Original Investigation

High-Risk Use by Patients Prescribed Opioids for Pain and Its Role in Overdose Deaths

Jane A. Gwira Baumblatt, MD; Caleb Wiedeman, MPH; John R. Dunn, DVM, PhD; William Schaffner, MD; Leonard J. Paulozzi, MD, MPH; Timothy F. Jones, MD

IMPORTANCE From January 1, 2003, through December 31, 2010, drug overdose deaths in Tennessee increased from 422 to 1059 per year. More of these deaths involved prescription opioids than heroin and cocaine combined.

OBJECTIVE To assess the contribution of certain opioid-prescribing patterns to the risk of overdose death.

DESIGN, SETTING, AND PARTICIPANTS We performed a matched case-control study that analyzed opioid prescription data from the Tennessee Controlled Substances Monitoring Program (TNCSMP) from January 1, 2007, through December 31, 2011, to identify risk factors associated with opioid-related overdose deaths from January 1, 2009, through December 31, 2010. Case patients were ascertained from death certificate data. Age- and sex-matched controls were randomly selected from among live patients in the TNCSMP.

MAIN OUTCOMES AND MEASURES We defined a high-risk number of prescribers or pharmacies as 4 or more per year and high-risk dosage as a daily mean of more than 100 morphine milligram equivalents (MMEs) per year. The main outcome was opioid-related overdose death.

RESULTS From January 1, 2007, through December 31, 2011, one-third of the population of Tennessee filled an opioid prescription each year, and opioid prescription rates increased from 108.3 to 142.5 per 100 population per year. Among all patients in Tennessee prescribed opioids during 2011, 7.6% used more than 4 prescribers, 2.5% used more than 4 pharmacies, and 2.8% had a mean daily dosage greater than 100 MMEs. Increased risk of opioid-related overdose death was associated with 4 or more prescribers (adjusted odds ratio [aOR], 6.5; 95% CI, 5.1-8.5), 4 or more pharmacies (aOR, 6.0; 95% CI, 4.4-8.3), and more than 100 MMEs (aOR, 11.2; 95% CI, 8.3-15.1). Persons with 1 or more risk factor accounted for 55% of all overdose deaths.

CONCLUSIONS AND RELEVANCE High-risk use of prescription opioids is frequent and increasing in Tennessee and is associated with increased overdose mortality. Use of prescription drug–monitoring program data to direct risk-reduction measures to the types of patients overrepresented among overdose deaths might reduce mortality associated with opioid abuse.

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Author Affiliations: Epidemic Intelligence Service, Centers for Disease Control and Prevention, Tennessee Department of Health, Nashville (Baumblatt); currently with Agency for Healthcare Research and Quality, Rockville, Maryland (Baumblatt); Tennessee Department of Health, Nashville (Wiedeman, Dunn, Schaffner, Jones); Department of Preventive Medicine and Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee (Dunn, Schaffner); Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Atlanta, Georgia (Paulozzi).

Corresponding Author: Jane A. Gwira Baumblatt, MD, Agency for Healthcare Research and Quality, Center for Quality Improvement and Patient Safety, 540 Gaither Rd, Rockville, MD 20850.

From January 1, 1990, through December 31, 2010, drug overdose death rates in the United States increased from 3.4 to 12.4 per 100 000 population, eclipsing motor vehicle death rates for the first time during 2009.[1] This increase was substantially attributable to an increase in prescription opioid-related mortality[2-6] because medical professionals have changed their prescribing of opioids in an effort to more effectively treat noncancer pain.[7] Prescription opioid pain relievers now account for more deaths than heroin and cocaine combined.[8] In Tennessee, drug overdose deaths increased from 422 during 2001 to 1062 during 2011, and opioid analgesic-related deaths increased from 118 during 2001 to 564 during 2011.[9]

