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The Opioid and Related Drug Epidemics in Rural Appalachia: A Systematic Review of Populations Affected, Risk Factors, and Infectious Diseases

Christine A. Schalkoff, MSPH¹, Kathryn E. Lancaster, PhD, MPH², Bradley N. Gaynes, MD, MPH³, Vivian Wang, BS², Brian W. Pence, PhD¹, William C. Miller, MD, PhD, MPH², Vivian F. Go, PhD, MPH¹

¹Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 302 Rosenau Hall, 135 Dauer Drive CB7440, Chapel Hill, NC 27599, USA

²College of Public Health, The Ohio State University, 250 Cunz Hall, 1841 Neil Ave, Columbus, OH 43210, USA

³UNC School of Medicine, Department of Psychiatry, University of North Carolina at Chapel Hill, 304 MacNider Hall, 333 South Columbia Street, Chapel Hill, NC 27514, USA

Abstract

Background/Aims—To examine trends in rural Appalachian opioid and related drug epidemics during the past 10 years, including at-risk populations, substance use shifts and correlates, and associated infections.

Methods—We conducted this review in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Seven databases were searched for quantitative studies, published between January 2006–December 2017, of drug use, drug-related mortality, or associated infections in rural Appalachia.

Results—Drug-related deaths increased in study states, and a high incidence of polydrug toxicity was noted. Rural substance use was most common among young, white males, with low education levels. A history of depression/anxiety was common among study populations. Prescription opioids were most commonly used, often in conjunction with sedatives. Women emerged as a distinct user subpopulation, with different routes of drug use initiation and drug sources. Injection drug use was accompanied by risky injection behaviors, and was associated with hepatitis C.

Corresponding Author: Christine A. Schalkoff, Department of Health Behavior, University of North Carolina at Chapel Hill, 302 Rosenau Hall, CB7440, 135 Dauer Drive, Chapel Hill, NC 27599, USA, caschalk@live.unc.edu.

Author Contributions:

CAS – Developed inclusion/exclusion criteria, conducted searches, served as primary reviewer for abstract/title and full-text review, extracted article data, synthesized results, and drafted manuscript.

KL – Developed inclusion/exclusion criteria, served as a secondary reviewer for abstract/title and full-text review, assisted with manuscript drafting, reviewed and edited manuscript.

BNG – Assisted with review strategy/inclusion and exclusion criteria, provided guidance during review process, reviewed and edited manuscript.

VW – Served as a secondary reviewer for abstract/title and full-text review, reviewed manuscript.

BWP – Reviewed and edited manuscript.

WCM – Conceptualized review, developed inclusion/exclusion criteria, oversaw review process, reviewed and edited manuscript.

VFG – Conceptualized review, developed inclusion/exclusion criteria, oversaw review process, reviewed and edited manuscript.

Conclusions—This review can help to inform substance use intervention development and implementation in rural Appalachian populations. Those at highest risk are young, white males who often engage in polysubstance use and have a history of mental health issues. Differences in risk factors among other groups and characteristics of drug use in rural Appalachian populations that are conducive to HIV spread also warrant consideration.

INTRODUCTION

The United States is currently facing a rise in drug-related deaths that has captured public health, media, and policy attention. According to the Centers for Disease Control and Prevention (CDC), over 630,000 Americans died from a drug overdose between 1999 and 2016,¹ and drug poisoning has now surpassed motor vehicle crashes as the top cause of injury-related mortality in the United States.² Rates of drug poisoning deaths have increased during the span of 1999–2009 from approximately 4 per 100,000 persons to 12 per 100,000, and the CDC estimates that drug overdose deaths have increased 137% since 2000.^{3,4} This increase in drug use and overdose arose from the prescription opioid epidemic, and has been linked with increases in both infectious and noncommunicable diseases – such as HIV, hepatitis C (HCV), and neonatal abstinence syndrome (NAS).^{5,6} The growing drug overdose and concomitant morbidity epidemics call for renewed attention to and understanding of unique regional trends in the United States.

While drug poisoning rates have increased nationally, particular geographical areas and populations have been disproportionately affected. Drug overdose deaths have been typically concentrated in primarily urban/metropolitan areas until recently. However, from 2009–2013, rural counties experienced the highest percent increase in age-adjusted drug poisoning death rates.⁴ The rural Appalachian region of the United States has been deeply affected by the drug epidemic during the last two decades.^{2,3,7} The Appalachian Regional Commission (ARC) recognizes 13 states that contain part of the Appalachian Mountain range: West Virginia, Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, and Virginia.⁸ However, the Appalachian region is further divided into subregions by the ARC, and consists of both rural and some metropolitan areas with differing sociodemographic characteristics. Of the estimated 25.6 million people living in Appalachia, approximately 6 million live in large metropolitan (greater than 1 million people) areas (such as Pittsburgh and Birmingham), and there continues to be an influx of individuals into these areas and out of rural counties.⁹ Appalachian counties overall are markedly less racially and ethnically diverse than the U.S. as a whole, with minority groups making up only 18.2% of the population, compared with the national average of 39%; however, metropolitan Appalachian regions are fueling a slight overall increase in racial and ethnic diversity in the past decade.⁹

In 2014 and 2015, three of the five states with the highest recorded rates of drug overdose deaths were in Appalachia, including West Virginia, Kentucky, and Ohio,³ and over a third of the 27 states that reported significant increases in drug overdose death rates from 2015–2016 were Appalachian states.¹⁰ The ARC reported that in 2015, deaths due to “diseases of despair”—such as drug overdose—in Appalachia occurred at a rate that was 37% higher than the rest of the United States.¹¹ Relatedly, a 2017 analysis of the U.S. counties most

vulnerable to HIV/HCV outbreaks linked to injection drug use concluded that vulnerable counties were overwhelmingly rural and heavily concentrated in the Appalachian region of the U.S., particularly in the states of Kentucky, Ohio, West Virginia, and Tennessee.⁶

Appalachia's classification as a High Intensity Drug Trafficking Area (HIDTA) through a 1988 Congressional program and subsequent targeting in a 2015 HIDTA Heroin Response Strategy initiative make the area a particularly important intersection of economic problems, unique cultural norms, and thriving drug trade.⁷ HIDTA areas are those which are "significant center[s] of illegal drug production, manufacturing, importation, or distribution" and in which "drug-related activities [are] having a significant harmful impact in the area."¹²

Given the surge in rates of drug-related morbidity and mortality in rural areas, particularly in rural Appalachia, we aimed to identify trends and correlates of drug use in this region to guide intervention development and understand ways in which the epidemic could shift in the future. This systematic review aimed to examine how drug epidemics in rural Appalachia have changed over the past 10 years, specifically: 1) How have drug-related mortality and nonfatal overdose in the region changed over time?; 2) Have the drugs and modes of use changed over time?; 3) Have the risk populations changed over time (proportion affected, age, race)?; and 4) Have rates of associated diseases changed over time?

METHODS

We conducted this review in accordance with Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.¹³ Overall studies were selected that focused on drug epidemics and illicit drug use in rural Appalachian regions in the United States.

Search Strategy

Seven databases (PubMed, Academic Search Premier, CINAHL, Health Source, Web of Science, PsycINFO, and SCOPUS) were searched for studies published between January 1, 2006 and December 16, 2017, in order to capture the most recent spikes in drug-related morbidity and mortality. Search terms included "Drug abuse," "substance abuse," "drug use," "substance use," "drug addiction," "substance addiction," "drug epidemic" "rural," "non-urban," "United States," "Appalachia," and "Appalachian." Searches by drug type (e.g. heroin, opioids, methamphetamine, etc.) were also conducted. Detailed search methods and all keyword combinations are available in Appendix 1. Initial searches produced 8,026 articles for screening.

Study Eligibility

Inclusion criteria for articles included the following: 1) peer-reviewed; 2) published between January 1, 2006 and December 16, 2017; 3) contained original research; and 4) presented information about drug use, drug-related mortality, or associated diseases in rural Appalachian populations. Articles that were purely qualitative were also excluded, as were review papers and case studies. Studies in which the only drug involved was marijuana or alcohol were excluded, as the recreational use of these substances is legal in some or all states. Lastly, studies that focused on treatment access or related drug use interventions were excluded, as our review did not focus on substance use interventions.

For the purposes of this review, we considered the Appalachian region to include the 13 states that are recognized as Appalachian states by the Appalachian Regional Commission.⁸

Studies that did not explicitly indicate a rural Appalachian study location were examined further in several ways. For papers in which county names were provided, we cross-referenced the counties with a list of rural Appalachian counties generated from Appalachian Regional Commission, Health Resources & Services Administration (HRSA), and state health department/HUD resources. For papers that did not include county-level information but specified a state geographic region, we consulted ARC Appalachian region boundaries, and inclusion or elimination was based upon whether the specified region fell within or outside of the Appalachian region. If no county or region was specified, such that study location could not be reasonably determined, then we excluded the paper. We excluded studies involving national samples, unless they included results that specifically pertained to rural Appalachia.

Review Process and Data Extraction

An abstract/title review and subsequent full-text review of the selected studies were conducted independently by two members of the research team, and any discrepancies were documented and resolved with a third team member. A hand review was then conducted of final articles, in which references of included papers were scanned for any additional articles that fit the defined search criteria.

The following information was extracted from each final study: study location, date of data collection, study design, research objective, study population and sample size, recruitment strategy, drugs involved, method of drug use, data collection method, outcome(s) measured, theoretical foundation (if applicable), key findings, and study limitations.

Quality Ratings

Following data extraction, the quality of evidence presented in the final articles was evaluated using a modified checklist from Sowa et al.,¹⁴ which was modified from Mirza and Jenkins.¹⁵ Studies were evaluated on a scale from 1–10 based on criteria including clarity of study aims, sample size, representativeness, use of a validated substance use measure, statistical analysis, and conflict of interest disclosure. Quality rating scores were produced independently by two members of the research team, and differences were discussed and resolved. Following Sowa et al., we classified articles as low quality (0–4), moderate quality (5–7), or high quality (8–10).

RESULTS

Appalachian State Trends: Overview of Studies

Fifty-seven studies met the criteria for inclusion (Figure 1). Most eligible studies were conducted in Kentucky (38), followed by Virginia (7), Pennsylvania (5), Tennessee (3), North Carolina (2), and New York (1) and West Virginia (1) (Table 1, Figure 2). Over 40% (44%, 25/57) focused predominantly on prescription opioids. Six studies examined poisoning/overdose trends (either fatal or nonfatal) in Appalachian states, 43 studies

examined current or lifetime substance use and correlates, 6 studies focused predominantly on diseases associated with drug use, and 2 studies involved other aspects of drug use epidemics, such as analysis of drug use networks or prescription claims. Thirty-three studies were classified as high quality, and 24 as moderate quality (Table 2).

