REVIEW ARTICLE

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Relationship between Nonmedical Prescription-Opioid Use and Heroin Use

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The nonmedical use of prescription opioids is a major public health issue in the United States, both because of the overall high prevalence and because of marked increases in associated morbidity and mortality.[1] In 2014, a total of 10.3 million persons reported using prescription opioids nonmedically (i.e., using medications that were not prescribed for them or were taken only for the experience or feeling that they caused).[2] Emergency department visits involving misuse or abuse of prescription opioids increased 153% between 2004 and 2011, and admissions to substance-abuse treatment programs linked to prescription opioids more than quadrupled between 2002 and 2012.[3,4] Most troubling, between 2000 and 2014 the rates of death from prescription-opioid overdose nearly quadrupled (from 1.5 to 5.9 deaths per 100,000 persons) (Fig. 1).

The pattern of nonmedical use of prescription opioids varies, from infrequent use once or twice per year to daily or compulsive heavy use and addiction. A key underlying characteristic of the epidemic is the association between the increasing rate of opioid prescribing and increasing opioid-related morbidity and mortality.[6-9] Pain has also been identified as a poorly addressed clinical and public health problem for which treatment with prescription opioids may play an important role.[10] Taken together, these trends suggest the need for balanced prevention responses that aim to reduce the rates of nonmedical use and overdose while maintaining access to prescription opioids when indicated.

In response to these interrelated public health problems, federal, state, and other vested interests are implementing a variety of policies and programs aimed at curbing inappropriate prescribing.[1,6,11-16] These efforts include educating health professionals and the public about appropriate use, implementing prescription-drug monitoring programs, taking enforcement and regulatory actions to address egregious prescribing (e.g., eliminating "pill mills"), and developing prescription opioids that incorporate abuse-deterrent technologies.

Although more rigorous evaluation is needed, there are some indications that these initiatives are beginning to show some success. A recent study showed that the rate of opioid prescribing in the United States stabilized between 2010 and 2012, with some medical specialties showing declines in the rate of opioid prescribing after consistent increases for a number of years.[17] States and localities that took the most decisive action are seeing a decrease in the availability of prescription opioids coupled with a decline in the rate of deaths from overdose.[13-15] Using national data, the Centers for Disease Control and Prevention reported that there were 16,007 and 16,235 overdose-related deaths in 2012 and 2013, respectively, involving opioid analgesic agents, down from a peak of 16,917 deaths in 2011; however, the 18,893 deaths reported in 2014 suggest continued concerns.[5] An-

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other study showed that abuse of prescription opioids increased between 2002 and 2010 and then plateaued between 2011 and 2013.[18]

Coinciding with these efforts to reduce nonmedical prescription-opioid use and overdose are reports of increases in the rates of heroin use (including both injection and noninjection routes of administration) and deaths from heroin overdose. According to national surveillance data, 914,000 people reported heroin use in 2014, a 145% increase since 2007,[2] and mortality due to heroin overdose more than quintupled, from 1842 deaths in 2000 to 10,574 deaths in 2014.[5] Some researchers suggest that the very policies and practices that have been designed to address inappropriate prescribing are now fueling the increases in rates of heroin use and death.[16,18] This is the key question addressed in this review.

Some persons certainly use heroin when they are unable to obtain their preferred prescription opioid; however, whether the increases in heroin trends in the overall population are driven by changes in policies and practices regarding prescription opioids is much less clear. As an alternative explanation, we explore the complexity and reciprocal nature of this relationship and review the pharmacologic basis for heroin use among people who use prescription opioids nonmedically, the patterns of heroin use among people who use prescription opioids nonmedically, the current trends in heroin use and their correlates, and the effects on heroin use of policies aimed at curbing inappropriate prescribing of opioids. A clearer understanding of these relationships will help to guide clinical practice and public health interventions and avoid the error of simply shifting the problem from one drug to another.

