with excessive daytime sleepiness complaints the currently recommended therapeutic strategies for the main aetiologies of excessive daytime sleepiness in this particular subpopulation.

**Keywords:** Adolescent; Sleepiness; Therapeutic Approaches; Sleep.

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Received: January 8, 2020;  
Accepted: February 20, 2020.

DOI: 10.5935/1984-0063.20190143

## INTRODUCTION

Excessive daytime sleepiness (EDS) may be defined as a tendency to fall asleep unintentionally during the day<sup>1</sup>. Although there may be an overlap, EDS must be distinguished from fatigue secondary to some somatic or psychiatric pathologies<sup>2</sup>. Among adolescents, the prevalence of EDS may reach 42%<sup>3</sup>, which seems to be higher than in the general population (19% to 27%)<sup>4,5,6</sup>. In addition, in this specific subpopulation, the presence of EDS is associated with a negative impact on school performance (learning difficulties, low school achievement, high rates of absenteeism and low school enjoyment)<sup>7,8,9</sup>. An increased risk of domestic or car accidents<sup>10</sup>, a decrease in extracurricular activities<sup>10</sup> and negative consequences in terms of somatic health (chronic low back pain, headache, abdominal pain, obesity, insulin resistance and blood pressure dysregulation), and psychic functioning (interpersonal difficulties [school friends or family], risk behaviours, aggressive behaviours, substance abuse and depression or anxiety disorders)<sup>11</sup>. Thus, in adolescents, EDS is a major public health problem.

Adolescence is a particular period of development characterized by significant physiological changes that may affect daytime functioning and sleep<sup>12</sup>. Indeed, during adolescence, pubertal maturation induces changes in sleep architecture (decrease in delta sleep)<sup>13,14</sup>, a decrease in vigilance during the beginning of the afternoon<sup>13</sup>, an evolution from the morning typology to the evening typology<sup>15</sup>, a tendency to fall asleep later<sup>16</sup> and an irregular sleep-wake rhythm (sleep deprivation during school periods and sleep recovery during weekends and holidays)<sup>17,18</sup>. The main consequences of these various physiological changes induced by pubertal maturation may be the development of physiological hypersomnia and delayed sleep phase favouring the occurrence of physiological EDS in adolescents<sup>19,20</sup>. However, in some cases, the presence of EDS in adolescents cannot be explained solely by these physiological changes induced by pubertal maturation. Indeed, in this particular subpopulation, EDS may also be induced by some pathologies or conditions (such as insomnia disorders, circadian rhythm disorders, chronic somatic pathologies, psychiatric disorders, movement disorders related to sleep, respiratory disorders related to sleep, parasomnias, hypersomnia disorders and use of drugs or medications)<sup>21</sup>. In order to differentiate this physiological or pathological EDS in adolescents, it is important to perform a complete clinical assessment including systematic clinical interview, physical examination, sleep diaries, use of specific questionnaires and possible confirmatory tests<sup>22</sup>. Finally, given these multiple aetiologies of EDS in adolescents, the implementation of targeted therapeutic strategies is essential in order to allow optimal management of this symptom and better prevention of its negative consequences<sup>23</sup>.

## OBJECTIVE

The aim of this review is therefore to provide health care professionals caring for adolescents with EDS complaints the currently recommended therapeutic strategies for the main aetiologies of EDS in this particular subpopulation.

## MATERIAL AND METHODS

### 1. Differential diagnosis of excessive daytime sleepiness in adolescents

#### a.) Assessment of excessive daytime sleepiness in adolescents

The main steps for assessing EDS (systematic clinical interview, physical examination, sleep diaries, specific questionnaires and possible confirmatory tests) in adolescents are summarized in Table 1<sup>24-30</sup>.

#### b.) The main causes of excessive daytime sleepiness in adolescents

In adolescents, the main causes of EDS may be divided into 3 categories (EDS with insufficient sleep, EDS with fragmented sleep and EDS with increased sleep need) and are available in Table 2<sup>31</sup>.

#### c.) Diagnostic algorithm of excessive daytime sleepiness in adolescents

In order to help healthcare professionals caring for adolescents with EDS complaints, an updated diagnostic algorithm based on the initial recommendations of the American Academy of Paediatrics is available in Figure 1<sup>32</sup>.

### 2. Therapeutic strategies for excessive daytime sleepiness in adolescents

#### a.) Excessive daytime sleepiness with insufficient sleep (Table 3)

- Sleep deprivation and inadequate sleep hygiene

In adolescents, the main therapeutic strategies applied in case of EDS associated with sleep deprivation and inadequate sleep hygiene may be the establishment of a bedtime determined by the parents<sup>33</sup>, a better management of the evening exposure to multimedia screens<sup>34</sup>, the management of comorbid pathologies (insomnia disorders, delayed sleep phase syndrome, substance abuse and depression or anxiety disorders)<sup>35</sup>, the use of individual or collective sleep educational programs (psychoeducation, cognitive-behavioural therapeutic interventions, family therapy, motivational interviews)<sup>36-39</sup> and the introduction of classes at a later start time (according to possible adaptations of school hours in the different national education systems)<sup>40</sup>. These different therapeutic strategies may be used alone or in combination to allow an increase in total sleep time in adolescents<sup>41</sup>.

- Insomnia disorders

The two main therapeutic strategies available are cognitive behavioural therapies (CBT) for insomnia and pharmacological treatments, which may be used alone or in combination<sup>42,43</sup>. Alongside these targeted therapeutic strategies for insomnia, it is