Drug-related Mortality and Nonfatal Overdose Trends

Across studies of both fatal and nonfatal drug overdoses, substantial increases were noted within several states, with a high incidence of overdoses involving multiple substances (polysubstance use). In four Appalachian states, drug-related deaths, particularly opioid-related deaths, rose dramatically from the late 1990s to early 2000s (Table 3).

In studies that compared overdose rates in urban and rural areas of Appalachian states, overdose cases in urban areas more often involved heroin or cocaine, while overdose cases in rural areas typically involved prescription opioids (particularly methadone, hydrocodone, and oxycodone).^{16–18} Beyond age, ethnicity, sex, and rurality, additional overdose correlates typically included lower education level, a history of chronic pain, a history of previous substance use and/or substance use treatment, and mental health disorders (such as anxiety, depression, and post-traumatic stress disorder).^{18,19}

Young, white men (often in the range of 25–54 years of age, with several studies reporting an average age between 30–39) were at greatest risk for fatal and nonfatal overdose in rural areas.^{16,17,19–21} Overdose deaths were most commonly accidental, and in most cases, polydrug toxicity was the cause of death; in cases of polydrug toxicity, prescription opioids were often found in combination with antidepressants or benzodiazepines.^{17–19} Whether people involved in mono- or polysubstance overdose had a prescription for the identified drugs was inconsistent across studies. In West Virginia, opioids were found in 93.2% of unintentional overdose deaths and approximately half of decedents had a prescription for the opioid.¹⁹ In contrast, most persons who died from methadone-related overdose in Virginia did not have a prescription at time of death.¹⁸

Drug Use Trends and Risk Populations

Rural substance use during the early- to mid-2000s among study populations consisted largely of the misuse of prescription painkillers, often used in conjunction with other medications, particularly benzodiazepines and antidepressants.^{17,22–29} In particular, oxycodone, hydrocodone, and methadone were among the most commonly used opioids among rural prescription opioid-using populations.^{30,31} Among prescription opioid users, distinct populations did emerge: chronic pain patients and nonmedical users, groups which show demographic and drug use differences. Pain patients were more likely to obtain prescription opioids from a healthcare provider, though they often co-used other medications (such as benzodiazepines or other types of prescription opioids) obtained illicitly; nonmedical users were more likely to obtain prescription opioids from a dealer or a friend.^{24,30,32}

Current or lifetime drug use trends and correlates in rural populations were similar to overdose trends across Appalachian states. Generally, populations affected by drug epidemics were younger (typically between 25–45 years of age), white, majority male, low-

income, and with lower levels of education and employment.^{24,29,33–35} Other common correlates reported included mental health issues, such as depression, anxiety, and PTSD, and chronic pain.^{18,21,26,27,36–39}

Injection Drug Use

Injection drug use was often commonly initiated with prescription opioids. Among people who inject drugs (PWID) in Kentucky, nearly 90% of PWID reported lifetime injection with prescription opioids and 68% injected with prescription opioids in the past 6 months. Approximately 60% of PWID initiated injection with prescription opioids; OxyContin was a common choice for injection initiation.^{40,41} In rural New York, 58% of PWID reported recent prescription opioid injection.³⁵

Injection often occurred in cohesive networks that also involved shared drug- and sex-related risk behaviors, such as syringe sharing and unprotected sex.^{40,42} Several studies examined risky injection practices and reported varying levels of injection risk behaviors, with estimates of syringe or needle sharing ranging from 25% to 97% of study participants.^{33,35,43} Injection drug use was also associated with anxiety and depression, and injectors were also more likely to report HCV/HBV than non-injection drug users.⁴³

Special Risk Populations

Women: Differences in overdose risk, drug type of choice, and initiation into drug use or injection drug use between men and women were also present across studies. Although hospitalizations and deaths were more prominent among males overall, overdose rates and cause of death (in the case of fatal overdose) varied by gender and age.^{17,19–21}

Hospitalizations for methadone poisonings in Kentucky among people aged 25–54 years were more common among men than women, but in those over 54 years, hospitalizations were more common among women.²⁰ Similarly, among people in Virginia who died of an opioid overdose, female decedents were older on average than male decedents (42.8 years vs. 38.5 years, respectively). Although most of these deaths were deemed accidental, women were more likely than men to have committed suicide.¹⁷ Women were also more likely than men to fit the profile of a pain patient or “doctor shopper” – a person who obtains prescription medications from prescribers and is more likely to administer the drugs orally. Conversely, “diverter” populations (consisting of people who obtain drugs from a nonmedical source and are more likely to pursue nonmedical routes of exposure) were more typically younger and male.^{17,19,32}

Regarding drug of choice, some evidence exists that rural Appalachian women were less likely than men to use illegal drugs, including heroin, crack, methamphetamine, and hallucinogens, although reports of methamphetamine use frequency were mixed.^{19,44,45} In Kentucky, women who inject drugs were more likely than men to have: initiated injection drug use due to social pressure, injected in the presence of a partner, received the drugs as a gift, had sex before or after injection, used a syringe provided by a partner, and used a previously used syringe. Men were more likely to have acquired the drugs and syringe themselves, and were more likely to have initiated with a friend or immediate family

member.⁴⁶ Whether men initiate drug use at a younger age than women is unclear; but men do not appear to initiate prescription drug use at a younger age than women.^{45,47,48}

Rural women who use drugs also had high rates of high-risk behavior and interpersonal violence (IPV) experiences. Over 90% of pregnant women undergoing detoxification in rural Kentucky reported experiencing IPV in their lifetime, which was substantially higher than women in the general population.⁴⁹ Incarcerated women in Appalachian Kentucky who reported violent victimization were more likely to report substance use; furthermore, sexual minority women were more likely to report violent victimization and multiple types of victimization than heterosexual women.⁵⁰ In the same cohort of incarcerated women, injection drug use was associated with risky sexual behavior, and initiation of drug use, initiation of first sex, and first arrest were all positively correlated in this population.^{37,51,52} Furthermore, earlier drug use and earlier age of first sexual encounter were associated with high-risk drug use as an adult, riskier sexual behavior, high-risk partners, and trading sex for drugs or money.⁵²

Adolescents: Only three studies focused on or included adolescent populations (5th-12th grade students) in rural Appalachian regions, with similar trends in substance use and related risks. These studies examined drug use among rural Appalachian high school students in grades 9–11,⁴⁸ 9–12,⁵³ and 5, 7, 9, and 11.⁴⁷ Alcohol was the most commonly reported substance, followed by painkillers or other prescription medications (between 30–35%).^{47,48} Nonmedical use of prescription medications among adolescents was associated with perceived availability of medications and friends' use of medications. Nonmedical use was less common among adolescents who perceived risk of nonmedical use or reported parental disapproval of nonmedical prescription drug use, adolescent school commitment, or community norms against drug use.⁵⁴ Adolescent sexual orientation was also associated with drug use—LGBQ (lesbian, gay, bisexual, and questioning) students reported drug use more commonly than heterosexual students.⁵³

Probationers/Criminal Justice Populations: Populations in the felony probation/criminal justice systems were similar in socio-demographics to the population most at risk for overdose death: white, young, and male, with low levels of education and employment.^{22,23,27,32,55} Among incarcerated women in rural Appalachian Kentucky, high-risk behaviors were common and included injection drug use, risky sexual behavior, trading sex for drugs or money, and having a sexual partner who also injected.^{37,51,52} Additionally, the probationer population also had a shift toward prescription opioid misuse, compared with other substances, comparable to the general rural Appalachian adult populations.^{22,23} Compared with pain patients, probationers were more likely to obtain drugs from a dealer rather than a prescriber; use of prescription opioids among probationers was also not associated with any medical condition, suggesting that they were using opioids for recreational purposes and not for pain.^{27,32} Prescription opioid use was linked with an increase in property crimes, but not violent crimes.²⁷

Associated Disease Trends

Several studies either focused primarily on the transmission of communicable diseases as it relates to drug use, or investigated transmission risk behaviors and associated diseases alongside drug use. Diseases covered included HCV, HIV, HSV-2, and neonatal abstinence syndrome (NAS). Reported HCV prevalence among PWID ranged from 34.0% to 54.8%, and HCV/HIV risk behaviors were common among PWID.^{35,40,42,56,57} Furthermore, rates of NAS births were higher in rural Appalachia than in non-Appalachian areas.^{58,59} Further key findings can be found in Table 4.

DISCUSSION

Results of this systematic review offer deeper insight into drug use trends and correlates in rural Appalachian populations. Overdose and overdose deaths in the U.S. at large have dramatically increased during the last 30–40 years, with particular increases since the late 1990s/early 2000s.^{1,4,7} With this increase in drug use and drug overdose deaths, a shift in the geographical regions and populations at risk has also been noted. In the 1980s and 90s, drug poisoning death rates were highest in African American populations and in urban areas.⁷ By the early 2000s, white populations demonstrated the highest accidental poisoning death rates,⁷ and rural Appalachia saw particularly rapid increases in drug use and overdose.⁴ While drug overdose death rates nationally increased more than 60% from the late 1990s to early 2000s, moving from a rate of 4.4 per 100,000 in 1999 to 7.1 per 100,000 in 2004,⁶⁰ results of this review indicate that rates in rural Appalachia during this time period often surpassed national trends (Table 3).

In rural Appalachia, those at highest risk for substance use and overdose appear to be young, white males, with low education and employment levels, and often a history of mental health issues. A high prevalence of prescription opioid use was evident in study populations, and polysubstance use (particularly the use of opioids and benzodiazepines) was also frequently reported. Within rural Appalachian drug users, several sub-populations emerged across studies, with differences noted between chronic pain patients and nonmedical users. Drug sources and drug use/injection initiation patterns also varied between men and women.

