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Health Services Research

Fourth Wave of Opioid (Illicit Drug) Overdose Deaths and Diminishing Access to Prescription Opioids and Interventional Techniques: Cause and Effect

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Background: In the midst of the COVID-19 pandemic, data has shown that age-adjusted overdose death rates involving synthetic opioids, psychostimulants, cocaine, and heroin have been increasing, including prescription opioid deaths, which were declining, but, recently, reversing the trends. Contrary to widely held perceptions, the problem of misuse, abuse, and diversion of prescription opioids has been the least of all the factors in recent years. Consequently, it is important to properly distinguish between the role of illicit and prescription opioids in the current opioid crisis. Multiple efforts have been based on consensus on administrative policies for certain harm reduction strategies for individuals actively using illicit drugs and reducing opioid prescriptions leading to curbing of medically needed opioids, which have been ineffective. While there is no denial that prescription opioids can be misused, abused, and diverted, the policies have oversimplified the issue by curbing prescription opioids and the pendulum has swung too far in the direction of severely limiting prescription opioids, without acknowledgement that opioids have legitimate uses for persons suffering from chronic pain.

Similar to the opioid crisis, interventional pain management procedures have been affected by various policies being applied to reduce overuse, abuse, and finally utilization. Medical policies have been becoming more restrictive with reduction of access to certain procedures, with the pendulum swinging too far in the direction of limiting interventional techniques. Recent utilization assessments have shown a consistent decline for most interventional techniques, with a 18.7% decrease from 2019 to 2020.

The causes for these dynamic changes are multifactorial likely including the misapplication of the 2016 Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for chronic pain, the relative ease of access to illicit synthetic opioids and more recently issues related to the COVID-19 pandemic. In addition, recent publications have shown association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. These findings are leading to the hypothesis that federal guidelines may inadvertently be contributing to an increase in overall opioid deaths and diminished access to interventional techniques. Together, these have resulted in a fourth wave of the opioid epidemic.

Methods: A narrative review.

Results: The fourth wave results from a confluence of multiple factors, including misapplication of CDC guidelines, the increased availability of illicit drugs, the COVID-19 pandemic, and policies reducing access to interventional procedures. The CDC guidelines and subsequent regulatory atmosphere have led to aggressive tapering up to and including, at times, the overall reduction or stoppage of opioid prescriptions. Forced tapering has been linked to an increase of 69% for overdoses and 130% for mental health crisis. The data thus suggests that the diminution in access to opioid prescriptions may be occurring simultaneously with an increase in illicit narcotic use.

Combined with CDC guidelines, the curbing of opioid prescriptions to medically needed individuals, among non-opioid treatments, interventional techniques have been affected with declining utilization rates and medical policies reducing access to such modalities.

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Conclusion: The opioid overdose waves over the past three decades have resulted from different etiologies. Wave one was associated with prescription opioid overdose deaths and wave two with the rise in heroin and overdose deaths from 1999 to 2013. Wave three was associated with a rise in synthetic opioid overdose deaths.

Sadly, wave four continues to escalate with increasing number of deaths as a confluence of factors including the CDC guidelines, the COVID pandemic, increased availability of illicit synthetic opioids and the reduction of access to interventional techniques, which leads patients to seek remedies on their own.

Key words: Opioid overdose deaths, rapid tapering, access to interventional techniques, Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, Drug Enforcement Agency, Food and Drug Administration, conflicts of interest

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The opioid and COVID-19 epidemic are interwoven with recent reports of escalating overdose deaths (1-7). The Centers for Disease Control and Prevention (CDC) published a document on understanding the epidemic (7). They characterized the rise in opioid overdose deaths as a triple wave epidemic, with description of 3 distinct waves (Fig. 1).

The first wave began with increased prescribing of opioids in the 1990s, with overdose deaths involving prescription opioids, natural and semisynthetic opioids, and methadone increasing since at least 1999 (8). The second wave began in 2010, with rapid increases in overdose deaths involving heroin (9), and the third wave began in 2013, with significant increases in overdose deaths involving synthetic opioids, particularly those involving illicitly manufactured fentanyl (10-12).

The market for illicitly manufactured fentanyl continues to change and it can be found in combination with heroin, counterfeit pills, and cocaine (13). The concept of the triple wave epidemic has been supported by others as supply and demand drivers of the US opioid overdose crisis (14). On the supply side, the iatrogenic sourcing of opioid pills, a new source form of refined heroin and an illicit opioid subclass, fentanyl, resurfacing from a new source. On the demand side, multiple social and structural root causes of opioid use that have led to popular dependency on opioids, starting with pills, leading to spillover effects driving heroin and subsequently fentanyl demand. As a result, multiple authors have described a fourth wave in the opioid crisis (15-17).

Ciccarone (15) described a fourth wave of high mortality involving methamphetamine and cocaine, along with availability and use of illicit fentanyl agents as the major drivers of overdose deaths. Moreover, the current rise in stimulant-related deaths appears intertwined with the ongoing opioid epidemic (15). Ciccarone (15) also noted that the COVID-19 pandemic is accelerating the overdose crisis, as well as its racial and economic inequities. He concluded that reducing morbidity and mortality will require significant expansion of resources for treatment and prevention.

Origins of the fourth wave of opioid crisis or epidemic are preliminary and based on individual opinions. None of the authors (4,15-18) have explored the significance of the rise in illicitly acquired opioid overdose deaths, diminishing access to prescription opioids as a result of misapplication of federal policies and barriers to interventional techniques. There are many possible contributing causes including significant increased availability of illicit drugs due to the relative ease of their manufacture and distribution, COVID-19, and diminishing access to prescription opioids and interventional techniques contributing (1,2,4,18-30)

Amid the ongoing national crisis of opioid related mortality and morbidity, extensive shifts in opioid prescribing trends have occurred over the years in the United States (19). While the CDC guidelines were prepared to help guide primary care providers they transformed into policies and regulations by multiple agencies often with maximum dose limits whether perceived harms of continued therapy outweighed perceived benefits for individual patients. This led to increased opioid tapering among patients prescribed long-term opioid therapy (25-35), yet opioid-related mortality has continued to increase (24). Subsequent

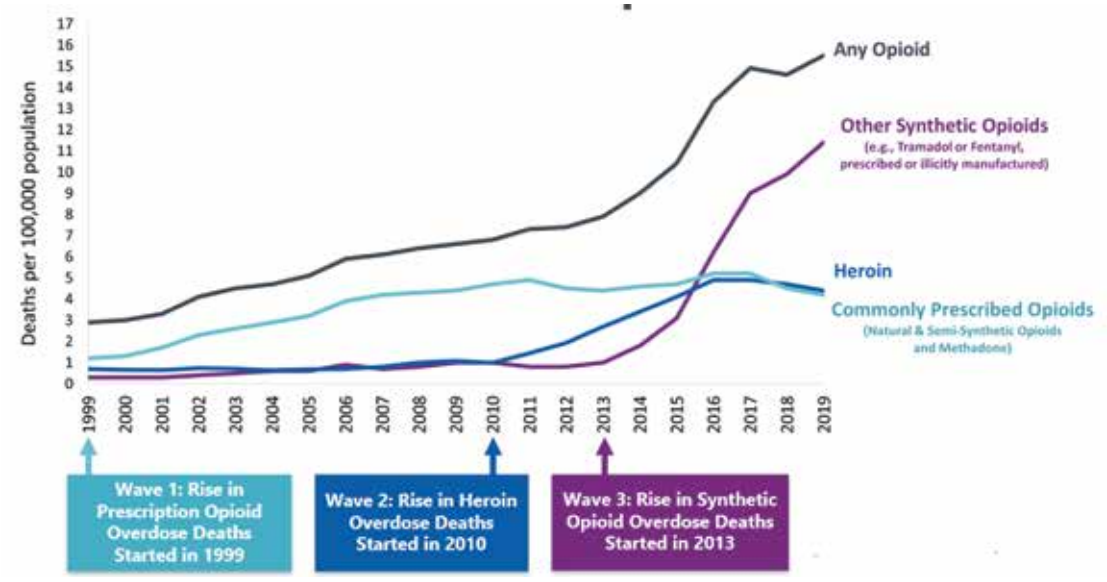


Fig. 1. *Three waves of the rise in opioid overdose deaths.*

Source: National Vital Statistics System Mortality File.

recommendations have advised caution in opioid de-prescribing (6,28-30). Poignantly, the Food and Drug Administration (FDA) has a clear warning regarding the potential hazards of rapid dose reduction in patients prescribed long-term opioids (28). Studies on opioid dose reductions in veteran populations (27) or specific regions (35) have focused on discontinuation and did not include sensitive indicators for tapering initiation, with small sample sizes (35-38). Consequently, patients and physicians have been facing continuous difficulties in reference to de-prescribing opioids (39). Recently, Agnoli et al (22) hypothesized that tapering the dose of patients receiving stable, long-term, high dose opioid therapy would be associated with increased risk of specific adverse events. An accompanying editorial by Larochelle et al (21) concluded that it is increasingly clear that opioid tapering needs to be approached with caution. Townsend et al (39) showed that the CDC guidelines were associated with approximately 20% reduction in dispensing opioids, with 15% reduction in MME, and over 10% reduction in high dose dispensing compared with a counterfactual no guideline scenario (39). Han et al (23) studied the most frequently misused opioids and differences in motivation for misuse between buprenorphine and norbuprenorphine prescription opioids as well as the trends and factors associated with misuse among individuals with or without opioid disorder. However, most who misused reported using prescription opioids and buprenorphine without having their own prescriptions for physical pain.

These recent publications underscore a multitude of issues related to, restriction of opioid dosages, forced opioid tapering, and increased access to buprenorphine-based opioid use disorder treatment. Studies also highlighted multiple issues related to conflicts of interest in developing guidelines, reducing the supply of prescription opioid production and free flow of opioids from other countries (40-64).