To address this problem, prescription drug-monitoring programs (PDMPs) have been established in most states, including Tennessee.[10] The Tennessee Controlled Substances Monitoring Program (TNCSMP) became operational in 2006, with the goal of monitoring the prescribing of controlled substances on the Drug Enforcement Agency Schedules II to V.[11] PDMP data have been used to determine the prevalence of use of multiple prescribers among persons dying of overdoses[12] and the association of patterns of high-risk prescription use with overdose death.[13] However, no studies have simultaneously measured the prevalence of such behaviors among the general population and their role among opioid analgesic-related overdose deaths. We conducted a descriptive study using data from the TNCSMP to describe prescribing patterns and a case-control study to better characterize the risk of opioid-related overdose death associated with high-risk behaviors.

Methods

The TNCSMP collects patient information for all prescriptions of controlled substances on the Drug Enforcement Administration Schedules II to V. Our analysis was limited to opioid prescriptions written for Tennessee residents, by Tennessee prescribers, and filled in Tennessee pharmacies from January 1, 2007, through December 31, 2011. We identified opioids using their National Drug Codes,[14] which encode the drug name, strength, dosage, form, and formulation for each drug prescribed. The quantity, number of days supplied, and the date the prescription was written and dispensed, are included for each prescription. The TNCSMP contains personal identifiers for patients, prescribers, and dispensers. We identified all prescriptions for noninjectable opioid medications dispensed to each patient using a unique patient identifier assigned by the database. Each refill was counted as a separate prescription. Prescriptions from veterinarians, military, Veterans Administration, Indian Health Service facilities, in-hospital dispensing, and mail-order pharmacies were excluded because the TNCSMP does not require reporting from these facilities. Prescriber specialty was determined by linking the TNCSMP data to the Tennessee Department of Health Board of Medical Examiners Licensure data. We determined the number of opioid prescriptions, prescribers, and pharmacies and the mean daily dosage for each patient.

To identify risk factors for unintentional opioid analgesic-related overdose death, we conducted a matched case-control study. A case was defined as an opioid analgesic-related overdose death that was unintentional or of undetermined intent from January 1, 2009, through December 31, 2010, in a Tennessee resident older than 10 years with 1 or more prescriptions in the TNCSMP database 12 months or less before death. Decedents were identified by searching death certificate data from the Tennessee Department of Health, Division of Health Statistics, Death Statistical System. Death certificates listing the underlying cause of death as unintentional drug poisoning (*International Classification of Diseases, 10th Revision* [*ICD-10*], codes X40-X44) or drug poisoning with undetermined intent (*ICD-10* codes Y10-Y14) were evaluated further. Of these, the subset with contributing causes of death identified as opioid analgesic poisoning (*ICD-10* codes T40.2, T40.3, or T40.4) alone or in combination with other drugs were counted as cases.

The first and last name, sex, and date of birth for deterministic linkage between the TNCSMP database and identified cases were used. For each case patient, 20 live controls matched by sex and age (controls with ages within the same decade of birth as case patients) were selected by random-number generation from patients older than 10 years with 1 or more opioid prescriptions during the 12 months before the date of death of the matched case patient (reference date). To ensure that all controls were living during the reference period, we matched their identifiers from the TNCSMP with death certificate files during 2009 and 2010 and excluded any matches.

