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Repurposed drugs for ALS are also of increasing interest, as evidenced by promising results from a phase 2 double-blind placebo-controlled study of AMX0035.<sup>10</sup> This combination of sodium phenylbutyrate and taurursodiol was designed to prevent neuronal death by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction. The mean rate of decline in ALSFRS-R total score was significantly slower with AMX0035 than with placebo. A separate phase 3 study of taurursodiol versus placebo is underway in Europe, and it is likely that an additional phase 3 trial of AMX0035 will be initiated in 2021.

Finally, the impact of the COVID-19 pandemic on clinical research in ALS has been considerable. There has been a significant shift to remote monitoring using telemedicine, as reflected in numerous publications over the past 6 months. COVID-19 has also necessitated a paradigm shift for the future design and execution of clinical trials, with a change in emphasis from in-clinic evaluation to home monitoring. Home monitoring opens opportunities for repeated testing of defined outcomes over shorter periods, providing a richer dataset of outcome measures that could, in future, reduce variance and improve reliability.

OH is the editor-in-chief of the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, and has consulted for Cytokinetic, Wave Life Sciences, Novartis, Orion, and Denali.

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## Sleep research in 2020: COVID-19-related sleep disorders

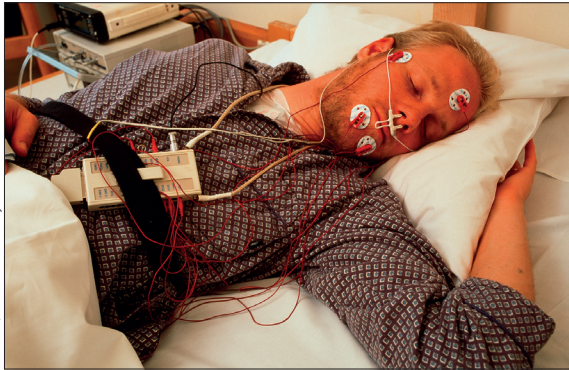


2020 has been an unprecedented year because a modified coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly from China to all continents, leading to the COVID-19 pandemic. The first studies of COVID-19-associated sleep disorders were reported in China. Huang and Zhao<sup>1</sup> collected information from a survey of 7236 volunteers (mean age 35.3 years [SD 5.6]). About a third of them were health-care workers. About 35% of these participants reported symptoms of general anxiety, 20% of depression, and 18% of poor sleep quality.<sup>1</sup> The participants who were most worried about the pandemic also reported the most symptoms. Health-care workers were clearly under great pressure, which was reflected in the high prevalence of mental-health symptoms that they reported.<sup>1</sup>

The increased prevalence of sleep disorders in 2020 has also been highlighted in several other publications from different countries. These studies examined the effect on sleep of SARS-CoV-2 infection and confounders related

to isolation, quarantine, anxiety, stress, or financial losses. According to a European task force, symptoms of insomnia could be related to psychosocial factors and to the confinements.<sup>2</sup> In Italy, anxiety related to COVID-19 was highly associated with disturbed sleep. In a survey of 2291 Italians, 57.1% reported poor sleep quality, 32.1% high anxiety, 41.8% high distress, and 7.6% reported post-traumatic symptoms of stress.<sup>3</sup> In the International COVID-19 Sleep Study,<sup>4</sup> different factors are being investigated using a harmonised set of questions. Insomnia, nightmares, sleep apnoea, fatigue, exhaustion, and REM sleep behaviour disorder are being investigated by this collaboration.<sup>4</sup> The hypothesis is that fatigue, sleepiness, and REM sleep behaviour disorder might be related to SARS-CoV-2 infection per se, whereas insomnia might be related mainly to confinement, anxiety, and other psychosocial factors.<sup>2</sup>

Although studies related to COVID-19 have dominated the field in 2020, other important investigations have



also been published. Untreated severe sleep apnoea is associated with poor health and cardiovascular morbidity and mortality. However, the cost-effectiveness of treating mild severe sleep apnoea with continuous positive airway pressure (CPAP) is still unclear. Two important randomised studies on the treatment of patients with severe sleep apnoea have been reported. The MERGE trial in the UK, which included 233 participants with mild untreated severe sleep apnoea (defined as having scores of 5–14 on the Apnoea–Hypopnoea Index [AHI]), showed that CPAP significantly improved quality of life (as measured by the Short Form Health Survey).<sup>5</sup> Although this study is methodologically robust, it does not provide final answers, and its follow-up time was short (only 3 months). Although 81% of the treated participants were willing to continue CPAP after completion of the trial, the improved quality of life might have been due to other factors. Effects of body-mass index, physical exercise, and sleepiness on quality of life were not analysed. All patients with untreated severe sleep apnoea should lose weight if they are obese, avoid excessive stress, and have a healthy lifestyle. CPAP can therefore not be routinely recommended for all cases of mild untreated severe sleep apnoea. In addition to their subjective quality of life, assessing daytime functioning in these patients is crucial.

