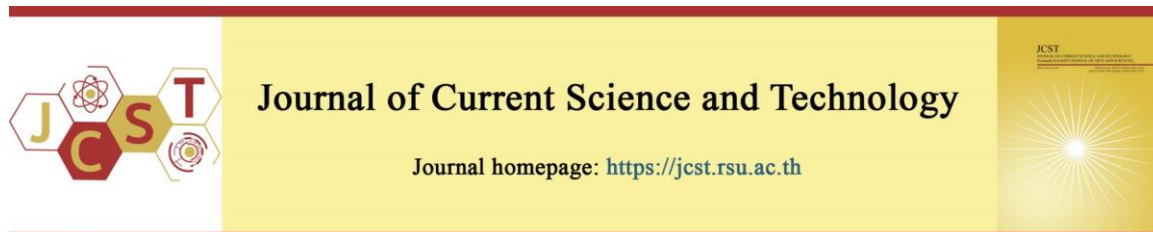


Cite this article: García Menéndez, S., Martín Giménez, V. M., Reiter, R. J., & Manucha, W. (2021, January). We are not alone: melatonin and vitamin D may be good company during COVID-19 pandemic. *Journal of Current Science and Technology*, 11(1), 158-170. DOI: 10.14456/jcst.2021.17



We are not alone: melatonin and vitamin D may be good company during COVID-19 pandemic

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Received 3 December 2020; Revised 6 January 2021; Accepted 11 January 2021
Published online 30 January 2021

Abstract

Loneliness and social isolation are associated with depression, anxiety and a progressive loss of higher cognitive faculties, mainly in older adults. In the current pandemic situation, with serious restrictions that limit interactions with members of our social circles, these cognitive alterations are becoming progressively more obvious in young adults, adolescents and even children. With the addition of eating disorders, sleep disturbances, and lack of exposure to solar radiation due to confinement, the condition can be considerably worse. Fortunately, there are two allies which from a psychological point of view, have many common features and could help to reverse some of the effects of social isolation; these molecules are melatonin and vitamin D. Their complementary functions on circadian rhythmicity may be useful in reestablishing mood balance. Thus, we suggest a re-education in new hygienic-dietary habits, especially related to the maintenance of adequate levels of melatonin and vitamin D, which may help prevent and possibly reverse the cognitive and psychological disorders until social contact is reestablished.

Keywords: anxiety; cognitive faculties; chronodisruption; depression; melatonin and vitamin D; SARS-CoV-2; social isolation.

1. Introduction

1.1 Social isolation affects cognitive faculties, or is it the other way around?

Social connections are known to be vital to survival throughout the animal kingdom and are dynamic throughout life. The consequences of social isolation and loneliness are increasingly a primary consideration in health care, disease prevention, and the degree of success in recovery processes (Matthews & Tye, 2019). One of the main consequences of confinement is the decline in cognitive faculties (Evans et al., 2019; Mengin et al., 2020). An example of this is being

observed in the recent pandemic caused by the SARS-CoV-2 virus, where the elderly are the first affected (Chu, Donato-Woodger, & Dainton, 2020). These sequelae arise both from the effects of social isolation (Chu et al., 2020; Su et al., 2020) and, secondly, the emotional disturbance associated with the experience of going through intensive therapy (Jaffri & Jaffri 2020). Everything seems to go in the opposite direction under these circumstances thereby emphasizing how important it is to maintain a socially active lifestyle (Malone, Liu, Vaillant, Rentz, & Waldinger, 2015; Röhr et al., 2020).

Although no psychological disorders were observed in the first weeks of isolation in countries such as China and Italy, when social restriction was several weeks long, disorders in various cognitive faculties became apparent (Su et al., 2020). Undoubtedly, these disorders were associated with reduced social interactions in young adults and adolescents and even in children. These included anxiety, post-traumatic stress disorder, depression, suicidal or addictive behaviors, domestic violence, eating, and sleeping disorders (Lopes & Jaspal, 2020; Ma et al., 2020; Mengin et al., 2020). Additionally, there are various problems of abuse of different drugs such as benzodiazepines or prescription opioids, without considering the cases of self-medication in single older adults in a situation of social isolation (Day & Rosenthal, 2020). The long duration of social confinement usually caused the psyche to undergo those changes (Su et al., 2020).

