

## REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

# Understanding Links among Opioid Use, Overdose, and Suicide

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**I**N THE UNITED STATES, DEATHS DUE TO SUICIDE AND UNINTENTIONAL overdose pose a major, and growing, public health concern. The combined number of deaths among Americans from suicide and unintentional overdose increased from 41,364 in 2000 to 110,749 in 2017 and has exceeded the number of deaths from diabetes since 2010.<sup>1</sup> The increase represents more than a doubling in the age-adjusted rate of deaths from suicide and unintentional overdose (Table 1), according to data from national surveillance systems.<sup>2</sup> Accordingly, both suicide and unintentional overdose have been the focus of large-scale prevention efforts, such as the National Strategy for Suicide Prevention<sup>3</sup> and the State Targeted Response to the Opioid Crisis grant program of the Substance Abuse and Mental Health Services Administration.

Both problems have connections with pain and opioid use.<sup>4-8</sup> The use of potentially lethal drugs such as opioids has a clear, direct relationship to the risk of unintentional overdose. Perhaps less well known, opioids also are linked to suicide risk.<sup>9</sup> Furthermore, opioid use disorders have a distinctly strong relationship with suicide as compared with other substance use disorders.<sup>10</sup> In all, more than 40% of suicide and overdose deaths in 2017 were known to involve opioids (Table 1), with many more likely to have had unrecorded opioid involvement.

The common theme of opioid use underlying suicide and overdose poses questions of how these problems may be related to one another.<sup>6</sup> This review describes what is known about the links between suicide and overdoses, with a focus on pathways through opioid use, issues of intent, risk factors, prevention strategies, and unresolved issues.

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## BIOLOGIC, MEDICAL, AND SOCIAL FACTORS AS LINKS

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Many factors promote the initiation and persistence of opioid use, but several specific pathways toward vulnerability to overdose and suicide are worth highlighting.

### PAIN AND RISK OF SUICIDE AND OVERDOSE

Pain causes alterations in the neurocircuitry related to reward, which result in vulnerability to suicide<sup>11</sup> and potentially to riskier use of opioids. This biologic mechanism is supported by epidemiologic data that have shown that chronic-pain diagnoses are linked to suicide,<sup>12</sup> and these associations are only partially explained by co-occurring mental health conditions.<sup>5</sup> Pain is also associated with opioid overdose, but in contrast to suicide, the limited analyses available suggest that this association is mediated by the quantity of opioids prescribed.<sup>7</sup>

### MEDICAL-SYSTEM DRIVERS OF OPIOID PRESCRIBING

Beginning in the early 2000s, opioids were increasingly used to treat chronic pain in the United States. This change came in response to concerns about the under-

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**Table 1. Rates of Death from Suicide and Overdose in the United States, According to Year.\***

Cause of Death	Age-Adjusted Rate per 100,000 Americans																	
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Suicide	10.4	10.7	10.9	10.8	11.0	10.9	11.0	11.3	11.6	11.8	12.1	12.3	12.6	12.6	13.0	13.3	13.5	14.0
Intentional overdose	1.2	1.3	1.4	1.3	1.4	1.4	1.5	1.6	1.6	1.6	1.7	1.7	1.7	1.6	1.6	1.6	1.5	1.5
Intentional overdose involving opioids	0.3	0.3	0.4	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Unintentional overdose	4.3	4.7	5.8	6.5	6.9	7.7	9.0	9.6	9.9	10.0	10.4	11.3	11.2	11.9	12.8	14.5	17.8	19.7
Involving opioids	2.2	2.4	3.1	3.4	3.6	4.0	4.8	5.0	5.3	5.5	5.7	6.3	6.4	6.9	7.9	9.3	11.9	13.5
Suicide and unintentional overdose combined	14.7	15.4	16.8	17.2	17.9	18.6	19.9	20.9	21.5	21.7	22.5	23.6	23.8	24.6	25.8	27.8	31.3	33.7
Involving opioids	2.5	2.7	3.5	3.7	4.0	4.5	5.2	5.5	5.9	6.0	6.3	6.8	6.9	7.4	8.5	9.8	12.5	14.1