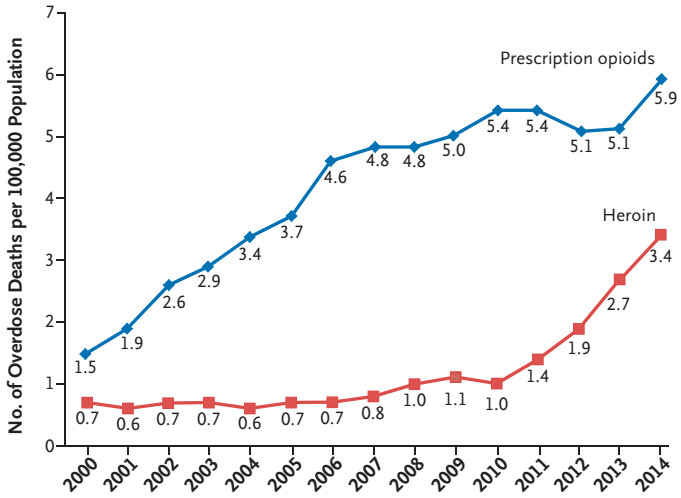

Figure 1. Age-Adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000–2014.

Data are from the Centers for Disease Control and Prevention.[5]

PHARMACOLOGIC SIMILARITIES OF HEROIN AND PRESCRIPTION OPIOIDS

Heroin is pharmacologically similar to prescription opioids. All these drugs produce their action through endogenous opioid systems that regulate a wide range of functions through three major types of G-protein–coupled receptors: mu, delta, and kappa, with particularly potent agonist activity at the mu receptor and weak activity at the delta and kappa receptors.[19,20] Mu-receptor activation by an agonist such as heroin or a prescription opioid triggers a complex cascade of intracellular signaling events, which ultimately lead to an increase in dopamine release in the shell of the nucleus accumbens.[19,20] The resulting burst of dopamine in this critical area of the reward circuitry becomes strongly coupled with the subjective "high" that is caused by drugs of abuse.[21]

The abuse liability of an opioid is determined by multiple factors, including the lipophilicity of the drug (i.e., its ability to cross the blood–brain barrier rapidly), its binding affinity for the mu receptor, and various pharmacokinetic and physicochemical characteristics (e.g., the ease with which it can be abused by means of injection and insufflation routes of administration).[22,23] Thus, although prescription opioids and heroin both have the potential to use similar pharmacologic mechanisms to induce euphoria (or analgesia), different opioid molecules have different euphorigenic properties and withdrawal-syndrome patterns.

These factors could also influence the potential for abuse of the various opioid drugs, because opioid drug–taking behavior is likely to be influenced by the balance between positive and negative subjective ratings engendered by a specific opioid. For example, a study involving heroin abusers showed that the reinforcing effects of oxycodone were similar to those produced by

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morphine or heroin, but unlike morphine or heroin, oxycodone produced no "bad" effects in the participants in the study.[23] Similar considerations may help explain why several prescription opioids — such as hydromorphone, fentanyl, morphine, and oxycodone — have a potential for abuse that is similar to, and in some cases even higher than, the potential for abuse with heroin.[22,23] Finally, these differential properties and effects are likely to interact with interindividual variability in powerful, complex, and incompletely predictable ways, so that some persons who abuse prescription opioids could find heroin less rewarding than prescription opioids, similarly rewarding, or even more rewarding.[24,25]

HEROIN USE AMONG PEOPLE WHO USE PRESCRIPTION OPIOIDS NONMEDICALLY

Studies that address the patterns of heroin use in nonmedical users of prescription opioids are mostly observational and descriptive (i.e., nonexperimental). Thus, conclusions about cause and effect are uncertain. Yet, certain consistent findings of a positive association between nonmedical use of prescription opioids and heroin use are highly suggestive and plausible, given the common pharmacologic principles described above.