**Table 1.** The main steps for assessing excessive daytime sleepiness in adolescents

Steps	Key points
Systematic clinical interview	<p>Assessment of usual sleep schedules for both the week and the weekend (sleep latency, nocturnal awakenings, bedtime, wake time and sleep duration)</p> <p>Systematic research for symptoms suggestive of sleep pathologies and inadequate sleep habits</p> <p>Interview of a family member to highlight possible symptoms or behaviours during sleep (snoring, sleep apnoea, parasomnias and abnormal movements)</p> <p>Assessment of daytime functioning (difficulty waking up, excessive daytime sleepiness, fatigue, mood, behaviour, school performance and napping)</p> <p>Research for personal or family antecedents of somatic, psychiatric and sleep pathologies</p> <p>Systematic collection of medications and substance consumptions</p> <p>Identification of life events that may influence sleep (such as divorce of parents, death of a family member or friend, family move and social problems)</p> <p>Differential diagnosis between EDS and fatigue secondary to some somatic or psychiatric conditions</p>
Physical examination	<p>Assessment of the body mass index to highlight the possible presence of overweight or obesity</p> <p>Complete otorhinolaryngological examination to look for an obstruction of the upper airways (micrognathia, midfacial hypoplasia, tonsillar hypertrophy, enlarged tongue base, “adenoid face”, deviated nasal septum, swollen inferior turbinates, high arched palate and mouth breathing)</p>
Sleep diaries	<p>Sleep diaries (completed over a minimum period of 2 weeks) may be used to assess regularity of sleep schedules, nocturnal awakenings/naps (frequency, distribution and duration) and variability between the week and the weekend as well as between the school periods and the holidays</p>
Specific questionnaires	<p>Subjective investigation of sleep (such as the School Sleep Habits Survey, the Paediatric Sleep Questionnaire and the Childhood Sleep Habits Questionnaire) and EDS (such as the Paediatric Daytime Sleepiness Scale and the Cleveland Adolescent Sleepiness Questionnaire)</p>
Confirmatory tests	<p>Actigraphy may be used for the diagnosis and therapeutic follow-up of sleep deprivation/fragmentation related to inadequate sleep hygiene, insomnia disorders and circadian rhythm disorders. However, since it is insufficiently accurate, actigraphy is not a suitable method for the detection of PLMs and fails to reliably identify breathing abnormalities (such as sleep apnoea) in adolescents.</p> <p>Multiple sleep latency tests are essential for the objective assessment of EDS and the diagnosis of central hypersomnia</p> <p>If in doubt about the presence of cataplexies, HLA typing and determination of cerebrospinal fluid hypocretin-1 levels may be used to complement the multiple sleep latency test for diagnosis of type 1 narcolepsy</p> <p>Given its lowest cost, polygraphy may be an alternative to polysomnography (gold standard) for the first-line screening of OSAS in some indications (absence of behavioural morbidity, high OSAS clinical presumption and absence of other sleep disorders)</p> <p>Polysomnography should be used to diagnose central sleep apnoea syndrome, upper airway resistance syndrome, obstructive hypoventilation, PLMs and parasomnias</p> <p>For the diagnosis of nocturnal epileptic seizures, a 24-hour EEG (16-32 channels) must be performed in addition to a full video-EEG-polysomnography</p> <p>Laboratory tests may be performed in case of suspicion of RLS and PLMs (iron status) or in case of suspicion of OSAS in adolescents with macroglossia (thyroid test)</p>

EDS = Excessive daytime sleepiness, PLMs = Periodic limb movements during sleep, OSAS = obstructive sleep apnoea syndrome, RLS = restless leg syndrome.

**Table 2.** Main causes of excessive daytime sleepiness in adolescents

Excessive daytime sleepiness with insufficient sleep	Excessive daytime sleepiness with fragmented sleep	Excessive daytime sleepiness with increased sleep need
<ul style="list-style-type: none"> <li>• Sleep deprivation</li> <li>• Inadequate sleep hygiene</li> <li>• Insomnia disorders (primary or secondary to somatic or psychiatric pathologies)</li> <li>• Circadian rhythm disorders (delayed sleep phase syndrome, non-24-hour sleep-wake schedule and sleep entrainment difficulties)</li> <li>• Use of stimulant medications/drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory disorders related to sleep (obstructive sleep apnea syndrome, upper airway respiratory syndrome, hypoventilation, central sleep apnoea syndrome)</li> <li>• Movement disorders related to sleep (periodic limb movements during sleep, restless leg syndrome, bruxism, head banging and body rocking)</li> <li>• Parasomnias (nocturnal terrors, confusional arousals and sleepwalking)</li> <li>• Somatic pathologies (asthma, eczema, cystic fibrosis, gastroesophageal reflux and epilepsy)</li> <li>• Environmental causes (noise, light and cosleeping)</li> </ul>	<ul style="list-style-type: none"> <li>• Neurological disorders (head trauma and increased intracranial pressure)</li> <li>• Hypersomnia secondary to medical disorders (infectious or metabolic diseases)</li> <li>• Use of sedative medications/drugs</li> <li>• Recurrent hypersomnia (depression, Kleine-Levin syndrome and menstrual-associated)</li> <li>• Central hypersomnia (idiopathic hypersomnia and primary or secondary narcolepsy)</li> </ul>

