EDITORIAL

Sleep Science

Struggling with comorbid sleep disturbances: insights from the ELSA-Brasil study

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The initial classification of sleep disorders were reported in 19th century using three categories: insomnia, hypersomnia and nightmare. In the following century (mainly in the last half of it), technological discoveries led to rapid advances in the understanding of sleep and recognition of several sleep disorders. Nowadays, the three systems of classification in use worldwide include the International Classification of Diseases (ICD, developed by World Health Organization), the Diagnostic and Statistical Manual of Mental Disorders (DSM, from the American Psychiatric Association) and the International Classification of Sleep Disorders (ICSD, produced by the American Academy of Sleep Medicine)[1-3]. All three systems had different strategies of sleep disorders classification with some confluence, but they are unanimous to present a huge number of sleep disorders in the humankind. Currently, there are more than 83 sleep disorders challenging not only sleep specialists but also non-specialists, frequently facing sleep issues in their clinical practice.

From the research perspective, we traditionally addressed sleep disorders as distinct compartments (Figure 1). Using this approach, considerable advancements were made in the last decades to understanding the major health consequences of sleep deprivation, long sleep duration, insomnia, sleep disordered breathing including obstructive sleep apnea (OSA), circadian disorders, sleep-related movement disorders, narcolepsy, parasomnias, etc. This traditional view made significant contributions for each sleep condition highlighting a myriad of consequences that made sleep an interdisciplinary area.

Figure 1. Classical view of the clinical approach of sleep disorders.

Despite the advances, researchers overseas are facing heterogeneous clinical presentations and prognosis related to each of the sleep disorders. For instance, even patients with severe OSA may not be at risk of cardiovascular events. Recent investigations pointed out that particular signatures such as daytime sleepiness[4] or higher burden of hypoxia[5] are more susceptible to the cardiovascular consequences than non-sleepy or OSA patients with mild hypoxia during sleep. In this complex scenario, a lot of attention has been devoted to explore potential phenotypes and biomarkers that predicts risk and response to therapies[6-8].

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Co-existence of sleep disturbances: common but largely unexplored!

Apart from these above mentioned strategies (phenotypes and biomarkers), a number of groups are noticing the potential relevance of exploring comorbid sleep disturbances. The bottom line is not promoting a 'competition' for comparing which one the most important is in terms of consequences but to figure out whether the whole 'package' provides more impairment than any individual sleep component. Moreover, one sleep disturbance may influence another in a bidirectional relationship[9]. We would like to provide two examples highlighting the potential relevance of the comorbid sleep conditions:

1) Comorbid insomnia and OSA (namely as COMISA)

In OSA patients, a recent meta-analysis showed that approximately a third of them presented insomnia (most of them presenting the difficulty maintaining subtype)[10]. In patients with COMISA, daytime symptoms scores tend to be higher and rates of psychiatric and cardiovascular comorbidities are reportedly more frequent[11]. Whether patients with COMISA have poor prognosis than insomnia and OSA, it remains to be determined. Besides, significant challenges in treating COMISA (for instance: hypnotics may worsen OSA; poor continuous positive airway pressure [CPAP] compliance is frequently observed in these patients) and order of treatment ("Should I treat OSA first and them observed insomnia symptoms or treat both simultaneously?") underscore the need of additional research and a comprehensive treatment in the clinical practice.

2) Comorbid short sleep duration and insomnia

Patients with insomnia presented sleep fragmentation as an obvious feature but the sleep duration (SD) is not frequent reduced in these patients[12]. When reduced, the combination with insomnia may have clinical implications than each condition in isolation. For instance, data from the Penn State Cohort[13] showed that the combination of short SD and insomnia were associated with a 3.8-fold chance of developing hypertension as compared to participants with no insomnia and usual SD detected by polysomnography. Of note, neither insomnia nor short SD *per se* was associated with incident hypertension after controlling to confounding factors. Increased metabolic disturbances and mortality associated with this comorbid association were also described by the same group[14-16].

