indicates that multiple forms of discrimination, such as racism and heterosexism, are associated with increased risk of mental health problems[9]. Additionally, our current understanding is limited about the potential intergenerational impacts of racism and their related epigenetic effects, with emerging evidence suggesting that these processes are likely to be operative[1].

Research on racism and mental health, to date, has focused more on documenting that racism matters than on identifying interventions to minimize the adverse effects of exposure to racism and reduce the occurrence of racism in the first place. Some evidence suggests that psychosocial resources such as social ties and religious involvement can reduce some of the negative effects of discrimination on mental health[6]. However, effectively addressing the multifactorial impacts of racism on mental health will require multilevel societal interventions that seek to build racial equity into homes, schools, neighborhoods and workplaces to minimize current racial economic gaps and improve socioeconomic and living conditions for the disadvantaged.

Interventions around resiliency and cultural/structural competency in the medical field have shown some promise, but more concerted attention is needed to address the multiple and interconnected systems through which racism operates[1,3]. Diversifying the mental health workforce in terms of including underrepresented racial/ethnic groups and professional experience (e.g., medicine, social work, religion) is also a necessary step towards addressing inequities in mental health care[3]. Comprehensive, coordinated, strategic initiatives are needed both within and outside of psychiatry and medicine to better understand, prevent and effectively intervene on the effects of racism on mental health.

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The epidemic of fentanyl misuse and overdoses: challenges and strategies

Fentanyl, a synthetic opioid with analgesic and anesthetic properties, is currently associated with one of the deadliest addiction crises in the US. Misuse of fentanyl (and fentanyl analogues) has been estimated to be responsible for 48,000 (out of a total of 83,335) overdose deaths in the 12 months ending in June 2020[1], a rate that has increased more than 29 fold since 2012, when the annual fatalities from fentanyl and its analogues were 1,615.

The cases of overdoses and deaths in the US are linked to illegally manufactured fentanyl, which rapidly penetrated the US illicit market since 2013. Though not as pervasively as in the US, increases in overdose deaths due to illicit fentanyl and its analogues have also occurred in Canada, in several European countries (including Estonia, Germany, Finland and the UK) and in Australia[2].

Fentanyl is relatively easy to synthesize and manufacture, and less difficult to traffic than heroin, since it requires much smaller volumes to transport across borders. It is, therefore, hugely profitable to drug dealers (50-100 times more than heroin), which can be expected to result in an expansion of the illicit fentanyl market across the globe.

The majority of opioid-related overdose deaths in the US are the result of fentanyl being ingested as a substitute for heroin or with drugs such as cocaine and methamphetamine that had been adulterated (cut) with the opioid, frequently without users being aware of this. Fentanyl, when used by itself or in combination with other drugs, can be taken orally, injected, snorted or smoked. Most heroin users do not report actively seeking fentanyl, and some are afraid of it but might have no choice because of the higher costs of uncontaminated heroin or its unavailability.

When fentanyl is used to adulterate other drugs (heroin, prescription opioids, psychostimulants), it increases their lethality. In the case of psychostimulants, this occurs not only due to the synergistic effects on the cardiopulmonary system, but also because stimulant users, who have no tolerance to opioids, are at very high risk of overdosing when ingesting fentanyl.

The unique pharmacological effects of fentanyl have contributed to its widespread misuse and are also the ones that make it a valuable therapeutic for anesthesia and for severe pain management. Fentanyl binds to mu-opioid receptors (MOR), which mediate the analgesic and the rewarding effects of opioid drugs, such as morphine and heroin, as well as their respiratory depressing actions[3]. However, fentanyl is much more potent at activating MOR-associated signaling than morphine (80-100 fold) or heroin (30-50 fold), and its higher lipophilicity leads to higher and faster brain uptake than for those other drugs. These properties underlie fentanyl's high potency as an analgesic and its rapid actions, which are beneficial for the treatment of breakthrough pain or other severe pain conditions. However, they are also responsible for its powerful rewarding effects, which can rapidly

result in physical dependence and in addiction, and for its severe and abrupt inhibition of respiration, which increases the risk for overdose.

