

An Unrelenting Epidemic of Deaths from Prescription Drugs in North Carolina

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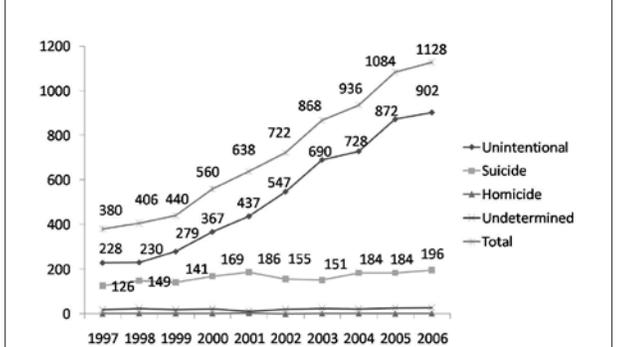
In the decade since 1997, more than 7,100 North Carolina residents have died from poisonings. At the beginning of the 20th century many victims were children who ingested toxic household products. By contrast, most of these recent victims were adults¹⁻⁴ and most died from an unintentional overdose of a prescription drug(s)⁵. The Centers for Disease Control and Prevention (CDC) recently released findings that suggest fatal accidental drug overdoses have reached epidemic proportions in the United States, including North Carolina. Most poisoning deaths now occur in rural states among adults who abuse or misuse prescription and illegal drugs. North Carolina is in the upper third of rural states with the highest percentage increase in unintentional poisoning mortality rates in the United States, 1999-2004. Fatal drug overdoses are now the second leading cause of death due to unintentional injury in the United States, exceeded only by motor vehicle fatalities⁶⁻¹¹. Public health epidemiologists have suggested that this epidemic of drug-related deaths can be reversed by using traditional injury prevention strategies¹²⁻¹⁴. These are primarily behavioral changes that include changing the way physicians prescribe controlled substances and the way patients take controlled substances for pain management. The approach also includes transforming how the general public views recreational drugs and the treatment of those who use them, as well changing how law enforcement practices drug diversion. The goal of the following report is to provide some descriptive statistics on the epidemic of drug-related deaths in North Carolina and information on the state's newest source of information on prescribed narcotics, the North Carolina Controlled Substance Reporting System¹⁵. The paper also suggests ways for physicians to use these data as a resource to improve the way they prescribe controlled substances to their patients with chronic severe pain.

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Historical Trends in NC Drug-Related Deaths

As illustrated in Figure 1, North Carolina has experienced a three-fold increase in the number of residents who died by poisoning in the past decade⁵. Deaths increased from 380 deaths in 1997 to 1,128 deaths in 2006, the most recent year of mortality data. The numbers of intentional fatal poisonings (suicides and homicides) and poisonings for which the medical examiner could not determine the intent of the victim (undetermined) have changed very little over the past 10 years. However, the number of deaths from unintentional overdoses has risen fourfold, from 228 in 1997 to 902 in 2006. These death certificate data sug-

Figure 1. Number of Fatal Poisonings by Manner of Death: NC Residents, 1997-2006



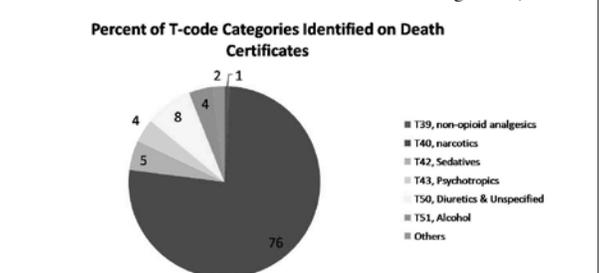
Source: NC State Center for Health Statistics, August 2007

gest that the sharp increase in the overall number of poisoning-related deaths is due to a dramatic increase in unintentional poisonings.

Types of Drugs Involved

Medical examiners in North Carolina run full panel toxicology screens whenever possible on almost every poisoning case they investigate, and have done so for decades. Therefore, changes in the drugs associated with drug-related overdoses in the last decade are real and not due to changes in investigative procedures. The substances recorded on death certificates as underlying or contributing causes of death since 1999 are coded by nosologists as *International Classification of Diseases and Related Health Problems Version 10 (ICD-10)* as external cause of injury codes and T-codes, respectively. These identify the substances determined by NC medical examiners to have caused or contributed to the death of the victim. They do not include an incidental drug(s) that the decedent took prior to death, was identified on the post-mortem toxicological screen, but did not cause or contribute to the demise. Figure 2 shows that in 2006 three quarters (76 per-

