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SEXUAL MEDICINE REVIEWS REVIEW

The Association Between Sleep Disturbances and Erectile Dysfunction During the COVID-19 Pandemic

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ABSTRACT

Introduction: There is increasing concern about the impact of the SARS-CoV-2 pandemic on mental and physical health. Among the many possible outcomes of COVID-19, reports of sleep disturbances, and erectile dysfunction are becoming prevalent worldwide.

Objectives: We sought to evaluate the recent literature on this subject to produce a narrative review of the topic.

Methods: We performed an extensive literature search to identify recent scientific findings on this subject.

Results: To date, the precise mechanisms that trigger pandemic related sexual dysfunction are not completely understood, although it has been suggested that psychogenic effects play an important role, in addition to the direct effects of the disease itself on those infected. There is evidence that the stress induced by the pandemic has had a significant impact on sleep, and sleep disturbances are known to induce erectile dysfunction. Other mechanisms which trigger this phenomenon, such as hormonal changes and previous health conditions, have been suggested to be associated with SARS-CoV-2 infection, and these factors may have a potential link to sleep disturbance.

Conclusion: The combined effect of COVID-19 and the psychogenic disorders triggered by isolation, grief, and anxiety might be associated with the increased prevalence of erectile dysfunction. This feature might be worsened by the onset of pre-existing or pandemic-induced sleep disorders. However, few studies explored this subject. Understanding this phenomenon is important for the strategic planning of treatments that could improve the quality of life of the population. **Andersen ML and Tufik S. The Association Between Sleep Disturbances and Erectile Dysfunction During the COVID-19 Pandemic. Sex Med Rev 2022;10:263–270.**

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Key Words: Sleep; Erectile dysfunction; COVID-19; SARS-CoV-2; Pandemic; Sexual behavior

INTRODUCTION

The absence of pathologies, physical and emotional well-being, and a good quality of life are some of the main factors that are essential for health. The current coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a global public health challenge, not only in relation to the disease itself, but also in respect of its impact on quality of life in general and the physical, emotional, and psychological health of the general population.

The pathophysiology of COVID-19 is complex, with a variety of symptoms, and outcomes having been reported in infected patients. In addition to the inflammatory unbalance known as the cytokine storm, which is closely associated with poor outcomes in respect of COVID-19, SARS-CoV-2 infection has frequently been related to neurologic damage,[1,2] as well as gastrointestinal, and cardiac pathology.[3] As the virus may infect a wide range of cell subsets, little is known about the long-term illness elicited by the infection. The increase in the number of variants of concerns (VOC) and the growing reports of different tissues that are susceptible to SARS-CoV-2 infection suggest that there is still a long way to go in respect of fully understanding the general health consequences of the pandemic.

The impact of the pandemic on mental health has become a growing concern. A recent study investigated the prevalence of stress symptoms and psychiatric disorders (including anxiety and depression) in the general Brazilian population through an online survey administrated between May 22, and June 5, 2020. The main findings revealed an increased prevalence of depression, anxiety, and stress symptoms unleashed by the pandemic, with the authors describing a steady growth in drug, tobacco, and

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food consumption.[4] The effects of the COVID-19 pandemic are caused not only by the infection itself, but also by a wide range of other factors, including changes in routine, the effects of social isolation and quarantine, and concerns about employment and loss of income, among others. Health professionals and individuals who cared for relatives and experienced grief or loss are among some of the most psychologically affected individuals.[5,6]

In addition to the psychological and physical consequences of COVID-19, recent evidence shows that the combined effect of stress, the viral neurotropism, and general symptoms of the disease (that include shortness of breath, fever, tiredness, dry cough, aches, and pain) can lead to a significant impairment in sleep quality.[7] Sleep is a behavioral and physiological event that is essential for life, and a bidirectional relationship between sleep and immunity/infectious diseases has previously been described in several studies.[7] As sleep deprivation/restriction is closely associated with the emergence of a diverse number of pathologies, the sleep disturbances induced by the COVID-19 pandemic are a cause of significant concern that need to be addressed.

METHODS

The literature review search was performed using the PubMed and Google Scholar databases, by using non−structured combinations of keywords related to three search domains: sleep (eg: sleep; sleep deprivation; sleep apnea; insomnia), erectile dysfunction (eg: sexual disorders, penile erection, erectile dysfunction) and COVID-19 (eg: COVID-19, SARS-CoV-2, coronavirus). Although the review was to a large extent based on studies identified using these key words, a narrative, rather than a systematic approach was used, as we considered that this would be the most suitable form to allow a discussion of the recent evidence, and the theoretical reasoning behind it. The articles were selected based on the relevance to the subject and we limited the search to English publications. Most of the studies described here were published in the last two years and reflects the scientific literature raised by the pandemic and its association with sexual dysfunctions.