Co-existence of sleep disturbances: insights from the ELSA-Brasil cohort

The ELSA-Brasil is an ongoing cohort study of civil servants from six different cities in Brazil, aimed to provide relevant information regarding the development and progression of clinical and subclinical cardiovascular diseases as well as diabetes[17-19]. Participants aged 35-74 years were eligible for the study. Specifically, the sleep in ELSA-Brasil was primarily installed in the Sao Paulo city[18]. Our sleep assessment consisted of the application of structured questionnaires. The assessment of OSA risk level was performed using the Berlin Questionnaire and NoSAS Score[18]. The Epworth Sleepiness Scale was used to assess excessive daytime sleepiness. The occurrence of insomnia was based on the Brazilian version adapted from the Clinical Interview Scheduled Revised (CIS-R), an instrument used to conduct a structured interview to verify the presence of psychiatric morbidity[17]. This questionnaire consists of 14 sections, including 1 section on reported sleep problems, which considers the frequency, duration and severity of symptoms in the last 7 days. Self-reported SD of each participant was based on questioning about the usual bed/wake time and the average SD in a typical week. The objective measurements included home sleep monitoring (polygraphy) and wrist actigraph. Overnight home sleep study was performed a standardized level-3 portable diagnostic device. We perform a validation of this strategy in participants from ELSA-Brasil[20]. The sleep duration was measured using a wrist actigraph over a period of seven consecutive days and nights, on the non-dominant wrist, in a typical week[18]. Thus, the ELSA-Brasil has the availability of OSA status as well as subjective and objective SD, daytime sleepiness and insomnia.

Our initial focus was to explore the factors independently associated with short SD and OSA, considering statistical models with the presence of these two sleep disorders concomitantly. We confirmed a high frequency of OSA (32.9%) and short SD (27.2%) observed in previous studies[21,22]. We observed that excessive daytime sleepiness was independently associated with short SD, but not with OSA. In contrast, cardiometabolic risk factors including obesity, hypertension and dyslipidemia were associated with OSA, but not with short SD[18]. Importantly, we did not observe significant interactions between OSA and short SD in potentially modulating these associations.

Figure 2 illustrates some of the comorbid possibilities in the ELSA-Brasil. Only 41% of the sample had none of the disorders, another 41%, 16% and 2% had one, two or three disorders, respectively. Approximately one third of the participants have OSA (33.1%), being the most frequent sleep condition followed by short sleepers (SD <6hours) with 26.9%, symptoms of insomnia (12.0%) and long SD (SD >8 hours) 6.6%. Figure 2 also indicates that approximately half of patients with OSA presented another sleep condition, being OSA and short SD the most common combination. Of note, COMISA may be varied from 54 participants only (limited to patients with moderate and severe symptoms of insomnia) to >300 participants when considered any kind of insomnia). Regardless of single or comorbid sleep disturbances, Figure 2 revealed a significant proportion of patients were not sleepy underscoring the heterogeneity of clinical presentation.

Statistical analysis challenges

To date, the results presented by the ELSA-Brasil study have been based on cross-sectional analysis. However, we are pursuing an integrated approach when considering different sleep disorders in our multinomial models with the including of an interaction term in the analysis. Computational tools such as cluster analyzes may help us to understand phenotypic subtypes among patients with different sleep disorders[23,24]. However, the

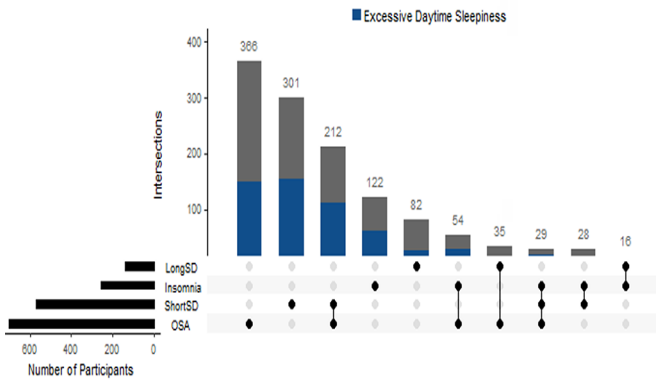

Figure 2. UpSet plot of intersections and aggregates among different types of sleep disorders in the ELSA-Brasil. The sizes of the subgroups of each disorder in isoltion are shown in the horizontal bar graph in the lower left corner of the figure. The mtrix layout at the bottom allows you to view the combination of disturbances, showing which sets are crossed. The main bar graph displays the sizes of the subgroups defined by the respective intersections and display the number of individuals with excessive daytime sleepiness for each subset. First point to be considered is the high frequency of sleep disorders.

challenge remains to determine how much an individual with a specific disorder or set of specific characteristics would benefit from personalized therapeutic interventions. This strategy could also help in identifying the undesirable presence of mutual reinforcement of negative effects ("positive feedback loop") that can occur when two or more disorders are present.

CONCLUSIONS

The Sleep Medicine field is not in its childhood anymore. Considerable advancements in the last decades pave the way for understanding the complexity of studying sleep disturbances. The coexistence of sleep disorders is common but largely under recognized and undertreated in the clinical practice. The ELSA-Brasil is not able to explore all myriad of sleep conditions but certainly addressing the most prevalent ones. Future longitudinal and interventional studies addressing combined treatment may help to understand the burden of comorbid relevant sleep conditions. The personalized approach, either for diagnosis, risk stratification and treatment is on the table pushing us to put the pieces together. After all, the "one size does not fit all" concept is also true for sleep!

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