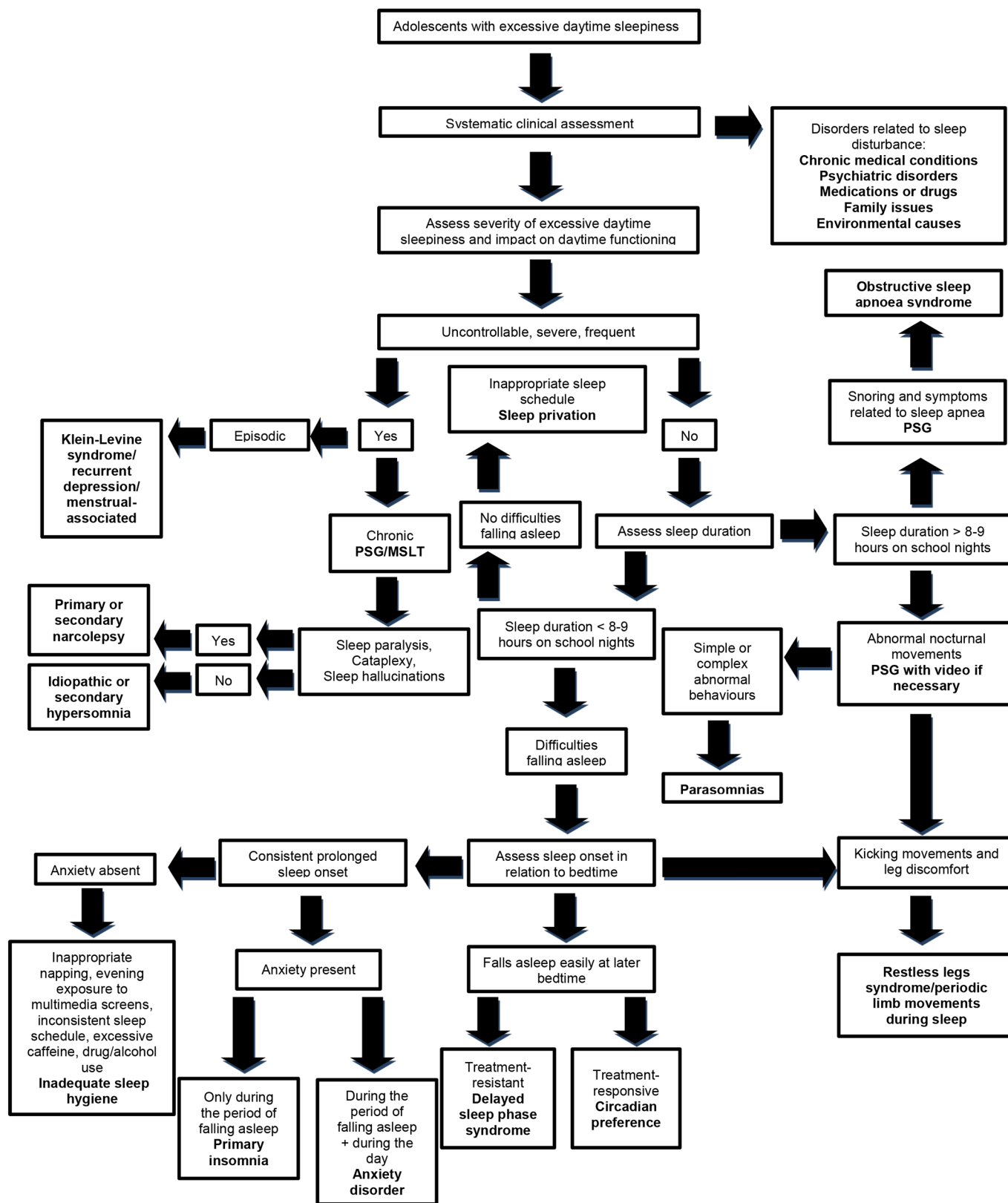


Figure 1. Diagnostic algorithm for excessive daytime sleepiness in adolescents. PSG = Polysomnography, MSLT = Multiple sleep latency test.

**Table 3.** Therapeutic strategies for excessive daytime sleepiness with insufficient sleep in adolescents.

Causes		Therapeutic strategies	Approved interventions for adolescents
Sleep deprivation and inadequate sleep hygiene	Individual measures	<ul style="list-style-type: none"> <li>• Bedtime determined by the parents</li> <li>• Reduction of evening exposure to multimedia screens</li> <li>• Management of somatic or psychiatric comorbidities</li> </ul>	Yes
	Family measures	<ul style="list-style-type: none"> <li>• Family therapy if family issues</li> </ul>	Yes
	Collective measures	<ul style="list-style-type: none"> <li>• Classes at a later start time</li> </ul>	Yes
	Individual or collective measures	<ul style="list-style-type: none"> <li>• Sleep educational programs</li> </ul>	Yes
Insomnia disorders	First-line treatment	<ul style="list-style-type: none"> <li>• Cognitive behavioural therapies for insomnia</li> </ul>	Yes
	Second-line treatment	<ul style="list-style-type: none"> <li>• Pharmacological treatments if failure or contraindication to cognitive behavioural therapies for insomnia</li> </ul>	No (off-label prescription)
	Complementary treatments	<ul style="list-style-type: none"> <li>• Management of somatic or psychiatric comorbidities</li> <li>• Adequate sleep hygiene</li> </ul>	Yes
Delayed sleep phase disorder	First-line treatment	<ul style="list-style-type: none"> <li>• Morning bright light therapy combined to evening melatonin</li> </ul>	No (off-label prescription for melatonin)
	Alternative treatment	<ul style="list-style-type: none"> <li>• Chronotherapy</li> </ul>	Yes
	Complementary treatments	<ul style="list-style-type: none"> <li>• Management of somatic or psychiatric comorbidities</li> <li>• Adequate sleep hygiene</li> </ul>	Yes
Use of stimulant medications		<ul style="list-style-type: none"> <li>• Adjustment of the dosage if necessary</li> </ul>	Yes
Misuse of stimulant medications/drugs	Individual measures	<ul style="list-style-type: none"> <li>• Cognitive-behavioural therapy and/or motivational interviewing</li> <li>• Management of psychiatric co-morbidities</li> </ul>	Yes
	Family measures	<ul style="list-style-type: none"> <li>• Family therapy</li> </ul>	Yes

also important to manage the somatic or psychiatric pathologies comorbid with insomnia disorders in order to enable optimal management of adolescents with insomnia disorders<sup>44</sup>.

### Cognitive behavioural therapies for insomnia

The CBT for insomnia are brief therapies (4 to 6 sessions) performed individually or collectively by trained psychologists or physicians<sup>45,46</sup>. These CBT for insomnia includes a variety of methods (stimulus control [adopt regular schedules, consolidate sleep to night-time and improve bed-sleep association], arousal reduction [quieting pre-bedtime activities and relaxation-imagery], cognitive therapy, improving sleep hygiene practices [increase behaviours and environmental conditions that promote improved sleep quality] and sleep restriction [temporary restriction of time spent in bed in order to make it more optimally matched to sleep duration of patient assessed by sleep diaries or actigraphy, which has the effect of improving the sleep efficiency]), that may be used alone or in combination<sup>47</sup>.

Currently, CBT for insomnia are recommended as first-line treatment of insomnia disorders in adults<sup>48,49</sup>. Regarding adolescents, several studies have also demonstrated the effectiveness of these therapies in the management of insomnia disorders, which suggests that CBT for insomnia may be a first-line treatment in this particular subpopulation<sup>50,51</sup>. However, in adolescents, one of the main factors limiting the effectiveness of CBT for insomnia is compliance with the strict protocols associated with this type of management<sup>35,52</sup>.