\* Categories were determined on the basis of the codes of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, that were obtained from death records. Suicide deaths were those with an underlying cause of death coded as X60 through X84, Y87.0, or \*U03. Unintentional overdose deaths were those with an underlying cause of death coded as X40 through X45. Deaths involving opioids were those with multiple cause of death codes recorded as T40.0 through T40.4 or T40.6. Data were obtained from the Centers for Disease Control and Prevention.<sup>2</sup>

treatment of pain, new clinical guidelines, and the declaration by the Joint Commission on the Accreditation of Healthcare Organizations of pain as the “fifth vital sign.”<sup>13</sup> Consequently, the average dose of prescribed opioids in the United States increased from approximately 100 to approximately 700 morphine milligram equivalents per person per year between 1997 and 2007.<sup>14</sup> The connections between the increased use of opioids medically and increases in overdoses was recognized toward the end of the first decade of the 2000s,<sup>8,15</sup> but only more recently has a connection to death by suicide been recognized.<sup>6</sup> In addition, given that opioid use disorders are linked to suicide and unintentional overdose,<sup>16,17</sup> iatrogenic increases in opioid use disorders may also be contributing to the increasing rates of suicide and overdose. These population-level associations are consistent with patient-level analyses showing that higher dosages of prescribed opioids are associated with higher rates of fatal and nonfatal overdose and suicide events.<sup>4,7,18,19</sup>

**LARGE-SCALE SUPPLY AND DEMAND**

There are two primary theories as to how opioid use functions as a common thread in the influence of large-scale factors on increasing rates of suicide and overdose deaths in the United States. One theory traces the causes to increased demand for opioids, and the other emphasizes the role of the supply of opioids.

First is the theory that both types of death represent “Deaths of Despair.”<sup>20,21</sup> This conceptualization posits that the rising rates of suicide and overdose among non-Hispanic, middle-aged white men are caused by the declining fortunes of the working class. In that framework, opioid use both within and outside of pain treatment is a way of coping with lack of opportunity. This theory is consistent with the declining opportunity for some as economic inequality rises<sup>22</sup> and posits that these large-scale (macro-level) social factors cause some persons to feel despair and turn to opioid use to cope. Opioid use then worsens depressive symptoms, which increase the risk of suicide, and directly causes death from intentional and unintentional overdose. However, when an opioid use disorder develops, it has a profound influence on the risk of suicide and overdose as well as an effect on factors such as increased social isolation, legal problems, and unemployment. Thus, it is challenging to study

this hypothesis without individual-level, longitudinal data.

An alternative hypothesis is that the increased availability of opioids is the underlying cause of increased nonmedical opioid use and opioid use disorders, which result in increased rates of suicide and overdose.<sup>23</sup> Previous drug “epidemics” have been based on the emergence of new drug forms (e.g., “crack” cocaine) or increased availability and have resulted in increases in adverse effects (e.g., poor birth outcomes<sup>24</sup>). Specific to opioids, a spike in heroin availability in the late 1990s and early 2000s in Australia dramatically increased overdose rates, and subsequent reductions in availability led to a decline in overdoses.<sup>25</sup>

As opioids became more available in the United States because of prescribing<sup>14</sup> and, more recently, because of influxes of heroin<sup>26,27</sup> and illicitly manufactured synthetic opioids,<sup>28</sup> the number of persons with opioid use disorders increased, as did the frequency of opioid use.<sup>29,30</sup> The timing of these increases relative to trends in overdose and suicide is consistent with a supply-focused hypothesis. Nonetheless, it is impossible to know how much of the increase in supply was a response to demand. For example, escalating problems with respect to prescription opioid use could have created demand for heroin use, given differences in price and drug effects<sup>31</sup> or because prescription opioids became less available for misuse.<sup>32</sup>

Among patients who receive treatment with opioid analgesics, the quantity prescribed is another way to conceptualize opioid availability. The association between higher dosages of prescribed opioids and higher risk of overdose has been replicated repeatedly.<sup>7,18,19,33</sup> A study involving patients at Veterans Affairs facilities also showed an association between higher prescribed dosage and higher rates of suicide death.<sup>4</sup>