Using national-level data, Becker et al. found that heroin users were 3.9 times as likely to report nonmedical use of opioids in the previous year, and 2.9 times as likely to meet the criteria for abuse or dependence on opioids, as persons who did not use heroin.[26] Grau et al. found that nonmedical use of multiple opioids was associated with transitioning to heroin.[27] Similarly, Muhuri et al. found that the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.[28] Additional studies involving persons from various geographic, economic, and drug-using backgrounds have shown similar associations.[29-33]

A limited number of small studies examined the sequence of and trajectories from nonmedical use of prescription opioids to heroin use. In 2003, Siegal et al. were among the first to suggest the pathway from nonmedical use of opioids to heroin use.[34] They found that in Ohio, 50% of persons 18 to 33 years of age who had recently begun using heroin reported having abused opioids, primarily OxyContin, before initiating heroin use.[34] A larger study involving young urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 showed that 86% had used opioids nonmedically before using heroin.[35] Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.[36-38]

Trajectory analysis of patterns of nonmedical use of prescription opioids suggests that persons most often start with oral nonmedical use of opioids. They move to more efficient routes of administration, such as insufflation, smoking, or injection, as tolerance to opioids develops and it becomes more costly to maintain their abuse patterns. By the time they initiate heroin use, usually through contact with drug users, sexual partners, or drug dealers, they view heroin as reliably available, more potent, easier to manipulate for nonoral routes, and more cost-effective than prescription opioids.[34-36,38-41]

In an effort to examine whether the findings from these small studies were consistent with findings in the broader population of nonmedical users, the sequence regarding initiation of use was assessed with the use of both treatment-population data and general-population data. Among heroin users entering substance-abuse treatment programs, Cicero et al. found significant shifts in the pattern of the first opioid used by those with recent onset as compared with those started using opioids 40 to 50 years ago.[41] Among persons who began their opioid use in the 1960s, more than 80% reported that their first opioid was heroin; conversely, in the 2000s, a total of 75% of users initiated opioid use with prescription opioids.[41]

Using national-level, general-population data, Jones found that in the period from 2008 through 2010, among people who used both prescription opioids for nonmedical reasons and heroin during the previous year, 77.4% reported using prescription opioids before initiating heroin use.[42] Similarly, Muhuri and colleagues found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.[28] Both studies showed that heroin use was most common among persons who were frequent users of

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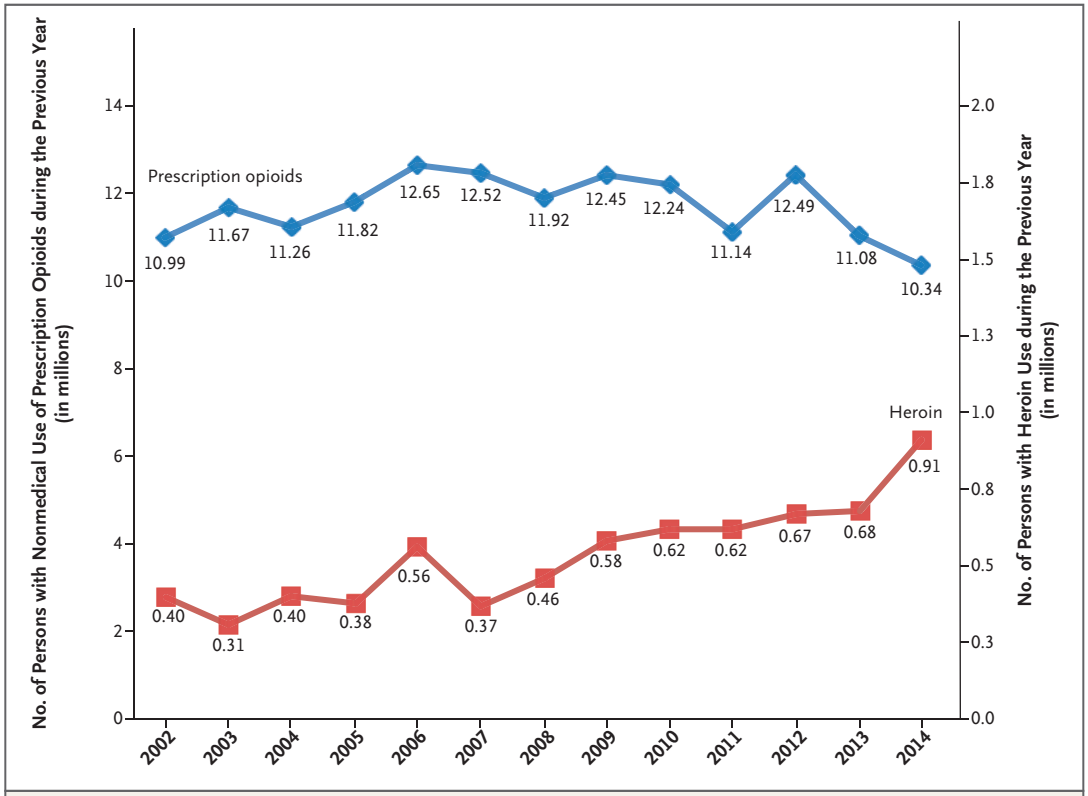