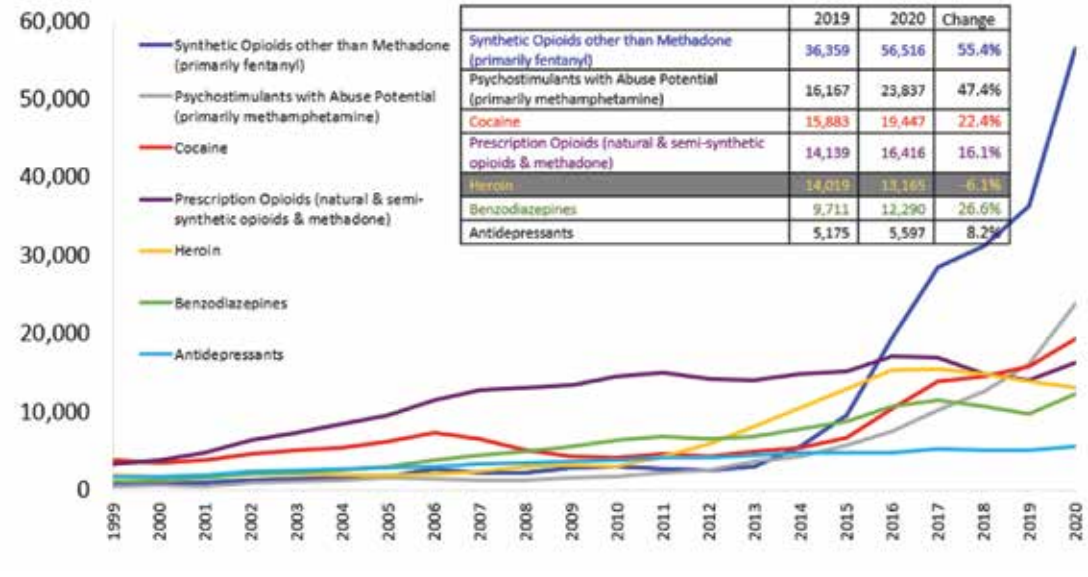
CDC guidelines indicate a lack of evidence for nonopioid techniques involving interventional pain management procedures (19). The issues related to interventional techniques in many ways date back to 2009 guidelines developed for the evaluation and management of low back pain. Ironically, at the time, opioids were recommended whereas interventional techniques were not. Publication from the Agency for Healthcare Research and Quality (AHRQ) (20) continued to influence interventional pain management through multiple guidelines and local coverage determinations (LCDs described as evidence-based, arguing against the role of interventional techniques in alleviating pain (20,46,51,52,65-83). The most recent LCDs published weren't free from these adverse recommendations (20,65,66,75-80). Ironically, the Best

Practices developed by the Interagency Task Force of HHS have been largely ignored despite their evidence-base, inclusiveness of numerous elements in opioid and other therapies, transparency and represented by a large number of participants (6). In prior publications the present group of authors have argued that the process was flawed with conversion of local anesthetic procedures into placebo controls and other issues (42,51,52,66,81). Claims based datasets have shown consistent decline in utilization patterns of interventional techniques (66-74,82,83). Specifically, there has been significant decrease in utilization patterns of percutaneous adhesiolysis procedures and vertebral augmentation procedures, followed by epidural injections, specifically interlaminar and caudal epidural injections (67-74,82,83). In fact, a recent survey showed an overall 18.7% decline in interventional techniques from 2019 to 2020, exacerbating the trend of decline of utilization of interventional techniques (67).

Opioid Epidemic and Prescription Opioid Deaths

Provisional data from the CDCs National Center for Health Statistics indicated that there were an estimated 100,306 drug overdose deaths in the United States during the 12-month period ending in April 2021, an increase of 28.5% from the 78,056 deaths during the same period the year before (84). Similarly, estimated overdose deaths from opioids increased to 75,673, in the 12-month period ending in April 2021, up from 56,064 the year before. More importantly, overdose deaths from synthetic opioids (primarily fentanyl) and psychostimulants such as methamphetamine also increased in the 12-month period ending in April 2021. Cocaine deaths also increased, as did deaths from natural and semi-synthetic opioids, such as prescription pain medications. Heroin deaths continued at a high level; however, there was a small dip in the death rate (84,85). In addition, during May 2020 to April 2021, 64% of deaths involved synthetic opioids other than methadone, mainly manufactured fentanyl, including both fentanyl and illicit fentanyl analogs (84-87). Morbidity and Mortality Weekly Report (86) reported that those opioids were introduced primarily as adulterants in or replacements for white powder heroin east of the Mississippi River. Illicitly manufactured fentanyls (IMFs) are now widespread in white powder heroin markets, increasingly pressed into counterfeit pills resembling oxycodone, alprazolam, or other prescription drugs, and are expanding into new markets, including in the western United States. This may have large consequences as overdoses related to illicit fentanyl will show up as prescription opioids including oxycodone, alprazolam, or other prescription drugs. In addition, approximately 4 in 10 IMF-involved deaths also involved a stimulant (Fig. 2), which has escalated to over 100,000 in the later data ending in April 2021 (85-87). The US data of drug-related overdose deaths from 2018 and 2019 showed an arrest of escalation and a dip in the curve towards reductions (88). However, this trend reversed with reports showing that 91,799 drug overdose deaths occurred in the US in 2020 as shown in Fig. 3 (88). Further, the primary drivers of increasing overdose deaths continue to be fentanyl, heroin, cocaine and psychostimulants while prescription opioid deaths have declined to the same or below the levels of cocaine, heroin, and methamphetamine (Fig. 4).

The CDC data brief from 1999 to 2020 (87) shows an increase in drug overdose deaths involving synthetic opioids other than methadone, which includes such drugs as fentanyl, fentanyl analogues, and tramadol, with different rates of change over time as shown in Table 1 and Fig. 5; however, the rates increased 56% from 2019 to 2020 from 11.4 to 17.8 per 100,000. Methadone deaths increased from 0.3 in 1999 to 1.8 in 2006 and 2007, then decreased through 2017 (1.0), and then increased again in 2020 to 1.1. Deaths involving natural and semi-synthetic opioids, which include oxycodone and hydrocodone, increased from 1999 to 2020, but did not change significantly from 2010 through 2020. However, compared with 2017 (4.4), rates decreased in 2018 (3.8), and 2019 (3.6), but increased in 2020. The rate of overdose deaths involving heroin was stable from 1999 to 2005, then increased from 2005 to 2016, and decreased from 2016 through 2020. The rate in 2020 (4.1) was lower than 2019 (4.4). In addition, overdose deaths involving cocaine and psychostimulants with abuse potential began in 2012 and continued through 2020. Deaths involving cocaine increased from 1.4 per 100,000 in 1999 to 2.5 in 2006, decreased to 1.4 in 2012, and increased with different rates of change over time to 6.0 in 2020, as shown in Fig. 6 (87). As described earlier, the age adjusted rate of drug overdose deaths involving psychostimulants with abuse potential, which include such drugs as methamphetamine, amphetamine, and methylphenidate, increased from 0.2 in 1999 to 0.4 in 2004, remained fairly stable through 2008, and then increased from 2008 through 2020 (7.5) with different rates of change over time (Fig. 6). The rate in 2020 was 50% higher than the rate in 2019.



	2019	2020	Change
Synthetic Opioids other than Methadone (primarily fentanyl)	36,359	56,516	55.4%
Psychostimulants with Abuse Potential (primarily methamphetamine)	16,167	23,837	47.4%
Cocaine	15,883	19,447	22.4%
Prescription Opioids (natural & semi-synthetic opioids & methadone)	14,139	16,416	16.1%
Heroin	14,019	13,165	-6.1%
Benzodiazepines	9,711	12,290	26.6%
Antidepressants	5,175	5,597	8.2%

Fig. 2. *National drug-involved overdose deaths by specific category.*

Redrawn and modified from CDC figure
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021. Accessed on 1/25/2022 https://www.cdc.gov/nchs/products/databriefs/db428.htm

	2010	2020	Change from 2010
Drug Overdose deaths	38,329	91,799	140%
Opioid prescriptions	251,088,904	142,816,781	-43%

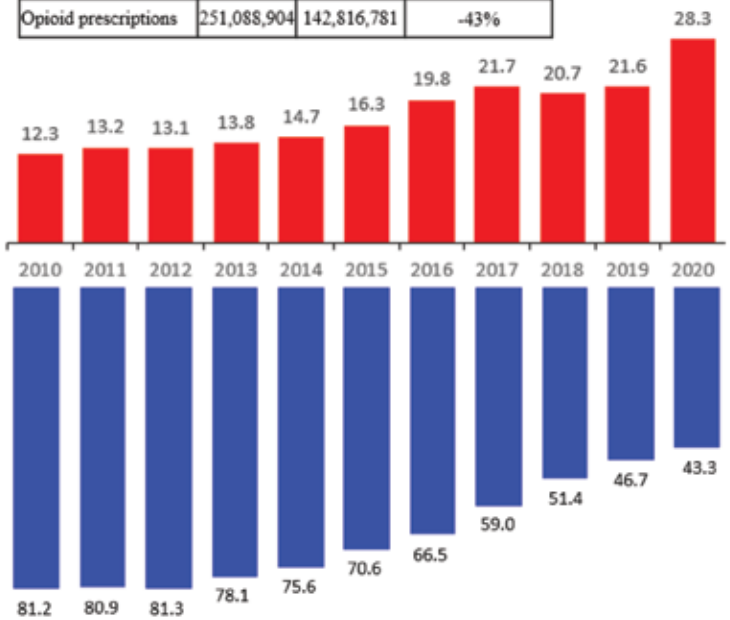


Fig. 3. *Reductions in opioid prescribing rates have not led to reductions in drug-related mortality rates.*

Source: https://www.cdc.gov/nchs/products/databriefs/db428.htm
https://www.cdc.gov/drugoverdose/rxrate-maps/index.html
Accessed on 1/25/2022

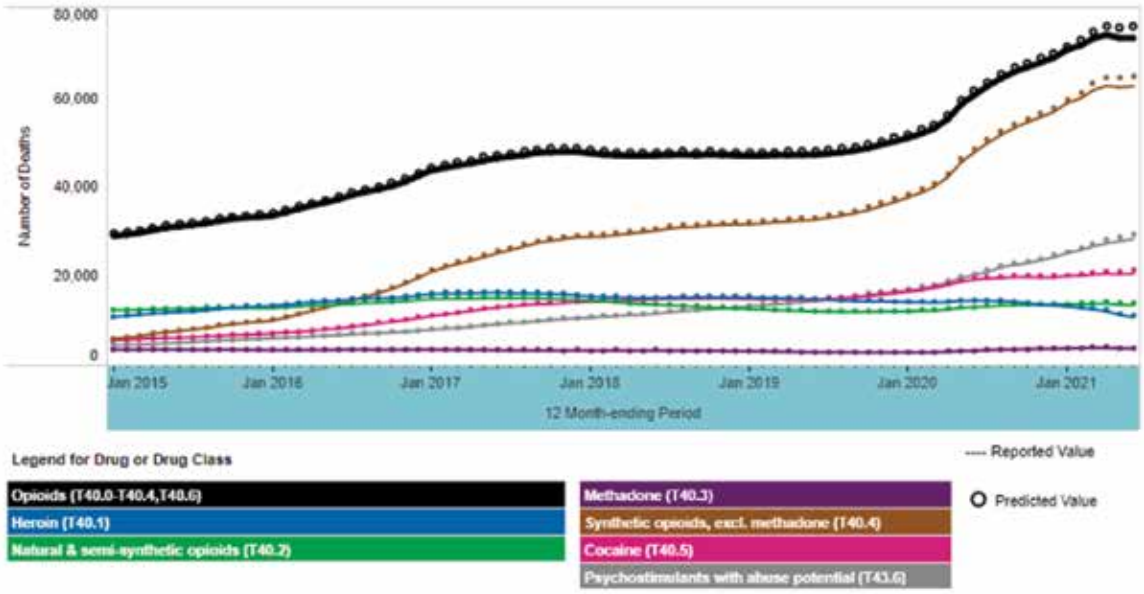


Fig. 4. *Twelve month-ending provisional number of drug overdose deaths by drug or drug class.*

Source: NCHS, National Vital Statistics System. Estimates for 2021 are based on provisional data. Accessed on 2/10/2020 https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

The data on prescription opioid deaths may be influenced by methadone deaths. The lower numbers may be achieved if methadone deaths are separated from prescription opioids, as methadone may be obtained by multiple means, with only a small proportion being from prescription opioids for the management of chronic pain (89). Peppin and Coleman (90) showed that in 2019, 7 times more methadone was administered or dispensed for opioid use disorder treatment than was prescribed for pain, yet all methadone-involved deaths were coded by the CDC as involving the prescribed form of the drug. The explanation for the error was related to an international program used by the CDC for reporting mortality and compiling and reporting drug overdose deaths (12). Thus, in 2019, with exclusion of methadone deaths, the prescription opioid deaths were 12,084 with 2,787 deaths attributed to methadone without considering methadone for opioid use disorder.

