DNA. In this system, the Cas9 endonuclease is guided by a single guide RNA to its complementary DNA sequence, where it induces a double-strand break, allowing editing. One major advantage of CRISPR-Cas9 over antisense oligonucleotides is that treatment with this sort of paradigm should require only one dose. However, a single-dose treatment also runs the risk that side-effects might be lifelong. A study[3] of a transgenic mouse model of amyotrophic lateral sclerosis that carried human mutant *SOD1* used adeno-associated virus 9 to deliver CRISPR-Cas9 and a single guide RNA designed to disrupt *SOD1*. Treated mice had reduced concentrations of mutant SOD1 protein, a delay in onset of symptoms of amyotrophic lateral sclerosis, and 25% longer survival, compared with untreated mutant mice. A similar approach is being investigated in animal models of Duchenne muscular dystrophy: building on earlier murine work, CRISPR-Cas9 components targeted to dystrophin in a canine model of Duchenne muscular dystrophy substantially increased concentrations of dystrophin.[4] Treated dogs also showed improved muscle histology. There is a long way to go before this therapy can be used in humans, and there are important hurdles to be overcome, including safety concerns, but these early studies are very promising.

Many of these exciting treatments for neuromuscular disorders are costly and raise concerns about the affordability of health care going forward, so it was a relief to see a successful trial of a comparatively inexpensive treatment for chronic inflammatory demyelinating polyneuropathy. In the PATH study[5]—a randomised, placebo-controlled, double-blind trial of subcutaneous immunoglobulin for chronic inflammatory demyelinating polyneuropathy—172 patients whose neuropathy was responsive to intravenous immunoglobulin were randomly allocated to placebo, low-dose subcutaneous immunoglobulin, or high-dose subcutaneous immunoglobulin. Relapse or withdrawal rates were significantly higher in the placebo group (n=36; 63% [95% CI 50–74]) than in the high-dose subcutaneous immunoglobulin group (n=19; 33% [22–46]) or low-dose subcutaneous immunoglobulin group (n=22; 39% [27–52]), and the treatment was well tolerated at both doses. Subcutaneous immunoglobulin offers a more convenient option for patients hitherto dependent on intravenous immunoglobulin, and can be administered at home, which improves quality of life and reduces costs associated with infusion-based treatments.

Overall, 2018 has seen innovation in the application and delivery of new therapies. Now that the ice is broken, the practical use of gene therapy in neuromuscular disease is a new area that should see huge strides in the next few years.

*Apeksha M Shah, *Ammar Al-Chalabi*
Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, London SE5 9RX, UK (AMS, AA-C); Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, UK (AMS); and Department of Neurology, King's College Hospital, London, UK (AA-C)
ammar.al-chalabi@kcl.ac.uk

AA-C is a consultant for Chronos Therapeutics, Mitsubishi-Tanabe Pharma, Cytokinetics, OrionPharma, and GlaxoSmithKline, and was Chief or Principal Investigator for clinical trials from Cytokinetics, OrionPharma, and GlaxoSmithKline. AMS declares no competing interests.

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Pain research in 2018: the year of translational studies

For decades, the traditional bottom-up approach in chronic pain research has consisted of investigation into mechanisms of pain in animal models, then attempted translation of the data obtained to the clinic.[1,2] However, because it is difficult to predict mechanistic conservation between animals and humans, several treatments developed on the basis of the mechanisms identified in animals have subsequently failed in humans.[2] A translational top-down approach to research has also been tried, consisting of stratifying patients on the basis of their sensory phenotypes (ie, specific combinations of signs and symptoms), with the hypothesis that

these phenotypes are surrogate markers for varying mechanisms. Despite promising preliminary results, this approach remains difficult to implement because of the complex relationship between phenotypes and underlying mechanisms.[1,2]

What if the mechanisms of pain could be assessed directly in patients? This approach seems increasingly feasible, as illustrated by several outstanding publications in 2018 concerning neuropathic pain. One major mechanism for peripheral neuropathic pain is increased axonal excitability in C nociceptors, particularly mechano-insensitive so-called silent nociceptors.[3] Thus far, silent nociceptors have been explored exclusively using microneurography, a very invasive technique consisting of direct electrophysiological recordings of nerve fibre activities. Jonas and colleagues[3] have developed for the first time a non-invasive psychophysical approach to selectively activate silent nociceptors using transdermal slow sinusoidal stimulation. Contrary to continuous electrical stimulation, which leads to nociceptor adaptation, this sinusoidal stimulation technique was shown to increase pain (rated on the numeric rating scale for pain) in 14 healthy people and in nine patients with neuropathic pain. This finding highlights the potential relevance of silent nociceptors as a surrogate, although indirect, marker of axonal excitability in patients with neuropathic pain.

Key determinants of axonal excitability include ion channels, particularly the sodium channel subtypes Nav1.7 and Nav1.8, which are expressed in primary afferent neurons. Thus far, gain-of-function variants of Nav1.7 have been associated to erythromelalgia and small fibre neuropathy, two rare and often inherited conditions. An important step forwards was taken in 2018 by Blesneac and colleagues,[4] who assessed whether individual Nav1.7 variants were associated with diabetic painful neuropathy. In a detailed phenotypic assessment of 111 patients with painful diabetic neuropathy and 78 patients with painless diabetic neuropathy, Blesneac and colleagues[4] identified 12 rare Nav1.7 variants exhibiting gain of function in ten patients with neuropathic pain, whereas none of the 12 Nav1.7 variants were found in the group without pain. Seven variants were novel and five had previously been associated with idiopathic small fibre neuropathy or erythromelalgia. Compared with other diabetic patients with neuropathic pain, patients who had any of these 12 variants had shorter disease duration, enhanced burning pain, and pressure evoked pain. Nav1.7 antagonists are now in early clinical development for treatment of peripheral neuropathic pain.[5] Enhanced analgesic effects of a topical Nav1.7 antagonist (about 7·5 µL of ointment per cm^2 of affected skin) compared with placebo have been reported in a proof-of-concept study of 54 patients with post-herpetic neuralgia who have a particular Nav1.7 polymorphism.[5] Thus, the combination of phenotypic and genotypic profiling might contribute to improved targeting of neuropathic pain treatment in future trials.

