Chapter

Sleep and Orofacial Pain: Physiological Interactions and Clinical Management

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Abstract

Sleep and pain are both vital functions on which wellbeing, health, and life itself depend. These two complex states interact in several ways serving homeostasis, but they are also regulated by a well-orchestrated, multi-oscillatory mechanism characterizing the Circadian Timing System. This interaction, which benefits critical physiological challenges, is also clinically crucial, as it mutually affects sleep and pain-related disturbances. It impacts pathophysiological pathways and relevant clinical aspects of many disorders. Furthermore, therapeutic success is frequently dependent on the adequate management of this cycle. The relationship of sleep and pain is undoubtedly of major relevance for diagnosis and successful management of various health conditions and disorders.

Keywords: sleep, orofacial pain

1. Introduction: basics of sleep-pain interaction

Sleep and pain interaction occur at several levels, both in physiology and pathology, and is influenced by a circadian timing system from which almost all functions in our body partially depend. Sleep and pain are both vital functions that ultimately contribute to general body homeostasis, and therefore to life success. Experience of pain motivates an individual to run away from potential physical injury and/or to stay protected and immobilized if an injury already occurred in order to promote and optimize recovery. While the escape-related response is tied to an increased state of arousal (being more awake), the response related to protection is linked to a state of rest (and sleep). Interestingly, sufficient sleep of good quality and pain have an inverse epidemiological relationship over the lifespan: sleep reduction, either in terms of duration or quality, increases from youth to old age, and at the same time pain-related complains follow a similar pattern. This relationship is clinically important since such negative interaction disturbs the internal milieu, and therefore impacts on prognosis of many disorders co-occurring with one or both of the symptoms of disturbed sleep and pain. Some of the most common pain-related conditions occur in the oro-maxillo-facial complex and are associated with emotional, psychological, and social disturbances that seriously compromise the patient's quality of life. Thus, orofacial pain may by itself directly and indirectly interfere with sleep quality and sleep duration and consequently increases the severity of concomitant conditions and even the pain-related outcomes. On the other hand, insufficient or inadequate sleep is known to contribute

to an increased pain intensity and a reduction of pain tolerance. A vicious cycle can then be perpetuated, and therefore an adequate knowledge on the sleep-pain interaction-related mechanisms should be an important part of learning and training in the domain of clinical sleep neurology, which is in the scope of this book.

2. Pain classification: physiology and physiopathology of orofacial pain

Nociceptive impulses generated by potential or actual tissue damage are just one of the types of input that are continually assessed and evaluated throughout the various levels within the central nervous system (CNS). Nociception provides the brain a chance to interpret pains and make behavioral adjustments to avoid further potential damaging stimuli [1].

First-order nociceptive neurons, whether they synapse in the spinal trigeminal nucleus or in the dorsal horn, excite the same type of second-order neurons that respond to nociceptive signals as well as a variety of sensory stimuli and are therefore called wide-dynamic range neurons. These neurons conduct nociception and other sensations through the brainstem and display varying degrees of arborization with structures throughout the reticular formation, where baseline physiologic processes are controlled before reaching the third-order neurons in the thalamus [2–5]. *Second-order neurons*, stimulated by the faster conducting A-delta fibers, arborize less than those receiving impulses from the slower conducting C-fibers. While the A-delta fibers release glutamate during this process, the C-fibers release a wide variety of neurotransmitters [6, 7]. The available information about the conduction velocity helps us to establish a connection between A-delta fibers and acute pain and between C-fibers and chronic pain.

Third-order circuits, which start in the thalamus and connect the sensory cortex with the basal ganglia and the limbic system, interpret nociceptive input [2, 8]. However, sometimes the pain source is difficult to locate even when pain is felt. For example, the cutaneous stimuli are easier to recognize than the stimuli from visceral organs and muscles just because dermis has much more free nerve endings. In response to pain interpretation, multilevel behavioral responses are coordinated, and descending motor commands are created. Whether nociception is delivered to the CNS through the spinothalamic tract or the trigeminal thalamic tract, pain perception evokes autonomic nervous system (ANS)-modulated cranial nerve responses [2, 9, 10].

Pain in the head and face often involves activation of the trigeminal ganglion nerves and the development of peripheral and central sensitization. The symptoms could be acute-like in toothache or chronic-like in migraine or temporomandibular disorders (TMD).

More important than a single nerve pathway, the expression "trigeminal system" alludes to a really complex course of action of, interneurons, nerve transmission fibers, and synaptic connection which process approaching information from the three divisions of the trigeminal nerve. This nerve is in fact a blended nerve containing both sensory and motor fibers. While sensory fibers innervate the face, conjunctiva, mucous membranes of the oral and nasal cavities, teeth, conjunctiva, dura mater of the brain, and intracranial and extracranial blood vessels, motor fibers support mostly the masseter, temporalis, and the other mastication muscles. Primary afferent neurons carry out sensory information from the face and mouth (except nociception) through trigeminal ganglion. The trigeminal-brain stem complex is the place where a synapse with a second-order neuron occurs. This complex receives simultaneously afferent axons from the upper cervical (C2, C3), vagus, glossopharyngeal and nerves and afferent input primarily from the trigeminal nerve (facial pain and headaches may be a consequence of this connection between the upper cervical nerves and the trigeminal spinal tract nucleus).

