A DEEPENING CRISIS

Triggered by aggressive marketing of prescription opioid drugs and false claims about their safety, the opioid crisis is now an epidemic that involves both prescribed and illicit drugs. Tackling it is more urgent than ever. By **Liam Drew**; *infographic by* **Alisdair Macdonald**.

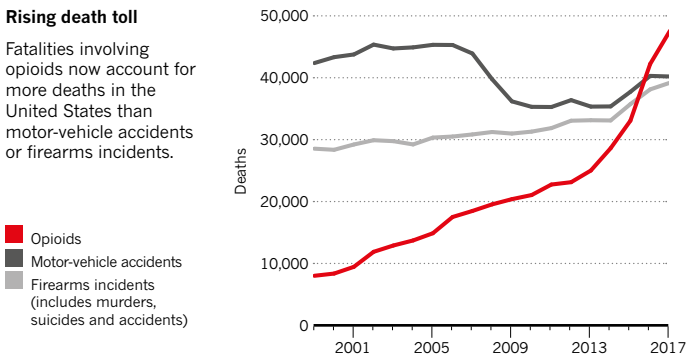
UPWARD TRAJECTORY

In the United States, opioid prescription rates have been falling since 2011. But in the same period, the number of opioid-related deaths has increased dramatically.

CDC

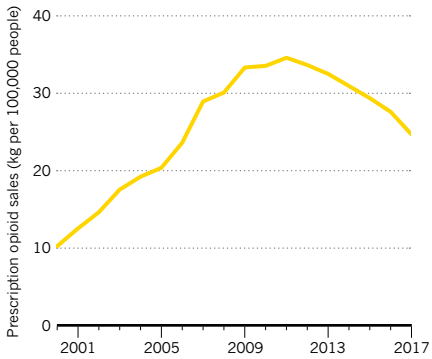
Rising death toll

Fatalities involving opioids now account for more deaths in the United States than motor-vehicle accidents or firearms incidents.



Falling prescriptions

For many years, the trend in opioid-related deaths in the United States correlated roughly with that in opioid prescriptions. But as opioid sales began to fall in 2011, the death toll continued to rise.



SHADAC/DEA

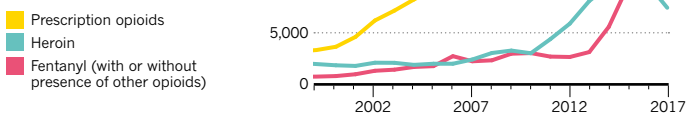
MOVING UNDERGROUND

Addictions to prescription opioids have helped to create a market for heroin, an illegal opioid often adulterated with the potent opioid fentanyl.

CDC

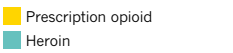
Three-act tragedy

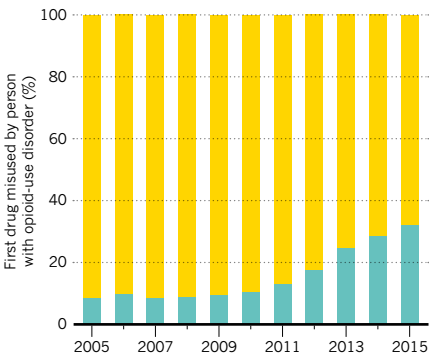
Deaths from prescription opioids have plateaued. After a sharp rise in deaths caused by heroin overdose, those linked to fentanyl are skyrocketing.



Shifting gateways

In the past, opioid-use disorders typically began with the use of prescription opioids, although many people progressed to illicit opioids. Since 2011, the proportion of addictions initiated by heroin has been rising.





