

Exploitation of Opioids in America: A Narrative Review of Multidisciplinary Studies

ABSTRACT

Opioids continue to ravage many socioeconomically disadvantaged communities across the nation of America. Opioids are pain relievers, but may become harmful when consumption is not regulated. Many overdose on this drug, and may commit actions that entirely change their life's trajectory for the worse. In this narrative review, information is presented from different sources on what has caused the opioid epidemic, the policies and initiatives that have been established to manage opioid overconsumption, and the sequence of events that occur internally when opioids are consumed. The main purpose of this review is to present the different factors that contribute to gradual opioid addiction, and how those addictions are counteracted. In terms of policies and initiatives, two of them were the Controlled Substances Act and the National Pain Strategy. Both policies were created to attempt to regulate the complex relationship between pain and opioid abuse. Without educational programs such as the Centers of Excellence for Pain Education teaching about opioids, and willingness to attempt nonopioid treatments for pain like methadone, the 13-25 year age range will be susceptible to the damages that opioid overdose can cause.

KEYWORDS: *opioids, opioid receptor, pain, fentanyl, OxyContin, overdose, policies, health*

INTRODUCTION

Government institutions such as the CDC have recognized the recent opioid epidemic that can be characterized into three categories seen in Figure 1, copied from (<https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html>). The opioid epidemic ranges from the 1990s-2020s, the first category being a rise in prescription opioid related overdoses in patients from the 1990s up until the 2010s where there is a distinct rise in overdose deaths related to heroin misuse. The most recent waves in relation to the opioid pandemic is the rise in fentanyl synthetics that have contributed to the rising opioid related overdoses since 2013. More recently, in the study Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016, it underscores how there has been a sharp increase in opioid related deaths since 2013 partly due to the introduction of illicitly distributed fentanyl that is laced with heroin (O'Donnell et al., 2017). It emphasizes the role fentanyl has played in overdose deaths examining how “fentanyl was detected in 56.3% of 5,152 opioid overdose deaths in the 10

states during July–December 2016”, but that of those deaths “fentanyl was determined to be a cause of death by the medical examiner or coroner in nearly all (97.1%)” (O'Donnell et al., 2017). Of these general statistics, in an article titled Drug Overdose Deaths Among persons aged 10-19 years- United States, it reported that “Median monthly overdose deaths among persons aged 10–19 years (adolescents) increased 109% from July–December 2019 to July–December 2021; deaths involving illicitly manufactured fentanyls (IMFs) increased 182%”(Lauren J. Tanz, 2022). Additionally, it highlighted how “U.S. drug overdose deaths increased 30% from 2019 to 2020 and 15% in 2021, resulting in an estimated 108,000 deaths in 2021.* Among persons aged 14–18 years, overdose deaths increased 94% from 2019 to 2020 and 20% from 2020 to 2021”(Lauren J. Tanz, 2022).The increasing trend of overdoses highlights the risk that illegally distributed fentanyl has played amongst the youth in the United States throughout the years.

Furthermore, in the study Opioid prescribed at discharge from emergency department among adults: United States 2006-2017, researchers tracked

the percentage of visits where opioid treatments were prescribed to patients suffering from chronic or acute pain from the ages of 18 and over throughout the course of two years, where the results of the study signify an increase of opioid treatments prescribed to patients, where some with morphine equivalent opioids prescribed at discharge “increased from 11.3% in 2006–2007 to 12.4% in 2010–2011 and decreased to 6.7% in 2016–2017” (Rui et al., 2020). Researchers evaluated and determined significant trends including how “hydrocodone and oxycodone experienced the largest increase from 15% to 31% in emergency department visits” and that overall “the percentage of ED visits by adults with opioids prescribed at discharge increased from 2006–2007 (19.0%) through 2010–2011 (21.5%), then decreased from 2010–2011 through 2016–2017 (14.6%)” (Rui et al., 2020). Apart from these trends, researchers have identified that “exposure to an opioid prescription in the ED has been identified as a potential risk factor for long-term use, with one study reporting that 17% of patients who filled their first opioid prescription for a minor painful condition were still receiving opioids 1 year later” (Rui et al., 2020). The long-term use for potent opioid analgesics reflect the addictive nature of opioids used in analgesics and the seriousness of its adverse effects on patients when prescribed at discharge. However, the trend signifying a decrease in opioids prescribed to patients reflects the awareness and precautions taken