While there was a decline in 2018 and 2019 with reversal in 2020, explanations are inadequate as prescription opioid use is declining rapidly with only 100 billion morphine milligram equivalents (MME) dispensed in 2020. This is a 60% decline from the 260 billion MME dispensed at the peak of the opioid epidemic in 2011. Reports also highlighted that between 2019 and 2020, there has been a decline in MME including the effects of disruption from the COVID-19 pandemic, making the 9th consecutive year of declines and the third year of double-digit change (Fig. 7). The number of prescriptions also declined from 2011 to 2019. Overall, prescriptions have decreased by 44% from 2011 to 2020, as shown in Fig. 3 (88,89). The opioid paradox of overdose deaths in prescribing also were highlighted in a recent publication by Kharasch et al (91). They described an "opioid paradox" in that opioid overdose mortality has continued to increase despite steady reductions in opioid prescribing (Fig. 8) (91-97). This is illustrated by an overall decrease in prescriptions both in numbers of patients exposed and average doses prescribed, but with a lack of decline of opioid overdose deaths, due to the increased rise of heroin and illicit fentanyl, and reversal of decline in 2020 of prescription opioid deaths.

The decline in use of prescription opioids in the United States has been noticed by global publications. In a recent publication, Jayawardana et al (98) in assessing global consumption of prescription opioid analgesics from 2009 to 2019 showed an overall decline of global opioid consumption contributed by US and Germany. They showed that it is primarily driven by the

US and Germany. They further showed that in 2009, Germany had the highest consumption rate of 2,649 MME per 1,000 inhabitants per day (2,019 MID), followed by the US (2,919 MID) and Canada (1,645 MID). Overall, the consumption rate declined by 58.3% in Germany, 48% in the US, and 36.8% in Canada from 2009 to 2019.

The analysis of quantification of opioid deaths showed a 13% increase from 2010 to 2020 and 16% from 2019 to 2020. In contrast, synthetic opioids other than methadone, primarily fentanyl increased 1,770% from 2010 to 2020, with an increase of 55% from 2019 to 2020. During the same period, psychostimulants with abuse potential (primarily methamphetamine) increased 1,186% from 2010 to 2020 and the rate was 47% higher in 2020 compared to 2019 (Figs. 2, 5 and 9). During the same period, cocaine increased 365% from 2010 to 2020, whereas it increased 22% from 2019 to 2020. In contrast, deaths involving heroin increased 334% from 2010 to 2020, whereas they decreased 6% from 2019 to 2020.

In addition to the worsening illicit drug

Table 1. *Number of national drug overdose deaths involving select prescription and illicit drugs from 2000-2020.*

	2000	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Total Overdose Deaths	17,415	38,329	41,340	41,502	43,982	47,055	52,404	63,632	70,237	67,367	70,630	91,799
Any Opioid[1]	8,407	21,089	22,784	23,166	25,052	28,647	33,091	42,249	47,600	46,802	49,860	68,630
Any opioid and Synthetic Opioids other than Methadone	205	1,002	961	944	1,219	2,493	4,806	9,299	12,556	13,491	13,596	16,465
Prescription Opioids[2]	3,785	14,583	15,140	14,240	14,145	14,838	15,281	17,087	17,029	14,975	14,139	16,416
Prescription Opioids AND Synthetic Opioids other than Methadone	167	939	889	861	1,015	1,489	2,263	4,055	5,444	5,417	5,876	8,626
Prescription Opioids WITHOUT Synthetic Opioids other than Methadone	3,618	13,644	14,251	13,379	13,130	13,349	13,018	13,032	11,585	9,558	8,263	7,790
Synthetic Opioids other than Methadone (primarily fentanyl)[3]	782	3,007	2,666	2,628	3,105	5,544	9,580	19,413	28,466	31,335	36,359	56,516
Heroin[4]	1,842	3,036	4,397	5,925	8,257	10,574	12,989	15,469	15,482	14,996	14,019	13,165
Heroin AND Synthetic Opioids other than Methadone	18	45	44	69	209	1,027	2,685	5,781	8,091	9,068	8,746	8,990
Heroin WITHOUT Synthetic Opioids other than Methadone	1,824	2,991	4,353	5,856	8,048	9,547	10,304	9,688	7,391	5,928	5,273	4,175
Cocaine[5]	3,544	4,183	4,681	4,404	4,944	5,415	6,784	10,375	13,942	14,666	15,883	19,447
Psychostimulants With Abuse Potential (primarily methamphetamine)[6]	578	1,854	2,266	2,635	3,627	4,298	5,716	7,542	10,333	12,676	16,167	23,837
Benzodiazepines[7]	1,298	6,497	6,872	6,524	6,973	7,945	8,791	10,684	11,537	10,724	9,711	12,290
Antidepressants[8]	1,798	3,889	4,113	4,259	4,458	4,768	4,894	4,812	5,269	5,064	5,175	5,597

Source: https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates (Accessed on 2/7/2022)
For technical information: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
[1]Any Opioid ICD-10 codes (T40.0-T40.4, T40.6)
[2]Prescription Opioids ICD-10 codes (T40.2-T40.3)
[4]Heroin ICD-10 codes (T40.1)
[5]Cocaine ICD-10 codes (T40.5)
[7]Benzodiazepines ICD-10 code(T42.4)
[8]Antidepressants ICD-10 code(T43.0-T43.2)

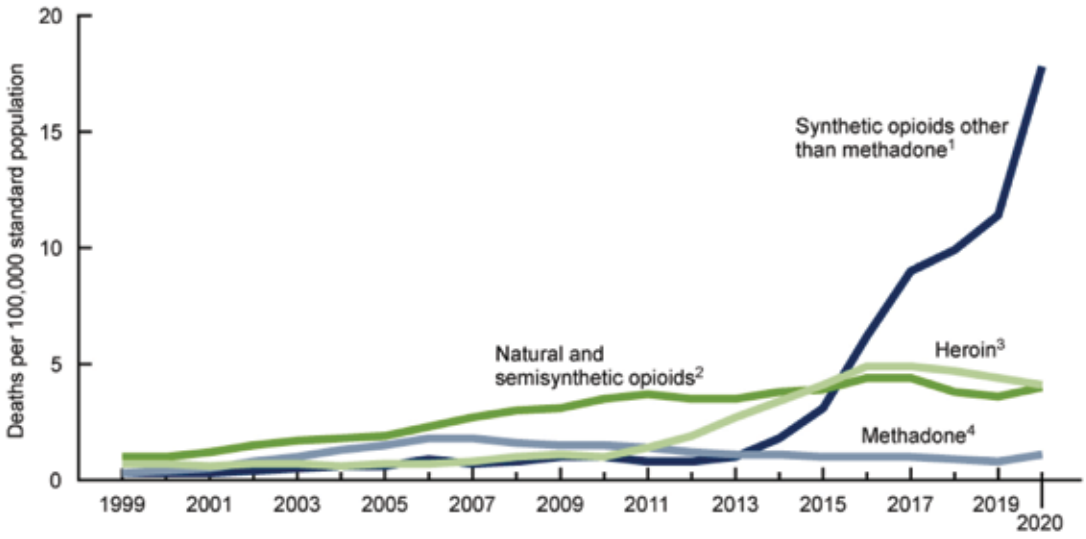


Fig. 5. *Age-adjusted rates of drug overdose deaths involving opioids, by type of opioid: United States, 1999–2020.*

Source: National Center for Health Statistics, National Vital Statistics System, Mortality.

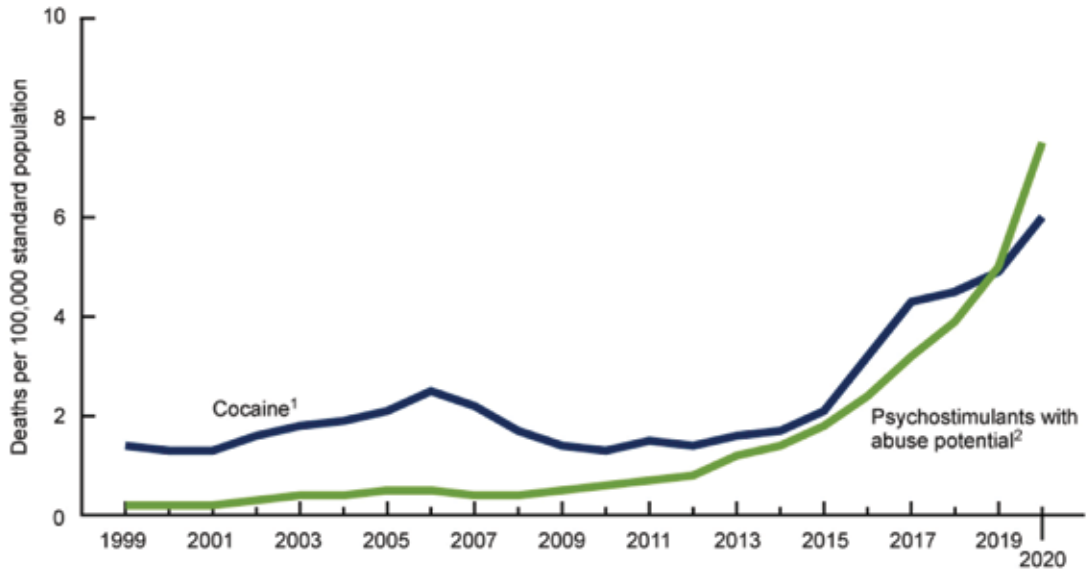


Fig. 6. *Age-adjusted rates of drug overdose deaths involving stimulants, by type of stimulant: United States, 1999–2020.*

epidemic with exacerbation related to COVID-19 pandemic, "Deaths of Despair: The Unrecognized Tragedy of Working Class Immiseration" has been once again discussed frequently (99). The terms deaths and despair come from Case and Deaton, who published rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st Century (100). They showed that the fastest rising death rates among Americans were from drug overdoses, suicide, and alcoholic liver disease, increasing between 56% and 387%, depending on the age cohort, over the past 2 decades, averaging 70,000 per year. They described