RESULTS

Sleep and Sexuality

Among the many consequences of sleep disturbances, there is growing evidence supporting the idea that sleep quality affects sexual function. In 2015, a study suggested that an increase of 1 hour in sleep length was associated with a 14% increase in sexual activity.[8] It has been widely reported that several psychological consequences of sleep disturbances, such as anxiety and depression, can lead to sexual dysfunction. However, it is not only the psychiatric outcomes related to sleep deprivation/fragmentation that can lead to sexual impairment, it can also result from the homeostatic unbalance, and changes in hormonal production which are associated with poor sleep.[9] Brain activity during sleep disturbances modulates the production of hormones, such as cortisol in order to reorganize the sleep-awake cycle. One potential consequence of this is a reduction in the production of hormones (eg estrogen and testosterone), which can lead to a decreased sex drive, impaired erectile function (ED), and reduced fertility.[10]

Sleep is essential for overall health, and some of the most common diseases associated with prolonged sleep disorders, such as cardiovascular/coronary diseases, obesity, and diabetes, are known to be related to decreased sexual satisfaction, low desire, and ED. The American Diabetes Association estimates that 35−50% of the men who live with diabetes experience sexual dysfunctions, mostly ED.[11-13] The same conditions associated with poor sleep quality may also exert influence over erectile function, thereby inducing worst outcomes in respect of sexual disorders, and a cycle of mutual negative effects.

For males and females, sex comprises several different elements that include desire (motivation or libido) and excitement (arousal) that lead to physical reactions (increased blood supply to the penis and clitoris), orgasm (associated with ejaculation in males) and resolution, which may be followed by dopaminergic signaling, and the activation of the reward system in the central nervous system. The impairment of any of these stages constitute what might be considered a sexual dysfunction, although a specialized professional must properly diagnose each circumstance in order to exclude confounding factors, such as associated comorbidities.

In recent years, many research groups have been dedicated to understanding the mechanisms by which lack of sleep can compromise sexual life, aiming to develop treatment strategies that may improve quality of life. The search for the term (Sleep AND sexual*[tiab]) in PubMed reveals that almost 3,000 articles were published on this topic between 1953 and 2021, which include literature reviews, original clinical articles with humans, and experimental approaches with animal models, with the number of articles increasing every year.

The most prevalent sexual disorders in male and female individuals include low sexual desire, impaired arousal, difficulty reaching orgasm or ejaculation and ED.[14] ED is probably the most common sexual disorder, and is particularly associated with sleep disturbances, since many sleep alterations can induce the physiological impairment of hormone production and affect blood pressure. This can impair blood flow to the penis and reduce its rigidity which is essential for intercourse. As mentioned above, psychological health, which plays an important role in maintaining sexual desire and, consequently, erection, can also be impacted by sleep disorders.[8]

Sleep and Erectile Dysfunction

To understand the mechanisms underlying ED and its association with sleep disorders, the physiology of erection must be considered. The constant contraction of smooth muscle keeps

the penis in a flaccid state. Penile erection requires the release of acetylcholine by the parasympathetic cholinergic nerve fibers and nitric oxide production by the non−adrenergic non−cholinergic nerve fibers (NANC) to produce smooth muscle relaxation, which enables the influx of blood into the lacunar spaces in the cavernosa area. This compresses the subtunic venules, impairing the outflow of blood in order to maintain the erection.[15,16]

Males commonly experience penile erection through either physical (reflexive) or visual/mental stimulation (psychogenic) or during nocturnal sleep. All of which require both physical and psychological homeostasis in different areas, including the central nervous system, the cardiovascular system, and in respect of hormonal production and emotions. Most stress-induced cases of ED are a consequence of the impairment of 1 or more of the systems that are associated with the organic induction of penile erection. General stress and anxiety or depression led to alterations in blood pressure, metabolic syndrome, and impairment in testosterone production.[17,18] Moreover, most of the antidepressants used in the treatment of these conditions are associated with loss of libido.[19]

