that high-income countries and low-income and middle-income countries are living two different epidemics. Whereas high-income countries deal with opioid-related deaths, low-income and middle-income countries have undertreatment of pain and suffering. The further the pendulum swings towards opiophobia, the harder it will be for low-income and middle-income countries to deal with their crises.

Various strategies have been implemented to treat patients with opioid use disorder. A combination of behavioural health services with substitution opioid therapy is considered the standard of care, preventing overdose and treatment dropout. Treatment usually uses one of or a combination of methadone, buprenorphine, and naloxone. Buprenorphine stands out because of its good tolerability and its effectiveness in managing withdrawal symptoms and blocking the subjective effects of other opioids. A new, subcutaneously extended-release, monthly administered buprenorphine treatment was approved in 2017 by the US Food and Drug Administration, which allows for a steady plasma concentration and mitigates the risk of misuse of take-home medications. A phase 3 study assessed two regimens of extended-release buprenorphine against placebo to establish its efficacy and tolerability.[6] Both regimens obtained more than 40% abstinence from opioids, whereas placebo achieved only 5%. Treatment success (>80% abstinence) was higher in buprenorphine groups, and withdrawal symptoms were less intense. The most common side-effects were headache and nausea. Some issues related to the injection site (pruritus and pain) were reported, but they were considered minor. Therefore, extended-release buprenorphine provides a promising option to manage opioid use disorder, minimising issues of adherence, diversion, and misuse.[5]

Although treatment with methadone and buprenorphine are well recognised, stigma and tight government regulation end up reducing implementation of opioid substitution therapy. In 2019, cannabidiol was studied as a potential treatment for opioid use disorder.[7] Data show that this medication was able to reduce anxiety, drug-craving behavior, and physiological responses (heart rate and salivary cortisol levels) to drug-associated cues.[7] No effect was observed on cognition or relevant adverse effects after treatment. Although these data are promising, little is known about the consequences of long-term use of medical cannabinoids regarding misuse and addiction.

There has been much progress since the beginning of the opioid epidemic, but there remains much more to be done. Perhaps a better understanding of the neurophysiology involved in addiction will provide a clearer path towards treatment. There is still a need for more advanced policies that allow a balance between prevention of opioid use disorder and adequate treatment for patients with pain. The struggle with opioids continues, with some seeking new analgesic options and safety, while many people around the world still miss the minimum necessary for pain relief.

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Advances in sleep medicine in 2019

Remarkable research findings have led to multiple advances in sleep medicine in 2019. Among the most important improvements, we would like to highlight the approval of new medication, the passing of legislation, improvements in our understanding of the effects of obstructive sleep apnoea, and advances in

our knowledge about prognosis in REM sleep behavior disorder (RBD).

Modafinil, armodafinil, and amphetamine-based stimulants are standard therapies for treatment of excessive daytime sleepiness, but might not adequately control symptoms or can result in intolerable side-effects. Solriamfetol (a selective dopamine and norepinephrine reuptake inhibitor) has been investigated for the treatment of excessive daytime sleepiness in patients with narcolepsy and obstructive sleep apnoea. Thorpy and colleagues[1] conducted a phase 3, double-blind, randomised, placebo-controlled study (NCT02348593) of solriamfetol in patients with narcolepsy. Patients were randomised into four groups, receiving placebo (n=58) or three different doses of solriamfetol: 75 mg (n=59), 150 mg (n=55), or 300 mg (n=59). After 12 weeks, a significant reduction in Epworth Sleepiness Scale score was observed for all three solriamfetol groups and a significant increase in mean sleep latency on Maintenance of Wakefulness Test was seen with solriamfetol 150 or 300 mg, compared with placebo. Headache, nausea, and reduced appetite were the most common side-effects. Based on these findings, and data from other studies in patients with obstructive sleep apnoea, the US Food and Drug Administration approved solriamfetol for excessive daytime sleepiness in patients with narcolepsy and obstructive sleep apnoea in March 2019.

A physiological circadian phase-shift results in a delay in sleep and wake up times during adolescence. This phase delay, combined with early school start times, results in insufficient sleep and other adverse consequences, including obesity, poor school performance, increased motor vehicle crashes, and depressive symptoms. In 2017, the American Academy of Sleep Medicine released a position statement calling for delaying school start times to 8:30 am or later, but this recommendation has been difficult to implement given conflicting interests of multiple stakeholders. Using actigraphy, Nahmod and colleagues[2] assessed the association between school start time and total sleep time, sleep onset, sleep offset, wake after sleep onset, and sleep quality. Adolescents (n=383) were divided into four groups based on school start times: before 7:30, 7:30 to 7:59, 8:00 to 8:29, and 8:30 am or later. The investigators found that school start time of 8:30 or later was associated with a significantly longer sleep duration of 34 min when compared with the before 7:30 group, 23 min for 7:30 to 7:59, and 21 min for the and 8:00 to 8:29 group. In October 2019, California became the first state to pass legislation mandating later school start times.