We can separate the trigeminal-brain stem sensory nuclear complex in two different structures: the trigeminal main sensory nucleus and the trigeminal spinal tract nucleus, also known as the nucleus of the descending tract of cranial nerve V [11]. The spinal tract nucleus is structured of three separate nuclei going from a rostral (superior) to caudal (inferior) direction: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis. Subnucleus caudalis is situated in the medulla, in some cases, stretching out to the dimension of C2 or C3 and it is the most important brain relay site of nociceptive information emerging from the orofacial area. Because the nucleus caudalis is anatomically continuous with, and structurally similar to, the spinal cord dorsal horn, and because it extends into the medulla as well, it is often referred to as the medullary dorsal horn [12]. Descending nerve fibers from higher levels of the CNS or medication can change or modulate incoming nociceptive signals to the subnucleus caudalis and projecting nociceptive signals on their way to the thalamus.

Inflammation and peripheral tissue injury increase the interaction between neuronal cell bodies and satellite glial cells within the trigeminal ganglion [13]. These interactions have been shown to play an important role in the induction and maintenance of peripheral sensitization of trigeminal nociceptive neurons. Under normal conditions, neuron-glia interactions in the trigeminal ganglia are involved in information processing, neuroprotection, and regulation of neuronal activity including the basal rate of spontaneous firing and threshold of activation to maintain homeostasis. While a transient increase in neuron-glia communication is associated with an acute response to inflammatory signals, stable gap junctions are formed between trigeminal neurons and satellite glia in response to sustained inflammation that is implicated in TMD's [14].

Astrocytes, which are specialized glial cells, and the most abundantly found cells in the CNS, perform similar functions to satellite glia [15]. This means that they facilitate the regulation of neuronal development, synaptic coupling, repair, and even nutritional support. On the other hand, astrocytes can monitor and control the concentration of ions, neurotransmitters, and metabolites, as well as water movement, and thus play a key role in modulating the excitability state of neurons both in the brain and the spinal cord [16]. Microglia, other important glial cells present in the CNS, act as immune cells to remove cellular debris and dead cells; they also release inflammatory mediators to promote healing [17, 18]. Glial cells are responsible for regulating the extracellular environment around neurons and hence neuronal activities, and their importance in regard to the underlying pathology of many inflammatory diseases is gradually becoming recognized. Therefore, they have emerged as important cellular targets for therapeutic intervention given their role in promoting peripheral and central sensitization and persistent pain [19].

3. Pathophysiological aspects of sleep-pain interaction

Understanding pathophysiological mechanisms of sleep-pain interaction requires first of all to be aware that some of those influences attributed to sleep could be in fact related to circadian modulation of both pain and sleep mechanisms.

3.1 Relationship between circadian timing system, sleep, and pain: a cyclic interaction

The circadian timing system is a complex neurophysiological network comprising a central biological clock, usually called the master pacemaker and several peripheral

oscillators, also known as peripheral clocks. The human master clock corresponds to a group of neurons located in the anterior part of the hypothalamus above the optic chiasm named the suprachiasmatic nucleus (SCN). Peripheral clocks are virtually present in all cells of the body. This time-related machinery dictates what we may consider an internal time which regulates almost all body functions in a 24-h periodic fashion. The Latin term "circadian" means circa-diem, about 1 day or 24 h, and this is because our clocks are adapted to the geophysical routine of the natural day-night cycle divided in the precise 24-h period of social time [20]. Both the period of human natural circadian rhythm and the sleep-wake cycle are not exactly 24 h but a little bit longer (more or less 24.6 h) consequently, a kind of hit on the clock should occur every day in order to get our body synchronized with social time. That is one of the main functions of melatonin, an hormone which is secreted in response to the absence of light and suppressed when light is present. The basic mechanism involves the activation or inhibition of photoreceptors in the eye's retina which activate/stop taking melanopsin to the suprachiasmatic nucleus stimulating or inhibiting melatonin secretion. Although mediated by these retinal ganglionic cell-related photoreceptors, the rods and cones also have photic inputs to SCN. Peripheral clocks within each cell have a mechanism which is identical to the clocks found in the SCN-isolated neurons. However, although in isolation each cell is time-autonomous, they tend to generate a single circadian pattern dictated by SCN when these SCN neuronal population couple with other cells via humoral and non-humoral pathways [21, 22].

For biological clocks to be successful, they should accurately keep time and adjust to environmental signals. This requires adequate coupling between the SCN and peripheral clocks. In the absence of SCN signaling, peripheral clocks become desynchronized. As there is a tissue-specific time control that is in part locally controlled, loss of synchronization usually propagates and disturbs the circadian rhythm of such tissue as it was shown to occur in the liver [23–25] as well as in other tissues and organs within the human body.

3.2 The circadian regulation of pain

Some important features of pain are regulated by the circadian timing system. For instance, pain sensitivity follows a rhythmic cycle modulated by the 24 h biological clocks. However, it remains unclear whether rhythmicity is derived from daily oscillations within the underlying causes driving the pain or from rhythmic oscillatory component of the neural processing of pain. Pain-related rhythmic influences, however seem to be independent of either subjective or objective responses suggesting that its modulation occurs on a basic physiological level. Interestingly, this 24 h related pain modulatory mechanism is also dependent of pain intensity which in turn affects pain sensitivity in such a manner that the more intense the pain is, the greater the change in its sensitivity across the day. On the other hand, the particular type of pain seems relevant for the clinical impact of its circadian modulation. A recent prototype of human daily pain sensitivity curve was proposed (**Figure 1**).