Figure 2. Nonmedical Use of Prescription Opioids and Heroin during the Previous Year among Noninstitutionalized Persons 12 Years of Age or Older, 2002–2014.

Data are from the Center for Behavioral Health Statistics and Quality.[2]

nonmedical opioids.[28,42] A recent study with data through 2013 showed that prescription-opioid abuse or dependence was associated with a likelihood of heroin abuse or dependence that was 40 times as great as the likelihood with no prescription-opioid abuse or dependence, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.[43] These studies suggest a clear link between nonmedical use of prescription opioids and heroin use, especially among persons with frequent nonmedical use or those with prescription-opioid abuse or dependence.

CURRENT TRENDS IN HEROIN USE AND THEIR CORRELATES

Heroin use has been increasing in the United States for the past 10 years, especially since 2007 (Fig. 2), an increase that has occurred in the context of broad use of multiple substances.[43] As seen in Table 1, in addition to the 138.9% increase in heroin use among nonmedical users of prescription opioids between the period of 2002–2004 and the period of 2011–2013, heroin use increased 97.5% among nonmedical users of other prescription drugs (stimulants, tranquilizers, and sedatives), 87.3% among users of cocaine, 57.3% among people who binge drink, and 45.4% among marijuana users.[43] Moreover, heroin users increasingly report abuse of or dependence on other substances.[43] There have also been shifts in the demographic characteristics associated with heroin use; the rate has increased particularly steeply among persons 18 to 25 years of age, and increases have been observed in both large urban areas and other geographic regions, in both sexes but more among women than among men, and in all races and ethnic groups but more among non-Hispanic whites than among others.[43]

Table 2 shows the sociodemographic, geographic, and substance-use groups that are associated with the greatest risk of heroin abuse or dependence during the previous year in the period of 2011–2013.[43] Other studies have shown

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Table 1. Annual Average Rates of Heroin Use during the Previous Year, According to Substance-Use Characteristic and Time Period, in the United States, 2002–2013.*

