

Opioid, Cocaine and Methamphetamine Overdose Crisis and Deaths in 2021

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Recent data reported by the Centers for Disease Control and Prevention (CDC) showed that 88,000 Americans have died from drug overdoses during the 12-month period that ended in August [1]. Compared to provisional, the August data is sharply higher than the CDC reported just a few months ago in December. Adding 27% more deaths to the interim drug overdose death rates reminds us that overdoses have increased in spite of our efforts [2]. The most recent data show the limitations of evidence-based and FDA-approved treatments for opioid use disorders, Narcan- an antidote to opioid overdose, reduced stigma, and improved treatment access. More patients with OUDs are currently being treated with medication-assisted therapy (MATs), and deaths continue to increase. Where is prevention ?

The opioid crisis in the United States has by necessity focused attention on the prevention of overdose deaths rather than opioid use disorder treatment and recovery. Over the last 15 years, deaths due to opioid overdoses are at least 500 000 Americans, which has already been reflected in decreased U.S. life expectancy. The COVID-19 pandemic has had an important role in undermining our progress by increasing the risk to Americans who use cocaine, methamphetamine, and opioid drugs as well as those with OUDs [3]. They are more dependent on emergency rooms, 911, EMTs, and face-to-face health care delivery [4]. Many Covid19-related changes have caused a worsening of the current OUD crisis [5]. Major cities may have called for a coronavirus quarantine to save lives from COVID 19 infections and to overwhelm our health system, but lives lost as those with SUDs and OUDs remained in lockdown [6].

As overdoses have increased, our health system has not been able to respond to the crisis adequately [7]. Experts have reported drug deaths, but regular users have had their use patterns and dealers change. Covid-19 changed the illicit heroin drug supply, and dealers have swamped many cities with fentanyl, methamphetamine, cocaine, and other drugs. Existing users have overdosed, users in remission have slipped, and new users have also increased. Increased use may be due to food insecurity, homelessness, stress, anxiety, craving, and treatment disruption, and increased legal and illicit drug access and prices are relevant factors. The age of first cannabis, tobacco [8], and alcohol use is decreasing. Covid19 stimulated teenage smoking, vaping, cannabis, tobacco, and alcohol use portends another generation with many substance use and psychiatric disorders [9].

OUD death rate reversal starts with naloxone

The COVID19-era opioid overdose epidemic represents a worsening of the drug overdose epidemic in the United States. Overdoses are now at levels that have never been seen or reported in our history [10]. The most recent CDC data indicate that we need to do much more to not repeat the loss of 88,000 Americans who have died from drug overdoses during the 12-month period that ended

in August. An unintended consequence of the change from prescription opioids to heroin and then fentanyl is that most of those with OUDs take illicit drugs and do not know what they took. Secondly, polydrug use is the most common finding for those reporting an overdose. Most overdoses occur in people with a SUD or OUD who have a history of overdose, have SUDs, have OUDs, taking other drugs, alcohol, and prescription medications. Benzodiazepines (e.g., Xanax) is a factor when mixed with opioids in at least one-half of the overdoses. Overdoses are also complicated by medicines used to treat a current medical or psychiatric problem. Third, psychostimulant death rates have been increasing, and both cocaine and methamphetamine deaths have been highlighted in recent CDC reports. Some of these deaths are due to fentanyl contamination. Some are due to the co-use of opioids and psychostimulants, and others due to the psychostimulants alone. 54% of all meth-related deaths in 2019 also involved opioids. By contrast, 75.5% of all cocaine-related deaths also involved one or more opioids in 2019 [11]. Increases in overdose deaths involving cocaine are primarily related to co-use overdose deaths involving cocaine and illicitly manufactured fentanyl [12]. The number of fatalities involving psychostimulants now exceeds the number of cocaine-involved deaths. Fentanyl plus cocaine or methamphetamine, or ecstasy are being reported in post mortem evaluations as increasing causes of overdose death [13]. Fentanyl is commonly detected in psychiatric emergency room patients [14]. Urine drug tests positive for cocaine or methamphetamine are also positive for nonprescribed fentanyl. Psychostimulant users who may be opioid-naïve are at a heightened risk of overdose when exposed to fentanyl [15].

Pitt and co-workers [16] reported that of all possible interventions, naloxone and making naloxone more available would make the most impact in reducing OUD deaths. Improving Narcan availability is the best chance of saving lives from overdose. An excellent place to start is by encouraging all patients with OUD to carry naloxone, for their loved ones to carry naloxone, and for their homes to have naloxone nearby in the bedroom or bathroom. But, it is unrealistic to expect all overdose patients to rescue themselves. Current and past OUD patients and their loved ones are a high-risk overdose group and should have naloxone nearby at all times. Naloxone can reverse an opioid overdose but is considered an intervention like cardio version or CPR rather than treating the underlying disease. There is no evidence suggesting that having an overdose and rescue changes the course of an OUD or substance use disorder. Fentanyl and other synthetic opioids are the primary drivers of the increase in overdose deaths.