3.3 Pain regulation by the homeostatic sleep drive

The sleep-wake cycle is the most conspicuous circadian rhythm in humans with a clear relationship with night (dark)-day (light) oscillation. Actually, sleep is itself regulated by a dual process comprising a circadian component and homeostatic one. This model presented by Borbely explains that we may predict a better sleep when it occurs at night and when we are tired compared to diurnal sleep and/or when we are full of energy.

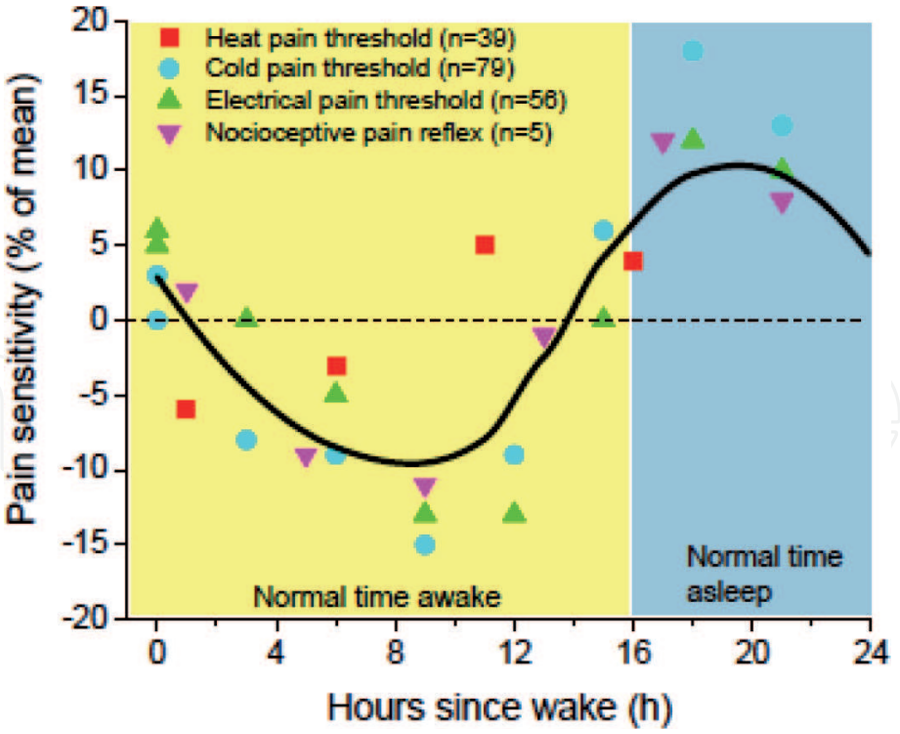

Figure 1.
Prototypical human "daily pain sensitivity" curve (adapted from [31]), the graphic illustrates the circadian profile of pain sensitivity to different pain modalities (thermic: heat and cold, electrical, and nociceptive) and their variation during the 24 h of social day.

The daily rhythm of pain sensitivity is affected not only by circadian rhythmicity, but also by sleep-related homeostatic drive. Actually, either acute and chronic pain are correlated with sleep duration and sleep quality, but while results from distinct basic studies point to a specific modulation of sleep with a wide range of results, there is a lack of human experiments to consolidate clinical knowledge. For instance, even with standardized protocols, there are significant variations in the results [26] which make interpretation sometimes difficult.

3.4 Neural pathways for pain are regulated by both circadian and homeostatic components

The dorsal root ganglia have a circadian rhythmicity since clock genes—those genes generating a near 24 h rhythm—are expressed there. The role of circadian regulation of the neural circuitry underlying pain also involves the rhythmic expression of genes that facilitate synaptic transmission as calcium channel subunits and NMDA glutamate receptor subunits [27]. On the other hand, there are some studies showing that the majority of afferents in this route are nociceptors, thus suggesting that the circadian pattern is of nociceptive origin [27, 28].

Painful stimuli and non-noxious mechanical sensitivity are differently modulated by the human circadian system since mechanical sensitivity peaks in the late afternoon (15–18 h); whereas, pain sensitivity peaks in the middle of the night (0–3 am). There is also a circadian component on inhibition of pain processing in the dorsal horn. It is however unclear what part of this inhibitory control is from the circadian machinery or dependent of the sleep homeostatic drive, since sleep deprivation is known to affect the higher levels of pain processing. Interestingly, pharmacological agents that copy that top-down inhibitory control such as morphine are ineffective after severe sleep deprivation [29, 30] and there is evidence suggesting a neutral response of fast pain processing in case of sleep deprivation. On the other

hand, cortical responses to fast pain also seem to diminish after disturbed sleep. The relative balance of circadian versus homeostatic components in pain processing may depend on the specific type of pain [31].

Although there is still a lack of knowledge on the orofacial pain-sleep interaction, basic and clinical evidence on both acute and chronic pain helps to elucidate the important role of these general components.

4. Orofacial pain diagnosis

The ability to understand and investigate the pathophysiologic processes underlying a disorder, depends on a valid, reliable classification system and common terminology to facilitate communication among clinicians, researchers, academicians, and patients.