### Pharmacological treatments

#### General recommendations

Before any prescription for pharmacological treatments in adolescents, it is important to take some precautions. Indeed, since there is no ideal hypnotic treatment for adolescents, the treatment must be selected according to the final diagnosis performed following a complete clinical assessment of the symptoms and a consideration of all possible differential diagnoses. Generally, pharmacological treatments for insomnia disorders should not be used as first-line or alone. Indeed, they must be short-term use in combination with non-pharmacological treatments after excluding substance abuse, inadequate sleep hygiene, use of self-initiated non-prescription sleep medications and presence of pregnancy.

In adolescents, the main indications of pharmacological treatments for insomnia disorders are the failure of non-pharmacological treatments (such as CBT for insomnia), the presence of medical illness with associated issues (such as pain control, concomitant medications and hospitalization), the adjunction with sleep hygiene/chronotherapy in circadian rhythm disturbances, the presence of an acute stressor (such as death in the family) and travels (such as prolonged plane rides with accompanying time change).

Finally, after setting clear and realistic goals with the adolescent and his family, the efficacy and possible occurrence of side effects should be regularly monitored when prescribing hypnotic therapy<sup>53</sup>.

## Medications

In literature, there are few studies investigating the efficacy and long-term effects of pharmacological treatments of insomnia disorders in adolescents<sup>54</sup>. Moreover, in adolescents with insomnia disorders, all pharmacological treatments are used off-label since none of these treatments are currently approved for this indication in this particular subpopulation<sup>55</sup>. However, despite this absence of approval due to the lack of empirical evidence, several pharmacological treatments are frequently used in adolescents with insomnia disorders<sup>56</sup>.

Finally, the American Academy of Sleep Medicine has published consensus statements for the appropriate use of these pharmacological treatments in adolescents<sup>53,55,57</sup>. Among these used medications for the pharmacological treatment of insomnia disorders in adolescents (Table 4)<sup>58-62</sup>, antihistamines seem to be a first-line treatment given their good acceptability in this particular population.

## Alternative medicines

Traditional Japanese medicine Kampo (derived from traditional Chinese medicine) is approved by the Japanese Ministry of Health, Labor, and Welfare for multiple indications

(such as sleep disturbances)<sup>63</sup>. Kampo medicine is mainly based on the use of acupuncture techniques, moxibustion (burning dried mugwort on particular points on the body), diet and herbal medications<sup>64</sup>. Among these herbal medications used in Kampo medicine, Yokukanasan, Kambakudaisoto and Daisaikoto are frequently used in the management of insomnia complaints due to their potential sleep-promoting effect without residual daytime drowsiness or performance impairment<sup>65,66</sup>. However, despite their empirical use in insomnia sufferers<sup>67</sup>, these herbal medications are not currently approved for the management of insomnia disorders in adolescents given the lack of studies investigating the efficacy and long-term effects of these herbal medications in this particular subpopulation<sup>68,69</sup>. Thus, in adolescents, the herbal medications from Kampo medicine should be used with caution in view of this lack of evidence<sup>70</sup>.

- Delayed sleep phase disorder

Therapeutic strategies are multiple<sup>71</sup>, but their long-term effectiveness largely depends on the degree of motivation of adolescents<sup>72</sup>.

- Chronotherapy<sup>73</sup>: The goal is to change the timing of sleep onset in order to progressively delay sleep onset until

**Table 4.** The most used medications for the pharmacological treatment of insomnia disorders in adolescents.

Drugs	Mechanism of action	Effects on sleep architecture	Side effects	Comments
Benzodiazepines • Clonazepam • Flurazepam, • Quazepam • Temazepam • Estazolam • Triazolam	Agonists of central GABAA receptors	Decreased nocturnal awakenings and suppression of delta sleep	Tolerance, dependence, residual sedation, cognitive or psychomotor disorders, anterograde amnesia, respiratory depression and withdrawal symptoms in case of treatment discontinuation	Short half-life molecules for sleep onset insomnia and long half-life molecules for insomnia maintenance
Alpha-receptor agonists • Clonidine • Guanfacine	Decreased release of norepinephrine	Decreased sleep latency	Dry mouth, hypotension, bradycardia and withdrawal symptoms (shortness of breath, hypertension and tachycardia) in case of treatment discontinuation	They may be used in daytime treatment of attention-deficit/hyperactivity disorder
Benzodiazepines-like • Zolpidem • Zaleplon	Similar action to benzodiazepines but shorter half-life time	Decreased sleep latency	Similar to benzodiazepines	Very few data on their use in adolescents
Atypical antidepressants • Trazodone	Antagonists of serotonin (5-HT <sub>2A</sub> /e) receptors	Decreased sleep latency, improved sleep continuity, decreased REM sleep and increased delta sleep	Residual sedation, cardiac arrhythmias, hypotension and priapism	They are particularly indicated in cases of comorbid depression
Antihistamines • Diphenhydramine • Brompheniramine • Chlorpheniramine • Hydroxyzine	Antagonists of histamine (H <sub>1</sub> ) receptors	Decreased sleep latency	Residual sedation, loss of appetite, nausea, vomiting, constipation, dry mouth, paradoxical excitation and risk of altered sleep quality	They are well accepted by adolescents and their parents
Melatonin	Targeted action on the circadian regulation of sleep	Reduced sleep latency and correction of some alterations of the circadian rhythm	Largely unknown (hypotension, bradycardia, nausea, headache and possible exacerbations of comorbid autoimmune diseases)	Melatonin may be used in adolescents with mental retardation, pervasive developmental disorders and neurological disorders
Herbal treatments • Passiflora • Valerian • German chamomile • Kava • Lavender	Modulation of central GABA receptors activity and induction of central nervous system depression	Potential sleep-promoting effects without residual daytime drowsiness or performance impairment	Largely unknown	The long-term efficacy and safety of herbal treatments are unknown



it matches a more conventional time. It involves subjecting the patient to a 27-hour sleep-wake rhythm (limit of possible entraining of the sleep-wake rhythm): the patient is asked to go to bed every day three hours later than the day before. The recycling of the sleep period is reached in 7 days. The patient must then strictly observe the fixed schedules for bedtimes and wake-up times.

- Bright light therapy<sup>74</sup>: The bright light therapy is based on the phase response curve. Morning exposure leads to a sleep phase advance whereas evening exposure is associated with sleep delayed phase. The light intensity necessary to allow an advance of the circadian phase must be between 2500 and 10000 lux. The duration of exposure to bright light therapy depends on the light intensity used.