While it is still too early to determine whether a prolonged duration of social confinement that usually causes the psyche to undergo these changes will be associated with changes at the neuronal level, the scientific evidence shows -for example, in pathologies that present symptoms of isolation or of affective flattening such as autism- a correlation with a reduction in the activity of neurons in specific areas as well as a decrease in the volume of certain brain nuclei (Hoogman et al., 2020). Cognitive-behavioral therapy is commonly used in these cases, but there are new alternatives that science shows could help the recovery of these patients. One of the alternatives that may be useful from a more immediate point of view is augmented reality technologies such as a virtual group bike ride. This practice is carried out in residential centers for the elderly and has brought many benefits that counteract the effects of social isolation (Appel et al., 2020; D'Cunha et al., 2020). Other alternatives with some limited results are animal therapy, new skills, social services, and others (Freedman & Nicolle 2020).

New treatments with a more molecular focus are currently being tested to control behavioral alterations, for example, in the regulation of genes responsible for epigenetic modulation using proven drugs. These immediate early genes (IEG) are known to play an essential role in neuronal plasticity, memory,

and behavior (Maes et al., 2020). For instance, vafidemstat (ORY-2001) in phase IIa trials appears to be capable of controlling some of these IEGs, correct memory deficits, ameliorate behavioral disturbances, and reduce neuroinflammatory processes (Maes et al., 2020). Perhaps this kind of drugs could soon be used to reduce the possible consequences of the social isolation we face today.

As a potential treatment for future emotional disorders that this pandemic may leave, attention could be directed at drugs that may influence the activity of the enzyme glycogen synthase 3 β (GSK3 β). The activity of this agent on dopaminergic systems of the medial prefrontal cortex is intimately involved in controlling higher cognitive functions (Bramson et al., 2020; Khlghatyan & Beaulieu, 2020; Li et al., 2020). The results of a study in knockout mice to silence the RNA of the enzyme demonstrated the participation of GSK3 β in the regulation of behaviors related to mood and emotions (Khlghatyan & Beaulieu, 2020).

Not only do concerns for the mental health of the population come from the effects of social isolation, but at the other extreme, those patients who have been infected by the SARS-CoV-2 virus and admitted to intensive care units and who manage to recover suffer from so-called post-intensive care syndrome (PICS) (Jaffri & Jaffri 2020). PICS, is characterized by physical disability, mental health problems, and cognitive impairment that require a multidisciplinary treatment team (Klok et al., 2020; Smith et al., 2020). Clearly, prevention and treatment of brain disorders not only should be made in those patients with cognitive deterioration caused by social isolation but also in those patients who have managed to overcome the SARS-CoV-2 infection, focusing mainly on the elderly (Chu et al., 2020; Ma et al., 2020).

To help prevent these loss-of-contact disorders, stimulating and developing a resilient attitude would be helpful. Resilience has become something of vital importance to better cope with the situation that the world population is currently experiencing (Vinkers et al., 2020). Moreover, this process may be accompanied by the regulation of certain habits that have been misdirected in this pandemic. One of the most common bad habits is poor regulation of the sleep cycle due to stress, i.e., chronodisruption;

which contributes with the cognitive disturbances.