A review of the literature regarding the classification of orofacial pain reveals a lot of classification systems with varying advantages and disadvantages [20–43]. Despite all these classifications, currently, the most accepted among the clinicians and researchers dedicated to orofacial pain is the Research and Diagnostic Criteria for temporomandibular disorders (RDC/TMD and DC/TMD).

The taxonomy of "Diagnostic criteria for temporomandibular disorders" (DC/TMD) is an evolution of the original "Research diagnostic criteria for temporomandibular disorders" (RDC/TMD). It uses a dual-axis system in which, on Axis I, the physical diagnosis is based on pathophysiology and grading of chronic pain and on Axis II depression, anxiety, and non-specific physical systems are scored, in order to determine the distribution of subtypes of TMD, psychological disorders and psychosocial dysfunction [32, 33, 44, 45]. It is important to emphasize that with the advent of the RDC TMD, it was possible to describe and compare appropriate TMD subtypes and psychosocial profiles using clearly defined and validated diagnostic criteria in groups of TMD patients, and is used in different parts of the world [34, 35, 46, 47].

An accurate orofacial pain diagnosis is obviously the first step to achieve the correct treatment for the patient. This means that the clinician must be aware of both the Axis I and Axis II of the DC/TMD. The diagnostic process involves defining the inclusion criteria that are specific to a disorder as well as ruling out specific disorders that can cause similar symptoms.

Establishing the correct diagnosis in orofacial pain is particularly difficult because of the complex inter-relationship of physical and psychological factors in the etiology of biopsychosocial chronic pain syndromes. Thus, the differential diagnosis is a critical process that—if failed—can often lead to an inappropriate treatment.

The broad categories included in the new guidelines for Assessment, Diagnosis, and Management of Orofacial Pain are as follows [36, 48]:

- Vascular and nonvascular intracranial pain disorders
- Primary headache disorders
- Neuropathic pain disorders
- Intraoral pain disorders
- Temporomandibular disorders

- Cervical pain disorders
- Extracranial and systemic causes of orofacial pain.

4.1 Vascular and nonvascular intracranial pain disorders

In this group, the differential diagnosis is essential since disorders like aneurysm, hemorrhage or hematoma, neoplasm, and edema can be life threatening and may require immediate care. The signs and symptoms include new or abrupt onset of pain, severe pain, and interruption of sleep by pain. In addition, non-pain symptoms may occur. Weight loss, ataxia, weakness, fever, changes in the neurologic examination, and neurologic deficits are common [37, 38, 49, 50].

4.2 Primary headache disorders

Migraine and tension-type headache (TTH) are considered the most prevalent among primary headaches. TTH affects 60–80% of the population while migraine has a prevalence of 15% (male 7.6%, female 18.3%) [39, 51]. Cluster headache is not very common (0.1%) [40, 41, 52, 53]; however, it is often misdiagnosed and mismanaged [42, 54]. Despite be a secondary headache disorder medication-overuse headache (MOH), it often co-exists with primary headache disorders, and consequently they are described together.

4.3 Intraoral pain disorders

Dental and other oral diseases are very prevalent conditions in the general population. Pain complaints are the primary reason why most patients seek care from dental or medical doctors. Thus, regardless of intraoral pain is not exclusively a result of dental disorders, it is essential that all complaints of pain in the mouth and face are carefully studied in order to know if there is a dental problem in its origin. There are a lot of common somatic intraoral pain disorders, which can originate from disease involving one or more broad anatomic areas: the teeth, the surrounding soft tissues (mucosa and gingiva, tongue, salivary glands), and bone.

4.4 Neuropathic pain disorders

Neuropathic pain is defined as a symptom caused by a lesion or disease of the somatosensory system, including peripheral fibers (Aβ, Aδ, and C fibers) and central neurons. Its prevalence is about 7–10% among the general population. Different causes of neuropathic pain have been described. Undoubtedly, there is a connection between neuropathic pain and population ageing as well as the increase of survival of cancer treatment and systemic diseases as diabetes mellitus. Indeed, imbalances between excitatory and inhibitory somatosensory signaling, alterations in ion channels, and variability in the way that pain messages are modulated in the central nervous system have been implicated in neuropathic pain. The challenge of chronic neuropathic pain is linked to the complexness of neuropathic symptoms, poor outcomes, and consequently difficult treatment options. The importance of the medication and other medical treatment is directly connected with the quality of life in patients suffering from

neuropathic pain. A multidisciplinary approach to the diagnosis and treatment of neuropathic pain is essential to achieve new and more efficient personalized intervention [43, 55].

4.5 Temporomandibular disorders

Temporomandibular disorder (TMD) is a general expression for pain, discomfort, and dysfunction of the masticatory muscles, the temporomandibular joints (TMJs), or both. TMD is the most common orofacial pain condition excluding dental pain. The main complaints from patients are regional pain in the face and periauricular area, limitations in jaw movement, and noise from the TMJs during jaw movements. Its prevalence is up to 15% in adults and 7% in adolescents. Long-term pain is the most important reason why patients with TMD seek treatment. Psychological disabilities are often associated with TMD. As peripheral mechanisms most likely play a role in the onset of TMD, a detailed muscle examination is recommended. The persistence of pain involves more central factors, such as sensitization of the supra spinal neurons and second-order neurons at the level of the spinal dorsal horn/trigeminal nucleus, imbalanced antinociceptive activity, and strong genetic predisposition, which also is included in DC/TMD. The etiology is multifactorial and still not clearly understood, but several biological and psychosocial risk factors for TMD have been identified. We have several treatment approaches to face temporomandibular disorders, including behavioral therapy, pharmacotherapy, physical therapy, and occlusal appliances. Evaluations indicated that the recently published Diagnostic Criteria for TMD (DC/TMD) are reliable and valid. These criteria cover the most common types of TMD and can be listed as follows.

