

Shining a Light on the Opioid Crisis

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Both natural and synthetic opioid drugs have been used as a popular therapy for chronic pain throughout history. However, their role as effective analgesics has been tainted by the potential for addiction, increased physical dependence, and often progressive reduction in drug efficacy.¹ Currently, Canada is home to a raging opioid crisis with epidemic proportions of overdoses and related deaths as a result of prescription opioids (POs), as well as illegal and more potent synthetic opioids.² In 2016, there were over 2500 opioid-related deaths across Canada, and more than 3000 deaths are expected by the end of 2017.^{3,4,5} The rise in morbidity and mortality stemming from PO misuse has led Health Canada to declare this issue a major public health crisis.

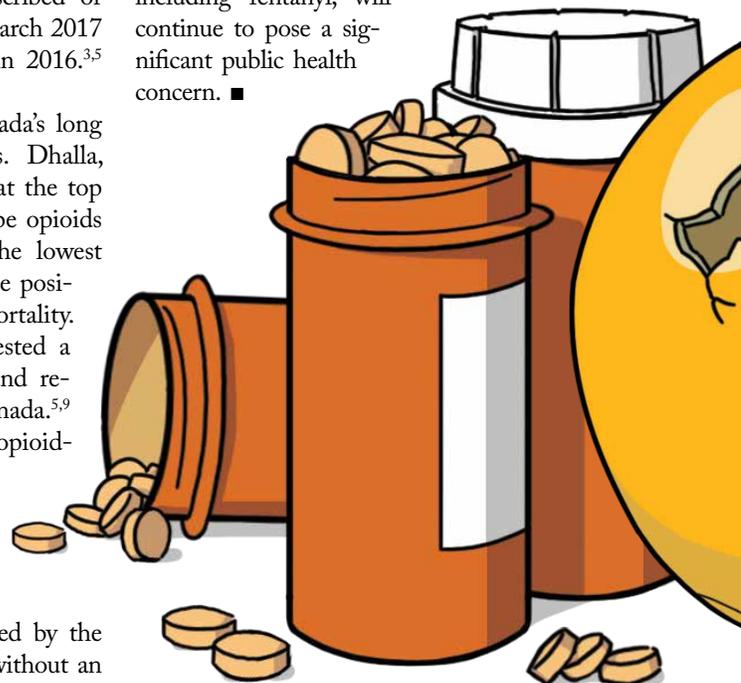
One of the most commonly used opioids, oxycodone, was patented and marketed in 1992 as OxyContin.⁶ As the cause of almost 50% of opioid-related poisoning deaths, OxyContin was delisted from most Canadian provinces' public drug formularies in 2012.⁵ This attempt to delegitimize OxyContin only gave way to increased use of other POs, particularly fentanyl. This represents a much greater concern because fentanyl is an extremely potent synthetic opioid, approximately 50-100 times stronger than morphine.⁷ Alarmingly, Canadian fentanyl consumption rates are among the highest worldwide, and the number of deaths involving prescribed or illegal fentanyl between January and March 2017 was double that of the same period in 2016.^{3,5}

This epidemic arises partly from Canada's long history of over-prescribing practices. Dhalla, Gomes and Juurlink demonstrated that the top 20% of family physicians who prescribe opioids did so 55 times more often than the lowest 20%.⁸ Overprescribing practices may be positively associated with opioid-related mortality. Many studies have consistently suggested a correlation between PO availability and related morbidity and mortality in Canada.^{5,9} In particular, one study examining opioid-related deaths between 2005 and 2011 reported significant correlations between PO dispensing and mortality due to oxycodone and fentanyl.⁹

Overprescription is further compounded by the fact that opioids have been marketed without an

upper dose threshold, despite limited evidence of their safety or effectiveness at high doses.¹ In fact, increases in dosage for long-term treatment plans may lead to the development of tolerance over time, presenting an overarching concern for many individuals dependent on opioid therapy for chronic pain.¹¹ Furthermore, a growing body of literature highlights the danger posed by morphine equivalent doses exceeding 200mg/day.¹⁰ The health repercussions are especially worrying for Ontario, given that this province has exhibited the highest annual rate of high-dose oxycodone and fentanyl dispensing between 2006 and 2011.^{10,11}

A report recently released by the Canadian Institute for Health Information warns that the opioid crisis presents a significant burden on the health-care system due to the rising number of Canadians seeking emergency care for overdoses.¹² As high PO availability and demand continue unabated in Canada, evidence-based population interventions are needed to understand and address the primary determinants and consequences of PO misuse.^{1,5,13} Given that opioid dispensing rates in Canada are much higher than those in other high-income countries, there is room for substantive reductions in PO prescription and improvements in physician and patient education.^{8,14} Unless measures are taken to address this crisis, the widespread availability of dangerous opioids, including fentanyl, will continue to pose a significant public health concern. ■



A Pastime in Peril?