The treatment of fentanyl addiction (fentanyl opioid use disorder or fOUD) is the same as for other opioid use disorders (OUD). It is based on the use of medications such as methadone (full MOR agonist), buprenorphine (partial MOR agonist) and naltrexone (MOR antagonist)[4]. These medications are the gold standard for OUD treatment, and multiple studies have shown that they prevent overdoses and relapse in patients exposed to fentanyl.

However, clinical cases and anecdotal reports indicate that it is much more challenging to treat patients with fOUD than with other OUD. There are greater difficulties in initiating buprenorphine treatment, resulting from buprenorphine-precipitated withdrawal[5] and lower rates of abstinence and retention after six months of buprenorphine treatment[6]. The slow clearance of fentanyl as a result of its accumulation in fatty tissues may require slower detoxification prior to buprenorphine or naltrexone induction, and the higher rates of tolerance and physical dependence associated with repeated fentanyl use might necessitate higher doses of methadone or buprenorphine than for other OUDs. Treatment of withdrawal symptoms during fentanyl detoxification might be aided, as for other opioids, by the use of the alpha-adrenergic drugs lofexidine and clonidine[7]. Overall, much more clinical research is needed to investigate how to optimally treat fOUD.

Like other opioids, fentanyl can result in overdoses due to its respiratory depressant effects. Signs of overdose include slow irregular breathing, slowing of circulation, sedation, acute respiratory distress, seizures, and coma. With repeated opioid exposure, individuals develop tolerance to the respiratory depressant effects of opioids (tolerance also develops for analgesia and reward), allowing them to tolerate much higher doses than naïve individuals[8]. Because tolerance to opioids decreases with interruption of use, whether during voluntary detoxification or incarceration, the relapse to opioid use after treatment discontinuation or after release from jail/prison is particularly dangerous.

Even for those who have developed tolerance to opioids, the very high potency of fentanyl, the impossibility of precisely dosing and the frequency with which drugs are mixed in the black market contribute to the high overdose risk associated with its misuse. As for other opioids, the treatment of fentanyl overdoses requires the timely delivery of naloxone (MOR antagonist) either via parenteral or intranasal administration[3]. Naloxone, which also has a very high affinity for MOR, displaces fentanyl from the receptor, thereby restoring breathing (as well as precipitating an acute opioid withdrawal).

Clinical cases and case reports have indicated that overdoses from fentanyl frequently require multiple naloxone administrations, due to the shorter duration of the action of naloxone ($t_{1/2}$: 1.3-2.4 hours) than that of fentanyl ($t_{1/2}$: 7 to 8 hours), prolonged further by the slow clearance rates of fentanyl in frequent users. Additionally, when fentanyl is injected rapidly, it can result in chest wall rigidity, which interferes further with breathing and exacerbates the risk of death; these effects are not MOR-mediated and might reflect noradrenergic and cholinergic mechanisms[9].

All this generates the need for further development of fentanyl overdose treatments, including higher-dose naloxone formulations, autoinjectors that automatically release naloxone with an impending overdose, longer-acting opioid antagonists (i.e., nalmefene), treatments against chest wall rigidity, and medications to stimulate respiration and oxygenation to help overdoses from the combination of opioids with alcohol, benzodiazepines or stimulants.

Modeling studies have revealed that the epidemic of opioid overdose deaths, including those from fentanyl, can be reversed by multi-pronged approaches that expand access to medications to treat opioid use disorders and increase retention in medication treatment, and by widely expanding access to naloxone for overdose reversals. It will also require strengthening the education of health care professionals in pain management, in safe use of opioids, and in how to screen and treat substance use disorders (including OUD).

Allocation of resources to implement these interventions is necessary, and timely surveillance systems that can serve as early warning signals for the presence of fentanyl or other opioids in a community would also be beneficial. In parallel, prevention interventions are needed to protect against opioid misuse initiation, recognizing that socioeconomic factors have contributed to the opioid crisis and that addressing them is necessary for preventing OUD and other substance use disorders in the long term.

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