

income), the *perfect storm* is created and serves as a catalyst for an opioid crisis [4]. While national data shows an overall increase in opioid use, rural areas are noted to have higher prevalence of opioid and naloxone use as well as opioid related deaths [5]. Until recently, existing bodies of literature have largely focused on opioid use in urban areas and have often used rural areas for comparative purposes. The aim of this review is to assess the current evidence concerning opioid use among rural dwellers.

METHODOLOGY

This systematic review is reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standards [6]. This method of reporting consists of an internationally recognized 27-item checklist developed to ensure quality in systematic reviewing. To identify literature for review, a detailed online search strategy was developed using the following databases: CINAHL Complete, Health Source, Nursing/Academic Edition, MEDLINE with Full Text, Psyc ARTICLES, Psychology and Behavioral Sciences Collection, Psych INFO and Social Sciences Full Text. These databases were searched with the intention of reviewing literature pertaining to opioid drugs and rural areas. Search terms “opioid AND rural” as well as “opioid addiction AND (rural or remote)” did not provide adequate search results. A different strategy including the terms: “rural n5 opioid” (rural within 5 words of opioid) was applied. This new strategy presented adequate results and was thus utilized in this review. The search was limited to English language and peer reviewed domestic or international articles published between the years of 2013-2018. This search produced 93 possible results. Four articles were duplicates and removed leaving 89 for further consideration.

A careful review of the abstract and methodology of each article resulted in deletion of 67 articles that were editorials, non-research, systematic reviews or did not pertain to rural populations. 22 articles were appropriate for final review (Figure 1).

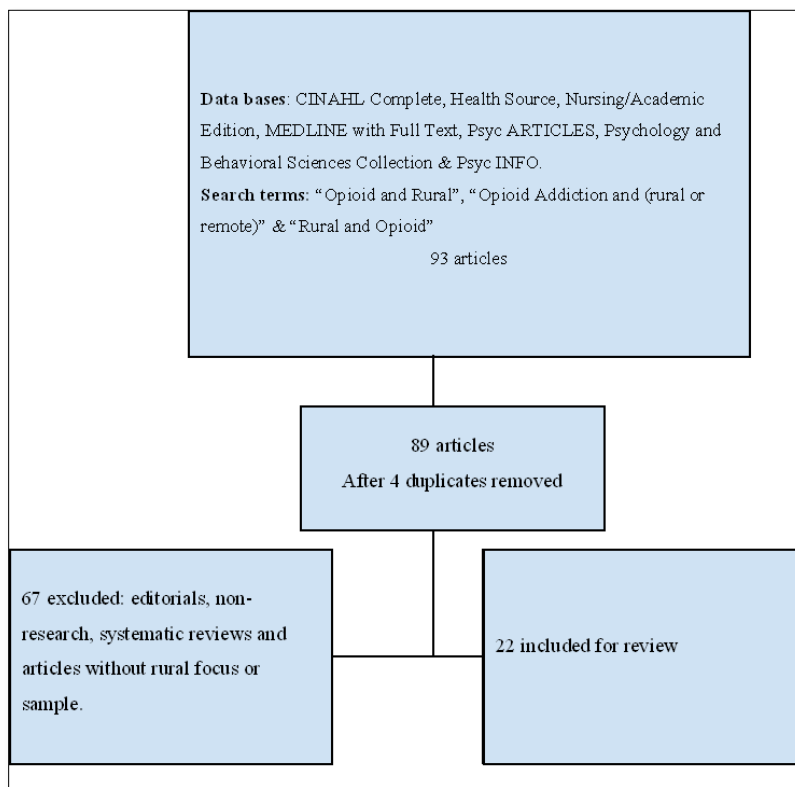


Figure 1. Search.

RESULTS

The literature in this systematic review was primarily descriptive or epidemiological in design (Table 1) [7-28] Table 2 provides information on sampling methodology and sample size on all of the studies. Sample sizes range from 28-75,964 with the studies with high sample sizes coming from secondary analysis of national data sets [9,28]. Slightly

less than half (10) used secondary data to conduct research [10,12-14,18-20,26-28]. Several articles used federal data to identify physician waivers for prescribing opioid treatments [13,14,20]. Three studies used the National Survey of Drug Use and Health (NSDUH) [19,27,28]. Finally, authors of two papers used the same data source (NSDUH) for the same time period (2011-2012) to release two different studies with different populations [19,27].

Table 1. Level of evidence with number of studies and citations.

Level of evidence	Number of Studies and Citations
I	Zero
II	One [7]
III	Zero
IV	Seventeen [8-23]
V	Zero
VI	Five [24-28]
VII	Zero

Table 2. Sample size and sampling methods.