Mechanisms in the CNS also play a crucial role in chronic pain. One key mechanism is descending pain modulation of nociception from the brain to the spinal cord dorsal horn.[6] Chronic pain might result from an imbalance in this system, either through enhanced facilitation or reduced inhibition. Most previous studies have focused on descending inhibition, which has been found to be decreased in patients with chronic pain compared with healthy controls. In 2018, an elegant study using functional MRI in patients with painful diabetic neuropathy conversely found that patients with pain had enhanced facilitation of the descending pathway, but those without pain did not.[6] A key area involved in descending modulation, the ventrolateral periaqueductal grey, had enhanced functional connectivity that positively correlated with spontaneous pain intensity, heat hyperalgesia, and brain responses to heat. This brain-based facilitation mechanism might also play a major role in painful neuropathies.

One future direction of research is to explore how brain mechanisms predict the analgesic effect of centrally acting drugs, such as cannabis-derived compounds. In a functional MRI study of 15 patients with chronic radicular neuropathic pain receiving single administrations of cannabis-derived δ-9-tetrahydrocannabinol (0·2 mg/kg) or placebo using a double-blind trial design, Weizman and colleagues[7] found that brain areas playing a key role in descending pain modulation and affective pain processing, such as the anterior cingulate cortex and the dorsolateral prefrontal cortex, were functionally involved in analgesia. Such analgesia was also predicted by higher functional connectivity in these areas. Whether these data extend to other centrally acting analgesics needs to be established.

Notably, a substantial overlap seems to exist in the brain areas involved in the response to active analgesics

and placebo analgesia. Placebo analgesia can affect almost all placebo-controlled clinical trials and the effect might sometimes exceed that of potent painkillers, including opioids. Vachon-Pressau and colleagues[8] reported the first large-scale brain imaging study using a double-blind design aiming to investigate the brain areas involved in placebo analgesia in 63 patients with chronic low back pain. Patients were randomly assigned into three groups to receive placebo, no treatment, or active analgesics. Patients receiving placebo had higher self-reported pain relief than those with no treatment and this was predicted by several psychological traits measured at baseline, such as increased emotional awareness. Authors further found that the response to placebo was predicted by modifications of the structure or function of key brain areas in pain modulation, encompassing the anterior cingulate cortex, sensorimotor cortex, prefrontal cortex, and periaqueductal grey—which play a role in the response to active analgesics—but also by brain characteristics not previously associated with analgesia, such as subcortical volume asymmetry. Thus, placebo responses in patients with low back pain were partially predictable by combining psychological and brain imaging models. Whether these models will be able to predict placebo responders in future clinical trials remains to be established.

Overall, these translational pain studies in 2018 have contributed to our understanding of pain and analgesia. We hope that they will also advance the therapeutic management of chronic pain, which is still a crucial unmet medical need.

Nadine Attal, Didier Bouhassira
INSERM U 987, Centre d'Evaluation et de Traitement de la Douleur, CHU Ambroise Paré, Assistance Publique—Hôpitaux de Paris, 92100 Boulogne-Billancourt, France (NA, DB); Université Versailles-Saint-Quentin, Versailles, France (NA, DB)
nadine.attal@aphp.fr

NA reports personal fees for consultancy from Merck Sharp and Dohme, Grunenthal, Sanofi Pasteur Mérieux, Novartis, and Teva; personal fees for serving on an advisory board from Aptynix; and speaker fees from Ipsen. DB reports personal fees for consultancy from Grunenthal, Novartis, and Teva; personal fees from Air Liquide for coordination of clinal trials; and speaker fees from Pfizer.

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Neurology met sleep medicine in 2018

In 2018, several mechanistic and interventional studies have illuminated our knowledge at the intersection between clinical neurology and sleep medicine. Narcolepsy due to hypocretin deficiency is a primary sleep disorder that can lead to excessive daytime sleepiness, and in which humoral immunological responses against hypocretin neurons are suspected. A study reported the detection of cytotoxic CD8+ T cells specific for hypocretin neurons in both peripheral blood and CSF in some patients with narcolepsy.[1] This finding reinforced the hypothesis of an autoimmune pathology in narcolepsy and identified these T cells as a potential diagnostic or prognostic biomarker. Regarding plasticity of hypocretin neurons, opioid effects were reported in both humans and mice. Hypocretin neurons were protected from neuronal death by long-term morphine administration in wild-type mice,[2] and neurogenesis was not the mechanism of hypocretin neuron protection. Additionally, morphine administration reduced cataplexy attacks in narcoleptic mouse models. Of relevance, about 54% more hypocretin neurons were found in five people with heroin addiction post-mortem than in control brains.[2] This translational finding indicates pathways to protect or even restore hypocretin function.

Two clinical randomised trials[3,4] tested the safety and efficacy of sodium oxybate for hypersomnolence and both trials reported positive results. In a randomised trial of 12 patients with Parkinson's disease who had excessive daytime sleepiness, sodium oxybate significantly reduced sleepiness compared with placebo, with a moderate


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