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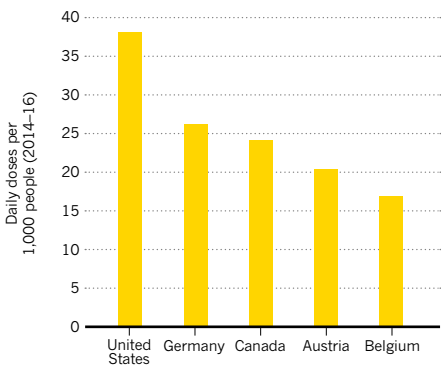
A SAFER PRESCRIPTION

Opioid prescription rates vary markedly between countries. Some nations use this class of drug widely for pain relief without high death rates.

OECD/INCB

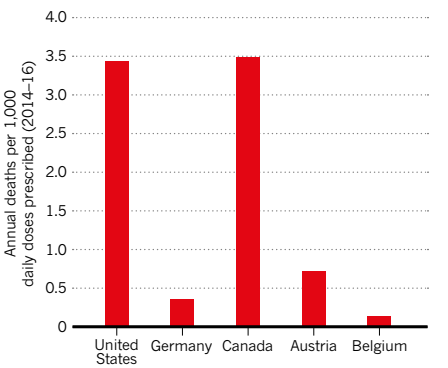
Leading prescribers

Although the United States prescribes the most opioids of all high-income countries, other nations also use prescription opioids in large quantities.



Variable relationship

Prescription opioid use varies between countries in terms of many factors. These include opioid strength, monitoring of patients and the level of social support available to users. Such differences could help to account for variations in mortality rate.



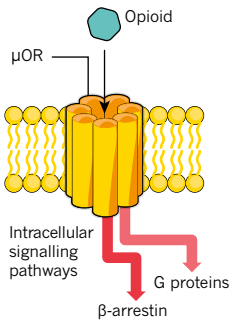
OECD/INCB

THE PATH TO PAIN RELIEF

Opioids can provide strong pain relief, or analgesia, but they are also extremely addictive. The benefits and risks of taking prescription and illicit opioids arise from the activation of a signalling system used by the brain to regulate numerous functions.

OPIOID RECEPTORS

There are several types of opioid receptor in cells. Prescription and illicit opioids activate the μ-opioid receptor (μOR), which inhibits the activity of neurons by two main signalling pathways.



The presence of μORs on the surface of many types of neuron throughout the central nervous system, as well as in the gut, mediates the diverse effects of opioids.

ANALGESIA

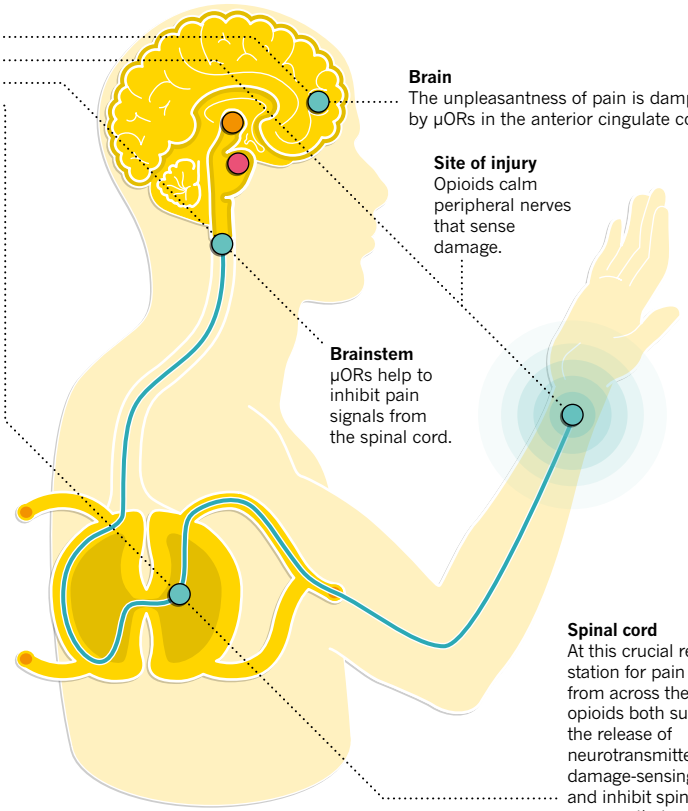
The painkilling power of opioids comes, in part, from their ability to block pain signals in several locations.