We determined the same exposures among case patients and controls that were measured for the general population as follows: number of medical professionals prescribing opioids, number of pharmacies dispensing opioids, number of opioid prescriptions,[15] and the total amount of drug dispensed and converted into morphine milligram equivalents (MMEs).[16] The number of prescribers, pharmacies, and prescriptions for each case patient and control were calculated for the 1-year period before the reference date. Only Tennessee prescribers and pharmacies were included. For analysis, we first categorized the number of prescribers and pharmacies into 1, 2 to 3, 4 to 5, and 6 or more and defined high risk as 4 or more prescribers or pharmacies. To calculate the mean daily dosage, all opioid prescriptions were combined and converted to MMEs and divided by 365 days. We categorized mean daily dosage into less than 20, 20 to 40, 41 to 80, 81 to 100, 101 to 200, 201 to 400, and more than 400 MMEs/d and defined high risk as a mean of more than 100 MMEs/d for a year. Patients with the defined high-risk factors were then compared with those without the defined high-risk factors for each category. Crude associations between unintentional and undetermined intent prescription opioid-related deaths and the defined high-risk factors were expressed as matched odds ratios (mORs). We also performed an analysis by opioid type to determine which opioids were associated with the highest risk of death. A conditional logistic regression model was used to compute adjusted odds ratios (aORs) for numbers of prescribers and pharmacies and daily dosage. Tests for trend in aORs and numbers of patients with each risk factor during the 5-year period

Table. Opioid Prescription Use in the Study Patients, Tennessee, 2007-2011

Variable	Patients, No. (%)				
	2007	2008	2009	2010	2011
Prescriptions per patient, No.					
1	889 728 (50.5)	952 783 (49.8)	966 579 (49.4)	955 195 (48.7)	954 170 (47.1)
2-12	769 966 (43.7)	829 432 (43.4)	852 465 (43.6)	858 444 (43.8)	902 282 (44.6)
13-24	83 073 (4.7)	105 577 (5.5)	112 268 (5.7)	119 142 (6.1)	135 650 (6.7)
≥25	18 401 (1.0)	25 624 (1.3)	24 934 (1.3)	27 142 (1.4)	32 449 (1.6)
Total	**1 761 168** (100)	**1 913 416** (100)	**1 956 246** (100)	**1 959 923** (100)	**2 024 551** (100)
High-risk factor					
≥4 Prescribers	102 271 (5.8)	121 044 (6.3)	127 874 (6.5)	134 324 (6.8)	154 666 (7.6)
≥4 Pharmacies	35 105 (2.0)	40 801 (2.1)	43 551 (2.2)	43 946 (2.2)	51 354 (2.5)
>100 MMEs	30 381 (1.7)	37 255 (1.9)	42 177 (2.2)	49 195 (2.5)	57 029 (2.8)
≥1 High-risk factor[a]	133 563 (7.6)	157 927 (8.3)	169 476 (8.7)	180 191 (9.2)	205 539 (10.2)
3 High-risk factors[b]	2471 (0.1)	3096 (0.2)	3611 (0.2)	4035 (0.2)	6044 (0.3)

Abbreviation: MMEs, morphine milligram equivalents.

[a] Defined as obtaining opioid prescriptions from 4 or more prescribers or using 4 or more pharmacies to fill opioid prescriptions or receiving more than 100 MMEs/d on average for a year.

[b] Defined as obtaining opioid prescriptions from 4 or more prescribers and using 4 or more pharmacies to fill opioid prescriptions and receiving a mean of more than 100 MMEs/d for a year.

were performed with the Cochran-Armitage test. Analyses were performed with SAS statistical software, version 9.3 (SAS Institute Inc). This study was approved by the Tennessee Department of Health Institutional Review Board.

Results

Descriptive Analysis

From January 1, 2007, through December 31, 2011, a total of 5 170 791 Tennesseans received 37 097 993 opioid prescriptions recorded in the TNCSMP database. A total of 20 489 Tennessee medical professionals wrote these prescriptions, and 2419 Tennessee pharmacies dispensed the medications. Prescriptions increased from 6 272 409 during 2007 to 8 449 105 during 2011, with a corresponding rate increase from 108.3 to 142.5 per 100 population (32% increase). Among approximately 37.1 million opioid prescriptions, the most commonly prescribed medications were hydrocodone (20.9 million [56%]) and oxycodone (7.3 million [20%]).