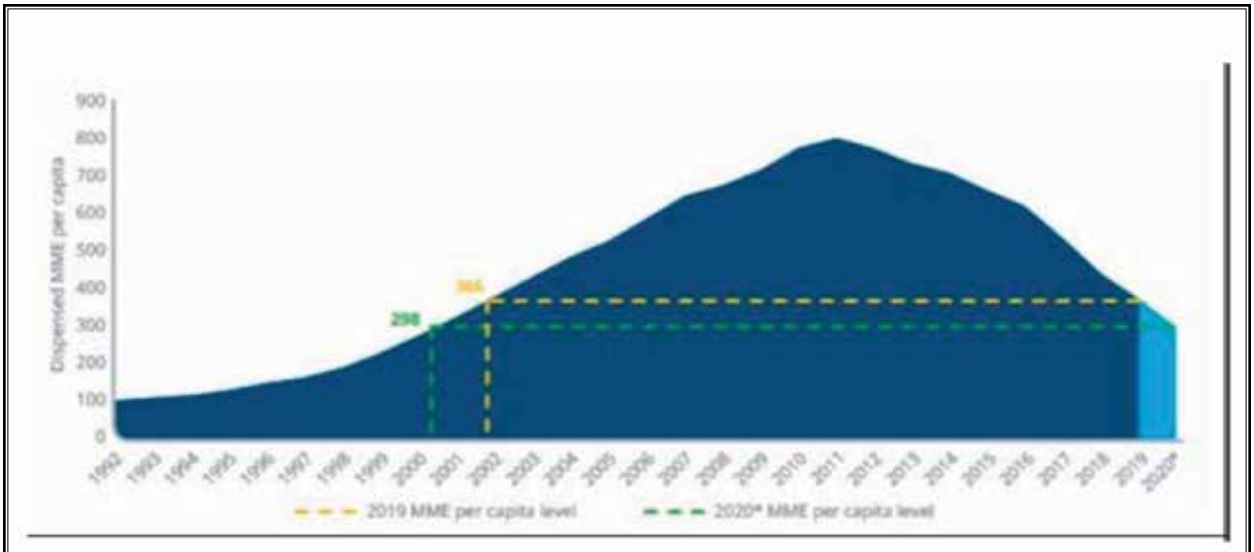


Fig. 7. *Prescription opioid use in morphine milligram equivalents (MME) per capita, 1992-2020*.*

Source: IQVIA Xponent, Mar 2020; IQVIA Prescription Audit; IQVIA Institute, Nov 2020.

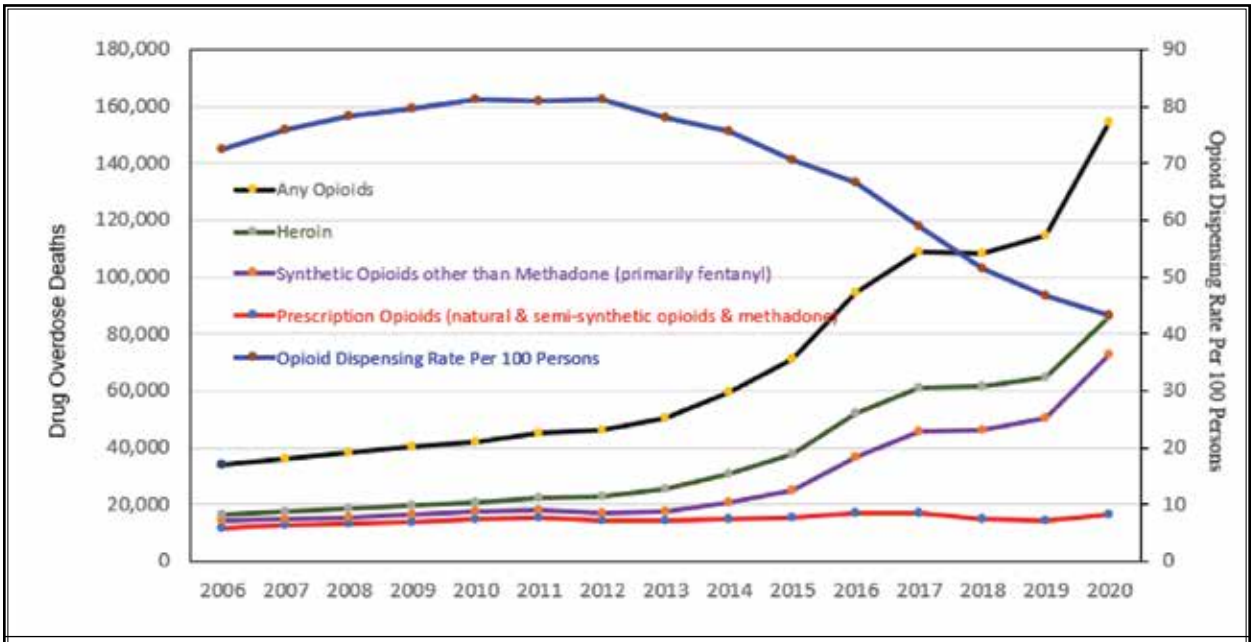
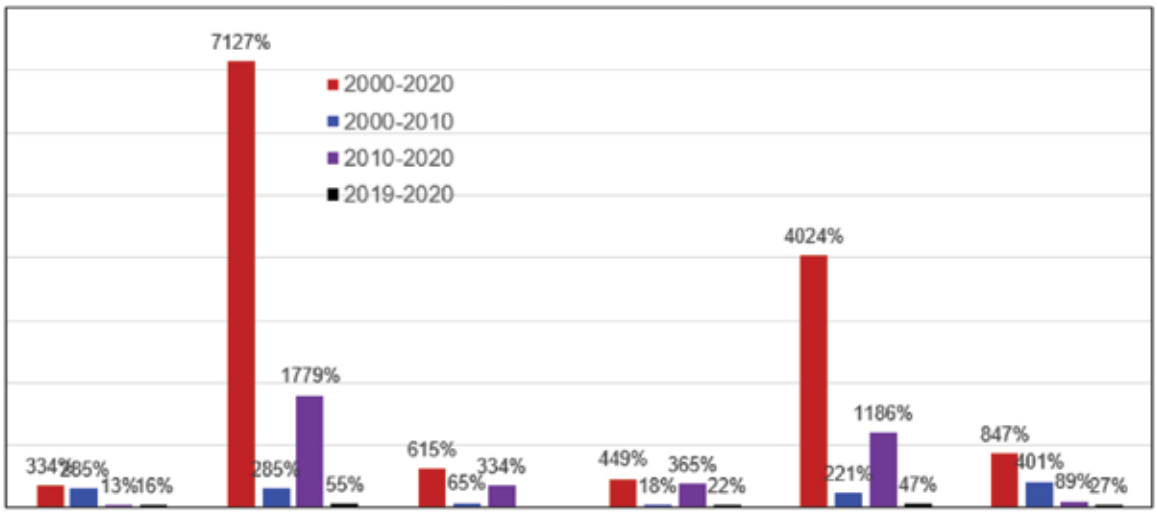


Fig. 8. *The opioid paradox. Opioid prescriptions are declining while opioid overdose deaths are increasing.*

Source: https://www.cdc.gov/nchs/products/databriefs/db428.htm
https://www.cdc.gov/drugoverdose/rxrate-maps/index.html
Accessed on 1/25/2022

that these effects are largely the result of economic hardship or the loss of work or wages, lack of education or low education, resulting in insecurity, deprivation, the loss of possibilities, the lack of belonging, hopelessness, and social maladjustment leading to negative emotions including loneliness, unhappiness,



	2000	2010	2017	2018	2019	2020	Change 2000-2020	Change 2000-2010	Change 2010-2020	Change 2019-2020
Prescription Opioids (natural & semi-synthetic opioids & methadone)	3,785	14,583	17,029	14,975	14,139	16,416	334%	285%	13%	16%
Synthetic Opioids other than Methadone (primarily fentanyl)	782	3,007	28,466	31,335	36,359	56,516	7127%	285%	1779%	55%
Heroin	1,842	3,036	15,482	14,996	14,019	13,165	615%	65%	334%	-6%
Cocaine	3,544	4,183	13,942	14,666	15,883	19,447	449%	18%	365%	22%
Psychostimulants	578	1,854	10,333	12,676	16,167	23,837	4024%	221%	1186%	47%
Benzodiazepines	1,298	6,497	11,537	10,724	9,711	12,290	847%	401%	89%	27%

Fig. 9. *Quantification of opioid deaths 2000-2020.*

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021. Accessed on 1/25/2022
https://www.cdc.gov/nchs/products/databriefs/db428.htm

worry, and stress that in turn led individuals to, in part, experience more pain and pain sensitivity, both physical and psychological. With the COVID-19 pandemic, the problem has been exacerbated as evidenced by the fact that 911 calls for opioid related use increased 250% between 2019 and early 2020 (99,100). Figures 10 and 11 show these factors with increasing mortality affecting mostly white middle-aged men. However, a multitude of these factors have been described to contribute to 5% to 15% of all drug deaths, 12% to 13% of illicit drug deaths, but virtually all of the suicide and alcohol deaths.

Contrary to the previous findings, recent data from the CDC (101) shows a substantial increase in overdose death rates in black men overtaking white men, now on par with American Indian or Alaskan native men, as the demographic groups most likely to die from overdoses (Fig. 12).

The COVID-19 pandemic has exacerbated the illicit opioid crisis, reversing the previously encouraging trends, but breaking the records with escalating overdose deaths. The literature has been replete with many of the adverse effects of COVID-19 related to lockdowns, as well as school and health care facility closures, but resulting in no benefit and expected to have prevented only 0.2% of the deaths due to COVID-19 (102-104). Further, free flow of opioids through the border have facilitated increased access to illicit drugs and subsequent deaths (105,106) Health care has been affected substantially due to COVID-19 and resulting in policies, specifically so chronic pain patients with increasing physical and psychological