This high prevalence of prescription opioid use in rural Appalachia can be attributed to increased opioid availability among rural white populations. A 2001 decision by the Joint Commission on the Accreditation of Healthcare Organizations to push for recognition of pain as the “fifth vital sign,” in conjunction with aggressive opioid marketing from pharmaceutical companies, new opioid products (including extended-release oxycodone), increased demand from patients, and regional variation in physician prescribing practices may have all contributed to an eruption of drug overdose deaths in rural Appalachian areas.⁶¹ Rural regions’ cultural and social traditions and ongoing economic struggles also likely contributed to increased drug use and diversion.⁶² Appalachian states have had a long history of alcohol and other substance abuse and illicit substance production, including a tradition of illicit moonshine and marijuana production.²⁴ At the same time, this region has experienced economic difficulties for decades; according to the ARC, 17% of Appalachian residents live below the poverty level (compared with 12.7% of Americans nationally), outmigration of working-aged residents in Appalachia continues to deplete the available

workforce, and the recent national recession resulted in an overall loss of all jobs gained since 2000 in the Appalachian region.^{11,63}

Appalachian culture could further increase susceptibility to substance use, though evidence for the precise mechanism is mixed. The traditional rural Appalachian culture of tangible social support, wherein people “tak[e] care of their own” in communities, could exacerbate drug epidemics through the sharing of drugs, particularly prescription medications.³⁴ Other evidence suggests that Appalachian counties may instead have low social capital (a construct including civic engagement, sense of community belonging, and community trust) compared to other regions in the U.S., and that this lack of social capital is linked to higher drug mortality rates.⁶⁴ More research is needed to understand potential connections between rural Appalachian culture and substance use.

The high prevalence of polysubstance abuse and simultaneous presence of reported mental health issues among drug-using populations has important implications for treatment programs in rural Appalachian areas. Polysubstance abuse requires a different, more complex treatment approach than monodrug use,⁶⁵ which may not be readily available in rural, low-resource areas. Access to mental health treatment services in rural areas is also challenging due to barriers such as cost, stigma, social norms, lack of transportation, and insurance issues,^{66,67} though integrated mental health treatment is critical. Furthermore, while the epidemic in rural Appalachia appears to disproportionately affect young, white men, other populations and overlapping groups – such as women, adolescents, and those in the criminal justice system – should also be carefully considered, as they demonstrate different risk factors and drug use behaviors, and may require tailored prevention and treatment approaches.

More studies of drug use and related comorbidities in rural Appalachia are needed. Studies included in this review were predominantly from Kentucky, making broader generalizations to other Appalachian areas difficult. Furthermore, the included studies collected data during the early- to mid-2000s, meaning that the results of this review may not fully represent the more recent scope of, or shifts in, drug epidemics in Appalachia. While results of this review suggest that prescription opioids are still the predominant drugs of use in rural Appalachia, the included studies may be failing to capture a more recent shift toward heroin and synthetic opioids, such as fentanyl and carfentanyl.^{3,68} Moreover, only 2 studies examined HIV among rural Appalachian PWID,^{42,57} and only 3 focused on HCV in this population^{35,40,69} – despite the fact that rural counties may be particularly vulnerable to HIV and HCV outbreaks, and that local health officials could benefit from an increase in such epidemiological studies and analyses.⁶ Additionally, while almost all of the studies included in this review had clear study aims, adequate descriptions of study data, and acceptable statistical analyses, only 13 out of the 57 provided a rationale for the size of the study sample, and only approximately half of the studies used sampling methods conducive to claims of generalizability (primarily Respondent-Driven Sampling) (Table 2).

CONCLUSION

Results of this review can help to inform substance use intervention development and implementation in rural Appalachian populations. Those at highest risk in these areas are young, white males who often engage in polysubstance use and commonly have a history of mental health issues. However, other groups (such as women and adolescents) may present a different set of risk factors and behaviors that should be considered during intervention design. Furthermore, while many rural Appalachian populations have remained isolated from HIV outbreaks, characteristics of social networks and drug use in these populations are conducive to rapid HIV spread, should the virus be introduced. More studies of recent drug use and drug use shifts in rural Appalachian populations, as well as associated diseases, are needed.

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Appendix 1. Databases and Keyword Searches

Database: Academic Search Premier

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limiters: Limited to 2006–2017 and peer-reviewed journals
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017 and peer-reviewed journals
5. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017 and peer-reviewed journals

Database: CINAHL

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017 and peer-reviewed journals
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017 and peer-reviewed journals
5. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017 and peer-reviewed journals

Database: Health Source

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017 and peer-reviewed journals
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
 - b. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - c. Limited to 2006–2017 and peer-reviewed journals
3. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017 and peer-reviewed journals
4. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian

- a. Limited to 2006–2017 and peer-reviewed journals

Database: PsycInfo

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017 and peer-reviewed journals
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017 and peer-reviewed journals
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017 and peer-reviewed journals
5. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017 and peer-reviewed journals

Database: PubMed

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017

5. Search terms: “Drug abuse” OR “substance abuse” OR “drug addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017

Database: Web of Science

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017 and article
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and article
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural
 - a. Limited to 2006–2017 and article
5. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017 and article

Database: SCOPUS

Searches/Keyword Combinations

1. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic”; AND rural OR “non-urban”; AND “United States” OR “U.S.A.” OR “U.S.” OR “America”
 - a. Limited to 2006–2017 and article
2. Search terms: Drug abuse AND rural AND United States
 - a. Limited to 2006–2017 and article
3. Search terms: Searched by drug type, separately (heroin, methamphetamine, opioid, cocaine); AND rural AND United States
 - a. Limited to 2006–2017 and article
4. Search terms: Drug abuse AND Appalachia OR Appalachian AND rural

- a. Limited to 2006–2017 and article
- 5. Search terms: “Drug abuse” OR “substance abuse” OR “drug use” OR “substance use” OR “drug addiction” OR “substance addiction” OR “drug epidemic” AND Appalachia OR Appalachian
 - a. Limited to 2006–2017 and article

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Figure 1.
Systematic review search and screening process.

Figure 2.
Density of eligible publications by state in the Appalachian region.

Table 1.

Summary of included studies.*

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Kentucky							
Schoeneberger et al., 2006	1999–2001	Drug users admitted to treatment programs in three regions of KY	Total: n = 478 Rural: n = 310 Very rural: n = 168	Cross-sectional	Amphetamine, cocaine, hallucinogens, heroin, inhalants, methamphetamine, prescription opioids, sedatives	Lifetime and past 30-day drug use, compared across rural and very rural areas	<ul style="list-style-type: none"> • Very rural and rural populations predominantly white (94%) and unemployed, with about 1/3 reporting chronic medical problems • Very rural drug users were less likely than rural drug users to report lifetime use of opiates, cocaine/crack, marijuana, and multiple drugs, and were older at age of first drug use • Alcohol use was higher in the very rural population, while illicit drug use was higher in the rural population; suggests that rurality could be protective for drug use and that illicit drug use in rural areas in 1999–2001 was a new problem
Havens, Oser, & Leukefeld, 2007	2001–2004	Felony probationers	n = 800	Longitudinal cohort study	Prescription opioids	Prescription opioid misuse	<ul style="list-style-type: none"> • Participants were mainly white males (population 66.5% male, 95.1% white) of about 32 years of age • During 2001/2002, one quarter of the sample reported misusing prescription opiates; by 2004, closer to half (44.1%) of participants reported misusing; rate ratios for misuse were significantly greater in 2003/2004 as compared to 2001 • Those who used prescription opiates were also significantly more likely to report use of cocaine and benzodiazepines; heroin use prevalence was low • Benzodiazepine use increased over time as well, while cocaine use remained stable – suggesting a shift from illicit to prescription drugs in this population
Havens et al., 2007	2001–2004	Felony probationers, rural KY and urban DE comparison	KY: n = 782 DE: n = 743	Cross-sectional	Prescription opioids	Prescription opioid misuse	<ul style="list-style-type: none"> • Rural population was mainly white, younger, married, and receiving income from disability • Rural participants were significantly more likely (9 times more likely) to use prescription opiates and sedatives/tranquilizers than urban participants; urban participants significantly more likely to use alcohol, cocaine, and heroin • Younger age, getting unemployment benefits, and lower education level were correlates of PO misuse
Oser et al., 2009	2001–2004	Felony probationers	n = 800	Cross-sectional	Cocaine/crack and other stimulants (amphetamines, methamphetamines)	Violence: Violent victimization and violent perpetration	<ul style="list-style-type: none"> • Victims were majority female (63.8%), perpetrators were majority male (73%) • Participants who reported use of cocaine/crack or stimulants were significantly more likely to have committed a violent offense

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Havens, Oser, & Leukefeld, 2011	2001–2004	Felony probationers, injection drug users (IDUs) vs. non-injection drug users (NIDUs)	n = 800	Cross-sectional	Cocaine, heroin, prescription opioids, sedatives	Lifetime IDU and risky injection behaviors	<ul style="list-style-type: none"> • 22.4% of the total sample reported lifetime injection drug use • IDUs were significantly more likely to report lifetime use of cocaine, heroin, amphetamines, and prescription opioids, to report anxiety and depression, and to report HCV and HBV infection, as compared to NIDUs • Among IDUs, 58.7% reported injecting prescription opioids, 68.7% reported injecting cocaine, and 21.2% reported injecting heroin • Among IDUs, 49.7% reported risky injection practices, and 97.1% reported distributive syringe sharing; only 8% of IDU reported consistently bleaching syringes • Among IDUs, those who injected cocaine were 15 times more likely to have participated in risky injection practices than those who did not, and those who injected prescription opioids were 14.7 times more likely to have participated in risky injection practices than those who did not • While no cases of HIV were reported (potentially due to low seroprevalence in the area and insulating/isolating effect of injection networks), the prevalence of risky behaviors means that if HIV is introduced, it could spread quickly
Havens, Walker, & Leukefeld, 2007	2004–2005	Rural residents, opioid analgesic injectors (OAI) and non-opioid-analgesic injectors (NOAI)	n = 184	Cross-sectional	Opioid analgesics, heroin, cocaine	Opioid analgesic injection	<ul style="list-style-type: none"> • Sample was 54.9% male, 98.4% white, typically around 30 years old • 35.5% of sample reported injecting opioid analgesics, vs. 9.8% for heroin and 7.1% for cocaine • 100% of those who indicated which opioid analgesic they injected reported injecting OxyContin, OAI also more likely than NOAI to use benzodiazepines • Higher prevalence of HCV and HBV among OAI than NOAI, and 25% of the total sample reported distributive needle sharing
Havens, Walker, & Leukefeld 2008	2004–2005	Rural prescription opioid users	Total: n = 221 Pain patients: n = 101 Nonmedical users: n = 120	Cross-sectional	Prescription drugs (prescription opioids, benzodiazepines)	Past 30-day prescription drug use	<ul style="list-style-type: none"> • Sample was 56.1% male, 98.6% white, around 30 years of age, 41.4% employed full-time; pain patients were significantly older than nonmedical users • No differences in nonmedical use of benzodiazepines or cocaine/crack • 62.9% of pain patients were also using opioids and/or benzodiazepines that the obtained illicitly, on top of what they were prescribed • The median reported age of first use of prescription opioids was a younger age than the median reported age of onset of pain – suggesting nonmedical use occurring before seeing a physician • High prevalence of nonmedical use of opioids among pain patients could indicate unmanaged pain