Understanding the large-scale causes of the increases in suicide and unintentional overdose is important for implementing a policy response. The demand-side hypothesis (i.e., the “Deaths of Despair”) argues for a focus on social and economic policies, whereas the availability hypothesis may argue for law enforcement and regulatory efforts to reduce access. In general, with evidence from individual-level opioid availability and supply changes in Australia, support for a supply hypothesis is stronger than that for a demand hypothesis with respect to how opioid use

relates to overdose. There is much less research with regard to suicide. Moreover, a complex, integrated theory for both outcomes is indicated. Even if one of the two pathways has a greater role, ignoring the potential influence of the other pathway may result in a policy response that causes harm. Furthermore, factors that sustain existing problems related to opioids may be different from those underlying the initial development of these problems. Observers of the Australian heroin shortage hypothesized that the reductions in overdose would have been unlikely without the comprehensive programs of addiction treatment and harm reduction in that country.<sup>25</sup>

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#### OVERDOSE INTENT

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An additional conceptual link between suicide and overdose emerges when we consider intentional overdoses, one type of suicide.<sup>6</sup> It is challenging to classify overdose events according to intent, and this is particularly true for those that are fatal.<sup>34,35</sup> Although the presence of a suicide note can make a determination relatively straightforward, such notes are found in fewer than a third of overdose deaths.<sup>35</sup> Furthermore, there is some evidence that intentionality of overdose events is dimensional, rather than categorical, and both fatal and nonfatal events may not be fully intentional or unintentional. For example, patients sometimes report that they cannot differentiate whether an overdose was a suicide attempt or unintentional.<sup>36</sup> In other cases, when a given patient survives an overdose, his or her perceived intent may change in retrospect. Consequently, intentional and unintentional overdoses may not be fully distinct outcomes.

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#### SHARED RISK FACTORS

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Research has identified several key factors, beyond opioid use, that are related to both suicide and overdose. The demographic characteristics that are associated with each cause of death are similar. Age-adjusted mortality rates in 2017<sup>2</sup> for both suicide and unintentional overdose in the United States were approximately twice as high among men as among women. In addition, death rates for both were highest in 2017 among people who identified as white or Native American and lowest among people who identified as

black or Asian. Rates were also highest during midlife (41 to 64 years of age) and lowest among older persons ( $\geq 65$  years of age). When we examined groups defined according to age, sex, and race (Fig. 1), there were several notable divergences between the two causes of death. Suicide rates remained high for white men 65 years of age or older, but rates of unintentional overdose declined dramatically after 64 years of age in this group. In addition, black and Native American men and women as well as white women had notably higher rates of unintentional overdose than of suicide during midlife. Some of these differences may reflect known racial biases in medical-examiner rulings.<sup>37</sup>

Most mental health conditions are linked to an increased risk of suicide.<sup>38,39</sup> Similarly, nearly all common mental health conditions are associated with unintentional overdose, including both overdoses of illicit drugs and medication-related overdoses.<sup>40</sup> In a study that compared patients who died by intentional overdose with those who died by unintentional overdose, the associations of substance use disorders were generally stronger for unintentional overdoses and the associations of other mental health conditions were generally stronger for intentional overdose.<sup>41</sup> Among the subgroup of patients receiving opioid analgesics, the association of mental health diagnoses and risk of overdose persists.<sup>42</sup>

Persons with substance use disorders should be given particular attention for prevention of both suicide and overdose,<sup>10,40</sup> and co-occurring mental health conditions within this group can further contribute to risk. Depressive symptoms that are reported by patients are associated with both suicide attempts and nonfatal overdoses in survey-based studies involving persons with substance use problems.<sup>43</sup> Given that people with opioid use disorders also are more likely than those without such disorders to meet criteria for additional mental health conditions,<sup>44</sup> the risk of both suicide and overdose is likely to be highest among those with these co-occurring conditions.