2. Could melatonin help in alleviating cognitive disorders?

Traumatic situations, whether related to personal life or caused by natural disasters, act by directly altering sleep regulation. During the current pandemic, many individuals have altered the timing of their daily routine, among many other perturbations (Cellini, Canale, Mioni, & Costa, 2020). Circadian disruption (chronodisruption) occurs when regular routines and internal rhythms are changed relative to the light:dark environment such that they are temporally desynchronized. These changes may induce alterations in body homeostasis, ranging from changes in cognitive abilities, behavior and performance (Rodrigues, Marques, & Gomes, 2019) to metabolic disorders (Cipolla-Neto, Amaral, Afeche, Tan, & Reiter, 2014; Rumanova, Okuliarova, & Zeman, 2020). The current social isolation caused by the pandemic may act as a catalyst for the disruption of the circadian rhythms. Thus, specialists in chronobiology have focused on this phenomenon (Erren & Lewis, 2020).

Melatonin is a ubiquitous ancestral molecule that has multiple functions in practically all living organisms. Of relevance to the current situation, the circadian secretion of pineal gland and possibly the synthesis of extrapineal melatonin (Acuña-Castroviejo et al., 2017) function as a chronobiotic, thus playing an essential role in the regulation of the circadian temporal internal order (Rodríguez et al., 2019; Cipolla-Neto et al., 2014).

The perturbed body homeostasis and allostatic load due to poor sleep hygiene have direct impacts at the cellular level (Egg et al., 2014; Acuña-Castroviejo et al., 2017; Bellanti et al., 2017; Ali et al., 2020; Mocayar Marón, Ferder, Reiter, & Manucha, 2020; Verma, Singh, & Rizvi, 2020) and the latter translate into a higher probability of developing pathologies ranging from metabolic disorders, cardiovascular diseases, immune system disorders, infertility, neurodegenerative deterioration and cancer (Al-Sarraf, Kasabri, Akour, & Naffa, 2018; Erren, Morfeld, Groß, Wild, & Lewis, 2019; Du & Holme, 2020; García Martín Giménez, Mocayar Marón, Reiter, & Manucha, 2020; Lateef &

Akintubosun, 2020; Morton et al., 2020; Schilperoort et al., 2020). The beneficial effects of melatonin would likely help to alleviate the disrupted circadian biology associated with the ongoing pandemic, which would be in addition to its evident antiviral actions (Feitosa et al., 2020) and could well be an effective antidote to the psychological consequences that social isolation is causing (Erren & Lewis, 2020; Mengin et al., 2020). While the benefits of its administration in animal models have been known for decades (Nie et al., 2017; Bano-Otalora, Madrid, & Rol, 2019; Jürgenson et al., 2019; Verma et al., 2020), the use of this molecule is increasingly being extended in various treatment schemes in humans (Agorastos & Linthorst, 2016; Xiao et al., 2019; Erren & Lewis, 2020; Galindo Muñoz et al., 2020; Latif Khan et al., 2020). Since the antioxidant, anti-inflammatory, and immunomodulatory properties of this molecule are well known, recently the scientific community has proposed it as a potential treatment against COVID-19 (Martín Giménez et al., 2020; Shneider, Kudriavtsev, & Vakhrusheva, 2020; Zhang et al., 2020). Beyond its ability to counteract the virus, its chronobiotic activity would likely be beneficial during the period of social isolation.

The promising dual effect of melatonin could also help with another primary concern in the healthcare community: gestational chronodisruption (Zhang et al., 2020). Maternal circadian rhythms provide essential circadian information to the fetal biological clock for synchronization and programming (Salazar et al., 2018). The recent pandemic caused by SARS-CoV-2 has forced alterations to social habits and, with it, the duration of exposure to natural light. This may have unfavorable consequences for pregnant women and their fetuses (Bagci, Sabir, Müller, & Reiter, 2020). Thus, while melatonin may help to overcome the psychological effects of the social isolation in the present generation, it may also be of benefit for the optimal health of next generation (Zhang et al., 2020). Of special interest, this chronobiotic may be assisted by another important molecule, vitamin D, in overcoming the negative effects of social isolation (Martín Giménez et al., 2020).