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Havens, Walker, & Leukefeld, 2010	2004–2005	Rural prescription opioid users	n = 221	Cross-sectional	Benzodiazepines, prescription opioids	Lifetime and past 30-day medical and nonmedical benzodiazepine use	<ul style="list-style-type: none"> • 92.3% of sample reported lifetime use of benzodiazepines, 67.9% reported past 30-day use; of those current users, 1/3 had a prescription • 58.4% of individuals who did not have a prescription reported receiving drugs from family/friends, and the prevalence of anxiety in those receiving benzodiazepines from family/friends was significantly higher than those who received the drugs from dealers • Individuals who reported past 30-day use were significantly more likely to report depressive symptoms than nonusers • Use of prescription opioids nonmedically, as well as use of other illicit drugs, was significantly higher among those who currently reported benzodiazepine use
Shannon et al., 2009	2006–2007	Women entering substance abuse treatment in rural Appalachia vs. non-Appalachian areas	Total: n = 2,786 Rural Appalachia: n = 872	Cross-sectional	Cocaine, hallucinogens, heroin, inhalants, nonprescription methadone, prescription opioids, sedatives/tranquilizers, stimulants	Past 12-month and lifetime substance use	<ul style="list-style-type: none"> • More women in rural Appalachian population were white and reported chronic physical pain, vs. non-Appalachian • Women in rural Appalachia were significantly less likely to use cocaine and methamphetamine compared to women in non-Appalachian areas, but significantly more likely to use opiates and sedatives/tranquilizers • High prevalence of depression in total sample (64.5%)
Bunn et al., 2010	2001–2007	Methadone-related poisoning cases	Hospitalizations: n = 1207 Poison Center: n = 1084 Deaths: n = 542	Descriptive analysis study	Prescription opioids (Methadone)	Methadone-related poisoning	<ul style="list-style-type: none"> • Peak methadone prescribing rate was seen in 2003 (27 prescriptions per 1,000 population) and decreased to 21 per 1,000 in 2007 • However, while prescribing peaked in 2003, the inpatient hospitalization rate increased significantly from 2001–2007, and the mortality rate increased significantly from 2001–2005 • The rural Appalachian region showed the highest hospitalization and mortality rates from methadone poisoning • Younger males (under 54) and middle-aged females (55–74) most likely to be hospitalized, methadone-related fatalities most frequently occurred in the 25–44 age group, majority among males, 99% whites
Christian et al., 2010	2006–2007	Health department clients screened for HBV/HCV	Total: n = 80 IDUs: n = 14	Cross-sectional	General injection drug use	HCV status	<ul style="list-style-type: none"> • 14 participants were IDUs, and of the 14, 8 were HCV-positive • Correlates/risk factors for HCV included injection drug use and sex with injection drug users
Cole & Logan, 2010	2001–2003	Women with protective orders against male partners	n = 756	Cross-sectional	Opioids, sedatives, other illicit drugs	Lifetime nonmedical use of opioids and sedatives	<ul style="list-style-type: none"> • Higher rates of nonmedical opioid and sedative use in rural IPV victims than in the larger state population

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Young, Havens, & Leukefeld, 2010	2008–2009	Prescription opioid users; rural vs. urban	Total: n = 212 rural: n = 101 urban: n = 111	Cross-sectional	Prescription opioids	Lifetime and past 30-day substance use, as well as route of administration	<ul style="list-style-type: none"> • Correlates of nonmedical use of opioids and sedatives included living in rural Appalachia, younger age, cumulative lifetime victimization, other illicit drug use, alcohol abuse, and reporting unmet health needs • 47.6% of participants were rural; median age of total sample was 37 years, 54% male, 51% white • Significantly more rural participants than urban were white (96%), and rural participants were also significantly younger and had less education and more severe drug use scores • 51% of rural participants reported lifetime buprenorphine use and 37% reported lifetime fentanyl use, while no urban participants reported use of these • Urban participants reported swallowing as the most common route of drug administration, regardless of substance; rural participants reported routes of administration that differ by substance – snorting the most common route for hydrocodone, methadone, OxyContin and oxycodone and injection most common for hydromorphone and morphine
Young, Havens, & Leukefeld, 2012	2008–2009	Prescription opioid users; rural vs. urban	rural: n = 101 urban: n = 111	Cross-sectional	Amphetamine, cocaine, hallucinogens, heroin, inhalants, methamphetamine, prescription opioids, sedatives	Lifetime and past 30-day drug use, age at onset of drug use	<ul style="list-style-type: none"> • 47.6% of participants were rural; median age of total sample was 37 years, 54% male, 51% white • Rural participants commonly reported lifetime use of oxycodone (92.1%), hydrocodone (88.1%), and cocaine (88.1%) as well as polydrug use (87.1%); they also commonly reported recent use of hydrocodone (76.2%), OxyContin (64.4%), other oxycodone (62.4%), methadone (54.5%) and polydrug use (73.3%) • Rural participants were significantly more likely to report lifetime use of illicit methadone, OxyContin, oxycodone, cocaine, and crack compared to urban participants, after adjusting for age, gender, and race • Rural participants were significantly more likely to report recent use of illicit methadone, OxyContin, and crack compared to urban participants, after adjusting for age, race, and gender
Havens et al., 2011	Unspecified	Rural drug users	n = 400	Cross-sectional	Heroin, illicit methadone, OxyContin, other oxycodone, hydrocodone, benzodiazepines, methamphetamine, cocaine	Non-fatal lifetime overdose and witnessed overdose	<ul style="list-style-type: none"> • Sample was 58.7% male and 93.7% white, with a median age of 31 • 28% reported lifetime non-fatal overdose and 58.2% reported lifetime witnessed overdose, median number of witnessed overdoses was 2 • Correlates that were independently significantly associated with non-fatal overdose included male gender, history of drug treatment, use of heroin and cocaine, greater number of years of injecting, injection of prescription opioids as well as illicit drugs, and mental health disorders

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Shannon et al., 2011	2008–2010	Rural drug users	n = 400	Cross-sectional	Cocaine, heroin, methamphetamine, prescription opioids	Lifetime and past 30-day substance use, age at first use	<ul style="list-style-type: none"> After adjusting for individual-level factors and social network characteristics, history of drug treatment, past 30-day injection with prescription opioids, having more members in one's support network, and PTSD were associated with non-fatal overdose Methamphetamine use, PTSD, and increased age were associated with witnessed overdose Lifetime use: compared to females, significantly more males reported use of heroin (39.6% vs. 27.3%), crack cocaine (79.6% vs. 64.9%), methamphetamine (50.2% vs. 33.9%), and hallucinogens (65.9% vs. 46.1%); significantly more females reported use of hydrocodone (99.4% vs. 96.2%) Past 30-day use: significantly more males reported use of any illegal drug, but no difference in prescription drug use by gender (OxyContin used by around 70%, hydrocodone around 80%, methadone around 60%, benzodiazepines around 84%) Males reported using cocaine and hallucinogens for the first time at a significantly younger age than females, but no difference was seen for age at first use of prescription drugs by gender
Jonas et al., 2012	2008–2010	Rural drug users	n = 503	Cross-sectional	Prescription opioids (OxyContin)	Social capital (effective size)	<ul style="list-style-type: none"> Sample was 94.2% white and 56.9% male, median age of 31, median educational attainment of 12 years; 28.0% used OxyContin daily After adjusting for gender, education, income, and daily marijuana/alcohol/hydrocodone use, daily OxyContin users were significantly more likely to have a higher effective size (2.31 times the odds of a higher effective size as compared to non-users) Those who use OxyContin daily were more likely to have more social capital among their network of other drug users
Lofwall & Havens, 2012	2008–2010	Rural drug users	n = 471	Longitudinal cohort study	Prescription opioids (Buprenorphine)	Past 6-month use of diverted buprenorphine	<ul style="list-style-type: none"> 70% of the sample reported lifetime use of buprenorphine, 46.5% reported use of diverted buprenorphine during the 6-month study period Sources of buprenorphine included dealers (58.7%), friends (31.6%) and family (7.3%) those who attempted but failed to access buprenorphine treatment had 7.31 times the odds of using diverted buprenorphine compared to those who did not attempt to access treatment
Young & Havens, 2012	2008–2010	Rural drug users; injection drug users (IDUs) vs. non-injection drug users (NIDUs)	Total n = 503 IDUs: n = 394 NIDUs: n = 109	Cross-sectional	Amphetamine, cocaine, hallucinogens, heroin, inhalants, methamphetamine,	Lifetime injection drug use and transition time to injection	<ul style="list-style-type: none"> Of the IDUs, 48% reported initiating injection drug use with OxyContin, 30% with stimulants (methamphetamine or cocaine), and 14% with other prescription opioids; additionally, those who initiated with OxyContin also reported the fastest