Characteristic	2002–2004		2005–2007		2008–2010		2011–2013	Percent Change		P Value†
	Rate (95% CI)	P Value	Rate (95% CI)	P Value	Rate (95% CI)	P Value	Rate (95% CI)	2008–2010 to 2011–2013	2002–2004 to 2011–2013	
								percent		
Binge drinking during previous month	3.7 (3.0–4.5)	0.001	4.1 (3.3–5.1)	0.02	5.2 (4.3–6.3)	0.38	5.8 (4.4–6.4)	12.30	57.3	0.006
Marijuana use during previous year	11.6 (9.5–14.1)	0.004	13.2 (10.6–16.4)	0.07	14.4 (12.6–16.6)	0.16	16.9 (14.4–19.8)	16.70	45.4†	0.004
Cocaine use during previous year	48.9 (40.2–59.3)	<0.001	57.6 (45.9–72.2)	<0.001	68.3 (55.4–83.9)	0.02	91.5 (78.2–106.8)	34.00	87.3†	<0.001
Nonmedical use of prescription opioid during previous year	17.8 (14.3–22.0)	<0.001	25.1 (19.9–31.7)	<0.001	34.0 (28.9–39.8)	0.048	42.4 (36.6–49.1)	24.80	138.9†	<0.001
Nonmedical use of other psychotherapeutic agent during previous year‡	23.1 (18.6–28.7)	<0.001	28.5 (23.1–35.1)	<0.001	41.6 (33.8–51.0)	0.48	45.6 (38.9–53.4)	9.70	97.5†	<0.001

* Data are from Jones et al.[43] The rate is per 1000 population in each analytic group. P values are for the comparison with the rate in the period of 2011–2013.
† The P values are for trend.
‡ Other psychotherapeutic agents included tranquilizers, sedatives, and stimulants.

that recent cohorts of heroin users entering treatment have been likely to be white, middle-class, and living in nonurban areas; this result mirrors the populations that have had the largest increases in rates of nonmedical use of prescription opioids since 2002.[2,41,42,44] These findings are generally consistent with those from a number of smaller studies.[34-40]

A key factor underlying the recent increases in rates of heroin use and overdose may be the low cost and high purity of heroin.[45,46] The price in retail purchases has been lower than $600 per pure gram every year since 2001, with costs of $465 in 2012 and $552 in 2002, as compared with $1237 in 1992 and $2690 in 1982.[45] A recent study showed that each $100 decrease in the price per pure gram of heroin resulted in a 2.9% increase in the number of hospitalizations for heroin overdose.[46] In addition, regions of the United States that are not typically centers for heroin distribution or availability have seen marked increases in recent years.[47,48]

In the context of marked increases in the rates of heroin use, it is important to note that only a small percentage of nonmedical users of prescription opioids initiate heroin use. Muhuri and colleagues found that 3.6% of nonmedical users initiated heroin use within 5 years after beginning nonmedical use of prescription opioids.[28] Jones et al. found that approximately 4.2% of persons who had used prescription opioids nonmedically during the previous year in the period of 2011–2013 also reported using heroin during the previous year.[43] Of note, given the large number of nonmedical users, even a small percentage who initiate heroin use translates into several hundred thousand new heroin users. Yet, taken in total, the available data suggest that nonmedical prescription-opioid use is neither necessary nor sufficient for the initiation of heroin use and that other factors are contributing to the increase in the rate of heroin use and related mortality.

EFFECTS OF OPIOID-PRESCRIBING INTERVENTIONS ON HEROIN USE

Multiple studies that have examined why some persons who abuse prescription opioids initiate heroin use indicate that the cost and availability of heroin were primary factors in this process. These reasons were generally consistent across

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time periods from the late 1990s through 2013.[34-41] Some interviewees made reference to doctors generally being less willing to prescribe opioids as well as to increased attention to the issue by law enforcement, which may have affected the available supply of opioids locally.[38,40] It should be noted that most of these studies were conducted before 2009 — a time when few policies targeting opioid prescribing were implemented.

It appears that the shift toward heroin use among some nonmedical users of prescription opioids was occurring before the recent policy focus on prescription-opioid abuse took hold. This observation is supported by data on heroin use reported to U.S. poison control centers that show increases starting in 2006,[18] as well as national surveillance data that show a rise in heroin use starting in 2007.[2] Similarly, a study examining hospitalizations for heroin overdose between 1993 and 2009 showed that the rate of such hospitalizations increased 69% between 1993 and 2006 and then rose more sharply, by 44%, between 2005 and 2009.[49] Furthermore, this study showed that these increases occurred in the context of continued increases in the rate of hospitalization for overdose of prescription opioids.