- Use of chronobiotic agents<sup>75</sup>: The aim is to use phase-shifters such as melatonin. Indeed, the exogenous melatonin phase response curve present a shift of 12 hours compared to the phase response curve to light. It is therefore advisable to administer the exogenous melatonin in the evening (five hours before the start of endogenous secretion of melatonin) in order to allow the resynchronization of circadian rhythms.

- Adequate sleep hygiene and management of comorbidities<sup>76</sup>: Limitation of use of multimedia screens in the bedroom (particularly in the hour before desired sleep time), establishing regular sleep patterns by parents, suppression of caffeine/energy-dense foods before desired sleep time, no exercise too close to sleep time and treatment for depression and anxiety.

Moreover, it has been shown that the combination of morning bright light therapy and evening melatonin are more practical and manageable than the chronotherapy alone<sup>78</sup>.

- Use of stimulant medications/drugs

When prescribing stimulant medications in adolescents, it is important to adjust the doses in case of sleep complaints in order to promote optimal sleep (quality and quantity)<sup>78</sup>. Concerning the misuse of stimulant medications and the abuse of stimulant drugs, the implementation of appropriate management in adolescents (family therapy, CBT, motivational interviewing and management of psychiatric co-morbidities) is essential in order to avoid the negative consequences related to this risk behavior<sup>79,80</sup>.

## **b.) Excessive daytime sleepiness with fragmented sleep (Table 5)**

- Obstructive sleep apnoea syndrome

In adolescents, an obstructive sleep apnoea-hypopnoea index  $\geq 5$  episodes per hour irrespective of the presence of comorbidities, an obstructive sleep apnoea-hypopnoea index of 1-4 episodes per hour associated with comorbidities (neurocognitive, behavioural, cardiovascular, metabolic and inflammatory) or factor predicting obstructive sleep apnoea syndrome (OSAS) persistence (overweight/obesity, male sex,

OSAS severity, African/American ethnicity, untreated tonsillar hypertrophy and narrow mandible), and the presence of complex conditions (such as major craniofacial abnormalities, neuromuscular disorders, achondroplasia, Chiari malformation, Down syndrome, mucopolysaccharidoses and Prader-Willi Syndrome) justifies the establishment of appropriate treatments in order to avoid the negative consequences related to OSAS<sup>81</sup>.

Finally, the European Respiratory Society and the French Society of Sleep Research and Medicine have published consensus statements (summarized below) in order to enable the best possible treatment for OSAS in adolescents<sup>81,82</sup>.

## **Surgical treatments**

In adolescents with enlarged tonsils and/or adenoids, the first-line treatment of OSAS is the adenotonsillectomy<sup>83</sup>. Indeed, this intervention is generally very well tolerated and effective since it allows a significant reduction in the obstructive sleep apnoea-hypopnoea index in 75% to 80% of cases<sup>84</sup>. Anaesthetic complications, immediate postoperative problems (such as pain and poor oral intake) and haemorrhage are the potential complications of the adenotonsillectomy<sup>85</sup>. However, in some cases, there may be a failure of this surgical treatment favoured by some risk factors such as obesity, initial severity of OSAS, family history of OSAS, asthma, neuromuscular diseases, craniofacial malformations and genetic abnormalities<sup>86</sup>.

## **Continuous positive airway pressure**

Continuous positive airway pressure (CPAP) involves air that is pressurized by an electronic device and delivered during sleep via a nasal or oronasal mask, acting as a pneumatic stent of the airway. In adolescents with OSAS, the main indications for treatment with CPAP are contraindications to surgical treatment of OSAS, presence of persistent OSAS after adenotonsillectomy, OSAS associated with obesity, craniofacial abnormalities and neuromuscular disorders<sup>81,87</sup>. Potential side effects of treatment with CPAP are nasal congestion, nasal bleeding, facial erythema (skin contact with the mask) and changes in the shape of the face<sup>88</sup>.

However, unlike surgical treatment that is curative, treatment with CPAP is a chronic treatment, which may lead to long-term problems of compliance and adherence to treatment in adolescents<sup>89,90</sup>. Thus, in case of treatment with CPAP in adolescents, the establishment of psychoeducation and regular monitoring is essential<sup>91,92</sup>.

## **Weight loss**

Along with these different treatments, overweight or obese adolescents must benefit from therapeutic strategies (diet and physical activity) allowing weight loss in order to reduce the OSAS severity<sup>93</sup>. Moreover, if these non-surgical weight loss strategies fail, bariatric surgery may be considered for adolescents meeting eligibility criteria (fail during at least 6 months of organized weight management attempts, physiological/psychological maturity and extreme obesity [BMI  $\geq 40$  kg/m<sup>2</sup>] with obesity-related comorbidities [such as OSAS treated by CPAP])<sup>94</sup>.