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Crosby et al., 2012	2008–2010	Rural drug users	n = 503	Cross-sectional	General injection drug use	Sexual risk behaviors and injection drug use	<p>initiation rates (median of 3 years from first use of OxyContin to injection)</p> <ul style="list-style-type: none"> • After adjusting for all other substance types, those who reported ever using OxyContin and stimulants had 6.7 times the odds of reporting a history of injection drug use than those who had not used those substances • 8.3% of the study sample reported having been diagnosed with an STD • Only 18.9% had ever injected heroin, and 7.7% had ever injected meth • 18.3% reported using a dirty needle in the past 6 months, 61.63% of the sample participants were linked to another sexual network member, but all of the participants were HIV-uninfected • Suggestion that this population is isolated from the HIV epidemic, but that if HIV were introduced into the network, it could spread quickly through sex and drug networks
Hall, Leukefeld, & Havens, 2013	2008–2010	Rural drug users	n = 503	Cross-sectional	Prescription opioids (methadone)	Illicit methadone use	<ul style="list-style-type: none"> • 94.6% of participants reported lifetime use of illicit methadone, and 46.3% reported high-frequency use (daily or weekly) in the past 6 months • Most common sources of illicit methadone were friends (46.0%), dealers (28.8%), family members (12.4%) and spouses/partners (8.8%) • High-frequency illicit methadone users were significantly younger than low-frequency users, and those who reported that they were taking medication for a physical problem were less likely to be high-frequency users, suggesting that methadone might be used to self-treat physical health problems
Havens et al., 2013	2008–2010	Rural drug users with history of injection drug use	n = 392	Cross-sectional	Injection drug use; cocaine, heroin, methamphetamine, prescription opioids	HCV status	<ul style="list-style-type: none"> • Sample was 58.9% male, 93.9% white, median age of 31 • 54.8% of the sample tested positive for HCV (compared to general population prevalence of <2% in the US), and 12.5% of the sample tested positive for HSV-2 • 88.7% of participants reported lifetime injection with prescription opioids, and 61.7% reported that they had initiated injection with prescription opioids • Injection of prescription opioids and injection of cocaine were both independently associated with HCV infection, and sharing syringes was also associated with HCV infection
Young et al., 2013	2008–2010	Rural drug users	n = 503	Cross-sectional	Cocaine, heroin, methamphetamine, prescription opioids	Risk network ties/structure	<ul style="list-style-type: none"> • The observed sex/drug network included various risk behaviors, including syringe sharing and unprotected sex • Average distance/“steps” between any two members of the network was approximately 6, and

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Young, Larian, & Havens, 2014	2008–2010	Rural drug users with a history of injection drug use	n = 394	Cross-sectional	General injection drug use	Injection drug use initiation	<p>17.7% of the sample was included in one main network component</p> <ul style="list-style-type: none"> • Suggests again, that while the overall network now may be insular/protective against HIV introduction, if HIV were to be introduced, it could spread quickly through the network • Sample was 59% male and 41% female, median age of initiation of injection was 24 • For both men and women, first injection was administered by a friend in the majority of cases (56% for men and 44% for women); however, 30% of women reported a partner administering the injection, and 26% of men administered the injection themselves • Compared to men, women were significantly more likely to have initiated because of social pressure, to have received the drugs as a gift, to have initiated in a partner's home and in a partner's presence, to have injected with a syringe that was previously used, to have used a syringe provided by a partner, and to have had sex before or after • Compared to women, men were more likely to have initiated with a friend or immediate family member, to have purchased drugs themselves, and to have gotten a syringe from a pharmacy/clinic
Smith et al., 2016	2008–2010	Rural drug users	n = 503	Cross-sectional	Cocaine/crack, heroin, methamphetamine, prescription opioids, tranquilizers/sedatives	Antisocial personality disorder status (ASPD)	<ul style="list-style-type: none"> • Prevalence of ASPD in the sample was 31.4% • Factors that were significantly associated with ASPD, after adjusting for covariates, included male gender, younger age, fewer years of education, having major depressive disorder, recent heroin use, and recent crack use
Stephens et al., 2016	2008–2010	Rural drug users	n = 499	Cross-sectional	Heroin, illicit methadone, OxyContin, other oxycodone, hydrocodone, crack, cocaine, methamphetamine, other amphetamine, benzodiazepines	HSV-2 status	<ul style="list-style-type: none"> • Sample was 57.1% male, 94.2% white, average age of 33 years • Prevalence of HSV-2 was in the sample 11.4% overall; 19.6% among women and 5.3% among men – weighted population estimates were 24.2% for women and 6.7% for men • After adjusting for covariates, female gender, older age, and greater frequency of unprotected sex were associated with positive HSV-2 status • 60.1% of the participants were linked to another participant in a sex network • Prevalence of HSV-2 in this sample was lower than generally reported among drug users, suggesting a possible rural isolative protective mechanism in Appalachia, but participants may be at increased risk for HIV were it to be introduced
Rudolph, Young, & Havens, 2017	2008–2010	Rural drug users	n = 503	Cross-sectional	Cocaine/crack, heroin, methamphetamine,	Injection status	<ul style="list-style-type: none"> • Examined mean geographic distance and mean social distance between participants

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Shannon, Havens, & Hays, 2010	2005–2007	Pregnant women undergoing inpatient detoxification or methadone stabilization; rural vs. urban	n = 114	Cross-sectional	Crack/cocaine, opiates, sedatives	Lifetime, past 12-month, and past 30-day substance use	<ul style="list-style-type: none"> • Social proximity to another injecting peer was more strongly associated with injection status than geographical proximity to injectors: for each additional socially proximal injecting peer, individuals had 19% increased odds of injection, whereas for each additional geographically proximal injecting peer, only 0.2% increased odds • Suggests that injections status more strongly related to behavior of socially proximal peers (people that an individual interacts with - through drug use, sex, social support, etc. - socially) than with the prevalence of injection among those who are geographically proximal • Average age of the sample was 25; 95.6% of participants were white, 86% unemployed, 93.9% reported a physical health problem, and 50.9% reported a mental health problem • 75% of the sample lived in a rural region; of those, 91% lived in Appalachia • Compared to urban residents, rural pregnant participants were significantly more likely to report use of illicit opiates (8.4 times more likely), use of illicit sedatives/benzodiazepines (3.3 times more likely), use of multiple illicit substances (2.8 times more likely), and injection drug use (5.9 times more likely) in the past 30 days (prior to detoxification)
Jackson & Shannon, 2012	2005–2007	Rural pregnant women undergoing inpatient detoxification	n = 95	Cross-sectional	Antidepressants, cocaine, heroin, prescription opioids, sedatives	Lifetime and past 30-day substance use	<ul style="list-style-type: none"> • Sample was 97% white, average age of 25, majority (around 60%) had less than college education • 92% reported lifetime use of prescription opiates, 88% reported use of illicit sedatives, 86% reported use of cocaine, and 55% reported use of illicit antidepressants • 94.1% reported using illicit opiates and 50.6% reported using illicit sedatives in the past 30 days • Participants reported using prescription sedatives and injecting drugs for the first time at age 22; 50% had ever injected drugs and 30.6% injected in the past 30 days
Shannon et al., 2016	2005–2007	Rural pregnant women undergoing inpatient detoxification	n = 77	Cross-sectional	Heroin, prescription opiates, sedatives, crack, cocaine	Interpersonal violence (IPV) and substance abuse	<ul style="list-style-type: none"> • Sample was 99% white, mean age of 25, majority had high school diploma or less, 89.6% unemployed • 91% reported lifetime IPV (89.6% reported lifetime psychological abuse; 64.9% reported lifetime physical violence) – much higher rates of IPV than the general population • 98.7% reported lifetime use of illegal opiates, 92.2% lifetime use of legal opiates, 87.0% illegal benzodiazepines, 85.7% crack/cocaine • 41.6% injected drugs and 81.8% reported using multiple substances

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Chubinski et al., 2014	2012	Kentucky adult residents, Appalachian county/Appalachian heritage vs. statewide	Statewide: n = 1,680 Appalachian counties: n = 505 Appalachian heritage: n = 623	Cross-sectional	Prescription opioids	Awareness of prescription opioid overdose and personal experience with prescription drug abuse	<ul style="list-style-type: none"> • However, no association found between past-year IPV and mental health, physical health, or substance use, apart from a significant association between IPV and past-year marijuana use • Compared with residents statewide, a significantly higher percentage of Appalachian participants reported an income below the federal poverty line, fair or poor health status, and having a chronic disease • 67% of Appalachian residents correctly identified drug overdoses as Kentucky's leading cause of unintentional deaths, vs. only 44% statewide • While there was no difference between Appalachian residents and statewide participants when asked about personal pain medication use, a significantly higher percentage of Appalachian residents reported that pain medication abuse affected their families or friends (46% vs. 33% statewide)
Havens et al., 2014	2010–2011	OxyContin abusers	n = 189	Retrospective cohort study	Prescription opioids (reformulated ERO/ OxyContin)	Reformulated ERO abuse	<ul style="list-style-type: none"> • Sample was 54.5% male, 97.9% white; 51.3% of the sample reported abusing reformulated ERO, 81.5% reported injecting drugs, and 96.1% of those reported injecting prescription opioids • In the past 30 days, the prevalence of reformulated ERO abuse was 33%, but the prevalence of immediate release (IR) oxycodone abuse was 96% • The prevalence of past 30-day reformulated ERO abuse was significantly lower than original ERO abuse (33% vs. 74%) • The frequency of reformulated ERO abuse was low (1.9 days/month on average), and this was significantly lower than reported IR oxycodone abuse and reported frequency of original ERO abuse • Results suggest that while ERO abuse decreased after reformulation, total opioid abuse was not affected/lowered due to continued abuse of IR oxycodone instead
Shannon, Perkins, & Neal, 2014	2009–2011	Individuals entering drug court services, rural Appalachian vs. urban	Total n = 583 rural Appalachian n = 301 Urban n = 282	Cross-sectional	Amphetamine, cocaine/crack, hallucinogens, inhalants, methamphetamine, opioids, sedatives/ tranquilizers	Lifetime and past 30-day substance use	<ul style="list-style-type: none"> • Study sample was 54.3% male and 85.4% white, average of 30 years of age; compared to urban participants, those in rural areas were significantly younger when they entered drug court, were significantly less racially diverse (almost all white), and were significantly more likely to report being unemployed and having a lower level of education • More rural Appalachian participants reported lifetime use of cocaine (84.0% vs. 68.5%), illicit opiates (95.7% vs. 57.0%), and illicit benzodiazepines (91.8% vs. 52.2%) compared to urban participants; rural participants also reported greater 30-day use of illicit opiates (57.4% vs. 10.9%) and illicit benzodiazepines (36.2% vs. 4.6%)