3. Could vitamin D help in alleviating cognitive disorders?

Low vitamin D levels and poor sleep quality are associated with the development of cognitive dysfunction in healthy people (Song & Wu, 2018). Hypovitaminosis D is a condition that increases the risk of developing cognitive impairment and dementia, especially in older people (Annweiler et al., 2015). Vitamin D deficiency is usually linked to a reduction in the volume of several hippocampal subfields and disrupted connections in hippocampal network of older people with mild cognitive impairment; which may worsen neurocognitive disease prognosis in these patients (Al-Amin et al., 2019).

Below normal vitamin D levels are also associated with an increase in the severity of negative symptoms in patients with schizophrenia (Graham et al., 2015). Moreover, a vitamin D deficiency is also related to neuronal integrity disruption, particularly in frontal brain regions, and may lead to the reduction of neuroprotection during cerebral ischemia, contributing to memory loss and other permanent deficits (Moon, Moon, Kwon, Lee, & Han, 2015). As another example, autistic children are more frequently deficient in vitamin D than are non-autistic children, which may exacerbate this psychiatric pathology (Guo et al., 2019).

Of particular interest, vitamin D supplementation attenuates the cognitive impairment observed in diabetic animals, possibly through the enhancement in cholinergic transmission at the prefrontal cortex level (Alrefaie & Alhayani, 2015). Vitamin D also reduces irritability and hyperactivity symptoms in children with autism spectrum disorder (Mazahery et al., 2019). Even in stroke patients, high vitamin D levels are associated with less cognitive impairment (Yalbuздag et al., 2015).

To highlight, vitamin D deficiency impairs the synthesis and release of serotonin. This neurotransmitter is responsible for the maintenance of multiple cognitive processes and brain functions related to mood. Therefore, serotonin dysfunction would lead to the exacerbation of neuropsychiatric disorders such as depression, among other associated alterations (Patrick & Ames, 2015). Suicidally-depressed individuals show significantly reduced vitamin D levels compared to depressed people who are not suicidal. Thus, the more exaggerated the vitamin D deficiency, the greater the manifested

depressive symptoms (Jo, Zhang, Emrich, & Dietrich, 2015). In young girls with severe hypovitaminosis D, vitamin D supplementation caused a reduction in the intensity of mood disorders associated with premenstrual syndrome. Some of these mood disorders included anxiety, irritability, sadness, and disturbed relationships (Tartagni et al., 2016). Severe vitamin D deficiency could also be responsible for developing psychiatric eating disorders such as bulimia nervosa and anorexia nervosa (Tasegian et al., 2016). Hypovitaminosis D may also be associated with greater anxiety levels, contributing to the increased future risk of psychosis (Kelley, Sanders, & Beaton, 2016; Bičíková et al., 2015). One study reported that mice with vitamin D deficiency showed greater vulnerability to the psychiatric effects of social stress (Groves, Zhou, Jhaveri, McGrath, & Burne, 2017). Vitamin D deficiency is also related to the development of agoraphobia, an anxiety disorder characterized by an irrational fear of entering open or crowded places, leaving one's own home, or being in places where escape is perceived to be difficult (Fond et al., 2019). Low vitamin D serum levels are often in patients with stroke and mood disorders. Likewise, hypovitaminosis D could increase the risk of developing depression in post-stroke individuals (Wu et al., 2016). Moreover, a potential relationship between vitamin D status and the probability of developing antenatal depression and/or postpartum depression has been suggested (Aghajafari, Letourneau, Mahinpey, Cosic, & Giesbrecht, 2018). Finally, it has been observed that the behavior, emotion, and attention of children may be negatively affected by a vitamin D deficiency (Wang et al., 2020).