Each year, approximately 2 million Tennesseeans (nearly a third of the state population) fill an opioid prescription. Among 34 604 194 prescriptions with data regarding sex, 58.7% were dispensed to females. Each year, the rate of prescription opioid use among female patients was 1.3 times that of male patients (30.4 vs 23.3 in 2007 and 30.0 vs 25.5 in 2011). Opioid-prescribing rates differed across the state. During 2011, the 2 largest urban centers, Memphis and Nashville, had the lowest prescription rates (76.1 and 106.2 per 100 population, respectively); the northeast region, with predominantly rural counties, had the highest rate (180.0 per 100 population).

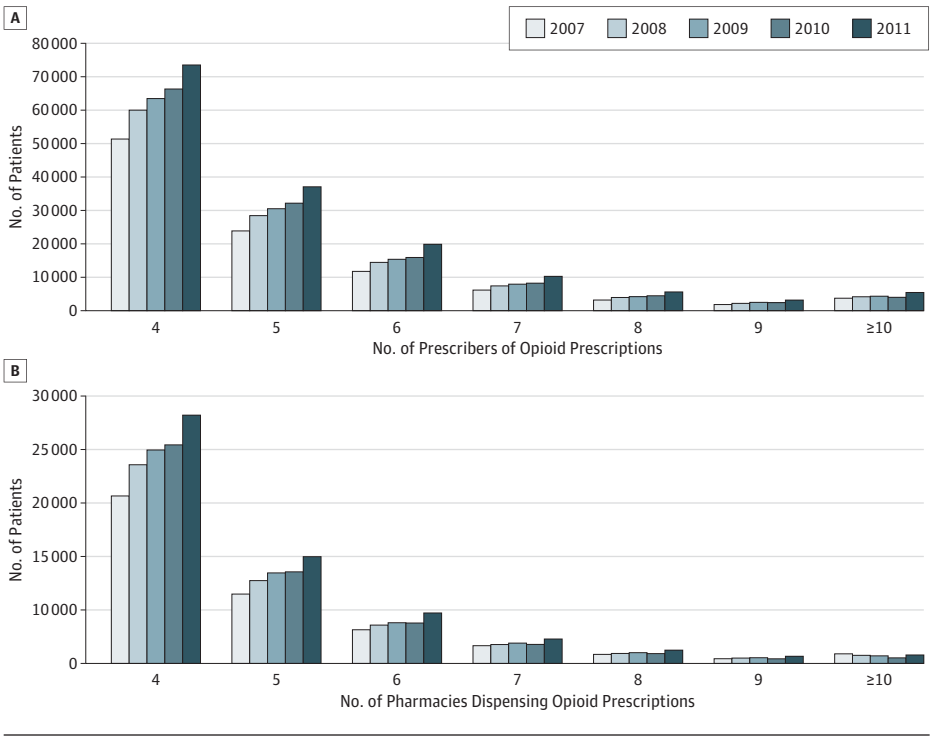
The percentage of patients receiving more than 1 opioid prescription increased every year, and by 2011 a total of 167 902 patients (8.3%) obtained 13 or more prescriptions per year (**Table**). During 2011, approximately 32 000 patients (1.6%) received 25 or more prescriptions. The number of patients receiving opioid prescriptions from 4 or more prescribers increased from 102 271 (5.8%) during 2007 to 154 666 (7.6%) in 2011 ($P < .001$). The 7.6% of patients who were treated by 4 or more prescribers during 2011 received 9 274 498 (25.2%) total opioid prescriptions, a mean of 60.0 prescriptions per patient. A total of 5501 patients (0.3%) received prescriptions from 10 or more prescribers (**Figure 1**A). The number of patients using 4 or more pharmacies increased from 35 105 (2.0% of total patients) during 2007 to 51 354 (2.5%) during 2011 ($P < .001$) (Table). Among these patients, 890 (1.7%) received opioids from 10 or more pharmacies during 2011 (Figure 1B). The total number of patients who received a prescribed mean dosage of more than 100 MMEs/d for a year increased from 30 349 (1.7%) during 2007 to 56 993 (2.8%) during 2011 ($P < .001$). Among these patients, 440 (0.8%) received a mean of more than 1000 MMEs/d. From January 1, 2007, through December 31, 2011, the number of patients with 1 or more high-risk factors increased steadily, and the number of patients with all 3 high-risk factors approximately doubled (Table).