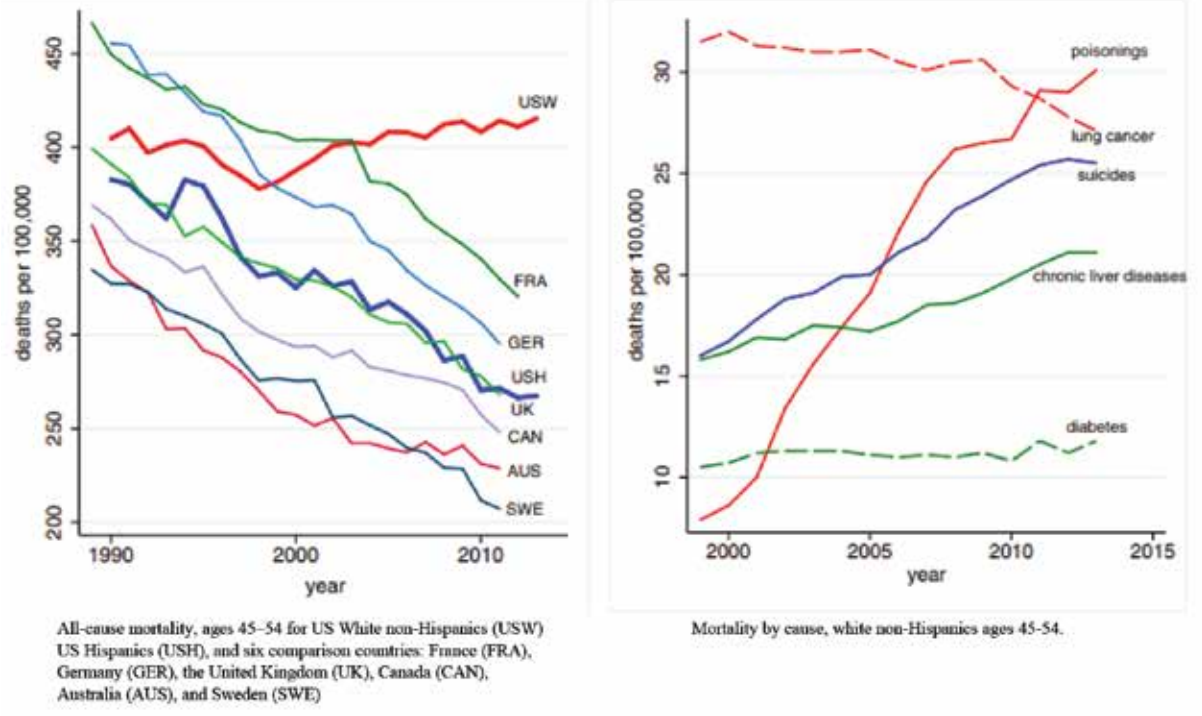


Fig. 10. *Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century.*

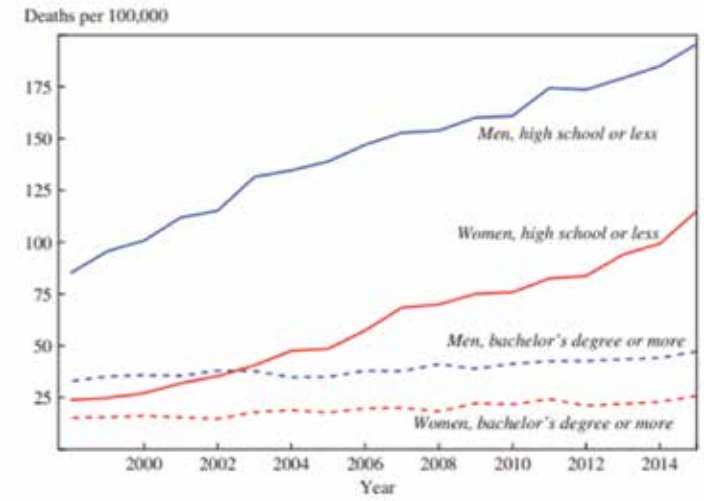


Fig. 11. *Deaths of despair for White Non-Hispanics age 50-54, by level of education, 1998-2015.*[a]
[a]Deaths of despair refer to deaths by drugs, alcohol, or suicide.

Sources: National Vital Statistics System; authors' calculations.

disability actually have reduced access to appropriate therapy (1,2,4,67,88,91,93,99,101-104,107-118). In fact, a recent survey of interventional pain physicians showed a significant decline in utilization of all types of services, resulting in potential reduction to access. Further, utilization patterns of interventional techniques showed a 18.7% decrease from 2019 to 2020 (67).

Tragic Failure of Current System

Historically, issues related to the opioid epidemic and the tragic failure of current systems to control opi-

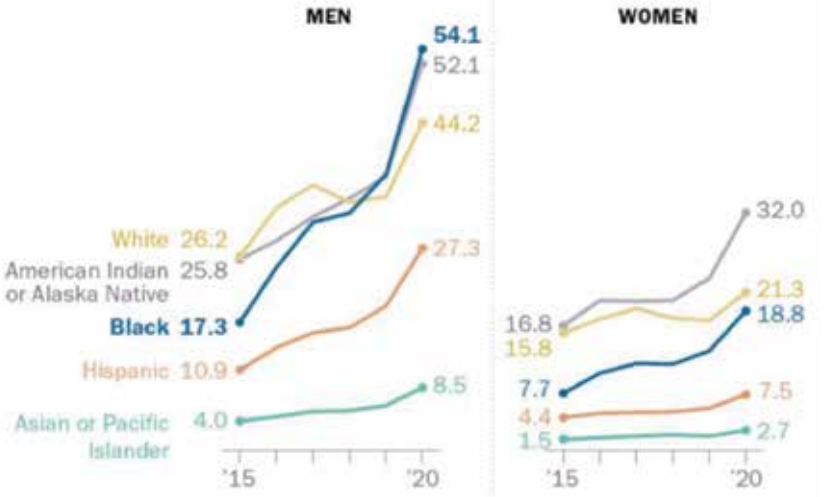


Fig. 12. *Drug overdose death rate among Black men in the U.S. more than tripled between 2015 and 2020.*

Note: All racial categories include people of one race, as well as those who are multiracial. For those who are multiracial, the CDC selects a single race to allow for consistent comparisons. All racial groups refer to non-Hispanic members of those groups, while Hispanics are of any race.
Source: Centers for Disease Control and Prevention

oid misuse included pharmaceutical company support of the use of prescription drugs to treat pain as the fifth vital sign (40). The explosion of the illicit fentanyl epidemic increases with the usage of heroin, and cocaine possibly reflect opioid under prescribing, as well as the undertreatment of pain when medically indicated (20,40,41,110).

Beginning and Escalation of Fourth Wave

The epidemic waves have been described in various ways (7,14). The CDC described the first wave began with increased prescribing of opioids in the 1990s (8). and the second wave beginning in 2010 with a rapid increase in overdose deaths involving heroin. The CDC descriptions of a third wave include the beginning of 2013 with a significant increase in overdose deaths involving synthetic opioids, particularly those involving illicit fentanyl (7,10-12) (Fig. 1). Subsequent assessment has led to the fourth wave of the opioid epidemic as described above. This has been traditionally described as polysubstance use and stimulants (16) and based on supply and demand (16,17).

In addition to the description of the three waves by the CDC showing prescription opioid overdose deaths, rise in heroin overdose deaths, and rise in synthetic opioid overdose deaths, the origin of synthetic opioid deaths leads to various regulations and guidelines. Coupled with the COVID pandemic, the fourth wave took shape.

CDC Opioid Guidelines

The CDC is the national public health agency of the United States. It is a federal agency under the Department of Health and Human Services (HHS). The agency's main goal is the protection of public health and safety through control and prevention of disease, injury, and disability in the US and worldwide (119). Its focus is on infectious diseases, foodborne pathogens, and environmental health; there is no specific statute for CDC to develop guidelines for any condition, including opioid prescriptions. There are multiple other agencies in HHS authorized to develop such guidelines, including HHS itself, United States Preventive Services Task Force (USPSTF), FDA, and Drug Enforcement Agency (DEA). The CDC also funded the AHRQ to conduct 5 systematic reviews, including opioid treatments for chronic pain, but also extending to non-opioid pharmacologic treatments for chronic pain, non-pharmacological treatments for chronic pain, treatments for acute pain, and treatments for acute episodic migraine.

The HHS, the agency of which FDA is part, based on the Comprehensive Addiction and Recovery Act (CARA) developed Pain Management Best Practices Interagency Task Force guidelines (6). The final report on pain management best practices was published on May 9, 2019. This task force utilized a total of 29 members with 12 public members, 9 organization representative members, and 8 federal members based on criteria specified in the CARA of 2016. The panel was headed by then Chief Medical Officer, Dr. Vanila Singh, an interventional pain physician, and included a large number of pain physicians and other experts.

Development of CDC Opioid Guidelines

The historical development of opioid guidelines dates back to the American Pain Society (APS) guidelines by Chou and Huffman (43). The initial publications were in the form of a book (43) and subsequently extended into multiple manuscripts (44-50). Manchikanti et al (51,52) published a critical review. APS guidelines were prepared essentially without an interventional pain physician (43,47). Essentially, early guidelines for APS stated there was no evidence for opioid therapy; however, at the time they appeared to recommend opioid therapy. APS guidelines were not supportive of interventional techniques. The "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic NonCancer Pain" (47) by the American Pain Society–American Academy of Pain Medicine (AAPM) opioid guidelines panel concluded that evidence is limited in many areas related to the use of opioids for chronic non-cancer pain. However, these guidelines provided recommendations developed by a multidisciplinary expert panel after a systematic review of the evidence. Notably, funding for these guidelines was provided mainly by APS, an organization that was eventually dissolved due to numerous conflicts of interest that have been well documented (120,121).

In 2011, a group including Von Korff, Kolodny, and Chou co-authored an article (54) with announcement of the creation of Physicians for Responsible Opioid Prescribing (PROP), "a non-profit organization with no pharmaceutical industry funding or ties," that would identify practical approaches to more cautious opioid prescribing in community practice. They noted that guidelines for long-term opioid therapy should not be developed by the field of pain medicine alone. Rather, experts from general medicine, addiction medicine, and pain medicine should jointly reconsider how to increase the margin of safety (54).

In July 2012, PROP filed a petition to the FDA (55) requesting the FDA to make three main changes to the labeling process for opioid analgesics, including strike the term moderate from the indication for non-cancer pain (essentially limiting opioids to severe cancer pain), add a maximum daily dose of opioid analgesia equivalent to 100 mg of oral morphine for treatment of all non-cancer pain and add a maximum duration of 90 days for chronic opioid therapy for non-cancer pain, after which opioid therapy would be discontinued. Soon after the submission of publication, the American Society for Addiction Medicine (ASAM) withdrew support (56,57). PROP approached multiple pain organizations including the American Society of Interventional Pain Physicians (ASIPP) to support this change; however, it was rejected by the board. AAPM also opposed the move (58) and multiple other societies including APS were critical. In September 2013, the FDA provided its response to the PROP petition to change opioid labeling and rejected the most important aspect of the PROP petition in reference to severity of pain, dose limitations, and limitation of duration of 90 days (59,60). However, FDA did make certain changes requiring new drug applications for long-acting opioids to conduct post-approval studies and clinical trials to assess known risks of misuse, abuse, hyperalgesia, addiction, overdose, and death (59). The FDA also determined that safety labeling of long-acting opioid analgesics needed to more effectively communicate to prescribers the serious risks associated with those drugs, and to describe the population more clearly in whom these drugs should be used in light of the serious risks (59,60). Further, they indicated that a new box warning for long-acting opioid analgesics and the addition of a phrase "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time" (59,60).

Subsequently, PROP had also reached out to the Federation of State Medical Boards (FSMB) to make changes in its revised model policy on the appropriate use of opioid analgesics in the treatment of pain (62). With these series of rejection, PROP approached CDC.

In 2016, CDC Director Frieden published an article in the New England Journal of Medicine with Houry as co-author (61) that included justifications for the development of CDC opioid prescribing guidelines. CDC guidelines were primarily intended for primary care physicians and meant to be voluntary; however, since then it has become the de facto standard of care for pain management in the US, with almost all boards of medical licensure, state legislatures, insurers, physicians, pharmacies, and other regulators (122). The CDC guidelines recommended opioid doses to be no more than 90 mg morphine equivalents (MME) per day. However, some providers have reacted by stopping prescribing opioids altogether rather than risk scrutiny from law enforcement or state medical boards (56,64). CDC guidelines were published despite major concern from bipartisan congressional members of the Congress as exampled by the letter from the Oversight and Regulatory Committee (53).