Vitamin D supplementation may significantly reduce negative emotions (Cheng, Huang, & Huang, 2020). It has been found to reduce psychological sequelae (stress, depression, and anxiety) observed in patients surviving natural disasters such as floods or earthquakes (Kaplan, Rucklidge, Romijn, & Dolph, 2015). One study also demonstrated that vitamin D has strong anxiolytic-like effects in an experimental rat model of long-term estrogen deficiency induced by ovariectomy (Fedotova, Pivina, & Sushko, 2017; Fedotova et al., 2017). Of additional interest is one report which indicated that skin exposure to ultraviolet

radiation improved circulating vitamin D levels and mood, especially in those who prefer the evening for performing their daily activities (Toledo et al., 2019).

From the analysis of the evidence summarized above, it is clear that vitamin D deficiency may induce brain disorders in previously healthy people under conditions that predispose them to psychological changes and may worsen or exacerbate the status or progression of existing psychiatric pathologies. In any case, vitamin D supplementation could prevent mood disorders that may develop or worsen during the COVID-19 pandemic (Patrick & Ames, 2015), especially considering that quarantine and imposed isolation to indoor places reduce sunlight exposure, which is important for the endogenous synthesis of vitamin D (Nair & Maseeh, 2012).

4. Conclusions and prospects

Herein, with the current pandemic situation we propose a feedback loop that

increases the likelihood of developing psychological impairments due to deficits in circadian organization (which can be minimized by regular melatonin use) and a relative vitamin D deficiency (Figure 1). SARS-CoV-2, a highly infectious virus, has forced social isolation to flatten the contagion curve. While this measure has provided protection against the spread of the virus, it is also generating parallel mental health problems that should not be ignored. One of the main consequences of social isolation is that it mainly generates stress, anxiety, and depression (Lopes & Jaspal, 2020; Ma et al., 2020, Mengin et al., 2020). This emotional change adds to changes in exposure to sunlight, and consequently, alterations in sleep cycles cause by chronodisruption that directly affects metabolic and psychiatric homeostasis (Erren & Lewis, 2020). In turn, this leads, among other things, to a dysregulation of the immune system and contributes to an increased vulnerability to the SARS-CoV-2 virus.

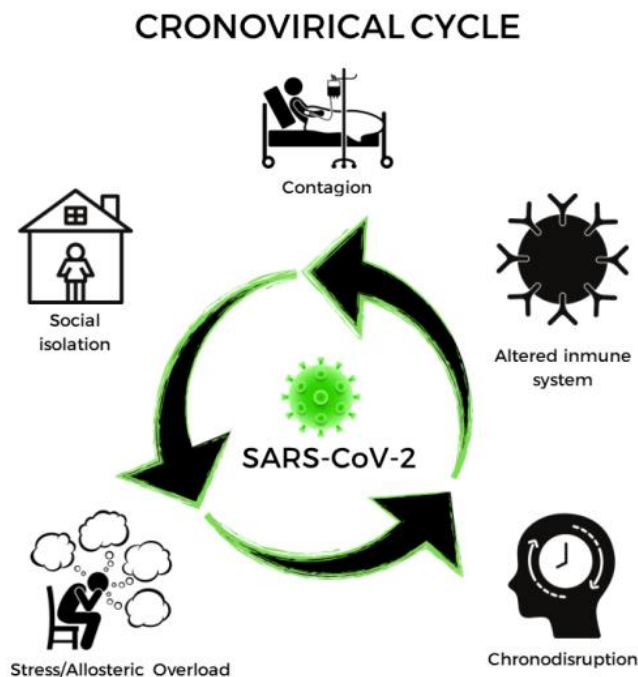


Figure 1. This cycle describes an interrelation between external and internal factors that increase the possibility of contagion with the COVID-19 virus.