RBD might precede the onset of parkinsonism by several years, sometimes even decades. The time-lag between RBD and motor symptoms of parkinsonism provides a unique opportunity for future trials of neuroprotective agents which might stop progression of neurodegeneration. Postuma and colleagues[3] assessed the risk and predictors for the development of neurodegenerative disease in the International REM Sleep Behaviour Study. The study recruited 1280 patients (from 24 centres) with idiopathic RBD. The investigators evaluated motor, sleep, cognitive, special sensory, and autonomic tests and did dopamine transporter single photon emission tomography (DAT-SPECT). The risk of phenoconversion to overt neurodegenerative disease was 6·3% per year and 73·5% at 12 years. Factors associated with increased risk of phenoconversion were: age, abnormal motor function, mild cognitive impairment, olfactory and colour vision abnormalities, erectile dysfunction, constipation, REM atonia, and abnormal DAT scan. These findings might help select patients when designing trials of neuroprotective agents in the future.

Obstructive sleep apnoea is characterised by intermittent hypoxia and sleep disruption, and has a role in cognitive impairment. MRI studies have shown loss of volume in the hippocampus in individuals with obstructive sleep apnoea, but direct tissue evidence was absent. In a histopathological study, Owen and colleagues[4] investigated the hippocampal cell layer thickness and myelination in autopsied brains of 32 individuals with obstructive sleep apnoea. They found that the hippocampal loss correlated with the severity of obstructive sleep apnoea. Multiple areas of the hippocampus (hilus and molecular layer of dentate gyrus; the CA1; layers of the entorhinal cortex) that have a role in memory circuits were affected. Decreased myelin staining was noted in layer six of the entorhinal cortex and deep white matter. Although continuous positive airway pressure users had less cortical atrophy, they had similar myelin loss compared with nonusers. These findings suggest that continuous positive airway pressure use can prevent some degree

of memory impairment, but other changes might be irreversible.

Obstructive sleep apnoea continues to be defined by the apnoea-hypopnea index. This metric does not capture the duration or severity of the ventilatory disturbance, which might have a substantial role in cardiovascular outcomes. Azarbarzin and colleagues[5] developed a novel metric to measure the ventilatory disturbance and assessed its association with cardiovascular mortality in the Outcomes of Sleep Disorders in Older Men and the Sleep Heart Health Study cohorts. The obstructive sleep apnoea specific ventilatory disturbance was calculated as the area under the curve associated with obstructive events, thereby taking into account the degree, frequency, and duration of oxygen desaturation. They found that this metric was independently associated with cardiovascular mortality, whereas the apnoea-hypopnea index was not. The time might have come to move beyond defining and quantifying obstructive sleep apnoea in terms of a single frequency metric—such as the apnoea-hypopnea index—and use other more sophisticated measures, which might better predict cardiovascular outcomes.

In conclusion, these studies in 2019 advanced our understanding of treatment of excessive daytime sleepiness, changed school start times, and improved our knowledge on the effects of obstructive sleep apnea on cognitive health, and that on neurodegeneration in RBD. Future research to define obstructive sleep apnea in terms of metrics or biomarkers that better predict cardiovascular outcomes will be useful.

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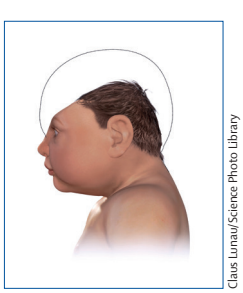
Neurological infections in 2019: challenges, solutions, and open questions

In 2019, groundbreaking progress has been made towards the understanding of the pathogenesis of neurological infections like bacterial meningitis or Zika virus-induced microcephaly, thanks to omics sciences—cutting-edge technologies that might also improve the diagnosis of neurological infections.[1] Furthermore, we now have a broader knowledge base on the global burden of neurological infections due to international collaboration projects. For example, meningitis is one of the four largest contributors of disability due to neurological disorders which, in turn, are the leading cause of disability worldwide.[1]

In genome-wide association studies, the genomes of people with diseases are compared with those of healthy controls to identify small genetic changes, single-nucleotide polymorphisms, that contribute to disease susceptibility and phenotype. A study on samples of human and pathogen DNA from culture-proven cases of pneumococcal meningitis revealed that variation in host genetics explains approximately 30% of the observed variation in pneumococcal meningitis susceptibility and almost 50% of the variation in disease severity.[2] In particular, variants in *CCDC33* were identified to be associated with susceptibility and variations near *UBE2U* and *ROR1* with severity of the disease. The bacterial genome was found to be crucial for determining the invasive potential but to have no effect on meningitis severity. The pneumococcal genes involved in invasiveness included *pspC*, *dacB*, *psrP*, and zmpD. These genes are promising candidates for the development of new pneumococcal vaccines.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Another sequencing approach, metagenomic next-generation sequencing of CSF, could revolutionise the approach to neurological infections, which currently