Evolution of Interventional Techniques Policies

"Pain Management Injection Therapies for Low Back Pain" (20) is a technology assessment report from AHRQ, the cost of which is not available (20). The authors followed the AHRQ Technology Assessment report with publication in the Annals of Internal Medicine (65) wherein active-controlled trials were converted into placebo-controlled trials in support of the idea that epidural steroid injections do not work. The present group of authors have previously described our concerns with that process. One frequently reported rationale for epidural steroids is that they reduce inflammation around nerve roots. However, this has not been proven and is considered a post hoc argument (123). Proponents of corticosteroids described efficacy, based on the hypothesis of inflammation, derived from postmortem studies and operative experience showing the inflammation of lumbar nerve roots. However, thus far, there is no definitive evidence to show a response from steroids based on inflammatory or noninflammatory radiculopathy. Consequently, multiple other factors play an active role. In fact, it has been reported that steroids have a reversible local anesthetic effect, producing the perceived benefit with epidural injections in addition to or rather than anti-inflammatory effect (124-133). In addition, other postulated mechanisms of actions of local anesthetic and steroids with their effect on multiple pathophysiologic mechanism or chronic pain include noxious peripheral stimulation, and excess nociception, resulting in the sensitization of the pain pathways at several neuronal levels, phenotype changes as part of neural plasticity, and excess release of neurotransmitters causing complex central responses including hyperalgesia windup (132,133). It is also important to note that local anesthetics alone were utilized without steroids from 1901 to 1953 (134-139), until the role of epidural steroids was described (138,139). Multiple studies have shown the therapeutic effects of sodium chloride solution injected into the epidural space (140). Further, multiple systematic reviews have shown the effectiveness of local anesthetics with or without steroids (141-146). Shanthanna et al (147) also clearly demonstrated that steroids may only have short-term effects and may be associated with significant risk. Manchikanti et al (66) published a comparative systematic review of Chou et al (65) identifying various deficiencies in the previous reviews as described above. These include conversion of active control into placebo control trials, inappropriate methodological assessment, and inappropriate inclusion of multiple studies leading to incorrect conclusions. The authors concluded that epidural lidocaine alone, or lidocaine in conjunction with steroids were significantly effective (66).

In part, based on these recommendations coverage for interventional techniques has been restricted through regulations and policies including the COVID-19 effect (Fig. 13) (67-74,82,83,107,109). Interventional

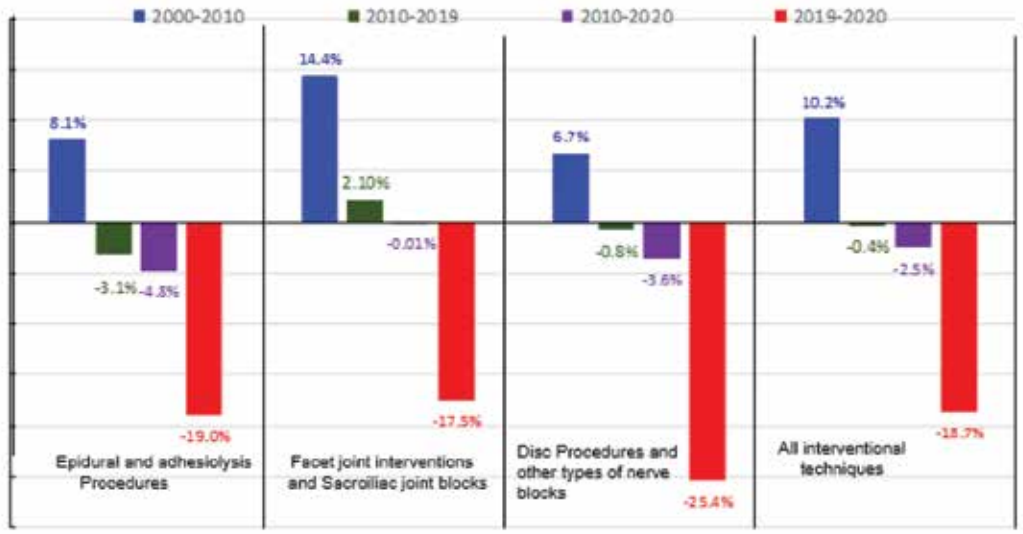


Fig. 13. *Comparative analysis of epidural and adhesiolysis procedures, facet joint interventions and sacroiliac joint blocks, disc procedures and other types of nerve blocks rates (geometric mean) , all interventional techniques.*

techniques have shown a 18.7% decrease in utilization patterns from 2019 to 2020. The decline or slowdown was reflected in all interventional modalities, except for spinal cord stimulation which has increased (Fig. 14), showing an increased utilization pattern. More recently, the new epidural LCD significantly curtails coverage policies with limiting indications and medical necessity to only radicular pain, limiting the frequency to 4 per year, per region, limiting the procedures for one year with an exception of collaboration with a primary care provider (75-77). Facet joint interventions also faced further restrictions with restriction of facet joint nerve blocks as a therapeutic modality only in patients where radiofrequency neurotomy cannot be performed (78). In addition, percutaneous adhesiolysis was not included in the epidural policy and a non-coverage policy was issued by Noridian and Palmetto Administrative Contractors (MACs) (79,80).

Opioid Tapering

Recent evidence has identified the opioid tapering practices leading to overdoses, as well as mental health crisis among patients prescribed long-term opioids (21,22). Agnoli et al (22) in a retrospective cohort study of more than 113,000 patients who were receiving stable, long-term opioid therapy reported that opioid tapering was associated with multiple adverse outcomes. They showed that in the period after opioid tapering, patients experienced an alarmingly high 9.3 overdose or withdrawal events for 100 person-years and 7.6% mental health crisis events for 100 person-years. These rates were estimated to be an increase of 3.8 treated overdose or withdrawal events per 100 person-years (95% CI, 3.0 to 4.6) and 4.3 treated mental health crisis events per 100 person-years (95% CI, 3.2 to 5.3) above the rate in patients who did not undergo opioid tapering. More rapid tapering was associated with a higher incidence of both outcomes. There have been multiple reports of this nature in the past, which was described as seemingly paradoxical increase in opioid related harms, such as suicidal ideation and completed suicide, among individuals undergoing opioid dose tapering. A potential mediating mechanism is that patients have developed physiologic opioid dependence and tapering, especially if rapid, may lead to opioid withdrawal, increased pain, and decreased functioning. Further, to alleviate these symptoms, some patients may use alternate, potentially riskier, substances obtained from nonmedical resources (21). They concluded that among patients prescribed stable, long-term, higher dose opioid therapy, tapering events were significantly associated with increased risk of overdose and mental health crisis.

An accompanying editorial by Larochelle et al (21)

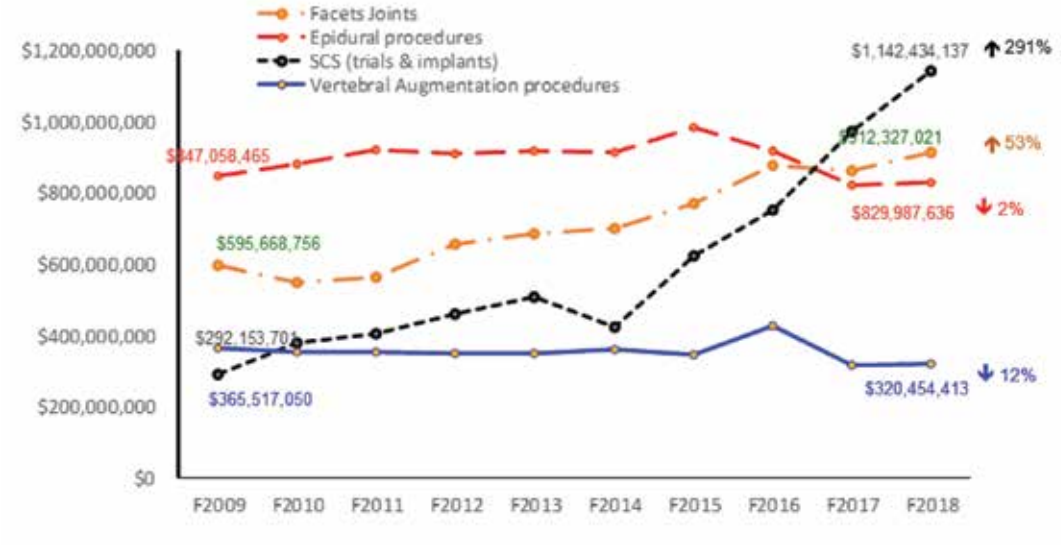


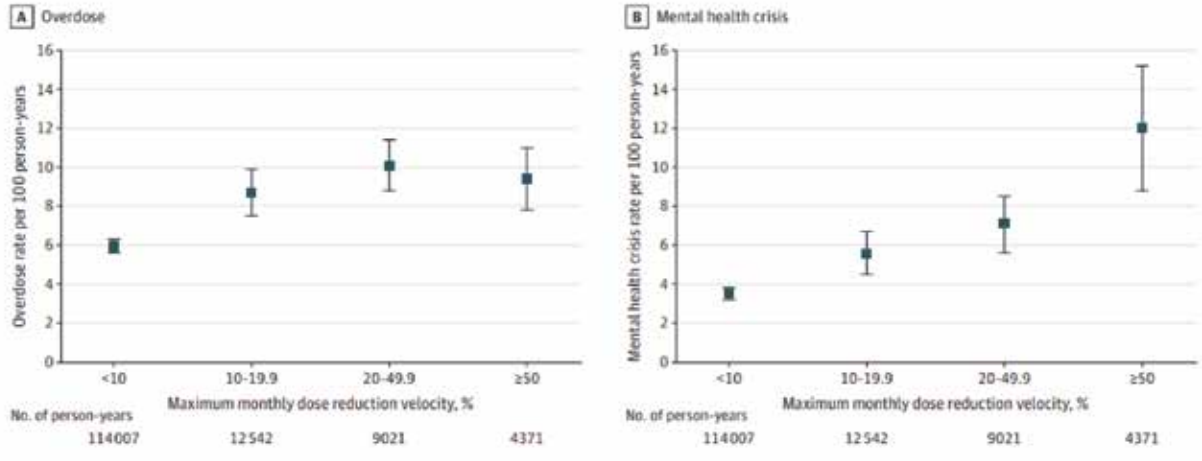
Fig. 14. *Total cost of facets, epidurals, SCS and vertebral augmentation procedures.*

Adapted from: Manchikanti L, Senapathi SHV, Milburn JM, et al. Utilization and expenditures of vertebral augmentation continue to decline: An analysis in fee-for-service (FFS) Recipients from 2009 to 2018. *Pain Physician* 2021; 24:401-415 (73).

titled "Opioid Tapering Practices – Time for Reconsideration", has cautioned that it is increasingly clear that opioid tapering needs to be approached with caution (Fig. 15).

Townsend et al (39), in a recent evaluation of CDC guidelines for opioid prescribing associated with reduced dispensing to certain patients with chronic pain, studied 450,000 patients with 4 common chronic pain diagnoses from 2014 to 2018, from a commercial claims database to examine associations between the release of guideline and opioid dispensing in a national cohort. They also examined whether any reductions associated with the guideline were larger for diagnosis for which there existed stronger expert consensus against opioid prescribing. Overall, the results showed that the guidelines were associated with substantial reductions in dispensing of opioids, including induction in patients' rates of receiving at least one opioid prescription by approximately 20 percentage points by December 2018 compared with the counterfactual, no guideline scenario. There was no variation in dispensing based on the strength of consensus. They suggested that although voluntary guidelines can drive changes in prescribing, questions remain about how clinicians are tailoring opioid reductions to best benefit patients. Further, these guidelines have transformed from their intended voluntary purpose to becoming mandatory for much of the population. Figure 16 shows the rate of one or more opioid prescription pills among commercially insured non-elderly US adults, with selected non-cancer pain, with and without CDC guidelines, by cohort 2014 to 2018. The study also showed the estimated effect was larger in the osteoarthritis or back and neck pain cohort with 21.5 percentage points, with the estimated effect being smaller in fibromyalgia or headache cohort with 17.8 percentage points. Additionally, this manuscript showed that CDC guideline was associated with a reduction in the combined cohort of 15.1 MME. In the combined cohort, the guideline was associated with a reduction in high dose dispensing of 10.3 percentage points by December 2018. However, they also noted that they found no evidence that there was a decrease in benzodiazepine dispensing in the comparison cohort or patients with diagnosed anxiety after the CDC guidelines were released.