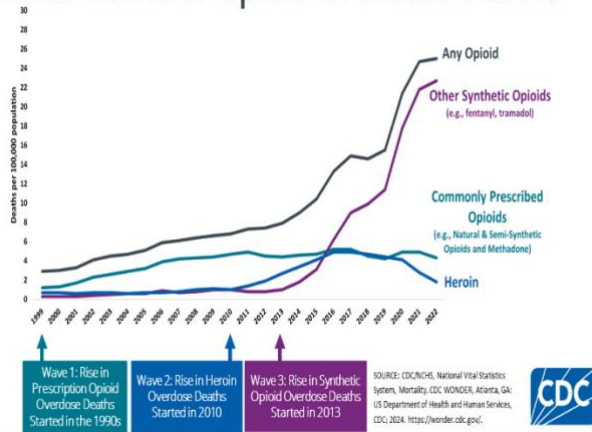
by departments to minimize opioid misuse by patients.

In order to battle the increasing opioid related overdoses in North America, states have enacted federal and state funded rehabilitation programs and have begun to experiment with new medications that react with opioids or can act as alternatives for opioid analgesics. This issue has called for an investigation over the leading causes of increased opioid addiction and how the US government has responded including integrating policies and addressing issues concerning opioid use between the years of 1970 and 2020, such as the National Pain Strategy (NPS), the Comprehensive Addiction and Recovery Act (CAR), and the Controlled Substances Act (CBA). By analyzing the policies incorporated by the government and how it has impacted opioid use through the years, we can determine the best approach to reducing the number of opioid related deaths and minimizing opioid misuse amongst adolescents and young adults.

METHOD

To investigate the primary causes, public policy initiatives, and the future prospects set to be implemented in order to approach the national opioid usage crisis across America, this narrative review was conducted to collect data from articles using PubMed, Scopus, and Google Scholar published between October 1973 to October 2024. Search terms used are as follows: ‘opioid epidemic,’ ‘detecting illicit opioid,’ ‘prescribed opioid abuse,’ ‘opioid addiction treatment,’ ‘future directions,’ ‘changes to addictive drug prescriptions’. Boolean operators such as ‘AND’ and ‘OR’ were used to filter and narrow the search. Articles and studies were implemented based on their applicability to certain aspects in relation to the opioid epidemic in individuals aged 13–25. Studies focused on both qualitative and quantitative perspectives, focusing on statistical data in relevance to observational experiences. Full text articles that were directly related to the opioid crisis, were published in peer-reviewed English journals. To rule out any

Three Waves of Opioid Overdose Deaths



irrelevance to the topic, three viewers carefully examined the abstract and title and checked for compliance of full text using the criteria to avoid disagreements related to its eligibility. The data collected from the chosen sources was summarized based on recurring patterns, themes, and concepts. Key findings were thematic subcategories: Causes, Policies & Initiatives, and Medication. Time restrictions applied a limitation to this study, because a survey could have been potentially created to use as valuable and first-hand data, but instead other sources were used.

CAUSES

One of the major causes of the opioid drug epidemic is the overprescription of various types of opioids by healthcare providers. From the 1800s to the early 2000s, physicians frequently prescribed opioid medications to patients in high doses, which contributed to the escalation of an opioid epidemic. In the 1800s, when opioid medications were initially introduced to the market, doctors had limited knowledge about the risks of the potentially addictive compounds in opioids, primarily due to pharmaceutical companies downplaying the serious side effects of these medications (Lyden & Binswanger, 2019). In the late 1800s physicians and health officials began shifting their views of opioids— from a useful drug option to recognizing it as a highly addictive drug correlated to triggering many serious health effects (Lyden & Binswanger, 2019). Ultimately, this led health regulatory institutes to seek regulation of opioid prescription and dispensation practices by adopting the Harrison Anti-Narcotic Act in 1915 (Lyden & Binswanger, 2019). With fear amongst doctors towards the risk of addiction, by the 1980s, opioids were mainly allocated for patients with severe cases such as cancer and terminal conditions. An opposing group of doctors rose to voice their concern about patients, specifically those without cancer, being undertreated for pain due to the growing fear of opioids (Lyden & Binswanger, 2019). In 1985 an editorial published in the *Advances in Alcohol and Substance Abuse* argued that doctors were too overly cautious with

supplying opioids and that it's quite rare for addiction to occur (Lyden & Binswanger, 2019). This idea was especially supported by the American Pain Society, which promoted movements for improved pain control, including a movement to recognize the importance of pain as a “fifth vital sign” (Lyden & Binswanger, 2019).