The mechanisms responsible for the influence of sleep disorders on ED remain uncertain. Among the many effects of lack of sleep are mood disorders, exhaustion, and variations in hormone production. Several studies have demonstrated that sleep deprivation can decrease testosterone production in animal models, leading to impaired sexual activity.[9,20] A similar profile was described in humans, with a study indicating a strong association between restricted sleep and reduced androgen concentrations in men, independent of age.[21] These studies suggest that alterations in the sleep cycle may exert a combined influence on sexual function that is caused by both psychological alterations and a physiological hormonal unbalance.[22] Although testosterone is the main factor associated with sexual performance, and a relevant factor for psychological health,[23] other relevant mediators, such as dopamine and cortisol, have important roles in driving sexual activity through the regulation of sexual desire (dopamine), and competition with testosterone production (cortisol).[9,24]

Studies have suggested that obstructive sleep apnea (OSA) may be the sleep disorder that is most associated with an increased risk of ED. In 2010 the epidemiologic study EPISONO found a prevalence of 32.9% of OSA in the population of the city of São Paulo, Brazil. The results indicated that 17% of the men diagnosed with OSA displayed symptoms of ED. It is important to emphasize that the age group in this study was from 20 to 80 years old. Some studies have indicated that this prevalence may be even higher than that found in the Brazilian study. The prevalence of ED in a Chinese cohort with 207 individuals diagnosed with OSA (44 ± 11 years old) was 60.6%,[25] while ED was found in 63.2% of the patients with OSA (average aged between 40 and 60 years old) in a survey carried out in 2016 in Turkey,[26] and in 51% of OSA patients (aged 18−70 years old) in a study from Spain.[27] Although the prevalence of ED varies according to different population studied, the data confirm the close relationship between OSA, and ED. In addition to decreased testosterone production, the reduced oxygen saturation induced by OSA may trigger sexual dysfunction. Prolonged hypoxia is related with ED symptoms,[28] and is probably one of its main causes.

Erectile Dysfunction, COVID-19 Pandemic and the Role of Sleep Quality

Since the beginning of the COVID-19 pandemic, there has been growing evidence of the increasing prevalence of ED in male individuals, either following the infection and/or resulting from the psychological stress associated with the pandemic.[29-32] Although there is increasing evidence that the pandemic has had a serious effect on sleep, little is known about how these sleep disturbances could be linked with the reported increase in the incidence of ED.

ED is known to be caused by several comorbidities, including those that originate from sleep disorders. OSA-induced physiological alterations in particular are known to be associated with ED. Parallel to this, studies suggest an important and significant bidirectional relationship between OSA and COVID-19 outcomes. A meta-analysis study of 21 articles exploring the relationship between OSA and COVID-19 published by Hariyanto and Hurniawan in April 2021 supported this hypothesis, reporting that OSA was associated with poor COVID-19 outcomes.[33] Another study revealed that patients diagnosed with OSA who exhibited a lower oxyhemoglobin desaturation index presented worse COVID-19 outcomes.[34] For the best of our knowledge, there is no description of OSA onset being triggered by COVID-19. Despite this, it is still reasonable to assume that the bidirectional relationship of the pathophysiology of both diseases could produce a combined effect, potentially worsening ED.

Severe OSA and COVID-19 share many clinical outcomes (eg excessive inflammation and a prolonged decrease in oxygen saturation), and both diseases have a worse prognosis when associated with comorbidities, such as diabetes, hypertension and cardiovascular conditions. Based on this, researchers have stressed the importance of monitoring the bidirectional relationship between sleep disturbances and COVID-19 to avoid or prevent severe outcomes.[35-39] As described above, sleep quality has been significantly affected by the COVID-19 pandemic, and this has been caused not only by organic alterations inherent to the infection itself, but by psychological-induced factors.

ED is usually attributed to either psychogenic or organic origins. However, this dichotomization has been discouraged, as it is hard to fully separate organic, and psychogenic conditions.[40] In practical terms, it is likely that most cases involve both possible etiologies, in a way that makes it difficult to consider any case as being exclusively organic or psychogenic. However, for didactical purposes, we elected to use these terms ("organic" and "psychogenic" erectile dysfunction), which should be understood by the readership as cases in which the cause of erectile dysfunction is mainly but not completely or exclusively attributed to one of