Contrary to popular street opinion, inexperienced and experienced users have opioid overdoses and die of an overdose. Opioid overdoses could be reversed if naloxone was available. But, overdoses do not generally occur in the hospital or pharmacy but most often when the user is with friends, at home, and with others present. Good intentions may be getting confused with reality. Most intravenous opioid injectors or users do not want to reverse their opioid-induced euphoria. In emergency settings, health providers often give naloxone, reverse an overdose, and save a person's life, only to have the

rescued yell at the rescuer. Friends, families, and good Samaritans need to reverse overdoses more than they currently do to impact overdose deaths positively.

Carry and give naloxone

Naloxone is considered a "pure" antagonist. Naloxone effectively displaces any full and/or partial agonists (e.g., heroin, oxycontin, fentanyl), occupying opioid receptors that produce euphoria, sedation, sleepiness, respiratory depression, bradycardia, analgesia, and small pupils. Thus, naloxone is an absolute wonder drug- a fast-acting, safe, easily administered opioid antidote capable of reversing opioid intoxication states and overdose [17]. Naloxone is given in emergency settings, regardless of the drug history. Naloxone usually fully reverses the opioid effects within minutes and can confirm a clinical diagnosis. There is little to lose and much to gain by simply giving naloxone in all overdoses. Whether a person or their friends say the overdose is due to cocaine, methamphetamine, or other drug is less critical than seeing pinpoint pupils, shallow pulse, and respirations reversed by naloxone. After a non-fatal overdose reversal, good Samaritans are reminded to call 911. Reversal and connecting individuals to a treatment facility that includes MAT [18] are essential to positive outcomes. A recent study's results suggest that the cost of effective prevention, intervention, and OUD treatment may be substantially offset by reducing the high direct medical cost of SUD hospital care [19].

Transition with urgency overdose reversal to evaluation, diagnoses, and treat the whole patient with OUD

Substance use costs to U.S. society are vast and difficult to estimate with precision, including productivity losses, loss of life, trauma to those left behind. Still, a recent study of hospital costs gave us a clue to the enormity of the costs of substance use disorders [19]. Volkow has suggested that evidence-based prevention and treatment interventions can reduce overdose mortality by 40%. However, opioid use disorder (OUD) is a chronic relapsing disorder that, while initially driven by brain reward activation, increasingly engages anti-reward neurocircuits [20] that drive adverse emotional states and relapse [21].

Brain changes in reward function occur over time as opioids are self-administered. Fentanyl may have more severe effects in producing anhedonia, depression, despair, and suicidal thinking than another opioid [22]. The higher the fentanyl dose exposure, the more profound the opioid-induced brain system disruptions, induced and resultant depressive complaints [23]. But these can be treated once they are diagnosed. But, it not surprising that many patients with OUDs are depressed and some overdose wishing to die [24]. Buprenorphine may have additional benefits in fentanyl use disorders [25], but methadone and Naltrexone are safe and effective for OUD and approved by the FDA. These medications are methadone (a full opioid agonist), Buprenorphine (a partial agonist), and

Naltrexone (an opioid antagonist). These medications are surprisingly old, but they remain, with exercise [26], Narcotics Anonymous, and counseling. I reviewed these in a paper in 1993 [27]. Detoxification treatments include Buprenorphine, clonidine-lofexidine [28], and methadone. Buprenorphine and methadone appear to be the most effective detoxification treatments [29].

MATs are safe and effective, reducing overdose in those patients who are treatment adherent [30]. Buprenorphine may be particularly well-suited for Reversal of anhedonia and withdrawal associated with fentanyl dependence [31]. Suboxone is the most prescribed of the MATs and the current mainstay of treatment for OUDs. Even if a patient fails in treatment with Buprenorphine, they will likely be given Buprenorphine again [32]. While X.R. naltrexone is equal in efficacy to Buprenorphine in the XBOT trial [33], Buprenorphine is easier to use clinically. Many outpatients do not finish detoxification to take the first dose of Naltrexone. Again, physicians tend to do better in terms of 5-year drug-free outcomes and return to pre-morbid functioning [34]. The efficacy of clonidine in opiate withdrawal states has improved and refined the medical approach to this condition. Also, the use of clonidine for opiate detoxification paves the way for naltrexone maintenance [35], which is quite crucial in patients who want to take an antagonist rather than an agonist or partial agonist [36].