Beyond the prescription practices, misleading marketing by pharmaceutical companies played a role in the opioid crisis. Pharmaceutical companies have a historical pattern in which they prioritize profits over the safety and health of the public by making exaggerated claims that misrepresent the efficacy and performance of their medication (Bowra et al., 2024). In 1996, Purdue Pharma introduced OxyContin, an opioid approved by Food and Drug Administration (FDA), and marketed to physicians as safe and effective in treating chronic pain (Bowra et al., 2024). Purdue established an aggressive marketing campaign, falsely promoting OxyContin as a low-risk and non-addictive option for physicians. To further promote OxyContin, Purdue established a bonus system that incentivized sales representatives to increase sales of higher-dosage opioids (Alam & Juurlink, 2016). Despite evidence disproving their claims that OxyContin has a low risk of dependence and provides a longer-lasting effect than any other branded opioids, the Purdue executives proceeded to mislabel the drug deceptively (Alam & Juurlink, 2016). Accordingly, in 2007, Purdue Pharma and three of its top executives pleaded guilty to misbranding and were fined over \$600 million by the West Virginia Attorney General (Bowra et al., 2024).

In response to the accessibility of opioids after new additional regulations, a shift to illicit opioids became more prevalent. Regulatory efforts implemented in the early 2000s increased to reduce the overprescription of opioids. Individuals who grew psychological dependence on the painkillers, either through misuse or prolonged use of the drug, turned to illicit substitutes. Illicit opioids like heroin became an alluring option due to their affordability in comparison to other street drugs (Ying Han et al.,

2019). In recent years, fentanyl, a powerful opioid anesthetic, has been synthesized in illegal laboratories with traces of other illicit drugs such as methamphetamine, cocaine, and heroin (Ying Han et al., 2019). Fentanyl has high potency, and is rapidly onset, giving very little time for individuals who underestimate its strength to seek immediate help (Ying Han et al., 2019). The rise in fentanyl sales on the streets contributed to the sharp exponential growth of the overdose mortality rate in the United States from early 2000s to present day (Ying Han et al., 2019). Furthermore, criminalizing individuals for illegal drug use meant that they could not receive proper healthcare to solve the root causes. The U.S. criminal justice system has very limited access to treatment plans for opioid use disorder, as federal prisons don't offer medications to assist opioid addicts (Csete, 2019). The lack of access to treatments is a violation of the health standards because incarcerated individuals have a right to the same healthcare as the general population (Csete, 2019).

Socioeconomic marginalization like homelessness, incarceration, or poverty is closely linked to opioid misuse, especially in adolescents. Social determinants make individuals more susceptible to chronic pain and distress because they likely face poor working conditions that are physically demanding or unsafe housing in a high-crime area that poses a threat to their lives, which can result in chronic physical and mental pain. With fewer options for adequate healthcare services and support, individuals turn to temporary fixes, opioids, to treat their chronic injuries, but in reality, opioids worsen physical and mental health in the long run (Nabarun Dasgupta et al., 2018). In a study conducted by Jenna Van Draanen et al. (2020), researchers found that 34/37 studies showed a strong connection between opioid misuse and socioeconomically disadvantaged individuals, proving that opioid addiction is not a random choice that individuals make but rather influenced by the socioeconomic environment that structures the access to getting proper health care. The healthcare system focuses on pharmaceutical fixes instead of focusing on the root causes that

contribute to the majority of opioid cases, which leaves hopeless individuals to fall deeper into their addiction cycle (Nabarun Dasgupta et al., 2018).

