Medications for opioid use disorder: bridging the gap in care

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For the past two decades, the USA has been in the throes of an opioid crisis marked by a rising number of deaths; in 2016, opioids were responsible for most of the nation's estimated 64 000 fatal drug overdoses.[1] The problem began with overprescribing of opioid analgesics in the 1990s, which exposed pain patients to the risks of addiction and produced large surpluses of pain pills that were diverted for misuse by the larger community. Additionally, the escalating numbers of opioid-addicted Americans led to increased HIV and hepatitis C transmission among people who misuse these drugs by injecting them[2] and increased numbers of infants born dependent on opioids as a result of the mother's opioid use (neonatal abstinence syndrome).[3]

The opioid crisis has been a moving target; while it began with the misuse of prescription opioids, this then opened the door to an increase in heroin use.[4] A decade ago, most people who misused opioids in the USA had initiated with prescription drugs, but now heroin is reported as the opioid of initiation more often than the most commonly prescribed opioids, oxycodone and hydrocodone.[5] There has also been an influx of new, more potent synthetic opioids such as fentanyl—often used to adulterate or replace heroin because it is cheaper to produce and easier to import—that has increased the danger for users and perpetuated the trend towards increasing opioid overdose deaths.[6] US Government authorities and the medical community are addressing the problem in a range of ways. In March, 2016, the US Centers for Disease Control and Prevention (CDC) revised its guidelines for opioid prescribing for chronic non-cancer pain, recommending alternative approaches in pain management and limitations on the dosing and duration of opioids when they are called for.[7] Law enforcement and diplomatic efforts are being made to stem the influx of synthetic opioids, which mostly originate in Chinese laboratories.[8] And to save the lives of people who overdose on opioids, most US states have taken steps to increase the availability of the opioid antagonist naloxone to police, emergency medical personnel, and opioid users themselves.[9] This safe and easily used medication can quickly reverse the effects of an opioid overdose and restore breathing if it is administered in time; and communities that have distributed naloxone to opioid users, their families, or potential bystanders have seen reductions in overdose deaths.[9] Naloxone is now available in an easy-to-administer nasal spray, although multiple administrations are sometimes necessary when overdoses involve fentanyl or other potent synthetics. Researchers are working to develop more potent and longer-lasting opioid antagonists to counter the fentanyl threat.

Addiction treatment is equally important in reducing deaths and infectious disease transmission, although historically in the USA such treatment has been hard to access, is not covered by most insurances, and is of variable quality.[10] Health-care reform efforts during the past decade have begun to increase access to evidence-based treatment for substance use disorders and to integrate that treatment into the larger health-care system.[11] Medications are the gold standard of treatment for opioid use disorder.[12] There are currently three medications approved by the US Food and Drug Administration (FDA), all of which target the μ-opioid receptor. Methadone and buprenorphine have agonist effects, addressing craving and withdrawal symptoms without producing euphoria and are used for long-term maintenance therapy.[12] By contrast, naltrexone is an antagonist at the receptor and prevents illicit opioids from having an effect.[12]

In the USA, medications are required to be given in conjunction with some form of counselling or behavioural therapy, called medication-assisted treatment (MAT), but there remains a vast gap between those who would benefit from MAT and those who receive it.[13] This gap reflects both lack of treatment capacity and an entrenched stigma against use of medications for opioid use disorder arising from the belief that these medications simply substitute one addiction for another. This belief, a holdover from early models of recovery that emphasised complete abstinence from all medications, reflects a misunderstanding of the pharmacological and therapeutic effects of these drugs. When an opioid user is treated with methadone or buprenorphine, the doses used do not produce euphoria or trigger the conditioned responses that generate craving.[12] These medications reduce withdrawal symptoms, improve mood, and help restore physiological balance—allowing the patient's brain to heal while he or she works towards recovery.[12]

Methadone, the first medication developed for opioid use disorder, is less expensive than the other

medications and is the most frequently prescribed medication for opioid use disorder globally.[14] However, in the USA methadone must be administered at specialty facilities separate from the regular health-care system, presenting access barriers. Methadone discontinuation requires careful tapering to avoid the severe withdrawal associated with abrupt termination.[15] Buprenorphine, which was approved for opioid use disorder in the USA in 2002, can be prescribed in office-based practices and is now usually given in a formulation with naloxone (BUP-NX) that provides some protection against misuse; it also has a lower risk for overdose than methadone.[16] Clinic visits are required frequently during induction and regularly throughout treatment. Patients with high opioid tolerance might experience withdrawal symptoms when treated with buprenorphine.[17] Overall, research suggests that methadone and buprenorphine are equally effective at reducing opioid use when used at medium-to-high doses.[18] The evidence also shows greater treatment retention and reduced opioid use with medications compared with detoxification alone,[19] and reduced overdose deaths with medications compared with psychosocial treatments alone.[20]