The results of the studies by Dart et al. and Cicero et al. suggest an association between the introduction of an abuse-deterrent formulation of OxyContin and increases in rates of heroin use.[16,18] Dart et al. found evidence that rates of heroin use increased after the introduction of the abuse-deterrent formulation, but they also reported that the rate of heroin use was increasing previously.[18] Cicero et al. found that a decrease in the rate of OxyContin abuse corresponded with an increase in the rate of heroin use over the 2 years after the introduction of the abuse-deterrent formulation.[16] However, in a follow-up study, Cicero and Ellis found that over the ensuing 18 months, the rates of OxyContin abuse no longer decreased whereas the rates of heroin use continued to increase.[50] Moreover, a separate study involving patients who were being screened for substance-abuse treatment showed no significant differences between the prevalence of heroin use before the introduction of the reformulation and the prevalence after the reformulated drug was available.[51]

Five recent quantitative studies provide additional insights into the relationship between opioid-prescribing policies and practices and heroin use and overdose. First was an analysis of deaths due to overdose in North Carolina be-

Table 2. Demographic and Substance-Use Characteristics Associated with Heroin Abuse or Dependence during the Previous Year in the United States, 2011–2013.*

Characteristic	Adjusted Odds Ratio (95% CI)	P Value
Sex		
Male	2.1 (1.4–3.0)	<0.001
Female	1.0	
Age group		
12–17 yr	0.3 (0.1–0.6)	0.001
18–25 yr	1.0	
≥26 yr	0.6 (0.4–0.9)	0.008
Race or ethnic group†		
Non-Hispanic white	3.1 (1.8–5.1)	<0.001
Other	1.0	
Geographic region of residence		
CBSA with ≥1 million persons	2.4 (1.5–3.6)	<0.001
Other	1.0	
Annual household income		
<$20,000	1.0	
$20,000–$49,999	0.5 (0.3–0.7)	0.001
≥$50,000	0.6 (0.3–0.9)	0.02
Insurance coverage		
No insurance	3.1 (2.2–4.3)	<0.001
Medicaid	3.2 (1.9–5.4)	<0.001
Private or other insurance	1.0	
Substance abuse or dependence in previous year		
None	1.0	
Alcohol	1.8 (1.2–2.9)	0.009
Marijuana	2.6 (1.5–4.6)	0.002
Cocaine	14.7 (7.4–29.2)	<0.001
Prescription opioid	40.0 (24.6–65.3)	<0.001
Other psychotherapeutic agent‡	1.6 (0.8–3.2)	0.22

* Odds ratios and 95% confidence intervals were calculated with the use of multivariable logistic-regression analyses. Data are from Jones et al.[43] CBSA denotes core-based statistical area.

† Race and ethnic group were based on survey respondents' self-classification of racial and ethnic origin and identification according to the classifications developed by the U.S. Census Bureau.

‡ Other psychotherapeutic agents included tranquilizers, sedatives, and stimulants.

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tween 2007 and 2013, which documented a shift toward an increasing risk of death due to heroin use.[52] However, the shift began in 2009, before changes such as the introduction of abuse-deterrent formulations of opioids were in effect.[52] The second study showed that heroin-related emergency department visits, hospital admissions, and overdose deaths in Wisconsin started to increase in 2007.[53] Furthermore, these increases in rates of heroin overdose were superimposed on continued increases in rates of prescription-opioid overdoses through 2012.[53]

The third study examined deaths from overdose in Florida through 2012.[13,54] Florida had a well-documented prescription-opioid problem.[54] Between 2010 and 2011, Florida instituted a series of major policy changes that were designed to reduce the inappropriate supply of prescription opioids. After these policies were implemented, prescriptions were curtailed and the rate of death from prescription-opioid overdose declined 27% between 2010 and 2012.[13,54] Moreover, these significant declines in prescription-opioid mortality were accompanied by an increase of only 60 deaths related to heroin, with the overall number of total deaths from overdose declining by 535 between 2010 and 2012.[13]