Another large randomised study was done in Spain. The ISAAC study recruited 2551 individuals.<sup>6</sup> Of the 1264 patients without excessive daytime sleepiness (Epworth Sleepiness Scale score [ESS]  $\leq 10$ ) and moderate-to-severe untreated sleep apnoea (AHI scores  $\geq 15$ ), 633 were randomly assigned to receive CPAP and 631 to receive usual care. The median follow-up time was 3.35 years. No significant differences in the occurrence of cardiovascular events were found. 98 (16%) of the

events were observed in the CPAP group and 108 (17%) in the usual care group. The hazard ratio was 0.89 (95% CI 0.68–1.17;  $p=0.40$ ).<sup>6</sup> Unfortunately, the investigators did not stratify patients with untreated severe sleep apnoea according to moderate (AHI scores 15–19) or severe (AHI scores  $\geq 30$ ) disease. Furthermore, they did not include patients with mild (ESS 11–14), moderate (ESS 15–17), or severe (ESS  $\geq 18$ ) daytime sleepiness and untreated severe sleep apnoea. Therefore, the results cannot be generalised to all patients with obstructive sleep apnoea, and certainly not to patients with moderate or severe (ESS  $>14$ ) daytime sleepiness. The results indicate that CPAP might not be necessary in patients without excessive daytime sleepiness (ESS  $\leq 10$ ) and AHI scores of 15 or lower. The findings from the ISAAC and MERGE trials thus point to different directions. What is more important: preventing cardiovascular morbidity for a 3-year period or improving quality of life for a 3-month period? This question remains open. Meta-analyses and studies addressing potential confounders are needed.

Further important findings in sleep medicine came from Hablitz and colleagues,<sup>7</sup> who showed that CSF distribution is under circadian control. Researchers in Copenhagen (Denmark) and Rochester (New York, USA) have proposed that interstitial ion signalling is crucial in controlling sleep and wakefulness.<sup>8</sup> These investigators have also proposed that ion homeostasis failure might contribute to neurological diseases and cognitive-behavioural disorders.<sup>8</sup> New studies done by Erlend Nagelhus and colleagues also show that Ca<sup>2+</sup> signalling is essential in the regulation of slow wave sleep.<sup>9</sup> All of these new studies support that astrocytes are key elements in the regulation of brain function. Emerging evidence indicates that disturbed sleep might be among the strongest risk factors for development of neurodegenerative diseases. Therefore, all physicians should incorporate questions about sleep hygiene and quality into their routine clinical practice.

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## Neurological infections in 2020: COVID-19 takes centre stage



Although there have been many contributions to advance our understanding of neurological infections in 2020, the year has been dominated by research focused on the neurological consequences of COVID-19. Multidisciplinary studies are ongoing to better differentiate the direct effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) versus its secondary effects (PMC7184392, NCT04386083, and CTRI/2020/07/026339). Nevertheless, it has become clear that there is a striking incidence of neurological involvement in this disease, the symptoms of which span reversible anosmia, stroke-related disability, and death.<sup>1–3</sup>

Dry cough, fever, dyspnoea, nausea, emesis, and fatigue are common symptoms of SARS-CoV-2 infection<sup>1</sup>—a profile shared with numerous viral infections. However, anosmia and ageusia, which have now been documented in ample research,<sup>1,2,4</sup> are symptoms more distinctive of SARS-CoV-2 infection than other common viral infections, and the implications of these symptoms drive our understanding of the unique pathophysiology of COVID-19. In one of the largest studies to date, 3191 individuals infected with SARS-CoV-2 were surveyed to assess the prevalence of anosmia and ageusia. 488 (15.3%) individuals were found to have one or both of these symptoms; in most cases, taste and smell were fully recovered 7 days after onset on average.<sup>1</sup> Smaller studies have shown anosmia to be much more prevalent and the heralding symptom of SARS-CoV-2 infection,<sup>5</sup> therein identifying a potential source of viral replication and CNS invasion.

Subsequently, hypotheses emerged regarding the potential for viral neurotropism and a direct route of entry into the CNS from the olfactory bulbs. In an imaging

study<sup>6</sup> of 23 patients with confirmed SARS-CoV-2 infection with clinical anosmia, SARS-CoV-2-related olfactory dysfunction was differentiated from other viral olfactory dysfunction in several crucial ways. Post-viral anosmia in the setting of upper respiratory tract infections is usually related to mucosal congestion and nasal obstruction, resulting in a conductive olfactory loss; however, few patients with SARS-CoV-2-related anosmia had sinonasal symptoms, suggesting that mucosal congestion is an unlikely aetiology for anosmia in these cases.<sup>6</sup> Olfactory epithelium support-cells residing in the olfactory cleft express the angiotensin-converting enzyme 2 receptor, identified as the binding antigen for SARS-CoV-2.<sup>6</sup> Imaging of the olfactory cleft showed olfactory cleft opacification in 17 (74%) of cases.<sup>6</sup> Moving proximally, olfactory nerve filia clumping, suggestive of inflammation, was observed in eight (35%) of patients, and olfactory bulb signal abnormalities, indicating degeneration or microhaemorrhage, were seen in 21 (91%) individuals. Within the CNS, hyperintense T2 or fluid-attenuated inversion recovery signals in the olfactory cortex were found in five (22%) individuals.

An association has been shown between SARS-CoV-2 infection and acute inflammatory demyelinating polyradiculoneuropathy (AIDP),<sup>7</sup> extending the viral pathogenic effects to the peripheral nervous system. In a case series of five individuals with AIDP and SARS-CoV-2 infection, the latency between respiratory symptom and neurological symptom onset was 14–30 days.<sup>7</sup> Most patients presented with the classical findings of AIDP, with ascending paraparesis and hyporeflexia, conduction blocks and increased latency on nerve conduction studies, and albuminocytological dissociation in the



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