POLICIES & INITIATIVES

Creating policy for opioids can be difficult due to opioids simultaneously being a source of pain alleviation and harm, if used without regulation. In order to regulate consumption of opioid products, there have been policies and initiatives created to counteract the over-consumption of opioids. Policies and initiatives such as the Controlled Substances Act (CSA), the National Pain Strategy (NPS), and the Comprehensive Addiction and Recovery Act (CARA) were created to assist with the complex relationship between pain and opioids (Gordon & Gross, 2018). These initiatives are listed in order of when they were enacted to present the differences that emerged in each policy. Before creating these policies, government officials needed awareness of the fact that individuals may increase their consumption of opioids to eliminate the pain they are experiencing (Gordon & Gross, 2018). Initiating the government's involvement in establishing policies and initiatives around the subject of pain, the Congress created the CSA in 1970 (Gordon & Gross, 2018). CSA was a piece of legislation designed to control the manufacturing, production and consumption of "certain controlled substances" (Gordon & Gross, 2018). Since the "CSA validated opioid medications as necessary components" for treating pain, there was a need for updates and changes due to concern towards potential increase in opioid usage to alleviate pain (Gordon & Gross, 2018). The NPS enacted a transition significant for United States' pain policies that were previously divided, and became more unified (Gordon & Gross, 2018). At both state and federal levels, there was more opioid allowance for "broader use in noncancer chronic pain", meaning that the NPS was moving towards opioids being used for more than just cancer due to opioid restrictions from 1980s to 1990s (Gordon & Gross, 2018). Returning to the NPS's benefits, the NPS "addresses the biopsychosocial aspects of pain previously

underrecognized” and emphasized new, improved treatments that were “evidence-based” in order to eradicate the use of opioids as much as possible (Gordon & Gross, 2018). The NPS aligned with the improvement of “patient experience”, population health, and “per-capita cost of health care” reduction (Gordon & Gross, 2018). This proposed improvement established the “Centers of Excellence for Pain Education” program to further expose individuals to other possible pain alleviation routes that may be more sustainable than consuming controlled-substances, such as opioids (Gordon & Gross, 2018). The NPS reduces the consumption of opioids through an economic advantage for consumers by establishing “legislation in support of ... state Medicaid coverage of nonopioid-based treatments” (Gordon & Gross, 2018). Medicaid coverage of nonopioid-based treatments reduces opioid usage because other treatments become more financially accessible. Unfortunately, attempted “public awareness campaigns about pain and safer medication use” by the NPS had not been completely exposed to the larger U.S. population (Gordon & Gross, 2018). Neither has “a significant impact on payment structures and reimbursement policies” been enacted per the NPS’s “recommendations for coalitions”, and those coalitions are important due to them increasing communication between communities, which is needed to spread awareness of opioid alternatives (Gordon & Gross, 2018). Though there is a mass amount of “literature on the efficacy of noncovered treatments for chronic pain”, these noncovered treatments are being overlooked due to policymakers not including these treatments in policies (Gordon & Gross, 2018). NPS’s limits include restricted funding and “absence of definitive timeline” for the NPS results to present themselves (Gordon & Gross, 2018). An absence of a definitive timeline is a limitation because the NPS’s initiatives are left to the people to implement in their lives to support their pain. In favor of the NPS, the CDC recognizes the “need for chronic pain management”, as well as a multiple solution approach to increasing nonopioid treatments’ popularity (Gordon & Gross, 2018). Continuing their support of the NPS, the CDC “requested \$85.6 million to combat opioid

overdose” (Gordon & Gross, 2018). Another piece of legislation created is CARA, “signed by Barack Obama in 2016 ... to address the opioid epidemic”, and it was later updated by adding the following: “increasing funding authorization”, “supporting the 3-day time limit quantity in acute pain prescribing supported by the CDC”, “reduced restrictions on medication-assisted treatment”, and harsher manufacturing penalties for illegal opioid distribution (Gordon & Gross, 2018). It is important to understand that these are not the only policies, but these policies attempted to support the complex relationship between opioids and pain for all in the U.S.