4.5.1 Temporomandibular joint disorders

1. Joint pain
    a. Arthralgia
    b. Arthritis
2. Joint disorders
    a. Disk-condyle complex disorders
        i. Disk displacement with reduction
        ii. Disk displacement with reduction with intermittent locking
        iii. Disk displacement without reduction with limited opening
        iv. Disk displacement without reduction without limited opening
    b. Other hypomobility disorders
        i. Adhesions/adherence
        ii. Ankylosis

1. Fibrous ankylosis
2. Osseous ankylosis

c. Hypermobility disorders

i. Subluxation

ii. Luxation

1. Closed dislocation
2. Recurrent dislocation
3. Ligamentous laxity

3. Joint diseases

a. Degenerative joint diseases

i. Osteoarthrosis

ii. Osteoarthritis

b. Condylolysis

c. Osteochondritis dissecans

d. Osteonecrosis

e. Systemic arthritis

f. Neoplasm

g. Synovial chondromatosis

4. Fractures

a. Closed fracture of condylar process

b. Closed fracture of subcondylar process

c. Open fracture of condylar process

d. Open fracture of subcondylar process

5. Congenital/developmental disorders

a. Aplasia

b. Hypoplasia

c. Hyperplasia

4.5.2 Masticatory muscle disorders

1. Muscle pain limited to the orofacial region
    a. Myalgia
        i. Local myalgia
        ii. Myofascial pain
        iii. Myofascial pain with referral
    b. Tendonitis
    c. Myositis
        i. Non-infective
        ii. Infective
    d. Spasm
2. Contracture
    a. Muscle
    b. Tendon
3. Hypertrophy
4. Neoplasms
    a. Jaw
        i. Malignant
        ii. Benign
    b. Soft tissues of head, face and neck
        i. Malignant
        ii. Benign
5. Movement disorders
    a. Orofacial dyskinesia
        i. Abnormal involuntary movements
        ii. Ataxia
        iii. Subacute

b. Oromandibular dystonia

i. Acute

ii. Deformans

6. Masticatory muscle pain attributed to systemic/central disorders

a. Fibromyalgia

b. Centrally mediated myalgia

4.5.3 Masticatory muscle disorders

1. Headache attributed to TMD

4.5.4 Associated structures

1. Coronoid hyperplasia

4.6 Cervical pain disorders

Cervical pain disorders represent a very common group of musculoskeletal conditions that can greatly influence the head structures. We can divide it in two groups: those that primarily originate in the muscles and those that predominantly originate in the cervical spine. These structures very commonly refer pain to the orofacial region [44, 56].

4.7 Extracranial and systemic causes of orofacial pain

There are also some associated structures that can cause orofacial pain such as the eyes, ears, the nasal-paranasal sinus complex, the salivary glands, and the throat. In these cases, the orofacial pain is a heterotopic pain. At the same time, systemic diseases like oromandibular dystonia, multiple sclerosis, and Lyme disease, often have orofacial manifestations. The importance of an accurate differential diagnosis is obviously tremendous.

5. General considerations about clinical and epidemiological aspects of sleep-pain interaction

Clinical evidence on sleep-general pain interaction comes essentially from insomnia patients. The severity of the insomnia is associated with pain sensitivity. In a recent study, we showed that prevalence of insomnia in orofacial pain patients was almost 40%; in more than 600 clinical patients, approximately 1 in 6 suffered from relevant insomnia corroborating this important relationship between pain and sleep disturbance [57]. In a review on comorbidities of chronic facial pain and obstructive sleep apnea, Olmos also stated that sleep disturbances may impact orofacial pain in a bidirectional way [58]. Patients with obstructive sleep apnea (OSA) or with other respiratory problems during sleep, one of the most common causes of disturbed and insufficient sleep, may actually present with more pain-related complaints and we have recently showed that in a large sample of patients with temporomandibular disorders and chronic orofacial pain 22% of patients presented with snoring which

is the most common sign of sleep apnea. Furthermore, when snoring and insomnia complaints are considered together, 6% of those patients presented with both symptoms increasing the likelihood of suffering from OSA [59]. The reasons for the higher prevalence of pain in patients with sleep disturbances were discussed previously in the pathophysiological section and could be related with either peripheral (e.g., release of proinflammatory cytokines and decrease in pain tolerance) or central mechanisms. Often medication, commonly prescribed for pain management, affects breathing during sleep and can even interfere with other common sleep-related disturbances. For instance, mechanical management for pain control may affect normal respiration predisposing to sleep related breathing disorders [60].

Sleep impairment and chronic pain are also independently related with increased depressive symptoms. It has been speculated that pain, sleep, and depression could share some neurobiological matrix. Anxiety, mood changes, and depressive symptoms are however a common feature in the sleep disturbed patient, chronic pain patient, and patient with comorbidly sleep-pain-related complaints. Therefore, in patients with these complaints, it is important to adequately address these three main aspects: *Sleep*, *Pain*, and *Psychology*.