The most prolonged duration of MAT therapy has the best outcomes. But, treatment is slow, and relapses are still common. Treatments for OUD are limited by poor adherence to treatment recommendations. Concurrent psychiatric, addictive, or medical diseases often are a root cause of dropping out and recidivism. Recent data suggest that overdose risk continues long after patients complete treatment with Buprenorphine [32]. Discontinuation of MAT is associated with high rates of relapse and an increased risk of overdose. Relapsing patients are often given the same MAT treatments again and again and again [20]. The risk of overdose and relapse remains even after years of stable recovery. Recovery can be a “remission” of the symptoms of an OUD, but not its elimination. MAT is conceptualized as analogous to the use of insulin for the patient’s life in the treatment of diabetes. No blood sugar or A1c testing is provided to prove this hypothesis. Whether the patients agree or not, they vote with their feet and generally do not follow a lifelong diabetes-like treatment plan. One controversial question is whether agonist treatment induces an opioid deficiency or represents proof that an opioid system dysregulation exists or both [37].

Progress has been made in adding successful, evidence-based psychological interventions and treatments to MATs. In a recent cost-effectiveness analysis, expanded access to MAT, combined with interventions used in most physician’s health programs psychotherapy (beyond standard counseling), overdose education and naloxone distribution (OEND), and contingency management (CM). When MAT is added to a successful therapy-based treatment program with CM, outcomes improve. Treatment for OUD in this study was

associated with cost-saving reductions in morbidity and mortality from OUD [38]. Other drug and alcohol problems [39] and co-morbid illnesses are often ignored [40] and undetected without a thorough face-to-face interview, examination, and testing. Treatment for OUDs has improved, but we have a long way to go [41].

Summary

OUDs are complex physical and emotional diseases with important mood and anhedonic deficits [20], concurrent medical & infectious diseases to evaluate and treat. OUDs are part of the SUD spectrum and primarily unique because we have a solid understanding of the neurobiology of opioid dependence, withdrawal, and FDA-approved treatments for OUDs [18]. Those take opioids, methamphetamine, and cocaine with SUDs to produce euphoria but, in regular use, change the brain to precipitate dysphoria, anhedonia, and depression. Sometimes they are used together as a speedball [42] or with alcohol and cannabis. Polysubstance use is the norm among current users wreaking havoc on the brain’s systems devoted to mood, anxiety, and enthusiasm. Deaths of despair [43] and overdoses are often related to co-existing major psychiatric problems. Still, relapse is the rule rather than the exception. Also, no one treatment works for everyone. Medical and psychiatric co-occurring disorders are common and, when untreated, can undermine success. The disproportionately high death rates suggest racial and economic barriers to treatment and inequities that need to be addressed and reversed [1]. Harm reduction may have less utility for OUD than tobacco, vaping, or alcohol efforts. Unlike alcohol use disorder, for which harm reduction measures to contain some of the immediate life-threatening negative consequences of a drinking relapse are readily implementable (e.g., don’t drive, don’t operate machinery, don’t go swimming after drinking), it is highly improbable that a person with opioid use disorder who has relapsed while alone will be able to implement naloxone reversal of opioid overdose successfully [44]. Naloxone must be carried by as many people as possible, especially those with a friend or relative with an OUD. Long-Acting Injectable Naltrexone [35], Methadone, and Buprenorphine are safe, effective, and approved by the FDA for OUDs with experts encouraging access changes to improve retention [45]. Buprenorphine is an effective medication reducing overdoses in patients with OUDs [46]. However, OUD treatment dropouts are commonplace. Brain and behavioral recovery take patience, time, and effort. Brain systems may return to pre-morbid function with enough time in treatment. Still, brain recovery appears to something that is accelerated by abstinence from drugs of abuse and alcohol [47], healthy eating, and novel regenerative treatment innovations [48] from exercise [26] to transcranial magnetic stimulation.

Outcomes in treating health professionals with OUDs and SUDs appear to be significantly better than for most other populations [34]. PHP treatment approaches should be employed in patients whether they are health professionals or not. Treating the patient with an OUD like we treat a physician with an

OUD [49] is a significant improvement that could improve everyone's treatment. PHP patients are provided with comprehensive medical-psychiatric-SUD evaluation, treatment, contingency management, and continuing managed-supervised care for five years. Such an approach reduces relapses and improves treatment engagement and efficacy by treating the whole person, comorbidities [50] and provide the best treatment, recovery, and return pre-morbid functioning [34].

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