**Table 5.** Therapeutic strategies for excessive daytime sleepiness with fragmented sleep in adolescents.

Causes		Therapeutic strategies	Approved interventions for adolescents
Obstructive sleep apnoea syndrome	Adolescents with enlarged tonsils and/or adenoids	<ul style="list-style-type: none"> <li>• First-line treatment: Adenotonsillectomy</li> <li>• Second-line treatment: Continuous positive airway pressure if failure or contraindication to adenotonsillectomy</li> <li>• Complementary treatments: Weight loss strategies</li> </ul>	Yes Yes Yes
	Adolescents with obesity, craniofacial abnormalities and neuromuscular disorders	<ul style="list-style-type: none"> <li>• First-line treatment: Continuous positive airway pressure</li> <li>• Complementary treatments: Weight loss strategies</li> </ul>	Yes Yes
	Adolescents with malocclusion and retrognathia	<ul style="list-style-type: none"> <li>• Alternative treatment: Orthodontic mandibular advancement</li> <li>• Complementary treatments: Weight loss strategies</li> </ul>	Yes Yes
Restless legs syndrome alone or combined to periodic limb movements during sleep	Mild severity	<ul style="list-style-type: none"> <li>• First-line treatments: Adequate sleep hygiene and avoidance of aggravating factors</li> <li>• Complementary treatment: Iron supplementation if serum ferritin &lt;50 mcg/L</li> </ul>	Yes No (off-label prescription)
	Moderate to severe severity	<ul style="list-style-type: none"> <li>• First-line treatments: Dopaminergic agents</li> <li>• Second-line treatments: Benzodiazepines, anticonvulsants, alpha-receptor agonists or minor opioids</li> <li>• Complementary treatments: Adequate sleep hygiene, avoidance of aggravating factors and iron supplementation if serum ferritin &lt;50 mcg/L</li> </ul>	No (off-label prescription) No (off-label prescription) No (off-label prescription)
			No (off-label prescription for iron supplementation)
Parasomnias	Sporadic episodes without dangerous behaviour	<ul style="list-style-type: none"> <li>• First-line treatments: Psychoeducation and adequate sleep hygiene</li> <li>• Complementary treatment: Therapy of scheduled awakenings</li> </ul>	Yes Yes
	Persistent episodes or episodes associated with dangerous behaviours	<ul style="list-style-type: none"> <li>• First-line treatments: Benzodiazepines (clonazepam)</li> <li>• Second-line treatments: Serotonergic agents</li> <li>• Alternative treatment: L-5-hydroxytryptophan</li> <li>• Complementary treatments: Psychoeducation and adequate sleep hygiene</li> </ul>	No (off-label prescription) No (off-label prescription) No (off-label prescription) Yes
Somatic pathologies		<ul style="list-style-type: none"> <li>• Establishment of targeted management for these specific aetiologies</li> </ul>	Yes
Environmental causes		<ul style="list-style-type: none"> <li>• Adequate sleep environment</li> </ul>	Yes

### Orthodontic mandibular advancement

Orthodontic mandibular advancement (OMA) (used only during sleep) allows advancing the mandible or the tongue, which increases the size of the upper airway. Although there is limited data on the effectiveness of OMA in the management of OSAS in adolescents, studies currently available in the literature suggest that OMA may be an effective treatment in adolescents with malocclusion and retrognathia<sup>95</sup>.

- Restless legs syndrome alone or combined to periodic limb movements during sleep

### Non-pharmacological treatments

In adolescents with restless legs syndrome (RLS) alone or combined to periodic limb movements during sleep (PLMs),

the establishment of healthy sleep habits and the avoidance of factors that may aggravate the RLS (such as insufficient sleep for age, irregular sleep schedule, pain, caffeine, nicotine, alcohol and medications [sedating antihistamines, serotonergic antidepressants and neuroleptics]), may be sufficient for mild forms or reduce the severity of symptoms for moderate to severe forms<sup>97</sup>.

### Pharmacological treatments

#### Iron Supplementation

Based on the evidence for relative iron deficiency in the pathophysiology of RLS alone or combined to PLMs, the use of iron supplementation in adolescents with serum ferritin < 50mcg/L may be considered as first-line treatment for mild forms and complementary treatment for moderate to severe forms<sup>97</sup>.



## Medications

Currently, there are no medications approved by the Food and Drug Administration for paediatric sleep disorders even though it has been shown that the lack of treatment of these disorders is associated with long-term negative consequences<sup>98</sup>. However, in the literature, there are studies supporting the long-term use of medications in adolescents with moderate to severe RLS alone or combined to PLMs<sup>99</sup>.

- Dopaminergic agents

In adults, the dopaminergic agents (carbidopa/levodopa, pramipexole and ropinirole) are the first-line treatment for moderate to severe RLS alone or combined to PLMs since they allow removing unpleasant sensations and PLMs<sup>100</sup>. However, in adolescents, several studies have shown that dopaminergic agents are also effective in treating moderate to severe RLS alone or combined to PLMs and could be a first-line treatment in this particular subpopulation<sup>101,102</sup>. The main side effects of these dopaminergic agents are the augmentation phenomenon (the worsening of symptoms of RLS as dopaminergic dosage is increased)<sup>103</sup> and the development of impulse control problems (such as impulsive gambling or shopping)<sup>104</sup>. If these side effects occur, it may be necessary to reduce the dosage or change medications<sup>105</sup>. Finally, it is important to note that there is little data on the long-term use of dopaminergic agents in adolescents<sup>106</sup>.

- Other medications

In adolescents, there are other treatment options for the treatment of moderate to severe RLS alone or combined to PLMs (benzodiazepines [clonazepam, temazepam and zolpidem], anticonvulsants [gabapentin], alpha-receptor agonists [clonidine] and minor opioids). However, even though they are frequently used in adolescents, these medications should be used with caution since they have never been validated and have not benefited from a paediatric investigation plan<sup>107,109</sup>.

- Parasomnias (nocturnal terrors, confusional arousals and sleepwalking)

## Non-pharmacological treatments

In case of sporadic episodes without dangerous behaviour, it is not necessary pharmacologically treat parasomnias in adolescents<sup>109</sup>. Indeed, the first approach is to reassure the patient about the benign nature of the episodes, to inform the parents not to awaken the patient in order to avoid the aggravation or the lengthening of the episodes, to secure the sleep environment (removal of obstructions in the bedroom, securing windows, sleeping on the ground floor, installing locks or alarms on windows, doors and stairways) and to avoid factors that may favour the occurrence of episodes (such as sleep deprivation, inadequate sleep hygiene, sleep disorders [OSAS and PLMs] and use of some medications/drugs [alcohol, hypnotics, antipsychotics, antidepressants, antihistamines]).

In some cases, if the parasomnias episodes always occur at the same time each night, the use of scheduled awakenings may be recommended to prevent the occurrence of parasomnias episodes. Finally, for other psychological interventions (such as hypnosis, relaxation therapy or CBT), there is currently no consensus regarding their use in the management of parasomnias in adolescents<sup>110-113</sup>.

## Pharmacological treatments

In case of persistent episodes despite adequate behavioural and psychological interventions or episodes associated with dangerous behaviours, it is recommended to introduce a pharmacological treatment with blunting effect on arousability to reduce the occurrence of episodes<sup>114</sup>.

## Benzodiazepines

Although they have never been officially approved for this indication, intermediate- and long-acting benzodiazepines (such as clonazepam) are frequently used as first-line treatment of parasomnia<sup>115,116</sup>. However, despite their good efficacy in the treatment of parasomnias, benzodiazepines should be used with caution in view of their potential side effects<sup>117</sup>.