Use of other medications and drugs in combination with opioids can further increase risk. Concurrent use of recreational drugs, such as alcohol and cocaine, increases the risk of death.<sup>45</sup> Within patient populations, specific prescribing

patterns are related to the risk of both suicide and unintentional overdose. Use of benzodiazepines among patients who have received prescriptions for opioids is associated with unintentional overdose,<sup>33,46,47</sup> and benzodiazepines are also associated with an increased risk of suicide.<sup>48</sup> Other central nervous system depressants, such as medications prescribed to treat insomnia, have not been well-studied but may potentiate the effects of opioids. In contrast, concurrent use of antidepressants, a well-established treatment for suicidality,<sup>49</sup> has also been shown to reduce the risk of drug overdose among patients with depression who were receiving opioid analgesics.<sup>33</sup>

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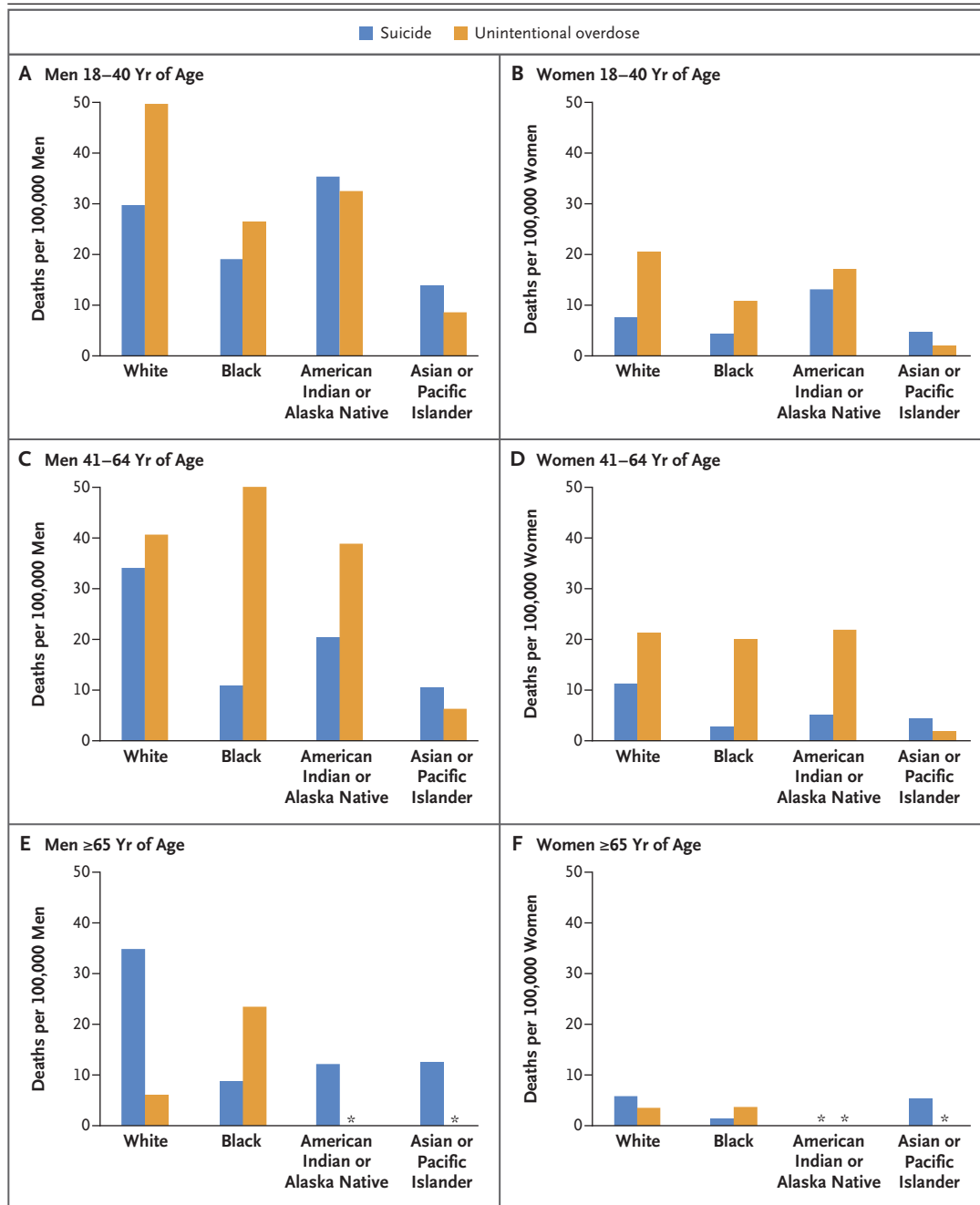
#### SHARED PREVENTION APPROACHES

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There are a number of potential prevention opportunities based on these shared conceptual links. The design and structure of the prevention strategies vary according to type of opioid exposure and whether they aid in identifying risk or preventing harm among those at risk. Table 2 positions each strategy within this framework.