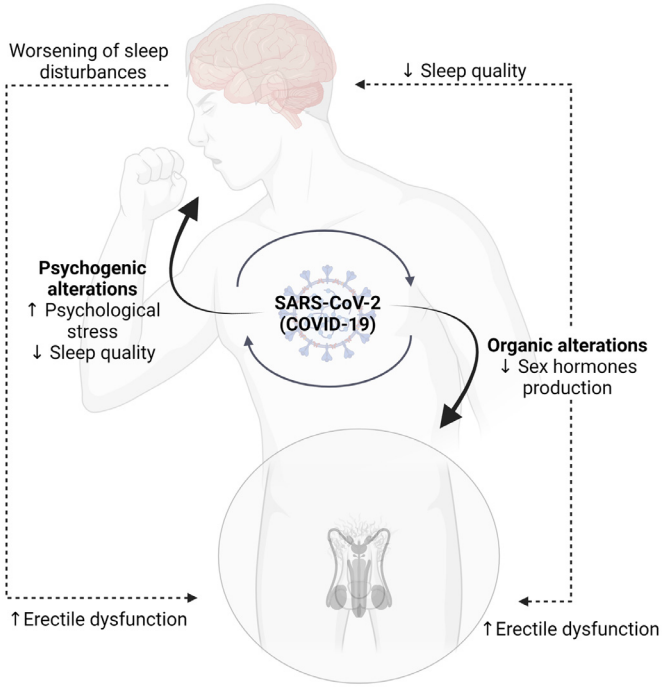


Figure 1. Relationship between sleep and ED dysfunction related to the COVID-19 pandemic. (Figure is available in color online at www.smr.jsexmed.org.)

these causes. Some of the most frequent conditions that are known to be closely associated with ED are metabolic diseases, such diabetes mellitus, obesity, hypertension, and cardiovascular diseases (eg atherosclerotic disease); prostate cancer treatment; endocrinal factors, including testosterone underproduction, and aging.[38,41] Anxiety (including performance anxiety), depression and treatment with antidepressants that inhibit serotonin reuptake are psychological precursors of ED.[42,43] The relationship between sleep disorders and ED is schematically presented in Figure 1.

Organic Erectile Dysfunction. Organic ED is induced by physiological alterations that promote the impairment of penile erection, which could be a consequence of the interruption of blood flow, hormonal changes, and impaired muscle tone. Some of the comorbidities mentioned above are commonly associated with sleep disorders (including OSA), and if not already present may be induced by COVID-19. SARS-CoV-2 infection is known to promote several physiological alterations. However, only a few studies have explored potential changes in the prevalence of ED during the COVID-19 pandemic, with most of these studies being clinical observations.

A survey that evaluated Italian male sexual health between April and May 2020 found a significantly higher prevalence of ED in patients diagnosed with COVID-19 (28%) compared to COVID-19-negative participants (9.3%) independently of other variables such as body mass index (BMI), age or mental health.[44]

The role of SARS-CoV-2 infection in the incidence of ED is a subject that is still under investigation; however, recent findings indicate that COVID-19 can influence both of the two main causes of ED, namely organic, and psychogenic-induced ED. In respect of organic origins, the combined effects of the common outcomes of COVID-19, such as increased viral load, and excessive inflammation might lead to ED. SARS-CoV-2 can affect both the male and female sexual organs, as the ACE2 receptor, the main entry point of the virus, is significantly expressed in many cell subsets, including in the testicles.[45] Some of the first studies on this topic did not find evidence of the virus in semen samples from infected men,[46,47] although later studies observed a high incidence of epididymitis in COVID-19 patients,[48] and postmortem biopsies from men who died from COVID-19 showed the presence of viral load in the testicles and germ cells. These results suggest a possible impact of the infection on reproductive health, spermatogenesis, hormone production, and even the potential for transmission during sexual intercourse.[49]

It is not clear how COVID-19 impacts testosterone production; however, a study revealed that 65.2% of 46 SARS-CoV-2-infected asymptomatic male subjects reported loss of libido,[50] and that there was a significant association between COVID-19 severity and decreased serum total testosterone levels in patients who had a pre-COVID-19 assessment of hormone levels. This suggests that this might be a consequence of the role of testosterone in regulating immune system activity.[51,52] In this respect, the parallel involvement of sleep disorders may be an additional factor that negatively modulates hormonal production, leading

to both the increased prevalence of ED, and the worsening of COVID-19. This may particularly be the case in respect of OSA, which as previously mentioned, has already been linked with ED, and worse COVID-19 outcomes.

It has been suggested that the changes observed in testicular pathology after COVID-19 may be induced by the abrupt inflammation, hyperthermia, and oxidative stress induced by the cytokine storm in association with hypothalamus-pituitary-gonadal axis abnormalities.[53] There is no information on whether the influence of SARS-CoV-2 on hormone production could be considered an evolutionary strategy for the virus prevalence; however, this phenomenon may be associated with the distinct outcomes of the disease observed in male, and female infected patients.

