The Opioid Industry's Legacy:

A Generation of Prescribed Suffering

Andrew Kolodny, MD, and Robert M. Bohler, PhD, MPH

The opioid industry's brilliant and multifaceted campaign to increase opioid prescribing has been the subject of books, documentary films, congressional investigations, and state litigation resulting in global settlements of more than $50 billion. From these sources, many have learned how corporate greed resulted in an epidemic of opioid use disorder (OUD) with devasting consequences for millions of American families. But the full extent of the opioid industry's far-reaching effort to manipulate the medical community, policymakers, and the public is still coming to light.

Recently, in the pages of this journal, we learned that the National Survey on Drug Use and Health (NSDUH), the federal government's primary tool for measuring the prevalence of OUD, was also influenced by opioid industry messaging. In the article, "Prescription Opioid Use Disorder Among Adults Reporting Prescription Opioid Use With or Without Misuse in the United States" by Han et al,[1] the United States Department of Health and Human Services (HHS) acknowledged a serious and long-standing flaw in the NSDUH that led to a massive undercount of OUD. The survey had been systematically excluding patients prescribed opioids from receiving its OUD assessment. Essentially, the survey's authors had accepted the opioid industry's message that OUD is exceptionally rare in patients who take opioids as prescribed.

HHS finally corrected the NSDUH methodology to allow for OUD assessments in all patients who were prescribed opioids in the past year. The recently reported findings from the revised survey are astonishing. HHS now estimates that 5 million Americans suffer from prescription opioid use disorder (POUD), defined as prescription opioid use leading to clinically significant impairment or distress.[2] This is more than triple the number of Americans with this disorder in 2019, before the methodological change. Even more surprising is that the majority (62%) of people with POUD do not misuse their prescription opioids. They take them as prescribed.[1]

The NSDUH followed *DSM-V* recommendations that require the exclusion of tolerance and withdrawal (2 of the 11 criteria used for making a diagnosis of OUD) when assessing patients who take opioids as prescribed. In theory, this should have made it more difficult to diagnose OUD in patients prescribed opioids than in individuals who obtain opioids on the black market. Still, the new HHS report found that millions of American adults who take opioids as prescribed were suffering from POUD.[1]

Many clinicians were taught to believe that POUD only exists in a subset of patients who misuse opioids. But these new findings make clear that millions of model patients who take opioids exactly as prescribed are nevertheless suffering from OUD. This important finding helps debunk pervasive industry-biased "educational" messages that downplay the risk of POUD and the consequences of physiological dependence. The findings also help debunk popular misconceptions about the opioid crisis itself.

To this day, industry-influenced educational materials on opioid prescribing routinely emphasize the distinction between physiological dependence and POUD. Physiological dependence is often mischaracterized as benign, clinically unimportant, and completely distinct from POUD. Although physiological dependence, which sets in within the first few days of opioid use, is not the same as POUD, the distinction is not as clear as many have been led to believe.[3,4]

One of the main reasons that opioids are highly addictive is that cessation of use produces withdrawal symptoms, reinforcing continued use. Opioid withdrawal symptoms can be severe, especially in patients who have used opioids for a prolonged period or were taking high doses. In the acute phase, withdrawal effects include flu-like symptoms, nausea, vomiting, diarrhea, pain hypersensitivity, insomnia, and severe anxiety that has been described as "a sense of impending doom." There are also protracted withdrawal symptoms that can last several months, including metabolic abnormalities, insomnia, fatigue, depression, and cravings to use opioids. The effects of physiological dependence and withdrawal help explain why millions of patients who take opioids as prescribed are suffering from POUD. Indeed, the *DSM-V* criteria most endorsed by patients who take opioids as prescribed in the new HHS report were "Unsuccessful efforts to cut down/control use" and "Craving/strong urge to use."[1(p4)]

Physiological dependence develops faster than many clinicians realize. After just 3 days of opioid use, discontinuation can produce withdrawal symptoms.[5] The rapid development of physiological dependence is associated with long-term use. For example, when opioids

are taken daily for 10 days, nearly 20% of patients are still taking opioids 1 year later.[6] The rapid development of physiological dependence is also associated with structural brain changes visible with magnetic resonance imaging and tensor-based morphometry.[7] After only 1 month of oral morphine, imaging studies detect decreases in gray matter volume in the right amygdala of individuals with low back pain.[8] These neuroplastic changes occur in regions of the brain that mediate affect, impulse, reward, and motivation.

Patients who initiate opioid use with extended-release products, like OxyContin, have the highest probability of becoming long-term opioid users.[6] This fact helps explain why opioid manufacturers engaged in a campaign to deceive prescribers, policymakers, regulators, and the public about the distinction between physiological dependence and POUD.

From 1996 until 2012, as opioid prescriptions soared, leading to parallel increases in POUD, academics, professional societies, pain organizations, and journalists with financial ties to opioid manufacturers disseminated a false narrative that millions of patients were benefiting from the increase in opioid prescribing. Opioid harms were portrayed as limited to so-called "abusers," and efforts to reduce opioid prescribing were characterized as punishing patients for the bad behavior of "addicts."[9] For example, a Forbes magazine article, written by journalist with financial ties to Purdue Pharma, appeared under the headline, "OxyContin doesn't cause addiction. Its abusers are already addicts."[10]

A key part of this false framing was exaggerating the distinction between physiological dependence and addiction. In 2001, an industry-funded and influential consensus statement called "Definitions Related to the Use of Opioids for the Treatment of Pain" was released by the American Pain Society, the American Academy of Pain Medicine, and the American Society of Addiction Medicine that drew a bright line between physiological dependence and addiction.[11] Even state medical boards were influenced by this false narrative. In 2004, the Federation of State Medical Boards, which accepted millions of dollars in funding from opioid manufacturers,[12] developed and disseminated a Model Policy that also exaggerated the distinction between physiological dependence and addiction and made undertreatment of pain punishable for the first time.[13] State medical boards across the country adopted the Model Policy.[14]

In recent years, an increasing number of clinicians have come to understand that the risks of long-term opioid use for chronic pain far outweigh the unproven and transient benefits. And many have become reluctant to maintain patients on high doses of opioid analgesics. But after decades of pervasive misinformation about physiological opioid dependence, these same clinicians may not appreciate how difficult it is for patients to discontinue opioid use or that many of these patients need treatment for POUD. This has left millions of patients at risk of experiencing severe opioid withdrawal or being forced to rely on exceptionally dangerous black-market opioids.

Unfortunately, media coverage and commentaries in medical journals often portray these patients as benefiting from long-term opioid use before falling victim to overly aggressive efforts to reduce opioid prescribing. The recently reported findings from the revised NSDUH help clarify that many of these patients have not been doing well and millions are suffering from POUD. They are not victims of efforts to promote more cautious opioid prescribing. Rather, they are victims of a campaign that promoted aggressive initiation of opioid use and that vastly minimized how difficult it is to discontinue use.

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Author Affiliations: Opioid Policy Research Collaborative, The Heller School for Social Policy and Management, Brandeis University, Waltham, Massachusetts (Kolodny); Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, Georgia (Bohler).

Corresponding Author: Andrew Kolodny, MD, 415 South St, MS 035, Waltham, MA 02453 (akolodny@brandeis.edu).

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