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Otis et al., 2016	Dec. 2012-Aug. 2015	Women from rural jail facilities in three rural Appalachian counties who met criteria for moderate risk for substance abuse and reported engagement in at least one sex risk behavior in the past three months	n = 400	Cross-sectional	Cocaine/Crack, hallucinogens, inhalants, methamphetamine, opioids, stimulants	Violent victimization and substance use	<ul style="list-style-type: none"> • After controlling for mental health and sociodemographic factors, those who entered drug court in rural Appalachia were significantly more likely to report using cocaine, illicit opiates, and illicit benzodiazepines than those in urban areas • Sample was predominantly white, 79.3% heterosexual and 21% in a sexual minority (not heterosexual), mean age of 32.8 years, average of 11 years of education • Compared to heterosexual women, sexual minority women were more likely to report using inhalants (p=0.005) and reported a significantly higher mean number of different opiate and stimulant drugs used (p<0.05) • Compared to heterosexual women, sexual minority women were significantly more likely to report experiencing multiple types of violent victimization, and were also significantly younger when first experiencing violent victimization • Sexual minority women had significantly higher average scores on two measures of injection drug use problems (significantly greater average # of people with whom they shared needles and significantly greater average # of people with whom they shared works, p<0.05) • Sexual minority women reported first injecting an illicit drug at a significantly younger age than heterosexual women • Sexual minority women were significantly more likely to indicate that they had ever overdosed as compared to heterosexual women (p=0.001) • In multivariate analyses, violent victimization was a significant predictor of scores on a measure of substance use problems
Staton et al., 2017a	Dec. 2012-Aug. 2015	Women from rural jail facilities in three rural Appalachian counties who met criteria for moderate risk for substance abuse and reported engagement in at least one sex risk behavior in the past three months	n = 400	Cross-sectional	Heroin, other opiates, stimulants, methamphetamine, buprenorphine, sedatives	Injection status	<ul style="list-style-type: none"> • 75.3% of sample reported lifetime injection, and 59.9% were recent injectors; 59% were positive for HCV • As compared to noninjectors, injectors (recent and past combined) were more likely to screen positive for HCV, more likely to have depression, had more lifetime sexual partners, and had significantly higher-risk living environments (e.g., more days of drug use by those living with them, more likely to have family members with drug problems) • Risky sexual behavior was also significantly associated with injection drug use – injectors were more likely to have a partner who injected drugs, and more likely to use drugs before sex as compared to noninjectors

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Staton et al., 2017b	Dec. 2012-Aug. 2015	Women from rural jail facilities in three rural Appalachian counties who met criteria for moderate risk for substance abuse, reported engagement in at least one sex risk behavior in the past three months, reported injecting drugs in the past year, and reported a past-year main male sex partner	n = 199	Cross-sectional	Unspecified	Injection partners and risky injection practices	<ul style="list-style-type: none"> • Average age of sample was 30.8 years, 99% of sample white, 77.4% heterosexual, average of 11 years of education, 58.8% single • 76.2% reported that their main sexual partner had ever injected • Compared to women who did not have a risky partner (partner with history of IDU), women with a risky partner were younger, reported lower relationship power, and were more likely to participate in shared injection practices • Relationship power also moderated injection sharing practices – women who had a risky partner and had lower perceived power in the relationship were more likely to demonstrate risky injection practices, but those with higher relationship power reported lower risk behavior (similar to women without a risky partner)
Tilson, Strickland, & Staton, 2017	Dec. 2012-Aug. 2015	Women from rural jail facilities in three rural Appalachian counties who met criteria for moderate risk for substance abuse and reported engagement in at least one sex risk behavior in the past three months	n = 400	Cross-sectional	Unspecified	High-risk drug use and high-risk sexual practices	<ul style="list-style-type: none"> • Average age of first sexual encounter was 14.7 years, average age of first drug use was 16.3 years, and average age of first arrest was 23.3 years; positive correlations between each of the three age of onset variables were seen (first drug use and arrest: $r=0.31$, first drug use and sex: $r=.28$, first sex and first arrest: $r=0.16$, $p<0.01$ in all cases) • Earlier drug use was associated with high-risk drug use as an adult (e.g. ever overdosing, ever injecting, injecting in past 6 months), having a sexual partner with a history of IDU or incarceration, trading sex for drugs/money, and using drugs before sex ($p<0.05$) • Earlier age of first sexual encounter was associated with more male partners, earlier IDU, overdose risk, injecting, trading sex for drugs/money, and having a sexual partner who injected ($p<0.05$) • Overall, initiation of the three events was related among rural high-risk women
Brown, Goodin, & Talbert, 2017	2008–2014	NAS births – Appalachian vs. non-Appalachian regions	n = 3,892	Ecologic	Opioids	NAS rates	<ul style="list-style-type: none"> • Statewide increase from 249 cases in 2008 to 1,054 in 2014 • The KY Appalachian region accounted for 52.0% of NAS births in the state between 2008 and 2014 • Rates of NAS births in the rural/Appalachian regions were 2–2.5 times higher than in metropolitan/non-Appalachian regions; rural NAS metropolitan/non-Appalachian regions; rural NAS birth rate reached 38.9 per 1,000, and reached approximately 25 per 1,000 in Appalachian counties
New York							
Zibbell et al., 2014	2012	Injection drug users	n = 123	Cross-sectional	Bath salts, cocaine/crack, heroin,	HCV status	<ul style="list-style-type: none"> • The sample was 68.3% male and 88.6% white; 68.3% were younger than 30 years old

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					methamphetamine, prescription opioids		<ul style="list-style-type: none"> • 68.3% reported sharing drug preparation equipment in the past year, 44.4% reported sharing needles in the past year • 58.0% reported injecting prescription opioids and 33.3% reported injecting heroin; these were the two most commonly reported drug types • After adjusting for covariates, factors significantly associated with HCV included prescription opioid injection and sharing preparation equipment in the past year; those who injected prescription opioids were 5 times more likely to have HCV than those who did not – suggesting that there are certain risks involved with prescription opioid injection preparation that result in higher HCV infection risk
North Carolina							
Modarai et al., 2013	2008–2010	North Carolina fatalities from unintentional drug overdose (?)		Ecological trend study	Prescription opioids	Opioid-related ED overdoses and unintentional drug overdose deaths	<ul style="list-style-type: none"> • Rural regions of the state showed higher rates of opioid sales and overdoses, compared to urban areas; southern and western regions of the state also had higher rates • Both opioid sales and opioid overdoses treated in EDs showed a significantly positive association from 2008 to 2010, as they both increased
Ballard, Jameson, & Martz, 2017	Spring 2014	High school students from two rural Appalachian high schools	n = 1,550	Cross-sectional	Cocaine, inhalants, methamphetamine, prescription drugs, steroids	Drug use and various risk measures (Risk for bullying victimization, suicide risk, school violence, sexual risk behavior)	<ul style="list-style-type: none"> • Sample was 51% female, 90% heterosexual, 90% white • 43.5% of students reported using at least one substance, 20.3% reported two, and 15% reported 3 • Compared to heterosexual students, LGBQ students were significantly more likely to report drug use (approximately 1.5 times the risk for reporting drug use as heterosexual students, $p < 0.0001$)
Pennsylvania							
Puskar et al., 2008	Unspecified	9 th –11 th grade high school students	n = 193	Cross-sectional	Cocaine, heroin, inhalants, LSD, PCP, prescription opioids, stimulants	Lifetime substance use	<ul style="list-style-type: none"> • Sample was 53% female, 86.5% white, and had an average age of 15.6 years • Following alcohol, the most commonly reported substance category was painkillers (30.6%); frequencies of stimulants, cocaine, tranquilizers, and heroin use were low • 37.3% of the sample reported never using any drugs, 36.8% reported lifetime use of just one drug, and 26.7% reported lifetime use of 2 or more drugs • No difference in drug use by gender, apart from marijuana
Karp et al., 2013	1989–2002	Monongahela Valley residents, aged 65+	n = 1,109	Prospective cohort study	Opioid and non-opioid analgesics	Opioid and non-opioid analgesic use	<ul style="list-style-type: none"> • Sample was 63.21% female, primarily white • Study consisted of a baseline wave in 1989, then 4 waves thereafter: opioid analgesic frequency across waves: 4.1%, 4.5%, 5.3%, 6.0%, 6.8%; non-opioid

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Cochran et al., 2015	2014–2015	Community pharmacy patients with opioid prescriptions; rural vs. urban	Rural: n = 98 Urban: n = 66	Cross-sectional	Prescription opioids	Opioid medication misuse risk and screening feasibility	<p>analgesic frequency across waves: 42.0%, 48.0%, 52.3%, 43.1%, 51.9%</p> <ul style="list-style-type: none"> • Among non-opioid analgesic users, 46.1% were classified as chronic users; among opioid analgesic users, 7.2% were classified as chronic users • Compared to non-users/inrequent users, chronic non-opioid users were significantly more likely to be female, report sleep disturbance, take 2 or more prescription medications, and have been diagnosed with arthritis; they are also less likely to consume alcohol and less likely to report good health • Compared to non-users/inrequent users, chronic opioid users were significantly more likely to be older, female, have less than a high school education, report poor health, take 2 or more prescription medications, and have been diagnosed with arthritis
Cochran et al., 2016	2014–2015	Community pharmacy patients with opioid prescriptions	n = 333	Cross-sectional	Prescription opioids	Opioid medication misuse	<ul style="list-style-type: none"> • Total sample was 56.4% women, average age 49.2; 52.5% had completed high school, and 68.7% were unemployed • Out of the total sample, 14.3% screened positive for risk of prescription opioid misuse, 7.3% had positive screening results for past-year illicit drug use, and 25.8% screened positive for depression • Compared to urban participants, rural participants reported a significantly lower average level of general health, and higher levels of pain that interfered with normal work • Those who screened positive for past-year illicit drug use had 12.96 times higher odds of screening positive for opioid medication misuse risk than those who did not
							<ul style="list-style-type: none"> • Total sample was 56.6% women, average age 50; 32.9% of rural participants had more than a high school education vs. 55.7% of urban participants • Out of the total sample, 15.1% showed prescription medication misuse, 22.4% reported hazardous drinking, and 26.8% had a positive depression screen • Compared to urban participants, rural participants reported significantly poorer general health • Compared to urban participants, a significantly lower proportion of rural participants reported seeking early medication refills or getting a buzz from their opioid medications • Rural participants who also used illicit drugs had 14.34 times greater risk of screening positive for opioid medication misuse compared with those who did not use illicit drugs or getting a buzz from their opioid medications