To assess risk among patients who have received prescriptions for opioids, several research teams have developed risk scores, which are electronic tools that calculate a specific patient's level of risk for suicide, overdose, or both on the basis of data from electronic health records.<sup>50-52</sup> Such an approach is agnostic to whether the risk factors are causal and serves to identify persons who could benefit from additional services. In the Veterans Health Administration, a risk score was developed for both suicide and overdose together and has been implemented nationally.<sup>50</sup> For patients who are identified as being at increased risk, an in-depth assessment of behavioral risk factors, suicidal thoughts or plans, and previous suicide attempts and nonfatal overdoses is an important clinical next step.

Counseling or psychotherapy that is delivered by mental health professionals to at-risk persons is an additional shared prevention approach. Cognitive behavioral therapy is an evidence-based treatment for the prevention of suicide.<sup>53,54</sup> There is emerging evidence that behaviors associated with overdose risk can be reduced among persons with medical and nonmedical use of opioids through the counseling method of motivational



**Figure 1. Rates of Death from Suicide and Unintentional Overdose in the United States, 2017.**

Categories were determined on the basis of the codes of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, that were obtained from death records. Suicide deaths were those with an underlying cause of death coded as X60 through X84, Y87.0, or \*U03. Unintentional overdose deaths were those with an underlying cause of death coded as X40 through X45. The asterisks in Panels E and F indicate unreliable estimates due to small numbers of deaths. Data were obtained from the Centers for Disease Control and Prevention.<sup>2</sup>



**Table 2. Interventions to Address the Risk of Suicide and Overdose Related to Opioid Use.**

Goal and Intervention	Population, Defined According to Level of Opioid Exposure and Misuse		
	Low-Risk Regimen of Prescription Opioids	High-Risk Regimen of Prescription Opioids or Opioid Misuse	Opioid Use Disorder or Illegal Opioid Use
<b>Identifying who is at risk for suicide and overdose</b>			
Determination of risk score on basis of medical record	+	+	
Assumption that high level of opioid exposure and misuse puts the patient at risk			+
<b>Preventing suicide or overdose among those identified as being at risk</b>			
Treatment for mental health conditions, when present	+	+	+
Cognitive behavioral therapy for suicide risk and motivational interviewing for overdose risk*		+	+
Patient-centered taper of opioid dosage†		+	
Overdose education and naloxone distribution*		+	+
Medication-assisted treatment‡			+

\* Although these interventions would ideally be available to all persons identified as having any risk of suicide or unintentional overdose, resource constraints are likely to preclude this approach. Given that these approaches can address risks specifically related to opioid use, they should be prioritized for those with riskier levels of use.

† Patient-centered tapering is based on an evaluation of the risks and benefits for a specific patient, at a reasonably slow pace of dosage reduction and with the patient's engagement in the treatment decision making.

‡ Treatments include methadone, buprenorphine–naloxone, and naltrexone.

interviewing.<sup>55,56</sup> Given the degree to which mental health problems are robust risk factors for both problems, it is likely that general mental health counseling and pharmacotherapy may reduce the risk of suicide as well as unintentional overdose. Addiction treatment and mental health clinics are well-positioned to provide these treatments, but providers of mental health care who are integrated into primary care practices may also provide this care.<sup>57</sup> Furthermore, behavioral pain-management interventions are associated with improvement in functional outcomes among those with pain.<sup>58</sup> It is plausible that improvements in pain-related domains through counseling could also reduce the risk of suicide and overdose.