In a large survey of 214,505 respondents, Han et al



A total of 109 223 patients and 139 941 person-years of follow-up are included in the analyses. Monthly outcome counts during follow-up were modeled as a function of the maximum monthly rate of dose reduction during any previous 60-day period. Thus, the less than 10% category may include patient periods prior to tapering, patients with gradual dose reductions, or patients with no dose change. Of the total cohort of 113 618 patients, 4395 (3.9%) were not included in these analyses due to an absence of follow-up time beyond the initial 60-day period or a dose increase of greater than or equal to 15% relative to baseline in the first 60 days. Plotted estimates are adjusted for patient age, sex, education, rurality of home address, commercial vs Medicare Advantage insurance, baseline opioid dose, co-prescription of benzodiazepines, study year, number of overdose events in the baseline period, baseline depression or anxiety, alcohol use disorder, drug use disorder, psychosis, and 24 other noncancer comorbidities included in the Elixhauser comorbidity index. Error bars show 95% CIs.

Fig. 15. *Adjusted event rates for overdose and mental health crisis events related to opioid tapering.*

Reproduced with permission from: Agnoli A, et al. Association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. *JAMA* 2021; 326:411-419 (22).

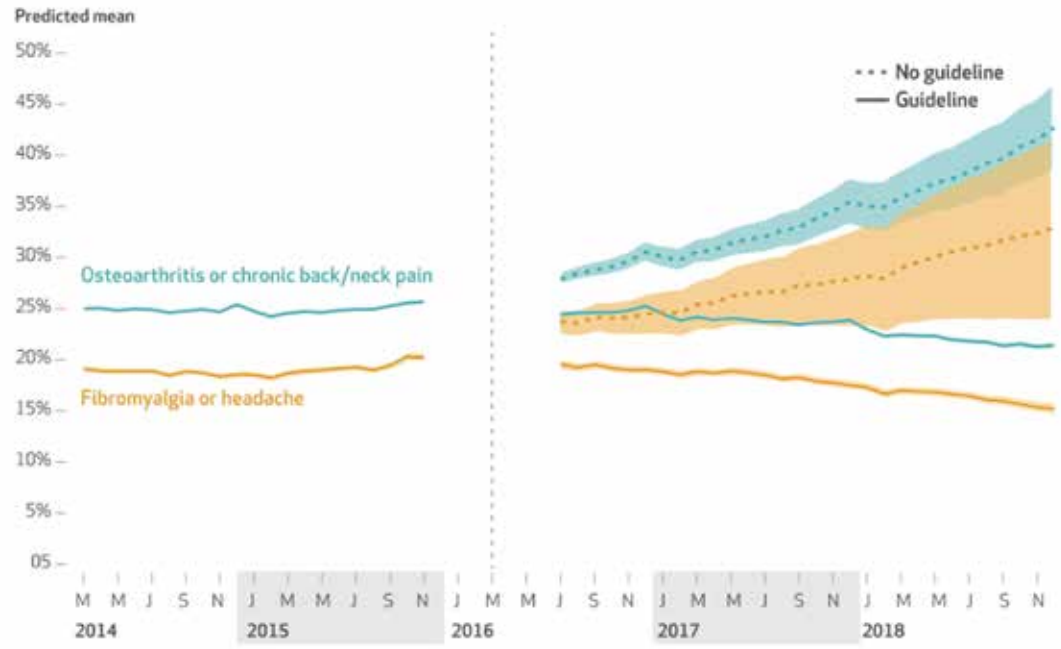


Fig. 16. *Predicted rate of one or more opioid prescription fills among commercially insured nonelderly US adults with selected noncancer pain with and without the Centers for Disease Control and Prevention guideline (observed versus counterfactual), by cohort, 2014-2018.*

Source: Authors' analysis of data from Optum's Clinformatics Data Mart, 2014–18. NOTE The vertical line indicates the release of the guideline, and the ungraphed portion indicates the implementation period between November 2015 and July 2016, which was not modeled.

Reproduced with permission from: Townsend T, et al. CDC Guideline for opioid prescribing associated with reduced dispensing to certain patients with chronic pain. *Health Aff (Millwood)* 2021; 40:1766-1775 (39).

(23) identified multiple drugs being reported using or misusing prescription opioids in the past 12 months. While use without misuse dominated the sample, the commonly misused opioids were hydrocodone, oxycodone, codeine, tramadol, among prescription opioids, and buprenorphine used for opiate use disorder and also methadone. Surprisingly, oxymorphone with small use was presented with highest use without misuse versus misuse ratio of 37.5, followed by buprenorphine of 29.2, methadone of 22.2, followed by others; hydrocodone was 11.6, oxycodone was 12.7, codeine was 10.1, tramadol was 7.8, morphine was 9.1, and fentanyl was 11.5. Overall, they concluded that among adults with opioid use disorder, the prevalence of buprenorphine misuse trended downward from 2015 to 2019. In 2019, nearly three-fourths of US adults reporting past year buprenorphine use did not misuse their prescribed buprenorphine. Figure 17 shows the use and misuse of various drugs utilized in pain management in opioid use disorder.

Multiple publications from advocacy organizations and Cato have looked at this (148,149). The Cato report (149) states that implementation of tapering and stoppage policies led to a rise in suicide and clinical stigmatization among chronic pain patients and patients with substance use dependencies. The Cato report (149) once again cast doubt on long-held assumptions about the opioid epidemic. They emphasized that there is no correlation between opioid-related mortality and the number of opioid prescriptions and that abruptly discontinuing opioids leads to adverse patient outcomes. Cato indicated that forcing physicians to reduce the number of prescriptions leads to a rise in counterfeit opioids. Recently in Kentucky, a federal judge deemed a pain management practice liable for the suicide of a patient unable to receive adequate pain relief, who then committed suicide as a result of the untreated pain (150). The judge in this case ruled that the physicians in the practice

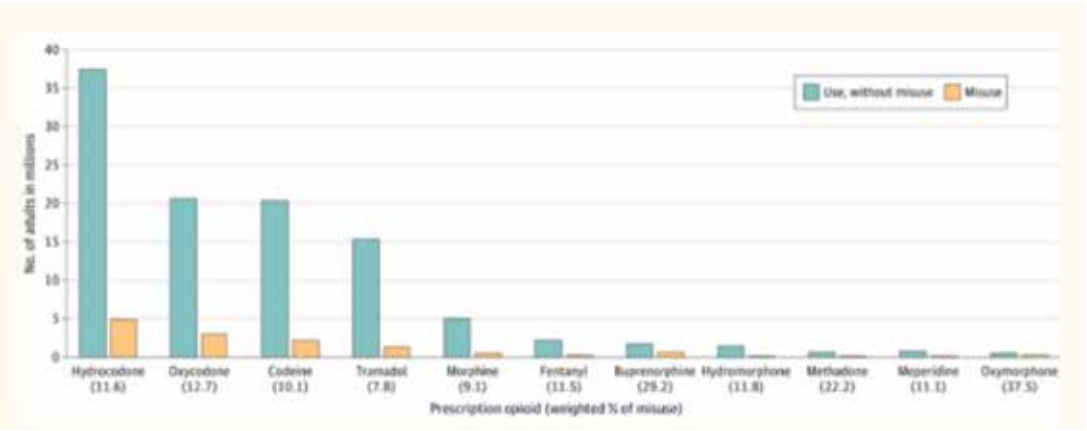


Fig. 17. *US adults who reported using or misusing prescription opioids in the past 12 months.*

Data are from 42,739 respondents in the 2019 National Survey on Drug Use and Health (NSDUH). The 2015-2019 NSDUH did not collect information on the use of illicitly manufactured fentanyl; the fentanyl data shown are for prescription fentanyl. For each type of prescription opioid, the denominator for estimating the proportion of misuse is the number of adults with use but no misuse plus the number of adults with misuse.

Reproduced with permission from: Han B, et al. Trends in and characteristics of buprenorphine misuse among adults in the US. *JAMA Netw Open*. 2021; 4:e2129409 (23).

were liable for the suicide because they inappropriately reduced the patient's opioid prescription dosage greater than 50% in one encounter (150). The AMA also issued an advisory that pain patients need to be treated as individuals (151).

Future Guidelines Revisions

The CDC has started the revision of the 2016 opioid guidelines (152). On April 17, 2020, they announced the opening of the docket to obtain comments concerning perspectives on and experiences with pain and pain management, including, but not limited to the benefits and harms of opioid use, from patients with acute or chronic pain, patients' family members and/or care givers, and health care providers who care for patients with pain or conditions that can complicate pain management. Overall, it received 5,392 comments from patients, physicians, medical organizations, and other stakeholders with feedback about its 2016 opioid guidelines. Multiple organizations including the AMA have expressed concern over the CDC guidelines and their misapplication (152-154).

However, the opioid guideline preparation workgroup has, in our opinion, thus far not been sufficiently transparent. The updated or expanded guideline is anticipated to be released in 2022.

The Role of Federal Agencies in Guideline Preparation

Multiple agencies including AHRQ, Centers for Medicare and Medicaid Services (CMS), and CDC are involved in providing funding and research regarding opioids and interventional techniques. Multiple organizations in HHS and outside have been established to assess health care technology. The National Center for Health Care Technology (NCHCT) functioned between 1978 and 1981. The Office of Technology Assessment (OTA) was created as an advisory agency to Congress covering a broad set of issues, including health care, and lasted from 1972 to 1995 (155). In 1989, the Agency for Healthcare Policy and Research (AHCPR) was created as an arm of the HHS (156). AHCPR undertook several initiatives, including creation of the National Guideline Clearinghouse (NGC) designed to summarize the available medical evidence on the appropriateness of treatments for various conditions (156). They produced 15 guidelines at an approximate cost of $750 million (157). In the mid-1990s, controversies arose after an agency-sponsored research team concluded that there was insufficient evidence to support certain spinal surgeries after which the agency issued practice guidelines for the treatment of back pain (157-160). The demise of the agency occurred in part due to strong opposition from spine surgeons, along with broader

questions about the value of the research that agency had funded and other factors (161). AHCPR ultimately survived with its funding for fiscal year 1996 reduced and the renaming of the agency as the Agency for Healthcare Research and Quality (AHRQ). AHRQ and effectiveness health care programs also received funding from multiple governmental and non-governmental organizations beyond $333 million in federal funding in 2018 (156). AHRQ and effectiveness research started with the Medicare Prescription Drug Improvement and Modernization Act (156,161). Some of the same questions which challenged AHCPR continue into the present day for AHRQ.