6. Assessment of sleep-pain interaction

While diagnostic aspects and evaluation of pain were discussed along this chapter and assessment of sleep was also detailed elsewhere in this book, it is important to consider some important diagnostic tools for an adequate assessment of the sleep-pain patient, such as self-reported questionnaires and polysomnography.

6.1 Self-reported measurements

An optimal use of self-report measures depends on the clinician's degree of expertise and on the specific goal. There are several screening, diagnostic, and follow up tools which can be used to properly evaluate and manage patients with sleep-pain interaction conditions.

Sleep evaluation involves several dimensions and patterns which should be differently assessed according to the main complaint and prior clinical suspicion. A sleep diary is the gold standard for subjective sleep assessment and is always a simple good way to start understanding better the usual sleep pattern of the patient. There is a consensus sleep diary (CSD) [61] that resulted for the collaborative work of both insomnia experts and potential users. This instrument is unique regarding the important related methodological issues that allow to evaluate insomnia in the research field and practical arena.

Other self-reported instruments commonly used are the Pittsburgh sleep quality index [62], to evaluate sleep quality, the Epworth Sleepiness Scale [63] to evaluate sleepiness which could be intended as an indirect measure of inadequate sleep, the Sleep Questionnaire to characterize sleep depth, and dreams and a the Sleep Disturbance Questionnaire to assess mental anxiety and physical tension. The Global Sleep Assessment Questionnaire (GSAQ) probably represents the best available screening tool for primary care practice. The chronotype as it could impact the sleep timing and the vulnerabilities for some pain sleep-wake cycle related impairments can be measured by the Morning-Evening Questionnaire [64], while states of sleepiness may be addressed by using the Stanford Sleepiness Scale [65] or the Karolinska Sleepiness Scale [66]. Visual analog scales oriented to sleep quality, sleepiness, or any other qualitative-measured dimension of sleep can also be used

and could provide important insights on the patient's status. For screening of specific high prevalent sleep disorders like sleep apnea or insomnia, there are available simple validated questionnaires as the Berlin Questionnaire [67] or the Stop-Bang [68] for sleep apnea and the Insomnia Severity Index [69], for insomnia.

6.2 Objective assessment

Polysomnography is the gold standard for sleep evaluation if movement disorders during sleep or parasomnias are suspected. In the case of disorders of central hypersomnolence, a Multiple Sleep Latency Test should be made after a PSG night in order to properly diagnose. Although PSG remains the gold option also to diagnose sleep disordered breathing, several simplified sleep studies are accepted and available. The American Academy of Sleep Medicine however recommends that PSG or home sleep apnea testing be used for diagnosis of uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. Important to note is that if a single home testing for sleep apnea is negative, inconclusive, or technically inadequate, PSG should always be performed for diagnosis in OSA. Furthermore, if a first PSG is negative and clinical suspicion for OSA remains, a second PSG should be considered [70].

7. Treatment of sleep-pain interaction

The orofacial pain diagnosis is clinical, but sleep studies may contribute to the objective establishment of orofacial pain interference with disturbed sleep.

The patient's evaluation should include the identification of risk factors as higher levels of anxiety, alcohol consumption habits, use of long-term medication, sedentarism, stress, and a compromise in the quality of life. Patients commonly complain from non-restless sleep and higher levels of fatigue, headaches, sleepiness, and anxiety.

Differential diagnosis could be difficult because of the occurrence of multiple sleep disturbances, which may mimic some aspects of pathological interaction between sleep and pain, either clinically or in a laboratory-based evaluation.

In patients with acute conditions, the efforts should be directed to the improvement of nocturnal complaints in order to avoid chronicity. In chronic patients, symptom relief is associated to a better quality of life.

Whenever possible, identifying the primary disturbance allows an approach directed to the etiological factors and sleep hygiene as well as management of sleep disturbances should be objectives to pursue.

Pharmacological management not only should always attend to the possible interaction with pain- and sleep-related mechanisms, but also to the influences of circadian oscillations in the symptoms and in the treatment effect (chronopharmacological characteristics).

7.1 Nonpharmacological interventions

Although medications have been widely used for managing both pain and insomnia, such drugs are not free from adverse effects which many times may actually worsen one or both conditions or even be responsible for therapeutic withdrawal symptoms. Cognitive behavioral therapy is largely used for insomnia (CBT-I) and for pain (CBT-P) related conditions and is recognized as an effective first option approach to both conditions.

7.2 Cognitive behavior therapy for insomnia (CBT-I)/disturbed sleep

Regarding sleep, cognitive behavior therapy for insomnia (CBT-I) proved to be superior to pharmacotherapy in several outcome studies [71, 72]. CBT-I consists of psychoeducation about sleep and insomnia, stimulus control, sleep restriction, sleep hygiene, relaxing training, and cognitive therapy.

Stimulus control techniques pretend to associate bed with a rapid sleep onset by teaching the patient to avoid habits other than sex and sleep in bed. Naps should also be avoided and regular sleep-wake schedules must be encouraged. Another important aspect is that the patient should learn only to go to bed when feeling sleepy and get out of bed if not asleep after 20 min [73].