Naltrexone, the antagonist treatment, is generally thought to be poorly tolerated, which mostly reflects the poor compliance reported among people with opioid use disorder treated with oral naltrexone.[21] To improve compliance, an extended-release naltrexone formulation, which requires a monthly injection (XR-NTX), was developed and approved by the FDA for opioid use disorder in 2010. Naltrexone can be prescribed and administered by any provider in the USA and does not cause euphoric effects, physical dependence, withdrawal, or respiratory depression and therefore poses no risk of diversion or overdose.[22] However, naltrexone has achieved the least penetration of all medications for opioid use disorder. One reason is that naltrexone induction requires that patients be fully detoxified to prevent the precipitation of withdrawal (so-called "detox hurdle"), which can require several days of tapering off opioid agonist medications. However, the widespread belief that antagonists are less effective than agonist treatments, despite the lack of comparative effectiveness data to substantiate this view, remains a barrier.[23] The US X:BOT trial, funded by the National Institute on Drug Abuse and reported by Joshua D Lee and colleagues[24] in *The Lancet,* and a trial done in Norway[25] suggest that BUP-NX and XR-NTX are similarly effective at increasing treatment retention and preventing relapse. Results of the US trial do not support the widespread belief that patients with more severe opioid use disorder require agonist therapy.

Ongoing research on the genetic and clinical features that influence treatment response will ultimately support personalised treatment selection. But for now, choice of medications should consider the patient's needs, comorbidities, and access to care. Despite the efficacy of the three currently available medications, they are not effective for all patients and each has drawbacks. Thus, the US National Institutes of Health is embarking on partnerships with the pharmaceutical industry to accelerate the development of new medications for opioid use disorder and improved formulations of the existing ones.[26] Two monthly extended-release formulations of buprenorphine are under review by the FDA, and future research will determine if they help improve treatment retention and outcomes. Research is needed on how to optimally initiate XR-NTX, since this is a major hurdle with antagonist treatment, and on how to reduce dropout rates, which remain high for all medications—about 50% by the end of the 6-month trial by Lee and colleagues.[24] Furthermore, researchers still need to establish appropriate treatment duration for people with different severity of opioid use disorder and to identify the most effective strategies for combined medication and psychosocial interventions. In parallel, implementation research is testing new models for increasing access to medications for opioid use disorder through the general health-care system (ie, emergency departments, primary care, infectious disease clinics) and criminal justice settings.

The opioid overdose epidemic is one of the worst American public health crises in recent decades, yet structural and attitudinal barriers have limited the reach of effective treatments for opioid use disorder that could help address it. These barriers are holdovers from an era when drug addiction was still seen as a moral failing best addressed by the legal system, not a medical condition best addressed through treatment. These barriers must be overcome to reverse the escalating numbers of deaths in the USA. Other countries where opioid misuse is on the rise should learn lessons from the US experience and ensure that effective treatments are widely available.