Analyzing this from a graphic perspective, some behavioral adjustment may

help to break this negative cycle (Figure 2). One of them involves changing underlying circadian

rhythms using a treatment scheme with melatonin and vitamin D (Martín Giménez et al., 2020). Another means to overcome the endogenous disruption arising from isolation is replacing bad habits with healthier ones under these unfamiliar conditions. As examples, mobile phone, tablet, computer, and TV use should be avoided where possible for at least 2 hours before sleep time. Blue light emitted by these screens maximally inhibits natural melatonin production at night (Wahl, Engelhardt, Schaupp, Lappe, & Ivanov, 2019). Daytime activities could also be adjusted since both low

and excessive daily activities negatively affect sleep quality (Gulia & Kumar, 2020). Performing daytime activities under natural light, aids not only in helping to correct circadian rhythms, but also in promoting the endogenous synthesis of vitamin D, a molecule that is highly beneficial (Patrick & Ames, 2015). Whether converting to healthier habits or by using exogenous treatments to adjust rhythms and metabolism, supplemental melatonin and vitamin D may improve psychological and physical wellbeing.

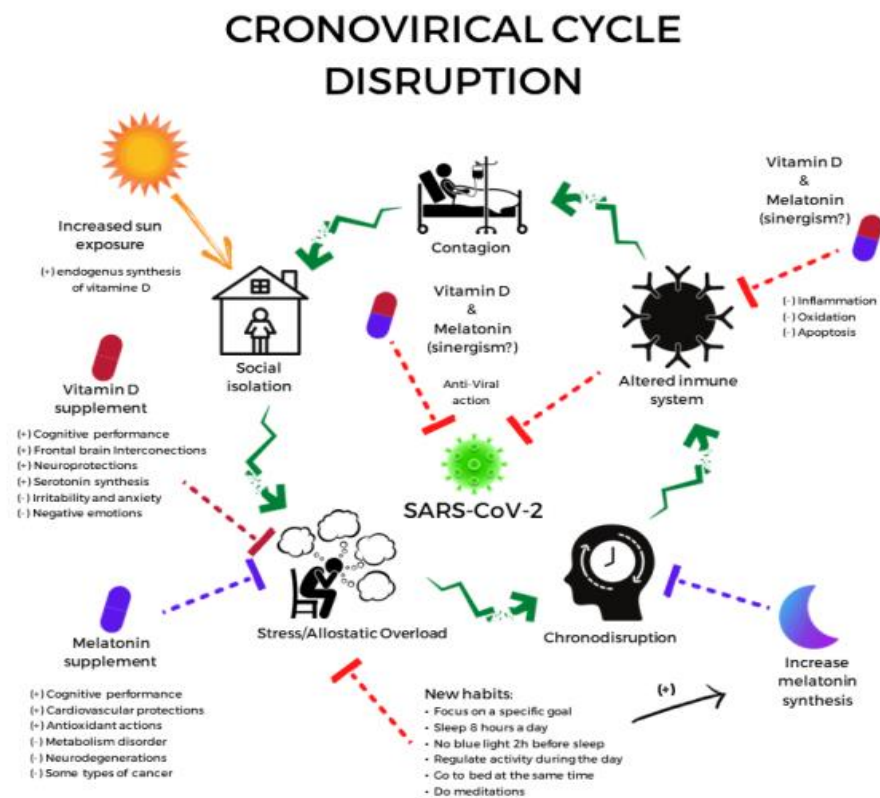


Figure 2. Representation of the breaking points of the COVID-19 virus contagion cycle (green arrows). The stimulating (blue fringes) or inhibitory (red dashed lines) actions of vitamin D and melatonin act synergistically on critical points in the cycle. The increases in the endogenous levels of these molecules can be achieved physiologically through changes in some habits, as well as through the external administration of these drugs.

This pandemic has tested our resilience in every respect. Consequently, to cope with current and future behavioral problems associated with social isolation, it is important to

use current scientific knowledge to benefit individual and community health. This strategy will enhance the possibility of avoiding lingering mental effects of this extreme situation.

5. Acknowledgements

This work was supported by grants from the Research and Technology Council of Cuyo University (SECyT), Mendoza, Argentina, and from National Agency for the Promotion of Research, Technological Development and Innovation ANPCyT FONCyT (Grant no. PICT 2016-4541, and IP-COVID-19-931).

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