In addition to the hormonal alterations induced by COVID-19, a recent study found the presence of viral particles in the vascular endothelial cells of the corpus cavernosum in penis biopsies in men that developed severe ED after SARS-CoV-2 infection. In these patients, a reduced expression of eNOS was also found. These results suggest that the infection causes widespread endothelial cell dysfunction, indicating that SARS-CoV-2 may directly affect reproductive, and sexual health leading to penile tissue damage.[54,55]

Recent findings reinforce the idea that "long COVID" is a common outcome in a significant proportion of convalescent patients and is characterized by the prevalence of several symptoms of the infection for longer periods than in most patients (>7 months after infection onset).[56] Therefore, it is possible that the sexual impairment induced by COVID-19, and the associated alterations in sleep cycles might be a prolonged effect.

Among the symptoms triggered by COVID-19, it has been proposed that anosmia and ageusia are factors that may contribute to the reduction of social bonds, sexual interest and intercourse engagement. This phenomenon may be a consequence of the inhibition of the perception of pheromones and chemical induction of the neural interactions that lead to sexual stimulation.[57]

Psychogenic Erectile Dysfunction. In addition to physical health problems, the COVID-19 pandemic resulted in an increase in the reports of psychological disorders. Salari et al. reported that in more than 20 studies that analyzed the psychological profiles of more than 70,000 individuals, the prevalence of anxiety was between 29% and 32%, while in 14 studies with a sample size of 44,531 individuals, the prevalence of depression reached almost 34% after the pandemic onset.[58] As mentioned, the incidence of anxiety, depression, and marital problems elicited by the pandemic can alter the sleep cycle, thereby increasing the prevalence of sleep disorders. The combined effects of pandemic-induced stress and impaired sleep quality could be responsible for the prevalence of ED.

In the general population, stress, anxiety, and depression are often undiagnosed, and sexual dysfunctions induced by these conditions are underreported.[59] Men with anxiety and depression are more likely to report ED, lack of libido, and frequently experience performance anxiety during intercourse.[60]

The prevalence of ED during the pandemic has been addressed by a few studies dedicated to analyzing the social and psychological impact of COVID-19 on sexual life. A recent review that explored the scientific literature on this subject found a prevalence of 63.6% of ED in healthcare professionals working during the COVID-19 pandemic, and this number was significantly higher compared to non−healthcare workers (31.9%).[61]

In the general population, the effects of quarantine imposed because of the epidemic promoted different consequences on sexual life. It is noteworthy that active sexual engagement during the pandemic is closely associated with a reduced incidence of anxiety and depression.[62] In this regard, the maintenance of a healthy sexual life is important for the prevention of psychological distress, highlighting the importance of unravelling the mechanisms underlying the prevalence of ED. One study reported that 49% of the sample of 2,149 individuals reported an improvement in their sexual activities. This trend was strongest in cohabiting couples, but men who reported a negative impact of the pandemic on their sex lives presented increased ED and orgasmic disorders that were associated with symptoms, such as anxiety, and insomnia.[63] However, other studies found that after the beginning of the pandemic, couples reported a reduced frequency of sexual engagement.[64-67] Prior to the pandemic, it was already known that increased stress affects several aspects of human health, including sexual function; however, there is a lack of studies dedicated to investigating psychogenic-induced ED during the COVID-19 pandemic.

The Consequences of Erectile Dysfunction During the Pandemic

Since the pandemic is an ongoing event, there is, as yet, little data demonstrating the lasting effects of the pandemic on the sex lives of the population. Evidence in respect of the sales of drug treatments for ED is inconclusive, with an Italian study reporting a decrease in sales during the first lockdown,[68] probably as a consequence of priority for income redistribution, while a US study highlighted an increase in sales.[69] It may be that the increase in sexual dysfunctions during the pandemic will in the long-term lead to an increase in the search for solutions to this problem, particularly in respect of drug treatments. An increase in the search for pornography has been described, that might be a consequence of isolation, and the fear of contracting COVID-19 from close contact with a partner.[70,71] Despite these recent data, the impact of the pandemic on sexual dysfunctions, including ED, is not yet fully completely understood.

CONCLUSION

Infection by SARS-CoV-2 in association with periods of social isolation and quarantine due to the pandemic has had a

significant influence on the physical and mental health of the population. Although there is evidence to suggest that the pandemic has been associated with an increased prevalence of sexual dysfunctions and sleep disturbances, there are only a few studies that have specifically explored the triad of sleep, sexual disturbances, and COVID-19. Understanding the combined effect of these conditions is important for the strategic planning of treatments that could improve the quality of life of the population.

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