It can hit as a piercing jolt, or sometimes as a dull ache that radiates through the body. Pain can be exquisite, or debilitating and chronic, which can destroy one’s quality of life.

Pain starts with a stimulus at the periphery of the body, which then travels through neurons to the brain. But the process is far more complex. A number of neuronal circuits are involved in pain transmission. Most of these circuits are plastic and can change when something goes awry. Once we understand these circuits, we can interfere and block them at the right level.

However, pain is not only a matter of neurons. The tissue around them plays an important role, too. Other cells—such as skin, immune, or glia cells, to name just a few—participate in the pathogenesis and also the resolution of pain. Nor is there a simple one-way street from the periphery to the brain. Powerful cognitive processes shape the way that we perceive pain. This perception is determined by our expectations and the situation in which we find ourselves. Clinicians need this knowledge to develop techniques for personalized treatment of chronic pain and to prevent pain from spiraling out of control.

Failed attempts to manage pain have contributed to the opioid epidemic in the United States. Understanding how opioids work, and how in some circumstances they might actually amplify pain, should lead to alternatives. As many states legalize the medical use of marijuana, hints are emerging that cannabis could be one, but research is complicated by strict federal regulations.