Sleep restriction pretends to limit the amount of time spent in bed in relation to the actual time asleep. In the first days, this will lead to a mild sleep deprivation which soon will increase the sleep drive and afterwards to a more consolidated sleep with better rest and efficiency. When the patient improves, time in bed will increase again [74].

Sleep hygiene contributes to more adequate behaviors near bedtime as avoiding caffeine or tobacco, intense exercise, or too much light, noise, and use of electronic devices [75].

Relaxation training will reduce cognitive and physical tension prior to bedtime. Techniques like hypnosis, meditation, and guided imagery can be used with more or less efficacy depending of personality and circumstances [76].

Cognitive therapy will help patient to have real beliefs regarding sleep and to adopt attitudes that will favor sleep. For instance, many patients lie in bed and think they will not sleep the whole night, making them worried about this. This technique also pretends to eliminate excessive rumination and negative thoughts, mainly in the bedtime [77].

Cognitive behavioral therapy is also available for other sleep disturbances such as sleep apnea, narcolepsy, sleep-wake circadian mismatch, and several pediatric disorders. Therefore, it could be used in several domains [78–80].

7.3 Cognitive behavioral therapy for pain (CBT-P)

Several psychological- and behavioral-related options showed to be effective for chronic pain, including CBT-P, acceptance and commitment, mindfulness, progressive muscle relaxation training, motivational interviewing, and goal setting to behavioral activation. CBT-P is effective in a manner that its principles are associated to identify and approach those negative or dysfunctional thoughts and behaviors that usually worsen patient's adjustment to chronic mechanisms of pain. It was shown to effectively reduce patient distress in patients with pain-associated conditions. Although it is expected that CBT-P also has impact on sleep in those patients, there are only few studies addressing this.

7.4 Combined cognitive behavioral therapy directed to both sleep and pain

A synergistic (CBT-I + CBT-P) approach was associated with significant greater improvements either in pain and sleep when compared with each isolated strategy. Fatigue, depression, and overall improvement in quality of live with less pain interference were observed in patients treated with this combination [81].

7.5 Pharmacological therapy

Reciprocal interaction between pain and sleep disturbance makes it important to concurrently address and treat both conditions in order to succeed. In some

patients, in which CBT is not successful or effective, pharmacological therapy is often required. Sometimes, also in the beginning of the therapeutic process, some classes of drugs are useful to optimize therapeutic adherence in both sleep and pain.

7.6 Opioids analgesics

Opioids may improve subjective sleep quality in some patients with chronic pain, but can also interfere with sleep in others, mainly if they have sleep related breathing disorders which may be aggravated by this class of analgesic drugs. Other well-known potential adverse effects are hyperalgesia, tolerance, and dependence. That is the reason to support the recommendation *against* the use of opioids for insomnia, although it could be effective in highly selected pain patients [82].

7.7 Benzodiazepine receptor agonists

This class of drugs binds to GABA (gamma aminobutyric acid)-A receptors and has sedative/hypnotic, amnestic, anxiolytic, muscle relaxant, and anticonvulsant effects. Many studies show that this GABA-mediated pharmacological activity favors sleep quality, reduces sleep latency, and wakefulness after sleep onset and improve total sleep time. Half-lives of BzRAS vary from short and intermediate to long, and therefore indications for sleep disturbance and insomnia depends of its clinical aspect (onset, maintenance, or end-stage insomnia) as well as their expected adverse effects (cognitive impairment, low attention levels, anterograde amnesia). Some controversies persist however regarding clinical improvements using these drugs on the long term. Long-term adverse reactions involve the increase in depressive symptoms, cognitive and psychomotor slowing. Its abrupt stop should not happen as rebound insomnia and seizures could appear or increase in intensity. Tolerance and dependence are also issues important to consider and in clinical practice it should be avoided to prescribe more than one benzodiazepine at the time since metabolites can combine and prolong sedation time. BzRAS should not be a first option in non-controlled patients with sleep disordered breathing as they can disturb respiratory responses and therefore increase severity of sleep-related respiratory disturbances. Finally, it is crucial to appropriately taper the BzRA in order to prevent associated deleterious effects in comparison of their probable short time advantage [83].

7.8 Non-benzodiazepine benzodiazepine receptor agonists

The agents from this pharmacological class are active at the benzodiazepine GABA complex, particularly on receptors in the ventrolateral preoptic nucleus. Due to their proven efficacy, reduced side effects and less risk for addiction, non-benzodiazepine receptor agonists (non-BzRAs) became the most commonly prescribed hypnotic agents for onset and maintenance insomnia in the recent years [84]. Zolpidem, zaleplon, and eszopiclone belong to this newest class of FDA-approved hypnotics. They improve sleep latency with fewer side effects given their shorter half-lives and receptor binding profile. While Zolpidem is currently the most prescribed drug for insomnia with no evidence of tolerance or rebound effect [85], Eszopiclone seems to have a similar safety profile but higher antidepressant and anxiolytic effects in patients with comorbid insomnia [86]. Regarding safety, behavioral effects of zolpidem, and zaleplon are much similar to triazolam and include sleep eating, sleep walking, and sleep driving. As recent data from zolpidem showed some negative cognitive impact on women, FDA recommended to lower the dose in females.