Allopathic physicians wrote most (56.2%) of the opioid prescriptions, followed by advanced practice nurses (11.7%). Dentists, physician assistants, and osteopathic physicians wrote the remaining prescriptions. Among physicians, primary care physicians (internal medicine and family medicine) wrote the largest number of prescriptions (56.5%). The mean numbers of prescriptions per physician per year were 745.5 and 412.7 for family medicine and internal medicine, respectively, compared with 320.5, 165.8, and 229.0 for surgeons, dentists, and advanced practice nurses, respectively. Each year, the number of opioid prescriptions written by primary care physicians increased, whereas the number written by surgeons and dentists remained stable.

Case-Control Study

During the 24-month case-control study period (2009-2010), 932 opioid-related overdose deaths occurred in Tennessee (a mean rate of 7.4 deaths per 100 000 population per year). Of those, 592 (63.5%) were patients in the TNCSMP, corresponding to a mean rate of 15.1 prescription opioid–related overdose deaths per 100 000 patients per year. Among case patients, 330 (55.7%) were men. The median age was 43 years (range, 18-92 years), 79% were 30 to 59 years old, and 576

Figure 1. Number of Patients Receiving Opioid Prescriptions by Prescribers and Pharmacies Dispensing Prescriptions



A, Patients receiving opioid prescriptions from prescribers. Each year patients with fewer than 4 prescribers account for more than 90% of the total patients (mean, 1.9 million per year). B, Patients receiving opioid prescriptions from pharmacies. Each year patients with fewer than 4 pharmacies account for more than 95% of the total patients (mean, 1.9 million per year).

(97.3%) were white and 16 (2.7%) were black. Among live patients with information contained in the database, we identified 11 840 sex- and age-matched controls. Among case patients, 227 (38.3%) received opioids from 4 or more prescribers, 145 (24.5%) used 4 or more pharmacies, and 140 (23.6%) received a mean of more than 100 MMEs/d. The corresponding figures for controls were 513 (4.3%), 196 (1.7%), and 172 (1.5%), respectively. Among case patients, 323 (54.6%) had 1 or more high-risk factors, and 35 (5.9%) had all 3 high-risk factors. The corresponding figures for controls were 709 (6.0%) and 12 (0.1%), respectively.

Opioid-related overdose death was associated with receiving opioid prescriptions from 4 or more prescribers (mOR, 15.4; 95% CI, 12.6-18.5), patronizing 4 or more pharmacies (mOR, 20.9; 95% CI, 16.3-26.8), and receiving a mean of more than 100 MMEs/d of opioids (mOR, 21.3; 95% CI, 16.6-27.4).

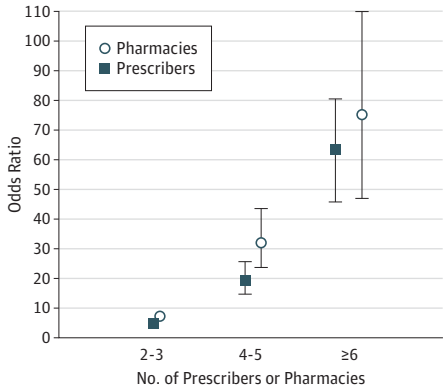
Having a prescription for 1 of the following 3 opioids conferred the highest risk of death: methadone (mOR, 20.5; 95% CI, 13.7-30.7), oxymorphone (mOR, 13.8; 95% CI, 8.6-22.3), and fentanyl (mOR, 13.6; 95% CI, 9.5-19.5). Increased risk was associated with the number of prescriptions (mOR, 1.2; 95% CI, 1.17-1.20; for each additional prescription). In a logistic regression model that adjusted for the number of prescribers, pharmacies, and dosage, the risk of overdose death was associated with 4 or more prescribers (aOR, 6.5; 95% CI, 5.1-8.5), 4 or more pharmacies (aOR, 6.0; 95% CI, 4.4-8.3), and more than 100 MMEs/d (aOR, 11.2; 95% CI, 8.3-15.1). Risk of overdose death increased with increasing number of pharmacies ($P < .001$) and prescribers used by the patient ($P < .001$) (**Figure 2**). Risk of overdose death was also significantly associated with increasing mean daily dosages, starting from 20 MMEs ($P < .001$), with an attenuation in this increase in risk seen at mean daily dosages of more than 400 MMEs (**Figure 3**).