MEDICATION DEVELOPMENT

One of the most significant properties of opioids is how they interact with the brain when developing medications and determining if they can reduce or treat opioid addiction. In the study *Untangling the complexity of opioid receptor functions*, it explains how “access to new molecular, genetic and computational tools have begun to elucidate the structural dynamics of opioid receptors, the scaffolding that links them to intracellular signaling cascades, their cellular trafficking and the distinct ways that various opioid drugs modify them” (Valentino & Volkow, 2018). This study has allowed for a more thorough understanding of how opioid analgesic (relief) medications interact with the mu opioid receptor agonists in the brain (Valentino & Volkow, 2018). For example, in the brain there are three opioid receptors that include the MOR, DOR, and KOR. According to the study, “though the MOR is the main target for opioid analgesics, the DOR and KOR also regulate pain and analgesia and the relative affinities of opioid analgesics for these receptors confers them unique properties” (Valentino & Volkow, 2018) In other words, when medication that has concentrations of opioids react with the receptors they have specific effects on a person's mood. While MOR agonists produce “euphoria and promote stress coping”, KOR agonists “produce dysphoria, stress-like responses and negative affect” (Valentino & Volkow, 2018).

By understanding the interactions between receptors and opioids, researchers can develop alternative analgesic medications that are not as harmful as opioid analgesic medications. However, the study underscores that receptors are much more complex and that researchers aimed to study receptors in both their inactive and active form. In their inactive form, “the crystal structures of the MOR, DOR, and KOR in the inactive conformation (i.e., bound to antagonists) identified the spatial organization of key molecules within the receptor that make up the binding pocket and determine ligand selectivity” (Valentino & Volkow, 2018). In their active form the receptors were more unstable, and as a solution researchers utilized nanobodies that are “single chain antibodies that mimic the G-proteins that couple to and stabilize receptors in an active conformation” (Valentino & Volkow, 2018). In simpler terms, when opioids are consumed they act as ligands, signaling molecules, so that they can bind to opioid (g- coupled protein) receptors (MOR,DOR,KOR) that each affect the production of neurotransmitters and hormones. When opioids have bonded to receptors, the opioids activate the receptor and induces a conformational change in the receptor, which makes it more difficult to understand the structure of the an opioid receptor. On the other hand, when receptors have not bonded to an opioid and are unactivated, its more manageable to understand the structure of opioid receptor.

This is why it was crucial for researchers to use nanobodies to identify the crystal structures of MOR and KOR in the active form, as they stabilized activated opioid receptors, which can be used to develop safer and more efficient MOR and KOR agonists.

Additionally, in the article Treatment of overdose in the synthetic era, it explains how the central nervous system plays a role in opioid overdose because the “neurons are particularly vulnerable to hypoxic damage resulting from depressed respiration”(Skolnick, 2022). A more sustained or profound hypoxia will also affect other CNS structures including epithelial cells of the choroid

plexus and glia” (Skolnick, 2022). This is relevant as the interaction between the MOR receptor and opioid agonists “drive opioid induced respiratory depression” (Skolnick, 2022). Respiratory depression is especially critical to think about as it “is responsible for opioid-induced fatalities as well as the short- and long-term morbidities linked to a non-fatal overdose” (Skolnick, 2022). Short and long-term morbidity refers to the brain damage that can occur when an individual suffers either hypoxia or anoxia (Skolnick, 2022).

One of the most recent medications that has been developed to react to brain receptors in order to reverse the effects of opioid related overdoses is naloxone. In the study, Assessing the Impact of Opioid Overdose and Opioid Antagonist Dosing to Support Medical Product Development, it explains that naloxone is an “opioid agonist” which “works by binding to opioid receptors in the central nervous system and blocking the effects of other opioids, such as heroin, morphine, oxycodone, and synthetic opioids like fentanyl” (Center for Drug Evaluation & Research, 2023). The information by the article highlights how researchers have used their understanding of neural receptors to develop medications that can react with receptors, however the study concludes that a primary limitation of incorporating naloxone is determining the appropriate dosage to give to patients (Center for Drug Evaluation & Research, 2023). It explains how naloxone and differing opioid compounds “differ in how quickly they bind to and dissociate from opioid receptors in the brain, their potency, and how readily their effects can be reversed by a given dose of naloxone” (Center for Drug Evaluation & Research, 2023). By analyzing the different properties of opioids and the interactions between opioid receptors, opioids, and naloxone researchers are able to identify the best dosages to prescribe to combat the effects of opioids. It is critical to understand the properties of agonists and MOR, KOR, and DOR receptors for the development of medications with reduced amounts of potency and decreases the overall likelihood of opioid misuse by patients by minimizing its harmful effects.