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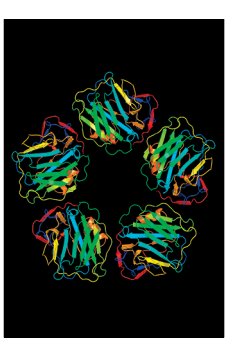
1 US Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. Provisional counts of drug overdose deaths, as of 8/6/2017. 2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf (accessed Nov 10, 2017).
2 Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. *J Acquir Immune Defic Syndr* 2016; **73:** 323–31.
3 Brown JD, Goodin AJ, Talbert JC. Rural and Appalachian disparities in neonatal abstinence syndrome incidence and access to opioid abuse treatment. *J Rural Health* 2017, published online July 7. DOI:10.1111/jrh.12251.
4 Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. Rockville, MD: Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, 2013.
5 Cicero TJ, Ellis MS, Kasper ZA. Increased use of heroin as an initiating opioid of abuse. *Addict Behav* 2017; **74:** 63–66.
6 Gladden RM, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths—27 states, 2013–2014. *MMWR Morb Mortal Wkly Rep* 2016; **65:** 837–43.
7 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep* 2016; **65:** 1–49.
8 O'Connor S. Fentanyl: China's deadly export to the United States. Washington, DC: US China Economic and Security Review Commission, 2017.
9 Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346:** f174.
10 Sharma A, Kelly SM, Mitchell SG, Gryczynski J, O'Grady KE, Schwartz RP. Update on barriers to pharmacotherapy for opioid use disorders. *Curr Psychiatry Rep* 2017; **19:** 35.
11 Clemans-Cope L, Epstein M, Kenney GM. Rapid growth in medicaid spending on medications to treat opioid use disorder and overdose. Washington, DC: Urban Institute Health Policy Center, 2017.
12 Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis* 2012; **31:** 207–25.
13 Williams R, Nunes E, Olfson M. To battle the opioid overdose epidemic, deploy the "cascade of care" model. *Health Affairs Blog*, March 13, 2017.
14 Whelan PJ, Remski K. Buprenorphine vs methadone treatment: a review of evidence in both developed and developing worlds. *J Neurosci Rural Pract* 2012; **3:** 45–50.
15 Maradiaga JA, Nahvi S, Cunningham CO, Sanchez J, Fox AD. "I kicked the hard way. I got incarcerated." Withdrawal from methadone during incarceration and subsequent aversion to medication assisted treatments. *J Subst Abuse Treat* 2016; **62:** 49–54.
16 Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug and Alcohol Depend* 2009; **104:** 73–77.
17 Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100mg of daily methadone. *Drug Alcohol Depend* 2007; **90:** 261–69.
18 Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; **2:** CD002207.
19 Friedmann PD, Schwartz RP. Just call it "treatment". *Addict Sci Clin Pract* 2012; **7:** 10.
20 Pierce M, Bird SM, Hickman M, et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction* 2016; **111:** 298–308.
21 Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011; **4:** CD001333.
22 Kjome KL, Moeller FG. Long-acting injectable naltrexone for the management of patients with opioid dependence. *Subst Abus* 2011; **5:** 1–9.
23 Nunes EV, Krupitsky E, Ling W, et al. Treating opioid dependence with injectable extended-release naltrexone (XR-NTX): who will respond? *J Addict Med* 2015; **9:** 238–43.
24 Lee JD, Nunes EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 2017; published online Nov 14. http://dx.doi.org/10·1016/S0140–6736(17)32812-X.
25 Tanum L, Solli KK, Latif ZE, et al. The effectiveness of injectable extended-release naltrexone *vs* daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; published online Oct 18. DOI:10.1001/jamapsychiatry.2017.3206.
26 Volkow ND, Collins FS. The role of science in addressing the opioid crisis. *N Engl J Med* 2017; **377:** 391–94.

Treatment concentration of high-sensitivity C-reactive protein

The landmark CANTOS trial evaluated the use of canakinumab, a monoclonal antibody targeting interleukin 1β, in 10 061 patients with previous myocardial infarction who had high-sensitivity C-reactive protein (hsCRP) concentrations of 2 mg/L or higher.[1] Interleukin 1β has multiple potential mechanisms that contribute to the pathogenesis of atherothrombotic cardiovascular disease.[2] Induction of interleukin 6 leads to the release of acute phase reactants including hsCRP. Thus, hsCRP serves as a surrogate marker of the overall inflammatory milieu,[2] often in situations where patients have multiple co-morbidities,[3] with a cumulative dose-response indicating a higher risk.[4]

CANTOS propelled the prevention field forward by showing that the inflammation-targeted therapy canakinumab (at 50, 150, or 300 mg subcutaneously once every 3 months) conferred a relative 15% reduction in major adverse cardiovascular events over a median of 3·7 years without altering the lipid profile.[1] Interestingly, there was also a significant 30% reduction in fatal cancer, balanced by a modest increase in fatal infection, with no difference in all-cause mortality. Thus, the observed reduction in the primary endpoint likely would not justify its routine use in all patients post myocardial infarction with elevated hsCRP.

So which patients, pending regulatory approval, might we consider canakinumab for? In *The Lancet*, Paul Ridker and colleagues[5] report that baseline demographics did not identify which groups of patients post myocardial infarction are most likely to benefit. Although women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