The fourth study, which examined opioid overdoses in New York, showed a 29% reduction in the rate of death from prescription-opioid overdose coupled with declines in the rates of overall and high-dose opioid prescribing in Staten Island, New York, in 2013 after the implementation of targeted and general public health initiatives, including a heavy focus on prescribing behaviors.[15] Importantly, these decreases were not offset by increases in mortality from heroin-involved overdose during the same time period.[15]

Finally, in an investigation of deaths related to heroin and prescription-opioid use in 28 states between 2010 and 2012, Rudd and colleagues found no association between declines in prescription-opioid–related mortality and increases in heroin-related mortality.[55] In fact, they found that increases in the rates of death due to heroin overdose were associated with increases in the rates of death due to prescription-opioid overdose in these states.[55]

Although none of these studies can disprove a potential relationship between policies that are aimed at decreasing the availability of inappropriately prescribed opioids and the motivation for heroin use in some people, the results of these studies consistently suggest that the transition to heroin use was occurring before most of these policies were enacted, and such policies do not appear to have directly led to the overall increases in the rates of heroin use.

CONCLUSIONS

Available data indicate that the nonmedical use of prescription opioids is a strong risk factor for heroin use. Yet, although the majority of current heroin users report having used prescription opioids nonmedically before they initiated heroin use, heroin use among people who use prescription opioids for nonmedical reasons is rare, and the transition to heroin use appears to occur at a low rate.

The transition from nonmedical use of prescription opioids to heroin use appears to be part of the progression of addiction in a subgroup of nonmedical users of prescription opioids, primarily among persons with frequent nonmedical use and those with prescription opioid abuse or dependence. Although some authors suggest that there is an association between policy-driven reductions in the availability of prescription opioids and increases in the rates of heroin use,[16,18] the timing of these shifts, many of which began before policies were robustly implemented, makes a causal link unlikely.

In the majority of studies, the increase in the rates of heroin use preceded changes in prescription-opioid policies, and there is no consistent evidence of an association between the implementation of policies related to prescription opioids and increases in the rates of heroin use or deaths, although the data are relatively sparse. Alternatively, heroin market forces, including increased accessibility, reduced price, and high purity of heroin appear to be major drivers of the recent increases in rates of heroin use.[46,56] Regardless of the causes of the high rates of both nonmedical prescription-opioid use and heroin use, in order to minimize overall opioid-related morbidity and mortality, efforts are needed to help people who are already addicted, in parallel with efforts to prevent people from becoming addicted in the first place.

Addressing the combined and interrelated

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opioid epidemics requires comprehensive action, including the prevention of the initiation of nonmedical use of opioids, interventions for persons who have clinically significant complications from opioid use, and improved treatment for those with opioid-use disorders. Prevention efforts should target the major risk factors for the initiation of opioid use, including the excess availability of prescription opioids; these risk factors may be addressed with policy and practice interventions such as the enhanced use of prescription-drug monitoring programs and the development of clinical guidelines to educate clinicians.[14,57] Universal family-based drug-abuse prevention, which has been shown to reduce the rates of initiation of nonmedical use of prescription opioids, may also play an important role.[58] Whether the opioid is heroin or a prescription medication, interventions to reduce morbidity and mortality include expanded access to naloxone in contexts in which overdoses occur[59-61] and increased use of effective treatment for opioid-use disorders, particularly medication-assisted treatment administered for an adequate duration.[62-65]

Fundamentally, prescription opioids and heroin are each elements of a larger epidemic of opioid-related disorders and death. Viewing them from a unified perspective is essential to improving public health. The perniciousness of this epidemic requires a multipronged interventional approach that engages all sectors of society.[14,66]

The views expressed in this article are those of the authors and do not necessarily represent those of the National Institute on Drug Abuse, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, or the Department of Health and Human Services.

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