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Cochran et al., 2017	Sep. 2015–June 2016	Community pharmacy patients with opioid prescriptions	n = 333	Cross-sectional	Prescription opioids	Prescription opioid misuse	<ul style="list-style-type: none"> Rural participants who also used illicit drugs had 14.34 times greater risk of screening positive for opioid medication misuse compared with those who did not use illicit drugs Rural participants with PTSD had 5.44 times greater risk for opioid medication misuse compared to those with no PTSD Rural participants with only a high school-level education or below had 6.68 times greater risk for opioid medication misuse compared to participants with higher education levels Sample was split into those classified as having 1) poor health, 2) mental health issues, and 3) hazardous alcohol use Compared to those classified as having poor health, those classified as having mental health problems had 6.23 times higher odds of having a positive screen for prescription opioid misuse Those classified as having mental health issues also had the highest percentage of positive screens compared to the two other groups (44.4% screened positive for opioid misuse) The mental health group was the only group associated with misuse; no relationship found between being in the poor health or hazardous alcohol group and screening positive for opioid misuse
Tennessee							
Collins et al., 2011	2009	5 th , 7 th , 9 th and 11 th grade students	n = 1,105	Cross-sectional	Pain medications, sedatives/anxiety medications, sleeping medications, stimulant medications	Lifetime and past 30-day nonmedical use of prescription drugs (NMUPD)	<ul style="list-style-type: none"> Total sample was 57% female and 90% white, with 37% reporting that in their lifetime, they had a prescription medication prescribed to them 35% of participants reported NMUPD, with pain medications most commonly reported (27%) Predictors of NMUPD included number of friends who were also using prescription drugs nonmedically and perceived availability of prescription drugs; protective factors included greater perceived risk of NMUPD, school commitment, community norms against NMUPD, and parental disapproval of NMUPD
MacMaster 2013	Unspecified	Rural female methamphetamine users living under the poverty level	n = 153	Cross-sectional	Methamphetamine	Methamphetamine use and treatment access	<ul style="list-style-type: none"> Mean age of the sample was 32.4, 58.9% did not have a high school degree, 76.2% reported a blood relative with a drug use problem 32.2% reported methamphetamine as their drug of choice, while 33.8% reported opioids as their drug of choice (particularly prescription opioids)
Erwin et al., 2017	2013–2014	Mothers and children with NAS in eastern Tennessee; urban	n = 706	Retrospective case-control	Opioids	NAS cases and opioid sources	<ul style="list-style-type: none"> In the 16-county area of eastern Tennessee studied, there were 339 NAS cases in 2013 and 367 in 2014

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
		Knox county vs. rural Appalachia					(rates: 22.5 per 1,000 live births in 2013, 28.5 per 1,000 in 2014) <ul style="list-style-type: none"> • In 2014, the rate of NAS in the rural Appalachian counties was 50% higher than in the urban area (Knox county) • Mothers with infants with NAS were significantly more likely to be older, single, white, have history of HCV and herpes, have smoked during pregnancy, and receive less prenatal care than mothers with non-NAS infants • Mothers with NAS infants were also more likely to use opioids that had been prescribed to someone else than to use illicit opioids (using diverted prescription medications rather than illicit drugs)
Virginia							
Wunsch et al., 2007	2000–2004	Prisoners and probationers in Southwestern district (District 28) with a history of drug/alcohol abuse	n = 233	Cross-sectional	Prescription medications, especially OxyContin	Drug abuse	<ul style="list-style-type: none"> • Sample was 75% male and 89% white, with a mean age of 32 for males and 30 for females • Compared to male use of prescription medications, females were more likely to abuse benzodiazepines and prescription opioids; 27% of men had abused OxyContin, compared to 45% of women • 75.8% of the overall sample reported polysubstance abuse • Compared with those who did not use OxyContin, OxyContin users were more likely to abuse other prescription opioids, methadone, benzodiazepines, and cocaine • Overall, 58.2% of men and 75% of women reported a psychiatric problem, such as depression or anxiety • Among those who used OxyContin, property crimes were committed significantly more often than among non-users, with no difference in violent crimes (suggesting that crimes were committed in order to obtain more drugs) • OxyContin use was not associated with medical treatment/chronic medical problems, suggesting abuse for euphoric effects, and not to manage pain
Wunsch et al., 2008	Unspecified	Southwestern VA (Western District) Substance abuse patients (SA), pain patients (Pain), and prisoners (CJ) with a history of OxyContin use	Substance abuse patients: n = 50 Pain patients: n = 34 Prisoners: n = 50	Cross-sectional	Prescription opioids (OxyContin)	OxyContin use and abuse	<ul style="list-style-type: none"> • Overall, majority of participants in all groups were white and had a high school education; a higher percentage of Pain patients were older and female compared to the other groups • Compared to the other groups, a significantly greater percentage of SA participants met criteria for abuse of opiates, as well as for abuse of at least one other additional substance; SA participants were also more likely to meet the criteria for abuse of sedatives/benzodiazepines • However, a high rate of opioid abuse was also present in the Pain patients (62%)

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Wunsch et al., 2009a	1997–2003	Residents in Western District who died of drug overdose	n = 889	Retrospective review of cases	Amphetamine, cocaine, heroin, methamphetamine, prescription medications	Drug poisoning (all drug types)	<ul style="list-style-type: none"> Participants in the SA and CI groups were more likely to have obtained OxyContin from a dealer, used someone else's prescription, or stolen it compared to Pain patients (who obtained it via a physician prescription) During the study period (1997–2003), there was a 300% increase in drug-related deaths, and a six-fold increase in the number of drug-related deaths in which opioids were involved <ul style="list-style-type: none"> The sample was 63% male and 96.8% white; female decedents were significantly older (42.8 years vs. 38.5 years); most deaths were among those aged 36–45 years, and 78.9% of deaths were accidental (though a higher percent of female vs. male deaths were classified as suicides); death rates were higher among rural populations, and polydrug toxicity was also more likely among rural individuals than non-rural (61.6% vs. 55.2%) 57.9% of deaths overall in this period were polydrug deaths 74.0% of deaths involved prescription opioids (most commonly methadone, hydrocodone, and oxycodone), 49.0% of deaths involved antidepressants, and 39.3% of cases involved benzodiazepines; only 2.4% of cases involved heroin, 12.0% of cases involved cocaine, and 1.4% of cases involved methamphetamine/amphetamine Heroin and cocaine were more likely to be found among decedents in urban areas, while prescription opioids were more likely to be found in rural areas In cases of single drug toxicity, methadone was most commonly identified (22.7% of cases) Benzodiazepines and anti-depressants were commonly found along with opioids
Wunsch et al., 2009b	1997–2003	Female residents in Western District who died of drug overdose	n = 330	Retrospective review of cases	Amphetamine, cocaine, heroin, methamphetamine, prescription medications	Drug poisoning	<ul style="list-style-type: none"> The overall sample was 95% white, with a mean age of 42.8 years and the greatest number of deaths in the 36–45-year-old age category Polydrug overdose was found in 56.4% of cases Opioids (72.4%), antidepressants (60.9%), and sedatives (48.8%) were most commonly identified; decedents had a prescription in 2/3 of cases of antidepressants and opioids, and 67% of cases of sedatives In 46% of cases, opioids, antidepressants, and sedatives were all identified, and the decedent had a prescription for all three medications Opioid-related deaths increased significantly over the study period Anxiety was documented in 20% of cases, and depression in 52.4% of cases

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Wunsch et al., 2013	1997–2003	Western district residents who died of methadone-related overdose	n = 246	Retrospective review of cases	Methadone	Methadone-related overdose	<ul style="list-style-type: none"> Between 1997 to 2003, there was a significant increase in methadone-related deaths (59.6% annual % change), and the majority of deaths were classified as accidental The sample of decedents was 75.2% male, 98.4% white, most commonly in the age range of 36–45 years, 27% disabled, with low education levels (34% did not complete high school, 47% had high school diploma but no further education) 45.1% of the decedents were from a metropolitan area, and 41.9% were from a rural area In 54.9% of cases, the cause of death was polydrug toxicity 40% of cases showed documentation of chronic injury, 19.5% had evidence of an anxiety diagnosis, and 41% had evidence of a depression diagnosis 63.8% of cases showed evidence of methadone Apart from methadone, the most commonly found drugs were sedatives/anxiolytics/muscle relaxants (56.9%), antidepressants (48.4%), and other opioids (30.1%); the most commonly found opioids were hydrocodone and oxycodone Majority of decedents did not have a prescription for the drug identified on toxicology
Thornton & Dettz-Allyn, 2010	2005	Attendants of the Remote Area Health Expedition	n = 139	Cross-sectional	Unspecified	Substance abuse	<ul style="list-style-type: none"> Sample was 61.9% female and 38.1% male, with a mean age of 41.3; sample was 91.4% white, the majority had less than a college education, and 75% were unemployed There was a strong significant association between unemployment and reported drug problems; overall, 15.3% reported drug problems
Weimer et al., 2011	Jan. 2004 – Dec. 2004	Western district residents who died of methadone-related overdose	n = 61	Retrospective review of cases	Methadone	Methadone or polysubstance overdose	<ul style="list-style-type: none"> Sample was 64% male and 36% female, with a mean age of 36; sample was 95% white In 2004, methadone was a direct or contributing cause of death in 34% of overdose cases A history of substance abuse was found in approximately half of decedents 67% of decedents had obtained methadone from an illicit source, 5% from an OPT, and 28% from a non-OTP physician; decedents who obtained methadone from illicit sources were younger than those using other sources (each 1-year increase in age was associated with an 8% decrease in the odds of an illicit source of methadone) Decedents with illicit methadone were less likely to also have antidepressants present, but other opioids were often found during toxicological analyses of these individuals
West Virginia							

Study	Year(s) of Data Collection	Study Population	Study Sample Size	Study Design	Drug Type(s) Included	Outcome Measure(s)	Key Findings
Hall et al., 2008, West Virginia	2006	Residents who died of unintentional drug overdose	n = 295	Cross-sectional	Prescription medications	Unintentional pharmaceutical overdose	<ul style="list-style-type: none"> • Total sample consisted of 295 deaths, and an overall unintentional pharmaceutical overdose death rate of 16.2 per 100,000 people was reported; 79.3% of decedents overdosed due to use of multiple substances • Methadone contributed to 40% of deaths – higher than any other substance • Opioids were found in 93.2% of deaths, although only 44.4% of these cases were found to have evidence of a prescription • The overdose rate of men was over two times that of women, and 67.1% of the decedents were male • 91.9% of the decedents were between age 18 and 54; greater death rates were associated with unmarried status, lower educational level, and increased poverty in county of residence • Out of the total sample, 63.1% of decedents had used prescription drugs without a prescription (diversion), and 21.4% of decedents had obtained medications through “doctor shopping” – having 5 or more clinicians write prescriptions for drugs in the past year • Compared to men, women were significantly more likely to have been doctor shopping • Out of the total sample, greatest prevalence of diversion was seen in the 18–24-year-old age category, and then decreased by increasing age category; doctor shopping was seen at the highest rate in the 35–44-year-old age group • Only 8.1% of the total sample showed evidence of both diversion and doctor shopping • Those who were categorized as doctor shoppers typically resided in higher-income counties and were more likely to administer drugs orally; the population categorized as diverters was heavily male (more than 2/3), young (half younger than 35), and likely to use a nonmedical route of administration

* Studies conducted using the same sample/cohort are grouped together and indicated with dotted-line borders

Table 2.