Discussion

Each year during 2007 through 2011 in Tennessee, approximately one-third of the population filled 1 or more prescription for an opioid analgesic. Increasing numbers of patients are receiving opioids from 4 or more prescribers or 4 or more pharmacies each year or are receiving high doses of opioids. Receiving opioids from a substantial number of prescribers or pharmacies are considerable risk factors for opioid-related overdose death. Increasing numbers of both prescribers and pharmacies and increasing mean daily dosage were substantially associated with increasing risk of overdose death among patients being prescribed opioids, consistent with previous studies.[13,17-19] Approximately half of the individuals prescribed and overdosing on opioids could have been identified in the PDMP records before their deaths using these criteria. These findings highlight the need for interventions using a multifaceted approach that targets patients, prescribers, and pharmacies to reduce mortality associated with opioid use. However, these interventions will need development and evaluation to determine their effectiveness.

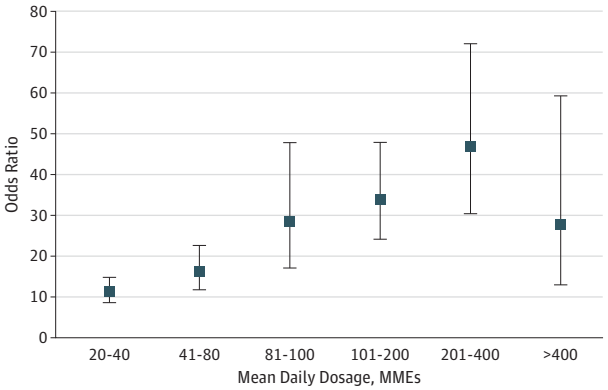
The study also found that patients receiving extremely high mean daily dosages (eg, >400 MMEs/d) have a decreased risk of opioid-related overdose death compared with patients receiving mean daily dosages of 201 to 400 MMEs/d. Among

Figure 2. Association of Number of Prescribers and Pharmacies With Risk of Unintentional Opioid Analgesic–Related Overdose Death



Reference was patients receiving opioids from 1 pharmacy or prescriber. Error bars indicate 95% CIs.

Figure 3. Association of Mean Daily Dosage of Opioid Analgesics With Risk of Unintentional Opioid-Related Overdose Death



Reference was patients receiving a mean of less than 20 morphine milligram equivalents (MMEs) per year. Error bars indicate 95% CIs.

these patients, diversion of opioids (defined as the transfer of a prescription drug from a lawful to an unlawful channel of distribution or use[20]) might reasonably be suspected. Persons unlawfully using prescription opioids commonly obtain them from friends, family, and drug dealers.[20-22] Patients with such prescription histories put themselves at risk, but might also have contributed to the deaths of others who had no opioid prescriptions in the TNCSMP (more than one-third of decedents did not have a prescription in the TNCSMP).