## Antidepressant therapy

Although few studies are available, there is evidence in the literature to support the use of serotonergic agents (selective serotonin reuptake inhibitors, tricyclic antidepressants and atypical antidepressants) as second-line treatment in the management of parasomnias<sup>118</sup>.

## Other drugs

In adolescents, an alternative to conventional pharmacological treatments may be L-5-hydroxytryptophan, which appears to be an effective and safe treatment for parasomnias in paediatric populations<sup>119</sup>.

- Somatic pathologies and environmental causes

Some somatic pathologies (asthma, eczema, cystic fibrosis, gastroesophageal reflux and epilepsy) and some environmental causes (noise, light and cosleeping) may induce excessive sleep fragmentation promoting the occurrence of EDS, which justifies the establishment of targeted management for these specific aetiologies<sup>31</sup>.

## c.) Excessive daytime sleepiness with increased sleep need (Table 6)

- Central hypersomnia

### *Narcolepsy*

## Non-pharmacological treatments

Behavioural measures of sleep hygiene (regular sleep schedules and avoidance of sleep deprivation) and use of programmed naps (< 15 min) may reduce EDS associated with narcolepsy in adolescents<sup>120</sup>.

**Table 6.** Therapeutic strategies for excessive daytime sleepiness with increased sleep need in adolescents.

Causes		Therapeutic strategies	Approved interventions for adolescents
Central hypersomnia	Narcolepsy with severe excessive daytime sleepiness	• First-line treatments: Psychostimulant medications	Yes (only for modafinil in adolescents aged over 16 years)
		• Alternative treatment: Sodium oxybate	Yes (only in adolescents aged over 16 years)
	Narcolepsy with moderate excessive daytime sleepiness	• Complementary treatments: Adequate sleep hygiene and programmed naps	Yes
		• First-line treatment: Sodium oxybate	Yes (only in adolescents aged over 16 years)
	Narcolepsy with refractory excessive daytime sleepiness	• Alternative treatments: Psychostimulant medications	Yes (only for modafinil in adolescents aged over 16 years)
• Complementary treatments: Adequate sleep hygiene and programmed naps		Yes	
Recurrent hypersomnia	Idiopathic hypersomnia	• First-line treatment: Pitolisant	No (off-label prescription)
		• Complementary treatments: Adequate sleep hygiene and programmed naps	Yes
	Kleine-Levin syndrome	• First-line treatments: Psychostimulant medications	No (off-label prescription)
		• Acute episodes: Psychostimulant medications or amantadine	No (off-label prescription)
		• Prevention of relapses: prolonged-release lithium or valproic acid	No (off-label prescription)
Mild depression	• Complementary treatments: Consistent sleep-wake schedules, avoidance of alcohol, absence of contact with infectious individuals and home surveillance	Yes	
Moderate to severe depression	• First-line treatment: Cognitive-behavioral or interpersonal psychotherapy	Yes	
Resistant depression	• First-line treatment: Psychotherapy combined to fluoxetine	Yes	
Use of sedative medications	Menstrual-associated	• Specialized psychiatric consultations for adolescents with resistant depression	Yes
		• First-line treatment: Hormone therapy	No (off-label prescription)
Misuse of sedative medications/drugs	Individual measures	• Adjustment of the dosage if necessary	Yes
		• Cognitive-behavioural therapy and/or motivational interviewing	Yes
	Family measures	• Management of psychiatric co-morbidities	Yes
Hypersomnia secondary to other disorders	Family measures	• Family therapy	Yes
		• Establishment of targeted management for these specific aetiologies	Yes

## Pharmacological treatments

Although there is few data available for paediatric populations, experts usually prescribe the same first- and second-line treatments as in adults since the benefit/risk ratio seems comparable<sup>121</sup>. However, before any prescription of medications, it is necessary to respect some rules of good practice (initial monotherapy and treatment at effective doses for a sufficient duration)<sup>122</sup>.

## Psychostimulant medications

In paediatric populations, psychostimulant medications are the first-line treatment of severe EDS associated with narcolepsy<sup>123</sup>. Among these psychostimulant medications, modafinil (modulator of the sympathomimetic systems)

should be used as first-line therapy given its safety and efficacy in paediatric populations<sup>124,125</sup>. Indeed, the side effects are usually mild (irritability, headache, nervousness, palpitations, nausea, allergic/coetaneous reactions and insomnia at the beginning of treatment) although some complications may be severe (Stevens-Johnson Syndrome, suicidal tendencies, mania, depression and hypertensive crises)<sup>126</sup>. If modafinil is not effective, methylphenidate (dopamine and catecholamine reuptake inhibitor) may be used as second-line therapy because its benefit/risk ratio is less favorable than modafinil<sup>127</sup>.

Finally, mazindol and amphetamines (sympathomimetic agents associated with increased release of norepinephrine and dopamine) are the last-line therapy of EDS associated with narcolepsy given their potentially severe side effects (severe

hypertension, pulmonary arterial hypertension, valvulopathy and angina)<sup>128</sup>. Given the potential cardiovascular complications of these different psychostimulant medications, it is essential to carry out a pre-therapeutic assessment (research for personal/family cardiovascular antecedents and electrocardiogram) before any prescription and to establish a regular cardiovascular monitoring during the whole duration of the treatment<sup>129</sup>.

### Sodium oxybate

Despite the limited data for paediatric populations, an alternative to psychostimulant medications is sodium oxybate (agonists of central GABAB receptors) that may be preferred in cases of moderate EDS, poor sleep quality or major disabilities related to cataplexy<sup>130-132</sup>. However, paediatric use of sodium oxybate may induce the occurrence of some side effects such as suicidal ideation, terminal insomnia, tremor, dissociative feelings and constipation whereas overdose of sodium oxybate may be associated with respiratory depression, bradycardia, delirium, myoclonus, hypothermia and coma<sup>133</sup>.

### Pitolisant

Finally, among the future prospects, the pitolisant (selective H3 receptor antagonists) could be a treatment for refractory EDS associated with narcolepsy in adolescents even if additional studies are necessary to validate this indication<sup>135</sup>.