7.9 Antidepressants

Antidepressants with sedative effect as tryciclic antidepressants (TCA), mirtazapine, and trazodone are often prescribed for insomnia comorbid with pain. Such pharmacological approach showed to relieve both insomnia, depressive, and pain-related symptoms. Often they are effectively used to treat neuropathic pain. Attention should be taken however regarding their differential effects on sleep. Imipramine and desipramine are less sedating and may disrupt sleep, amitriptyline, nortriptyline, trimipramine, and doxepine lead to a reduction in sleep latency, increase of sleep efficiency, and increase in sleep duration [87]. Those properties should be taken into account either on the prescription time or in the evaluation in order to control comorbid conditions.

Doxepin is approved as a hypnotic in doses from 1 to 6 mg and as an antidepressant in doses from 150 to 300 mg. At hypnotic doses, it reduces wakefulness after sleep onset, increases sleep efficiency, and total sleep time without next day impact on diurnal excessive sleepiness [88].

The adverse effects of TCAs are mainly due to anti-adrenergic and anticholinergic effects: orthostatic hypotension, xerostomia and xeropthalmia, constipation, and cardiac electric changes (delays in conduction). The risk of those side effects are age-related and particular care should be taken when prescribing TCAs to patients with comorbid depression and suicidal ideation because they are extremely lethal in overdose [89].

Trazodone, a type 2 serotoninergic, histaminergic and alfa1-adrenergic antagonist acts by inhibition of serotonin reuptake. As other antidepressants, trazodone has a hypnotic function at low doses whereas antidepressant effects occur at higher doses. It improves sleep in elderly, depressed, and anxious patients and patients with post-traumatic stress and has shown clear benefit in several painful conditions. Side effects include sleepiness the next day, rebound insomnia, orthostatic hypotension, xerostomia, and priapism [90].

Mirtazapine, a sedative antidepressant agent, at doses of 15–30 mg, improves sleep onset, total sleep time, sleep efficiency, and wakefulness after sleep onset. Additionally, it has a positive impact on pain (recurrent headache and postherpetic neuralgia), mood, and appetite [91].

7.9.1 Selective serotonin (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI)

This class of drugs is both effective for depression and pain, but it is linked to sleep disruption. So, whenever needed, attention should be paid to avoid its use in the evening hours [92].

7.10 Antipsychotics

Despite the limited evidence, some off-label atypical antipsychotics drugs (olanzapine, quetiapine, and risperidone) are used for managing sleep disruption and insomnia. Self-reported and objectively evaluated outcomes suggest efficacy in increasing sleep duration, slow wave sleep and decreasing sleep latency. However, long-term safety and efficacy studies should be done in order to corroborate these findings. Meanwhile, even in low dose (<150 mg/day) quetiapine was associated to xerostomia and dizziness. Some cases of hepatotoxicity, restless legs, and akathisia were also reported. Risperidone was associated to somnolence and sialorrhea and olanzapine is suggested to be related to a degree of sedation which impacts morning rising time [93].

7.11 Anticonvulsants

GABA analogs Gabapentin and pregabalin are two anticonvulsants often used to treat chronic pain with comorbid insomnia and studies suggest positive effects on sleep outcomes as sleep latency and wakefulness after sleep onset as well as in deep slow wave sleep. Both are effective as adjuncts in depression and anxiety. Frequent adverse effects are dizziness, diurnal sedation, gastrointestinal problems, and peripheral edema [94].

7.12 Melatonin

Some studies show that melatonin, an hormone for regulating mammalian circadian biology exerts anti-nociception effects in animal models and humans, and a recent metanalysis strongly supports the utilization of melatonin on anti-nociception against many types of pain [95]; thus, suggesting that melatonin directed to comorbid condition should be effective without any major adverse effects.

7.13 Anti-histamines

The majority of over-the-counter agents used for sleep contain first generation anti-histamines with complementary anticholinergic effects. Those agents are associated to a fast development of tolerance and the lack of long-term studies on these agents requires some caution particularly because of the link to diurnal sedation and impaired cognitive function [96].

7.14 Placebo effect

One relevant aspect not sufficiently discussed is the placebo effect, which can be sometimes one of the most important pieces of the treatment. Conceptualization of the placebo phenomenon has significantly changed during the last decades and this armamentarium is now intended as related to the patient's perception of a treatment. Of course, this is directly related to the patient's previous experience and the patient-practitioner relationship and confidence as well as with expectations, emotions, and beliefs. However, all those factors impact on cerebral function and release of endogenous opioids. Moreover, the placebo effect has a psycho-neurobiological base, since brain image studies performed in healthy volunteers show increased cortical activity particularly in the dorsolateral prefrontal cortex and orbitofrontal cortex, possibly associated with expectations of pain relief. On the other hand, the placebo analgesia is related to decrease of the neural activity in structures like thalamus, insula, and the anterior cingulate cortex, which constitute the so-called pain matrix [97]. The endogenous opioid system is probably involved in the placebo analgesia mechanism since opioid antagonists were shown to block the placebo effect [98]. Interestingly, the placebo mechanism was shown also to interfere with insomnia, even when patients did know they were taking a pharmacologically inactive substance [99]. It is of crucial importance for clinicians to be aware of how the placebo components may affect (enhance or reduce) the outcome of active treatment in chronic pain patients in order to separate either the therapeutic effect from the placebo one and to optimize treatment outcome.

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