The most commonly prescribed opioids were hydrocodone and oxycodone, which comprise approximately three-quarters of all opioid analgesics prescribed, consistent with national and other state trends.[23,24] However, methadone was associated with the highest risk of death. Methadone dispensed at retail pharmacies and reported to the TNCSMP is primarily prescribed for pain control, and it has been reported to have an increased potential for causing overdose death when used for this indication.[5,25,26] We did not analyze the risk of overdose death associated with combinations of opioids or combinations with benzodiazepines or alcohol, but the increased risk of overdose death with these combinations has been well established.[7,27] The risk factors noted might represent heavy use of opioids or a combination of opioids and benzodiazepines because sedative use is also a risk factor for drug overdose.[13] Because high opioid use has been at the forefront of political and media attention in Tennessee and nationally, we focused specifically on this issue. This is a complex issue with many associated risks, and future studies could focus on the risk of opioid-related overdose death associated with concomitant use of benzodiazepines and opioids or combinations of opioids.

More females than males received opioid prescriptions, but most overdose decedents were male. Some studies found that men are more likely to use prescription drugs nonmedically[28] and more likely to use opioids by nonoral routes.[29] This might explain the increased risk of death among males. Most decedents were non-Hispanic whites, out of proportion to the percentage of whites among the Tennessee population (81.1%), making the death rates among whites substantially greater than among blacks. One explanation is that blacks and Hispanics may be less likely to be prescribed drugs or to use prescription pain relievers nonmedically.[30] Although we did not examine the geographic distribution of high-risk opioid use, the highest prescribing rates in our study were reported among rural communities. Nonmedical use of prescription pain relievers is associated with lower socioeconomic status and receipt of Medicaid.[31] This might explain the higher prescribing rates among rural communities, which tend to be poorer than urban communities. These results are consistent with other studies[31,32] that report higher rates of prescription abuse and overdose deaths among rural and small urban communities. Tennessee has among the lowest median household incomes in the country,[33] yet it ranked third highest in opioid consumption per capita in the United States during 2010.[8]

In our study, primary care physicians prescribed most of the opioids, consistent with a recent study[34] that used a commercial prescription database with detailed prescriber information. We determined that primary care physicians accounted for the increasing prescription rates after 2007, whereas prescribing by dentists and surgeons remained consistent. This increase in prescription opioid use is likely a result of the long-term treatment of chronic pain rather than the time-limited treatment of acute pain provided by dentists and surgeons.[21]

Our study had some limitations. The proportion of patients prescribed opioids among the population was likely underestimated. The TNCSMP became operational during 2006, and although pharmacy reporting was required within 30 days, no penalties for not reporting were enacted. In addition, the TNCSMP does not require reporting from methadone treatment programs, federal facilities, hospital pharmacies, or out-of-state pharmacies that fill prescriptions for Tennessee residents. The true number of opioid prescriptions dispensed is therefore even greater than the number reported. In addition, PDMP data are only a proxy for opioid use; diversion of opioids and other illicit uses are not reported.

Conclusions

The use of the TNCSMP was voluntary until implementation of the Tennessee Prescription Safety Act, which mandated prescribers to check the database before prescribing controlled substances, in 2013. It is expected that high-risk behavior will decrease with increased monitoring; however, studies have not established whether PDMPs or laws against high-risk use effectively curtail such behavior. Despite this limitation, the TNCSMP can be used to analyze trends in opioid prescribing and to identify patients at risk for overdose death. The TNCSMP might help physicians navigate decisions involved in treating patients with chronic pain at risk for addiction and mortality and identify patients with these risk factors for intervention. In addition, the TNCSMP could be used to develop multiple preventive interventions to combat the growing problem of prescription opioid use and abuse.

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Acquisition of data: Baumblatt, Wiedeman.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Baumblatt, Dunn, Schaffner, Paulozzi, Jones.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Baumblatt, Wiedeman, Dunn, Jones.
Administrative, technical, and material support: Dunn, Schaffner.
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Correction: This article was corrected on May 5, 2014, for an error in the Table footnote.

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