### Idiopathic hypersomnia

Currently, there is no specific treatment for idiopathic hypersomnia in paediatric populations. Indeed, as in adults, the treatment of EDS associated with idiopathic hypersomnia in adolescents is essentially based on psychostimulant medications (modafinil and methylphenidate) in view of the lack of efficacy of non-pharmacological measures (behavioural measures of sleep hygiene and programmed naps)<sup>135</sup>.

- Recurrent hypersomnia

### Kleine-Levin syndrome

Considering the few studies in the literature, there is currently no consensus for the treatment of Kleine-Levin syndrome<sup>136</sup>. However, some non-pharmacological measures for episode prevention (consistent sleep-wake schedules, avoidance of alcohol and absence of contact with infectious individuals) and management (home surveillance) may be used in addition to pharmacological treatments<sup>137,138</sup>. During acute episodes, psychostimulant treatments (modafinil, methylphenidate and amphetamine) and amantadine (antiviral) appear to have a beneficial effect on symptoms such as EDS<sup>137,138</sup>.

For the prevention of relapse in case of brief and frequent episodes, prolonged-release lithium or valproic acid (thymostabilisers) seems to be the most effective preventive medications despite limited data<sup>137,138</sup>. Finally, since the Kleine-Levin syndrome has a benign clinical course with spontaneous disappearance of symptoms in the majority of cases, the use

of these pharmacological treatments should be considered only for patients with frequent occurrence of attacks and severe behavioural disorders inducing major professional and social disabilities<sup>139</sup>.

### Depression

In adolescents, the diagnosis of depression may be difficult and requires confirmation during a full assessment by psychiatrist specialized in adolescents<sup>140</sup>. In depressed adolescents with EDS, treatment should be selected according to the depression severity following this specialized psychiatric consultation for adolescents<sup>141</sup>. Indeed, in cases of mild depression, it is recommended to focus on cognitive-behavioural or interpersonal psychotherapy whereas for moderate to severe depression, psychotherapy should be combined with antidepressant treatment<sup>142</sup>. Currently, the recommended first-line antidepressant therapy for adolescents is fluoxetine that present the best risk/benefit ratio<sup>143</sup>. In case of failure of treatment with fluoxetine, depressed adolescents should be referred to psychiatric consultation specialized for adolescents with resistant depression to consider different therapeutic alternatives<sup>144</sup>.

### Menstrual-associated

In cases of EDS associated with menstruation, some studies have demonstrated a response to hormone therapy<sup>145</sup>.

- Use of sedative medications/drugs

When prescribing sedative medications in adolescents, it is important to adjust doses in case of side effects (such as EDS) in order to allow optimal daytime functioning<sup>146</sup>. Concerning the misuse of sedative medications and the abuse of sedative drugs, the implementation of appropriate management in adolescents (family therapy, cognitive-behavioural therapy, motivational interviewing and management of psychiatric co-morbidities) is essential in order to avoid the negative consequences related to this risk behavior<sup>79,80</sup>.

- Hypersomnia secondary to medical or neurological disorders

Some somatic or neurological disorders (traumatic brain injury, cancer, Prader-Willi syndrome, myotonic dystrophy, Smith-Magenis syndrome, Norrie disease, Coffin-Lowry syndrome, Neiman-Pick disease type C, encephalopathies/encephalitis and rapid-onset obesity with hypothalamic dysfunction and autonomic dysregulation syndrome) may induce EDS, which justifies the establishment of targeted management for these specific aetiologies<sup>147</sup>.

### DISCUSSION

Since there are no medications approved by the Food and Drug Administration for the main disorders associated with EDS complaints in paediatric populations (including adolescents)<sup>32,55,57</sup>, all pharmacological treatments discussed in this review are currently off-label used, which may lead

to medico-legal difficulties when using these treatments in this particular subpopulation<sup>149</sup>. This absence of approved pharmacological treatments for the main disorders associated with EDS complaints in paediatric populations, including adolescents, is due to the insufficient number of scientific studies available in the literature<sup>32,55,57</sup>. Indeed, in this specific subpopulation, the performing of scientific studies is more complicated than in adults for ethical reasons<sup>149</sup>. The main consequence of this insufficient number of scientific studies is the extrapolation of data obtained in adults for paediatric populations (including adolescents)<sup>149</sup>. However, while there is some debate that adolescents may be treated as adults in some indications, they are different populations with their own particularities<sup>149</sup>.

This lack of pharmacological treatments approved for the main disorders associated with EDS complaints in paediatric populations (including adolescents) means that it is absolutely recommended to use non-pharmacological interventions in first-line, since they are currently the only approved interventions for the main disorders associated with EDS complaints in this particular subpopulation<sup>32,55,57,150</sup>. However, in case of disorders associated with moderate to severe EDS complaints not controlled by these non-pharmacological interventions, the question of off-label use of pharmacological treatments is raised with all possible medico-legal consequences for the prescriber<sup>151</sup>.

Thus, in this review, in order to take into account these different limitations and avoid as much as possible extrapolations from other populations (children or adults) than adolescents, we have tried to limit ourselves only to pharmacological treatments and non-pharmacological interventions already been studied in adolescents (including on small samples) or associated with major clinical interest (lack of approved therapeutic alternatives or failure of first-line recommended interventions), in the management of disorders related to EDS complaints in adolescents.

## Perspectives

Given the insufficient number of scientific studies in adolescents, it seems essential to carry out additional scientific studies on the use of pharmacological treatments in order to benefit from approved pharmacological treatments for the main disorders associated with EDS complaints in this particular subpopulation.

## CONCLUSIONS

Complaints of EDS are common among adolescents. However, the aetiologies of this EDS are multiple, which justifies a systematic medical assessment before any medications prescription in this particular subpopulation. In addition, given the limited data for most of the medications used for EDS in paediatric populations, caution is recommended in case of pharmacological treatment and non-pharmacological approaches should be preferred where possible. In adolescents, the implementation of comprehensive and targeted therapeutic

strategies of EDS is essential to avoid the negative consequences associated with this major health problem.

## DECLARATIONS

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and material:** Not applicable.

**Conflicts of interest:** The authors have no conflicts of interest with the work carried out in this study.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors' contributions:** All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work

## ACKNOWLEDGEMENTS

I want to thank Christelle Bouchart (MD) for her support and the sleep laboratory team from the Erasme Hospital for technical support.

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