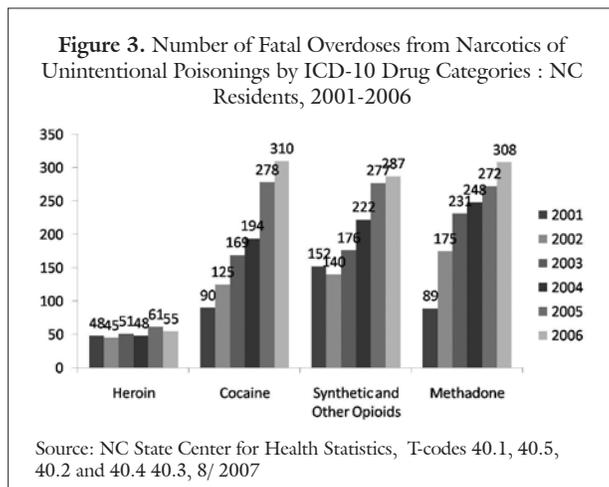
Figure 2. Substances Reported by Medical Examiners for Unintentional and Undetermined Intent Fatal Poisonings: NC, 2006



Source: NC State Center for Health Statistics, May 2007

cent) of the substances that caused or contributed to these unintentional deaths were narcotics (NC State Center for Health Statistics, 2007). Alcohol and the other non-biological substances contributed to approximately 7% of the deaths.

Figure 3 illustrates the diversity of controlled substances that have resulted in fatal drug overdoses in the past five years, based on T-codes recorded on death certificates. Heroin caused or contributed to relatively few fatal drug overdoses in North Carolina



since 2001, accounting for 6% of deaths in 2001 (48 deaths) and 13% in 2006 (55 deaths). Cocaine was implicated in 24% of the accidental drug-related deaths in 2001 and 32% in 2006 (310 deaths). Methadone (primarily prescribed for pain management and not to treat opioid addiction^{1,3,16-17}) caused or contributed to 23% of the drug overdoses in 2001 (89 deaths) and was identified in 32% of the deaths in 2006 (308 deaths). The narcotics and hallucinogens in the remaining category of 'synthetic and other opioids' (for example codeine, fentanyl, hydrocodone, morphine, and oxycodone) were identified in 40% of the drug-related deaths in 2001 (152 deaths), but only 30% in 2006 (287 deaths). Thus, in 2006, the categories of drugs that caused or contributed to the accidental drug overdoses were approximately equally divided among cocaine (32%), methadone (32%) and the other synthetic and unspecified opioids (30%). Both cocaine and methadone-related deaths increased threefold from 2001 to 2006. Deaths from the synthetic opioids increased twofold, in spite of their universally recognized and highly publicized potential for addiction and diversion. These data suggest, as do data from other states^{6-11,17-19} that legal drugs kill more people than illegal drugs. It is because 93% of the unintentional and undetermined intent poisonings in North Carolina are caused by biological products (Figure 2), and the majority of them are prescribed controlled substances (Figure 3), that we can conclude that most unintentional poisonings are now the result of accidental drug overdoses.

Methadone-Related Deaths

One question raised by statistics on the drugs that cause or contribute to unintentional poisoning fatalities in North Carolina is, 'Why methadone?'. Methadone is prescribed for pain management less often than other opioids in the state. Based on data from the North Carolina Controlled Substances Reporting System, hydrocodone and oxycodone were dispensed to outpatients in North Carolina 38 times more often than methadone²⁰. Yet in 2006, methadone was implicated in one third of the accidental fatal drug overdoses (Figure 3). Hydrocodone, oxycodone and all other synthetic opioids combined were cited in about the same percentage (30%) of deaths¹⁵. This suggests methadone is more lethal than the other opioids.

Methadone was originally created during World War II in Germany as an alternative to morphine, which was not available for use by the Germans on the battlefield. Methadone has many positives as a painkiller. It has fewer side effects than many of the other opioids. It is cheap—often less than \$15 per month in contrast to the \$300 to \$400/month for hydrocodone and oxycodone preparations. Methadone does not produce euphoria, which some had mistakenly thought would make it less likely to be diverted and abused. There are also many down sides to the drug. Methadone has a very long half-life (8-96 hours), but the duration of its analgesic action is considerably shorter (4-8 hours). The initial dosing of methadone is difficult and not all physicians are aware of its varying equivalence to other opioids^{17,21}. The cross tolerance between methadone and other opioids is incomplete, thus complicating the transition of a patient from another opioid to methadone. Finally, methadone, like many opioids, can cause severe respiratory depression and death.