Quality ratings of included articles.

Authors	Publication Year	Clear Study Aims	Sample Size (Rationale Provided)	Representative Sample	Inclusion and Exclusion Criteria	Response Rate Documented	Validated/ Reliable Measure of Substance Use or Outcome	Measure of Substance Use/ Outcome by Individual Substance Type	Adequate Description of Data	Adequate Statistical Analysis	Conflict of Interest Statement	Total
Ballard, Jameson, & Martz	2017	1	0	0	1	1	1	0	1	1	0	6
Brown, Goodin, & Talbert	2017	1	1	1	1	0	1	1	1	1	1	9
Bunn et al.	2010	1	0	1	1	0	1	1	1	1	1	8
Christian et al.	2010	1	0	0	1	1	0	0	1	1	1	6
Chubinski et al.	2014	1	0	1	0	1	0	1	1	0	0	5
Cochran et al.	2015	1	0	0	1	1	1	1	1	1	1	8
Cochran et al.	2016	1	0	0	1	1	1	1	1	1	1	8
Cochran et al.	2017	1	0	0	1	1	1	1	1	1	1	8
Cole & Logan	2010	1	0	0	1	1	1	1	1	1	1	8
Collins et al.	2011	1	0	1	1	1	0	1	1	1	1	8
Crosby et al.	2012	1	0	1	1	1	1	0	1	1	1	8
Erwin et al.	2017	1	0	0	1	0	1	1	1	1	1	7
Hall et al.	2008	1	1	1	1	1	1	1	1	1	1	10
Hall, Leukefeld, & Havens	2013	1	1	1	1	0	1	1	1	1	1	9
Havens et al.	2007	1	0	0	1	0	1	1	1	1	1	7
Havens et al.	2011	1	0	1	1	0	1	1	1	1	0	7
Havens et al.	2013	1	1	1	1	1	1	1	1	1	1	10
Havens et al.	2014	1	0	0	1	1	1	1	1	1	1	8
Havens, Oser, & Leukefeld	2007	1	0	0	1	0	1	1	1	1	0	6
Havens, Oser, & Leukefeld	2011	1	0	0	1	0	1	1	1	1	1	7

Authors	Publication Year	Clear Study Aims	Sample Size (Rationale Provided)	Representative Sample	Inclusion and Exclusion Criteria	Response Rate Documented	Validated/ Reliable Measure of Substance Use or Outcome	Measure of Substance Use/ Outcome by Individual Substance Type	Adequate Description of Data	Adequate Statistical Analysis	Conflict of Interest Statement	Total
Havens, Walker, & Leukefeld	2007	1	0	0	1	0	1	1	1	1	1	7
Havens, Walker, & Leukefeld	2008	1	0	0	1	0	1	1	1	1	1	7
Havens, Walker, & Leukefeld	2010	1	0	0	1	0	1	1	1	1	1	7
Jackson & Shannon	2012	1	0	0	1	0	1	1	1	1	0	6
Jonas et al.	2012	1	1	1	1	0	1	1	1	1	1	9
Karp et al.	2013	1	0	1	1	1	1	1	1	1	1	9
Lofwall & Havens	2012	1	1	1	1	0	1	1	1	1	1	9
MacMaster	2013	1	0	0	1	0	1	1	0	0	1	5
Modarai et al.	2013	1	0	1	1	0	1	1	1	1	1	8
Oser et al.	2009	1	1	1	1	0	1	1	1	1	1	9
Otis et al.	2016	1	0	1	1	1	0	1	1	1	1	8
Puskar et al.	2008	1	0	0	1	0	1	1	1	1	1	7
Rudolph, Young, & Havens	2017	1	1	1	1	0	1	1	1	1	1	9
Schoeneberger et al.	2006	1	0	0	1	0	1	1	1	1	1	7
Shannon et al.	2009	1	1	1	1	0	1	1	1	1	1	9
Shannon et al.	2011	1	0	0	1	0	1	1	1	1	1	7
Shannon et al.	2016	1	0	0	1	1	1	1	1	1	1	8
Shannon, Havens, & Hays	2010	1	0	0	1	1	1	1	1	1	1	8
Shannon, Perkins, & Neal	2014	1	0	1	0	1	1	1	1	1	1	8
Smith et al.	2016	1	1	1	1	0	1	1	1	1	1	9
Staton et al.	2017a	1	0	1	1	1	0	1	1	1	1	8

Authors	Publication Year	Clear Study Aims	Sample Size (Rationale Provided)	Representative Sample	Inclusion and Exclusion Criteria	Response Rate Documented	Validated/ Reliable Measure of Substance Use or Outcome	Measure of Substance Use/ Outcome by Individual Substance Type	Adequate Description of Data	Adequate Statistical Analysis	Conflict of Interest Statement	Total
Staton et al.	2017b	1	0	1	1	1	0	0	1	1	1	7
Stephens et al.	2016	1	1	1	1	0	1	1	1	1	1	9
Thomton & Deitz-Allyn	2010	1	1	0	1	0	0	0	1	1	0	5
Tillson, Strickland, & Staton	2017	1	0	1	1	1	0	0	1	1	1	7
Weimer et al.	2011	1	0	1	1	0	1	1	1	1	1	8
Wunsch et al.	2007	1	0	1	1	1	1	1	1	0	1	8
Wunsch et al.	2008	1	0	0	1	0	1	1	1	1	1	7
Wunsch et al.	2009a	1	0	1	1	0	1	1	1	1	1	8
Wunsch et al.	2009 b	1	0	1	1	0	1	1	1	1	1	8
Wunsch et al.	2013	1	0	1	1	0	1	1	1	1	1	8
Young & Havens	2012	1	1	1	1	1	1	1	1	1	1	10
Young et al.	2013	1	1	1	1	0	1	0	1	1	1	8
Young, Havens, & Leukefeld	2010	1	0	0	1	0	1	1	1	1	1	7
Young, Havens, & Leukefeld	2012	1	0	0	1	0	1	1	1	1	1	7
Young, Larian, & Havens	2014	1	0	1	1	0	1	0	1	1	1	7
Zibbell et al.	2014	1	0	0	1	0	0	1	1	1	1	6

Table 3.

Summary of key fatal and nonfatal overdose studies and findings.

Study	Location	Study Design	Sample Size	Key Findings
Bunn et al., 2010	Kentucky	Descriptive analysis	n = 2833	<ul style="list-style-type: none"> • Methadone-related poisoning/hospitalization rates increased significantly from 2001–2007 statewide, with rural Appalachian areas showing the highest hospitalization and mortality rates • Rural Appalachian counties reached methadone-related death rates of more than 10 per 100,000 population
Hall et al., 2008	West Virginia	Cross-sectional	n = 295	<ul style="list-style-type: none"> • 2006 unintentional pharmaceutical drug overdose rate was 16.2 per 100,000 population • 79.3% of decedents overdosed due to polysubstance use, and opioids were found in 93.2% of deaths • Overdose rate of men was twice that of women
Modarai et al., 2013	North Carolina	Ecological trend study	Not given	<ul style="list-style-type: none"> • Both prescription opioid sales and opioid-related ED overdoses significantly increased from 2008–2010 statewide, with rural Appalachian areas displaying some of the highest rates
Wunsch et al., 2009a	Virginia	Retrospective review of cases	n = 889	<ul style="list-style-type: none"> • From 1997–2003, the Western District of Virginia saw a 300% increase in drug-related deaths and a six-fold increase in number of drug-related deaths involving opioids • Close to 60% of deaths were due to polysubstance use, and three-quarters involved prescription opioids
Wunsch et al., 2009b	Virginia	Retrospective review of cases	n = 330	<ul style="list-style-type: none"> • Among women in Virginia's Western District who died of drug overdose between 1997–2003, 56% of cases involved polysubstance use • Opioids were found in 72% of cases, followed by antidepressants (61% of cases) and sedatives (49% of cases) • A significant increase in female opioid-related deaths over the study period was reported
Wunsch et al., 2013	Virginia	Retrospective review of cases	n = 246	<ul style="list-style-type: none"> • Between 1997–2003 in Virginia's Western District, methadone-related deaths significantly increased; annual % change was 59.6% • 55% of cases involved polysubstance use • Apart from methadone, the most commonly found co-occurring drugs were sedatives (57% of cases), antidepressants (48% of cases), and other opioids (30% of cases)

Table 4.

Summary of key disease trend findings.

Disease/ disorder	Key Studies	Study Location(s)	Key Findings
HCV	Christian et al., 2010 Havens et al., 2013 Zibbell et al., 2014	New York, Kentucky	<ul style="list-style-type: none"> • HCV prevalence among PWID ranged from 34.0% to 54.8% • Correlates of HCV among PWID included injection of prescription opioids, injection of cocaine, and sharing of injection equipment • Prescription opioid injection/preparation is associated with greater HCV risk, as compared to other drug types
HIV	Crosby et al., 2012 Young et al., 2013	Kentucky	<ul style="list-style-type: none"> • Lack of HIV in rural Kentucky is suggestive of a potential rural isolative protective effect • However, HIV risk behaviors were common (~20% in the past 6 months), suggesting rapid spread of HIV possible if introduced
HSV-2	Stephens et al., 2016	Kentucky	<ul style="list-style-type: none"> • HSV-2 seroprevalence among rural Appalachian KY PWID: 11.4% • Correlates of HSV-2 included female gender, older age, and greater frequency of unprotected sex
NAS	Brown, Goodin, & Talbert, 2017 Erwin et al., 2017	Tennessee, Kentucky	<ul style="list-style-type: none"> • Rates of NAS births 2–2.5 were times greater in rural Appalachian counties compared to urban/non-Appalachian areas; reported rates reached approximately 25 per 1,000 in Appalachian counties • NAS mothers more likely to be older, single, white, and have a history of STDs than mothers of non-NAS infants • NAS mothers more likely to use diverted prescription opioids than illicit opioids