DEPENDENCE

Opioid dependence results from the euphoric and rewarding effects of taking opioids, as well as from wanting to escape the effects of withdrawal. μORs in several brain regions contribute. Crucial μORs are found in the midbrain, from where they trigger the release of the neurotransmitter dopamine in the nucleus accumbens.

OVERDOSE

μORs in the brain's respiratory centre suppress breathing. Overactivation of these receptors through an overdose of opioids can lead to death.



Brain
The unpleasantness of pain is dampened by μORs in the anterior cingulate cortex.

Site of injury
Opioids calm peripheral nerves that sense damage.

Brainstem
μORs help to inhibit pain signals from the spinal cord.

Spinal cord
At this crucial relay station for pain signals from across the body, opioids both suppress the release of neurotransmitters from damage-sensing nerves and inhibit spinal neurons that convey pain signals towards the brain.

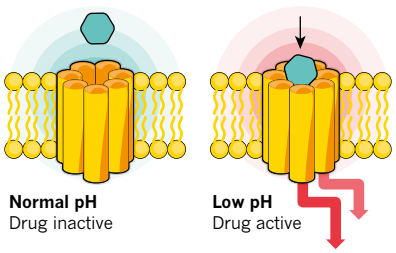
PAINLESS REVERSAL

Halting the opioid crisis will require action on several fronts, including these three crucial areas.

ALTERNATIVE PAINKILLERS

The search for effective non-opioid painkillers continues, and new ways of targeting μORs could deliver safer opioids.

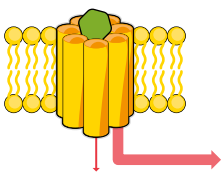
Opioids that are pH-sensitive might activate μORs only in inflammed tissue.



Normal pH
Drug inactive

Low pH
Drug active

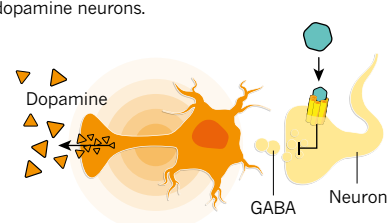
Opioids that mainly activate the G-protein signalling pathway might be less addictive.



Activated μOR sends signals mainly through G-protein pathway.

DECREASING DEPENDENCE

Opioid dependency is a long-term, relapsing medical condition. The feelings of euphoria and reward that help to trigger it are caused by a spike in dopamine levels. Opioids induce this effect by halting the release of GABA, a neurotransmitter that inhibits dopamine neurons.



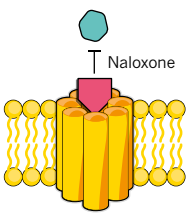
Several approaches might help to tackle opioid dependency.

- **Widened treatment programmes**
  Providing a weaker opioid in combination with counselling and social support can be an effective treatment for dependency, but access to such programmes is often limited.
- **Improved monitoring**
  Better oversight of people taking prescription opioids could enable earlier intervention.
- **Fresh treatments**
  Neuroscientists are studying opioid-induced changes in neurons to develop new treatments.

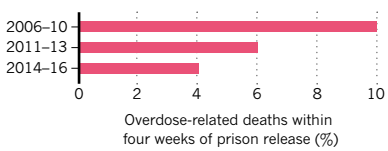
HARM REDUCTION

Abruptly withdrawing prescription opioids can lead people to use illicit drugs.

Needle-exchange services, fentanyl-contamination testing kits and naloxone (a medication that blocks the effects of opioids) can reduce disease transmission and overdose among opioid users.



In 2011, Scotland launched a programme to issue naloxone to opioid-dependent people on their release from prison. The scheme has contributed to a decrease in overdose deaths that occur in the month following release.



S. M. BIRD & A. MCAULEY *LANCET* **393**, 316–318 (2019).