The signs and symptoms of opioid-induced respiratory depression are often unrecognized by the lay public. A systematic review of all of NC medical examiner records of fatal methadone overdoses between 1997 and 2001 often indicated that the decedent died many hours after the ingestion of the methadone and that someone heard the decedent snoring loudly prior to finding the person dead the following morning³. Research has also shown that methadone can cause serious cardiac conduction effects, including QT interval prolongation and Torsades de Pointes²¹. Because of the inherent increased potential for lethality in methadone when prescribed for pain management, the FDA began requiring a 'black box' warning for the drug in November 2006²¹. It remains to be seen whether this warning has reduced the prescribing of or mortality from methadone. Mortality statistics on drug-related deaths in North Carolina for 2007 will not be available until August/September 2008.

Prescription Profiles from the NC Controlled Substances Reporting System

Until the passage of enabling legislation to imple-

"Ninety-three percent of the unintentional and undetermined intent poisonings in North Carolina are caused by biological products and the majority of them are prescribed controlled substances"

ment a narcotic prescription drug monitoring system in 2006, North Carolina did not have a means of reporting or monitoring the outpatient prescribing of controlled substances. In August 2007, the NC Controlled Substances Reporting (CSR) System began collecting data on Schedule II through V controlled substances that are prescribed by NC physicians to NC residents and dispensed from pharmacies in the state. (Schedule I narcotics—those defined as having no medical applications and by definition illegal—are monitored by law enforcement.) The data in the CSR system include most of the data elements routinely collected by most NC pharmacies and submitted to billing vendors who facilitate third party reimbursement. The primary goal of the CSR System is to provide NC medical care practitioners with a tool to help determine the appropriateness of prescribing a controlled substance(s) to their patients or the need to refer their patients for more specialized treatment of chronic severe pain or substance abuse. Upon request, the CSR System generates prescribing profiles of controlled substances for eligible medical care practitioners and pharmacists on all patients in the database who have legally bought these drugs from a pharmacy (or other participating agency) in the state. Any medical care practitioner in the state with a DEA license to prescribe controlled substances can apply for access to his or her patient data in the CSR system by contacting the CSR System manager in the NC Department of Health and Human Services Division of Mental Health/Developmental Disabilities/Substance Abuse Services (Johnny.womble@ncmail.net). A secondary goal of the CSR System is to generate anonymous epidemiologic profiles of outpatient prescribed controlled substances in the state¹⁵.

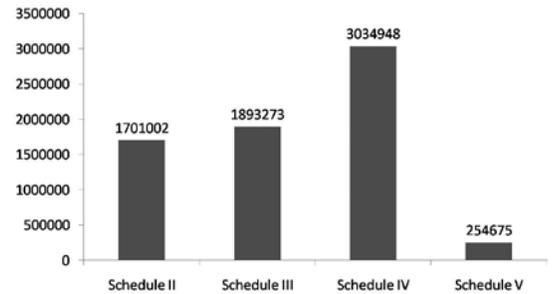
The CSR System provides the first opportunity to review what categories of controlled substances are prescribed and purchased in the outpatient setting for all patients, not just for the patients on the state's Medicaid and Medicare rolls. Preliminary CSR System data from July to December 2007 indicate that slightly

less than 1.2 million prescriptions for Schedule II-V controlled substances are dispensed every month by NC pharmacies, outpatient facilities and practitioners to NC residents²⁰. This suggests that, in a state of 8.7 million residents, there were nearly 14 million

prescriptions for controlled substances written and dispensed in 2007. These prescriptions varied by Schedule, which is a classification system that attributes each drug's potential for addiction and abuse in descending order of likelihood. For example, a Schedule III drug is less likely than a Schedule II to be abused, and so forth.

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Figure 4. Outpatient Prescriptions to North Carolinians for Controlled Substances Dispensed in North Carolina: July – December 2007



TOTAL SCRIPTS = 6,916,296 for Jul-Dec 2007

Source: NC Controlled Substances Reporting System; March 2008. C. Sanford 05/12/08

Between July and December 2007, 44% of prescriptions in the CSR System were for Schedule IV controlled substances; 27% were for Schedule IIIs; 24.5% were for Schedule IIs; and 3% were for Schedule Vs (Figure 4). Seventy percent of NC residents who obtained a controlled substance from an outpatient pharmacy in July 2007 were dispensed a prescription for one drug; 19% were dispensed two prescriptions for drugs; and 10% were dispensed three to five prescriptions. Just one percent of patients took home more than five prescriptions for a controlled substance.