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Mounting evidence has suggested a linkage between American football and chronic traumatic encephalopathy (CTE). Recently, a study examining the deaths of 111 National Football League (NFL) players found an overwhelming 110 CTE cases.¹ CTE is a neurodegenerative disease associated with repeated blows to the head. Normally, tau proteins in the brain provide a scaffold for neurons, but repeated head trauma causes hyperphosphorylation of these proteins, which then aggregate to form neurofibrillary tangles (NFTs).² NFTs can progressively spread throughout the brain over many years and disrupt function in critical regions, such as the hippocampus (responsible for memory and emotion), the amygdala (aggression), and the frontal cortex (cognition and executive functions). As a result, CTE symptoms include memory loss, aggression, and suicidal behavior.

Although CTE is well-known for its presence in high-profile NFL players, like the late Aaron Hernandez, a two-year study on high school football players suggests that CTE-associated pathology can be found in young, amateur athletes as well.³ Given that more than 1.1 million high school athletes play football in the United States, the impact of CTE may be more widespread than commonly assumed. Moreover, a recent study published in *Nature* suggests that playing football from a young

age can result in more severe long-term symptoms of CTE.⁴ Specifically, the investigation

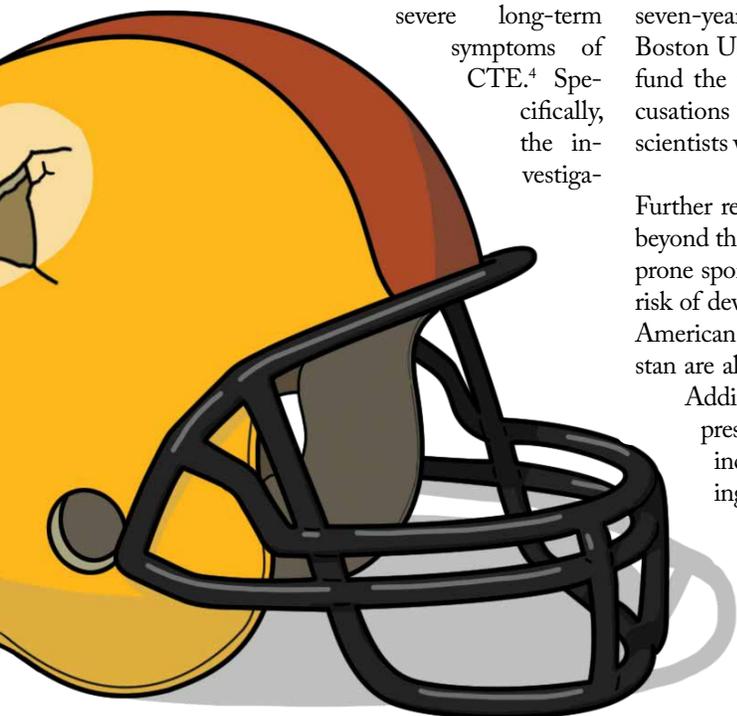
noted that athletes who began playing before age 12, in comparison to those who started at or after this age, faced triple the odds of depression and more than double the odds of executive dysfunction, as characterized by poor impulse control, working memory, and cognitive flexibility. Nevertheless, studies providing evidence of the link between football and CTE have many limitations, including small sample sizes, and self-selected participants often with greater-than-average concern for their health. Moreover, these studies focus on the correlation, rather than the potential causal relationship, between football and CTE.⁴ Such considerations have prompted researchers to recognize the need for prospective, longitudinal studies in validating the causal link between football and CTE.

Research on CTE is an increasingly popular field because of its social impact and widespread applicability. Results from previous studies that linked CTE and football have already facilitated a \$1 billion settlement between the NFL and players who suffer from concussion-related diseases.⁵ However, a major difficulty facing future studies on CTE is that a definitive diagnosis can only occur through a post-mortem brain autopsy, highlighting the need for research on potential diagnostic tools. A reliable, in-vivo diagnostic method may come from a seven-year, \$16 million study conducted by Boston University.⁵ The NFL was initially set to fund the study but later backed out amidst accusations that it attempted to direct funding to scientists with previous connections to the league.

Further research on CTE may have implications beyond the football field. Athletes in other injury-prone sports, such as hockey and wrestling, are at risk of developing CTE.⁶ 20% of the two million American troops deployed to Iraq and Afghanistan are also affected by traumatic brain injuries.⁷

Additionally, tau proteins and NFTs are present in other neurodegenerative diseases, including Alzheimer's disease. Accordingly, diagnostic tools and treatments developed for CTE may lead to breakthroughs for other diseases as well. ■

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