Reduction in opioid dosage is a controversial strategy relevant for people who receive prescriptions for potentially risky medication regimens or who exhibit signs of opioid misuse. On the basis of an analysis of deaths from opioid overdose,<sup>59</sup> the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain<sup>60</sup> recommends against escalating

dosages for new patients above 90 morphine milligram equivalents, and this same threshold has been interpreted as a goal for tapering efforts. A reduction in the quantity of prescribed opioids may function as a “means restriction” by reducing patients' access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients' access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity.<sup>61</sup> However, whether tapering changes the risk of either suicide or overdose is unknown.

The distribution of naloxone, an opioid-overdose antidote, reduces opioid-related emergency department visits.<sup>62</sup> Naloxone is ideally provided to someone who lives with a person at risk for overdose. Although naloxone distribution for layperson administration has been championed largely as a solution for unintentional opioid overdoses, it is also relevant to reversing suicide attempts.

Finally, improving access to medication-assisted therapy, which is the combined approach of medication (methadone, buprenorphine–naloxone, or naltrexone) and counseling for opioid use disorders, may reduce rates of suicide and overdose.<sup>63</sup> Several decades of research show that medication-assisted therapy can reduce mortality, and this is especially true for overdose-related mortality.<sup>64</sup> However, both suicide and overdose still occur even when at-risk persons receive these treatments. The risks of death among those receiving medication-assisted therapy are highest when the medication is initiated and when the treatment is suddenly stopped.<sup>64</sup> Prevention should involve addressing these critical transition periods.

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#### UNRESOLVED ISSUES AND CONTROVERSIES

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Several areas that need more research should be prioritized owing to their potential to influence policy and system interventions. First, there is concern that opioid tapering has resulted in patients' transitioning to heroin use<sup>31</sup> or resulted in uncontrolled pain, which increases suicidality.<sup>65</sup> However, evidence for these relationships, beyond case reports, is lacking. As noted above, a study involving patients at Veterans Affairs facilities showed that higher prescribed dosages are associated with greater suicide risk than lower dosages.<sup>4</sup> This same study also showed that rates of suicide among patients who were prescribed opioids for any length of time and stopped were similar to those among patients in ongoing treatment at low dosages (1 to 20 morphine milligram equivalents) and lower than rates among patients receiving higher dosages ( $\geq 21$  morphine milligram equivalents). The findings of this study are not suggestive of suicide-related harm from discontinuation.

It is premature to conclude that discontinuation of prescription opioids leads to suicide or heroin use independent of risk factors that predated (or directly caused) the decision to discontinue. Nonetheless, abrupt discontinuation is physically unpleasant and potentially distressing. Protocols to reduce opioid withdrawal and provide alternative pain management are critical. In addition, only a small number of patients are

transitioned to medication-assisted treatment at the point of opioid discontinuation,<sup>66,67</sup> but this should be a common care transition for patients with opioid use disorders.

Second, most research that identifies a risk of overdose and suicide is based on data from medical claims or records. Even well-designed risk scores have only moderate predictive value.<sup>50,51,68</sup> One possible measure that could improve risk detection is the level of opioid misuse. Several measures have been validated (e.g., the Current Opioid Misuse Measure<sup>69</sup>) to assess misuse, but none are used commonly enough to permit study in connection to suicide and overdose. Cohort studies that involve high-risk patients might help to fill this knowledge gap.

Third and finally, both suicide and overdose continue to result in a substantial burden of deaths in the United States, despite many clinical initiatives and numerous changes in state and federal policy. Prevention efforts may not have addressed important causes of suicide and overdose. Alternatively, efforts may have been effective for addressing harms related to prescription opioids, because deaths due to commonly prescribed medications have stabilized, but the "wave" of heroin use and use of illegal synthetic opioids masked the effects.<sup>70</sup> Regardless, it is clear that prevention efforts have been insufficient.

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#### SUMMARY

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Rates of suicide and unintentional overdose in the United States have climbed during the past two decades. Opioid use plays a critical role in fueling both of these public health problems. Consequently, interventions that address the shared causes and risk factors, such as programs to improve the quality of pain care, expand access to psychotherapy, and increase access to medication-assisted treatment for opioid use disorders, have the potential to be high-value investments by addressing both problems simultaneously.

Dr. Ilgen reports serving as cofounder of and owning shares in Arborsense. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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