Hydrocodone and oxycodone were the most frequently prescribed controlled substances between July and December 2007. There is little reason to expect the pattern to have varied for the second six months (January – June, 2008). The top 20 controlled substances prescribed in July-December 2007 are listed in Table 1. This table

Table 1. Top 20 Controlled Substances Dispensed in North Carolina: July – December 2007*

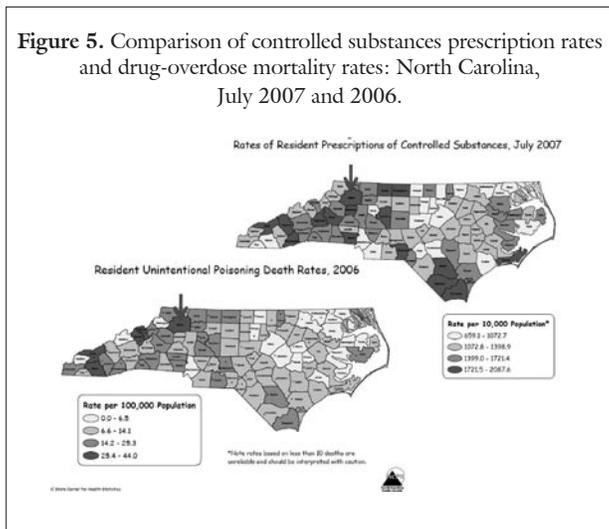
Controlled Substances	No. Scripts	Controlled Substances	No. Scripts
1. Hydrocodones	2,014,652	11. Adderall	148,416
2. Oxycodones	935,394	12. Concerta	144,143
3. Alprazolam	712,680	13. Temazepam	111,520
4. Zolpidem TA	430,623	14. Phenteramine	108,851
5. Clonazepam	421,155	15. Lunestra	102,874
6. Propoxyphene	401,674	16. Amphetamine Salts	80,047
7. Lorazepam	364,569	17. Fentanyl	77,252
8. Diazepam	247,763	18. Methadone	70,284
9. Lyrica	162,604	19. Morphine Sulfates	68,296
10. Ambien	151,317	20. Codeine compounds	45,545

Preliminary data, The Controlled Substances Reporting System, March 2008 (20)

is important, not only for its description of what outpatient controlled substances were prescribed during the CSR system's first year of operation, but as an example of how a reasonable expectation of a direct correlation between the prevalence of available drugs

and the ranking of deaths from accidental overdoses of those drugs does not hold. Assuming a one-to-one correlation, one would expect most of the deaths from unintentional drug overdoses to be caused by those drugs that are most frequently prescribed. However, according to data on NC death certificates, these drugs only caused or contributed to one third of fatal accidental drug overdoses. Meanwhile, methadone, while only the 18th most frequently prescribed controlled substance, was mentioned as a contributing factor in another third of deaths. These data suggest that much more research is needed on the benefits and adverse effects of all of the controlled substances that are currently being prescribed to patients with the best of intentions.

A review of the combined data from death certificates and the CSR System suggest that the relationship(s) between the availability and lethality of controlled substances in our state is complex and probably multifactorial (Figure 5). Some counties in which there are high prescribing rates of controlled substances have high mortality rates from accidental drug overdoses. For example, Wilkes County (identified with an arrow on each map) have high rates of fatal accidental drug overdoses and high rates of prescriptions for controlled



substances^{5,20}. Diametrically opposite patterns also occur. For example, Hyde County in 2006 had a high unintentional poisoning rate but a very low rate of prescriptions for controlled substances in 2007. What is undisputable is the annual increase in the number (and the rates) of NC residents who are dying from accidental drug overdoses from controlled substances, the variation in these death rates by age, race, sex and county, and the variation in the outpatient prescribing profiles of controlled substances within the state. Much research is obviously needed to establish the role of these and other factors in the causal pathway. Analyses of emergency department data, death certificate data, medical examiner records, physician and pharmacist requested CSR system patient prescription

profiles, and de-identified epidemiologic reports from the CSR system will go a long way to improving our understanding of how best to prescribe controlled substances in the out-patient setting. Without access to and use of these data to support the practice of pain management, the epidemic of unintentional drug overdoses will continue unabated.

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