DEA issued multiple opioid production quotas (162-164). By 2020, the DEA annual quotas have brought production levels down more than 50% below 2016 levels.

External Influences and Conflicts of Interest

There appear to be conflicts of interest amongst the regulatory agencies as they pertain to opioids and interventional techniques. Yudkin, Richter, and Gale elegantly quoted, "The most entrenched conflict of interest (COI) in medicine is a disinclination to reverse a previous opinion (165)." The Institute of Medicine (IOM) (166) extensively described the role of bias and COI and the need to minimize them. IOM defined conflict of interest as, "A set of circumstances that creates a risk that professional judgment or actions regarding the primary interest will be unduly influenced by a secondary interest". Despite a known primary interest in terms of financial conflicts, IOM also stressed the importance of secondary interest, such as pursuit of professional advancement, future funding opportunities and recognition, and the desire to do favors for friends and colleagues, as potential conflicts. Further, such descriptions have been provided in the past, illustrating hidden conflicts of interest including by agencies which advise the policymakers and those preparing reviews for these organizations (42,81). Further, the Institute for Transitional Medicine and Therapeutics (ITMAT) has described confluence (not conflict of interest) in which they describe conflicts of interest as representing a complex ecosystem that requires development of a uniform approach to minimize bias in clinical research across the academic sector. They showed that the term conflict of interest is pejorative, disclosure policies have focused on financial gains only, whereas in academia, the prospect of fame, may be even more seductive than fortune (167).

Conflicts of interest were reported with the publication of the book "Managing Chronic Low Back Pain" by Chou and Huffman (43) funded by the APS, at a cost of over $1.4 million. The first guideline was published in 2009, which included multiple authors from APS.

The CDC was criticized for a lack of transparency in the drafting of the opioid prescribing guidelines since it had not disclosed which outside advisors it consulted during drafting of the prescribing guidelines for physicians (56,57). Other additional concerns included a 48-hour period for stakeholders to submit comments. This was later changed to a 30-day open comment period. The guideline committee had superficial involvement of ASIPP. The initial draft was published, which included interventional techniques; however, the final version removed the language in support of interventional techniques as non-opioid treatments.

On August 29, 2016, soon after the publication of the CDC opioid guidelines, a group of scientists from the CDC itself expressed integrity concerns about the agencies data and "current state of ethics, noting that "it appears that our mission is being influenced and shaped by outside parties and rogue interest" (64). They reached out to the Chief of Staff, Office of the Director for the CDC, stating that the CDC "data were clearly manipulated in irregular ways for political purposes" (64). Subsequently, they published an article concerning CDCs manipulation of data in a variety of projects, again alleging that the CDC was being influenced by corporate and political interests in a way that compromised its data collection (64).

In reference to disclosures, Kollas (56) reports that among the significant requirements, there is a statement as follows: experts could not serve if they had conflicts that might have a direct and predictable effect on the recommendations.

Summary

The COVID-19 pandemic of 2020 now entering 2022 continues to overshadow and increase the escalating crisis of drug overdoses and inappropriate techniques to prevent drug overdoses, which may be in fact, along with increased availability and distribution of illicit opioids, causing the escalation of the epidemic beyond its third wave. The tragic failure of systems has been described extensively (40). During the first and second waves and to some extent, the third wave, drug manufacturers, drug dealers, drug distributors, and over prescriptions have been targeted. Consequently, the direction of the drug epidemic has changed and

now we are entering the fourth wave. Wave one described the rise in prescription opioid overdose deaths which was also associated with the second wave, with a rise in heroin and overdose deaths from 1999 to 2013. The third wave was associated with a rise in synthetic opioid overdose deaths. Prescription opioid deaths had decreased in 2018 and 2019 with reversal of trend in 2020 as shown in Table 1 and Figs. 4 and 5. At the same time, opioid prescriptions have decreased 44% from 2011 through 2020, whereas overdose deaths continued to increase up to 94,134 in the period ending in 2020 (Fig. 3) (88). Some of these phenomena have been attributed to the COVID-19 pandemic. However, it is beyond the opioid epidemic. In a sense, the opioid epidemic is a misnomer -- it should be called the "illicit drug epidemic", which includes illicit fentanyl, heroin, and methamphetamine. Consequently, the fourth wave of the opioid epidemic starting in 2016 may be attributed to numerous factors (Fig. 18). These interrelated factors include COVID-19, increased availability of illicit drugs and reduced access to interventional techniques. One of the important factors in creating the fourth wave are the CDC guidelines and the subsequent saga of regulatory atmosphere with either forced tapering, overall stopping of opioid prescriptions, reduced opioid prescriptions with reduced dosages, leading pain sufferers to the streets in search of illicit sources to control their pain and a tragic increase in subsequent deaths. This has been evidenced by Agnoli et al (22) in a recent manuscript showing significant evidence of adverse effects related to opioid tapering, increasing opioid overdosing with 9.3 overdose or withdrawal events per 100 person years and 7.6 mental health crisis events compared to 5.5% and 3.3% in patients who were not forced into tapering. These increases were 69% for overdoses and 130% for mental health crisis events (22). The authors of this manuscript have cautioned against tapering and raised multiple questions about the potential harms of tapering. Agnoli et al (22) also showed adverse effects based on the amount of dose tapering. They showed that increasing the maximum monthly dose reduction velocity by 10% was associated with an adjusted incidence rate difference of 1.09 for overdose and of 1.18 for mental health crisis as shown in Fig. 15. An accompanying editorial by Larochelle et al (21) also noted that opioid tapering needs to be approached with caution. They described that achieving the goals of minimizing risks, yet also improving pain and function, will require individualizing care and evidence-based approaches with more nuanced strategies that embrace the clinical complexity of the population of patients with chronic pain. Numerous comments were submitted to HHS during the guideline preparation about the CDC guidelines and adverse consequences developed in these patients. Consequently, multiple guidelines also have been developed for ta-

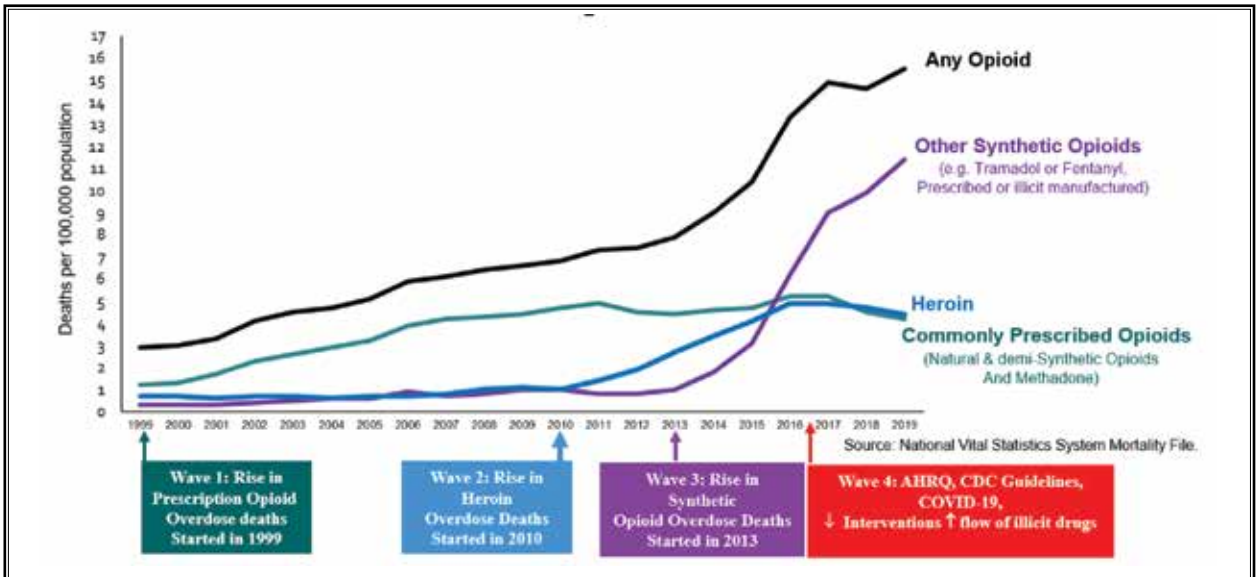


Fig 18. *Four waves of rise in opioid overdose deaths.*

Redrawn and modified from CDC figure

pering purposes. However, these do not carry the same significance as the CDC guidelines, which are mandated in some states and by multiple agencies.

Opioid dose tapering has been extensively performed since the 2016 CDC guidelines (19) were published. An unintended consequence was an increase in deaths attributable to some extent to fentanyl resultant from poor pain control and addiction management. Similarly, the study by Han et al (23), showed significant misuse patterns in all groups of opioids related to relieving physical pain. This reduced access to opioids is occurring in the backdrop of guidelines or policies aimed at limiting use of not only opioids, but of interventional techniques and other interventions. These factors, intertwined with COVID-19 and relatively easy access to non-prescription opioids are contributing to a fourth wave of the illicit drug epidemic, despite a reduction in opioid prescriptions and dosages.

Due to multiple factors involved, the fourth wave continues to escalate with an increasing number of deaths despite decreasing prescription opioids and other modalities of treatment.

Conclusion

The United States is entering what can be termed as the fourth wave of the opioid crisis. ASIPP took a strong position in the earlier waves of the opioid crisis, expressing our concerns with the easy and widespread availability of prescription opioids and the negative consequences this would have on patients and society. What were at one-point unpopular positions, e.g., that some pharmaceutical companies were using their immense resources to support these activities, are now accepted as fact. The authors are proud of the role ASIPP played in bringing this challenge to light. In 2022, we are faced with a more nuanced situation that requires careful attention. Patients with legitimate somatic pain are being challenged by the faulty application of guidelines outside of their intended purpose. Moreover, these same patients are potentially denied appropriate access to interventional pain therapy.

The Center for Disease Control is developing a second set of guidelines. There are lessons that should be learned from 2016 including the reality that these guidelines can be broadly misapplied with incontrovertible detriment to chronic pain patients. It is our hope, and the expectation we will lobby for, that the CDC can improve their process by including pain physicians as occurred with the Pain Management Best Practices Interagency Task Force and making the guideline process more transparent. Safer prescription opioids and better access to proven interventional techniques will inure to the benefit of chronic pain patients and hopefully impact this tragic fourth wave. Unfortunately, federal agencies continue to depend on AHRQ publications with a most recent publication from April 2020, once again, encompassing the principles of previous reviews potentially resulting in further calamity (168).

Author Contributions

All authors contributed to preparation to the manuscript, reviewed, and approved the content with final version.

Conflicts of Interest

Dr. Singh is an Independent Board Member with Virpax, Director, Bio Delivery Sciences International (BDSI) since November 2019, and Independent Director, Lucid Lane since April 2020.

Dr. Staats receives grants from Boston Scientific, Halyard, and St. Jude, an honorarium from Nevro, Halyard, Medtronic, and St. Jude, patents from NeurogesX, royalties from multiple books and NeurogesX, and has investment in Electrocore.

Dr. Soin is the founder and CEO of Soin Neuroscience, which is developing a spinal cord stimulator to treat spinal pain and has a patent for Soin Neuroscience, Jan One, and Avanos and a patent pending for Soin Therapeutics.

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