Two medications that have been used by hospitals to treat withdrawal symptoms and promote opioid recovery is methadone and buprenorphine. In the article, Methadone, it describes how methadone has been used in treatment programs for people who have been identified as dependent on heroin or morphine, and that while possessing the pharmacological properties of morphine, it has more gradual and less intense withdrawal symptoms that opioid medications have and prevents the euphoric effects produced from other opiates (Sim, 1973). The results of this study concluded that patients who underwent treatment with methadone reported improved productivity compared to being dependent on heroin and morphine.

Additionally, in the article Buprenorphine Treatment for Opioid Use Disorder: An Overview, it highlights how methadone, a synthetic opioid analgesic, hallmarked “the agonist treatment strategy for addiction treatment that include slow absorption, which reduces the tendency to produce a rush or “high,” and slow elimination, which avoids the rapid emergence of withdrawal symptoms (Shulman, 2019). Both of these texts illustrate how methadone has been an effective medication that has both discouraged opioid misuse and can be used in the field of medicine to prevent the reliance of potent and addictive opioid analgesics. Apart from methadone, the article introduces the use of buprenorphine, which was developed as an “opioid analgesic with less abuse potential” and therefore trials began under the Addiction Research Center at the Federal Narcotics Hospital over buprenorphine as an alternative to methadone (Shulman, 2019). The study found that buprenorphine had a “unique profile as a mu-opioid receptor partial agonist, producing less tolerance and less intoxicating effects” which included “less respiratory depression compared to full agonists, as well as a blockade of opioid effects at adequate doses” (Shulman, 2019). Moreover, the article explains how the kappa receptor produce dysphoric effects, and since buprenorphine was classified as a “kappa-opioid receptor antagonist” it might “oppose the dysphoria that accompanies withdrawal from opioids, or exert

antidepressant effects” (Shulman, 2019). By reducing the intense dysphoria and stress that comes with withdrawing from opioids, buprenorphine decreases the likelihood of overdoses and prevents opioid analgesics misuse. The evidence from the article supports the efficiency of buprenorphine during medically-supervised withdrawals from opioid misuse, and provides insight as to why buprenorphine should be considered more seriously worldwide to treat opioid misuse and be more accessible, despite the strict regulations set in place because of fears of the risk of diversion, sedation, and overdose.

DISCUSSION

The research we conducted indicates that opioid abuse can have a profound impact on people’s lives, whether it involves individuals directly misusing opioids or being indirectly influenced by others’ misuse. Even though there is a rising amount of research on opioid use among youth and young adults, there are still many gaps. Primarily, there is a major lack of longitudinal studies. Thus, more data that follows young people over time is needed to understand how early exposure to opioids affects their development, mental health, and future substance use. There is also limited data on preventative strategies for these age groups. While there is a substantial amount of information focusing on what is going wrong, there is much less evidence about what preventative measures are being taken, emphasizing the need for individualized prevention and treatment methods, as adolescents and adults experience addiction differently. As for future implications, limiting the availability of opioids, both medical and illicit, would contribute to decreasing the number of opioid-related deaths in the United States as well as the number of addicts. In addition, expanding the reach and accessibility of treatments for opioid use disorder, such as naloxone, buprenorphine, and methadone, would be beneficial not only for individuals struggling with opioid addiction, but also for the general population (Center for Drug Evaluation and Research, 2023). Nonetheless, despite its findings, our research is not

without its limitations. A significant limitation is that drugs are constantly evolving, making it hard for research to keep up. By the time a study is designed, conducted, peer-reviewed, and published, drug trends may have already shifted, constantly changing public health.

CONCLUSION

Overall, the opioid crisis is a growing issue for adolescents and adults aged 13-25 in the United States. Addressing this public health concern is essential for preserving health across the nation. It requires an extensive approach that balances education, regulation, and individual care. Efforts must focus on expanding treatment options and minimizing dependence on opioid use. Policymakers, healthcare providers, and communities need to collaborate to develop effective, long-term solutions, such as making opioids less available and making opioid abuse treatments more available to the public. Additionally, programs can be implemented to provide individuals with external resources such as counseling, job opportunities, and community support networks. Ultimately, the United States can work towards promoting a collective effort to prioritize public health and combat the opioid crisis through the use of appropriate information and prevention strategies, as well as effective treatment approaches and practices.

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