Articles	Sample Size	Sampling
Andrilla et al. [8]	N=2,577	Purposive sampling/convenience sampling
Berends et al. [9]	N=28	Convenience sampling
Brown et al. [10]	N=3,892	Convenience sampling (NIS data with random sampling)
Cedra et al. [12]	Residents of 18517 zip codes 2001-2011	Convenience sampling
Cochran et al. [11]	N=33	Convenience sampling (regional sample)
Dick et al. [13]	N=unknown (second analysis from multiple data)	Convenience sampling
Hirschak and Murphy [14]	803 zip codes and subsequent populations	Convenience sampling
Hutchinson et al. [24]	N=78	Convenience sampling
Kapoor [25]	N=64 medical records	Convenience sampling
Karp et al. [15]	N=1,109	Convenience sampling
Monnat & Rigg [27]	N=32,036	Convenience sampling
Mosher et al. [26]	NIS/US Census America Community Survey data Secondary analysis	Convenience sampling
Netherland and Hansen [16]	N=100 press articles	Random Sampling
Pattison-Sharp et al. [17]	N=633 school nurses	Convenience sampling
Prunuske et al. [18]	N=2,745	A multistage sampling (the original survey used a systemic random sampling)
Rigg and Monnat [20]	N=47,440	Convenience sampling
Rosenblatt et al. [20]	N=18,225	Purposive sampling/convenience sampling
Smith et al. [21]	N=503	Respondent-driven sampling (a variant of snowball sampling)
Tran et al. [7]	N=308 (169+139)	Prospective, cluster-randomization sampling, based on power analysis
Wang et al. [28]	N=75,964	Complex sampling (weight)
Young et al. [22]	N=75,964	Probability cluster sampling
Zibbell et al. [23]	N=123	A modified snowball sampling

Rural

Although rural was used in the search terms, 64% of the articles sampled rural and urban populations. The remaining 36% of the articles discussed rural only (Table 3). Another factor that varied greatly between studies was the definition of the term rural (Table 4). Some articles defined rural based

on codes such as zip codes, Rural-Urban Continuum Codes (RUCC) or Urban Influence Codes (UIC). Other articles used abstract quantifiers such as perceived social and health status of underserved areas and simply the name of a region, such as Appalachia. Additionally, several articles identified rural areas as those considered underserved in access to health and social services or provided no definition of rural.

Table 3. Rural or urban subjects, location or study focus and citation.

Rural/Urban Classification	Number of Articles	Citations
Rural Only	8	[7-10,15,21-25]
Rural/Urban	14	[10-14,16-20,26-28]

Table 4. Defining rural in studies reviewed.

How Rural was Defined?	Number of Articles	Citations
Defined rural by zip codes or specific areas	6	[7,9,12,14,15,18]
Defined rural as social and health underserved areas	4	[10,11,24,25]
Defined rural as non-metropolitan areas	3	[19,21,26,27]
Defined rural using Rural-Urban Continuum Codes (RUCC)	4	[13,21,22,28]
Defined rural using Urban Influence Codes (UIC)	3	[2,17,20]
No specific definition of rural	2	[16,22]

Place

Two studies were conducted outside of the United States, in Australia; New South Wales and Vietnam [7,9]. All remaining articles were conducted in the United States. A few locations are mentioned more than others. For example, two groups conducted their studies in Cortland County, NY [20,23]. Three groups of authors conducted their studies in Kentucky [10,21,22]. Both upstate NY and the eastern region of KY are part of the Appalachia Mountain Range and presented as rural in the research.

Similarities and differences in findings

Findings indicate that there is little research regarding interventions for opioid drug abuse in either rural or non-rural locations. The intervention that received the most attention in the review of literature was the number and distribution of Medication Assisted Treatment (MAT) for opioid use and misuse. The major intervention reported in the literature was regarding efforts to increase the number of providers who can prescribe MAT for opioid use disorder in both rural and more metropolitan areas [8,13,14,20].

The Comprehensive Addiction and Recovery Act (CARA) originally authorized physicians to prescribe buprenorphine in the treatment of opioid use disorders and have been expended to include prescribers such as nurse practitioners, and physician assistants. This law was enacted in 2016 for the purpose of opioid abuse prevention and treatment. Following the enactment of CARA, there were moderate

increases in the number of providers with waivers. At the conclusion of 2017, 33,876 physicians, 3,534 Nurse practitioners and 912 Physician assistants had received waivers to prescribe Buprenorphine [29]. More research is warranted in this area so interventions can be developed and implemented to increase the knowledge of prescribers and to make the use of MAT readily available. There was a dearth of literature focused on prevention of opioid abuse.

Another area deserving further research is the use of Fentanyl on the streets. Fentanyl is an opioid used to treat pain and can be used as an anesthetic drug when combined with other substances. In the literature reviewed for this paper, there was no mention of Fentanyl. However, prior to completion of this manuscript, a National Public Radio story was released that focused on the use of Fentanyl on the streets and the high overdose rates associated with its use [30]. The media indicates that Fentanyl is being used illegally on the streets along with other opioids such as Heroin. Antidotal evidence indicates overdose deaths are higher with the use of Fentanyl, which is often combined with Heroin as an additive. This is referred to as the third wave in the opioid crisis stating that prescription drug misuse was the first wave, heroin the second and Fentanyl is the third. The story did not indicate if there is a rural/urban difference in Fentanyl misuse. The incidence of misuse of Fentanyl is occurring most frequently in the eastern part of the United States [30]. The above news release can be traced back to a National Vital Statistics report from the U. S.

Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics report in 2019 [31]. This warrants further study and research into the effects of this specific drug in relation to the opioid crisis.

Opioid use is increasing as supported by more than one article. For example researchers illustrated that opioid poisoning almost doubled between 2001-2011 in the state of California [12]. An international report examined four rural sites in an area of Australia and found an increase in individuals on opioid maintenance treatment over a period of four years [9]. The increase was more than 30% for three of the sites over the four years and this study referred to opioid misuse as a global crisis. No single study refuted the existence of an opioid crisis.

The questions of whether opioid use has increased more in rural than urban environments is still under debate. Research results indicated that Neonatal Abstinence Syndrome (NAS) increased 2-2.5 times per 10,000 births in rural and Appalachian counties compared to urban and non-Appalachian Kentucky counties between 2008-2014 [10]. In 2013, Kentucky NAS was more than double the national rate. Moreover, opioid facilities were further from rural and Appalachian areas compared to micropolitan/metropolitan and non-Appalachian areas ($p < 0.001$) [10]. Similarly, the conclusion of one national study was that rural adolescents had 35% greater odds than their urban counterparts in Prescription Opioid Misuse (POM) [27]. The opioid misuse was reported as 6.8% rural, 6% small urban and 5.3% for urban adolescents. Although there is a clear trend of less POM in areas of increasing population; reporting the level of residency in three levels may have slightly inflated the odds of rural misuse over the more traditional two level comparisons. A spread in prescription opioid poisoning hospital discharges, from rural and suburban/exurban to urban areas, was found in a California state wide study [12]. One study utilized primary care patient record forms to examine the difference between rural residency and non-rural residency in obtaining opioid prescription for Non-Malignant Chronic Pain (NMCP) and found that “rural residents had higher odds of having an opioid prescription than similar non-rural adults. Rural residency was the strongest predictor for having an opioid prescription and a diagnosis for NMCP” (p.5) [18].

Although there were some studies that reported an increase of opioid use in rural areas over urban, there were a few studies that did not support this hypothesis [11,19,28]. One national study reported that prescription opioid misuse was more common in urban than rural areas; while another found no difference between the two [19,28]. Rigg and Monnat [19] speculated that previous studies finding more opioid misuse in rural areas may have had too small or a specific geographical limit in sample.

In addition to demographics, several surveys used self-report, paper and pencil instruments to measure attributes for a wide array of variables, such as alcohol disorders, chronic diseases, depression, drug abuse status, health status, mental status, opioid misuse, pain, quality of life, psychological distress, post-traumatic stress disorder and sleep disorders.

Two articles used pain scales [7,25]. One study utilized a visual analogue scale for pain assessment, with respiratory rate and blood pressure to conclude that ketamine is equitable to morphine in its analgesic effect in emergency situations where evacuation is particularly difficult [7]. One study had three pain measures, appropriate to their population of rural patients with chronic pain [25]. The first measure was a structured pain interview. The Wisconsin Brief Pain Inventory, measure of pain intensity and interference and the pain catastrophizing scale both were reported as having good psychometrics [25]. Most authors used more than one instrument for data collection.

Social determinants of health

Increase in opioid use was sometimes associated with other health disorders and socio-economic factors. Patients receiving opioid medications in rural settings have poorer overall health, higher pain levels, lower levels of education and higher rates of unemployment than their urban counterparts [11,15]. Similarly, another study showed that rural individuals who reported good health were less likely to use opioid prescriptions for non-medical reasons than those who reported poor health [28]. Studies showed that lower income and manual labor were associated with an increase in prescription opioid poisoning or prescription opioid misuse [12,19].

In addition to the general health deteriorations that are associated with opioid use or misuse, one study found an association between the hospital discharge diagnostic code, prescription opioid misuse and major psychological distress [20]. Another showed an association between Anti-Social Personality Disorder (ASPD) and hydrocodone, crack or powder cocaine, marijuana, alcohol and heroin use [21]. One study reported significant association between HCV (Hepatitis C Virus) and a network of non-medical prescription opioid users [23]. Similarly, another found a strong association between prescription opioid analgesics and positive HCV [24]. In addition, arthritis was associated with opioid use in two different studies [12,15].

The issue of ethnicity/race and opioid use is conflicting and may be shaped by media that emphasis the *newness* of rural opioid reports [16,18,19,28]. In exploring opioid prescription risk factors in a sample with Non-Malignant Chronic Pain (NMCP), race was reported as a factor; “being non-Caucasian was a strong predictor of having an opioid prescription and a diagnosis for NMCP” (p 5) [18]. In a study that was not limited to chronic pain patients, black and non-Hispanic residents were less likely than white urban

residents to use prescription opioids for non-medical reasons [28]. Yet another concluded that white urban residents were significantly more likely to misuse prescription opioids [19]. A content analysis of a random selection of 100 popular media articles on the opioid crises reported "...a consistent contrast between criminalized urban black and Latino heroin injectors with sympathetic portrayals of suburban white prescription opioid users (p. 664) [16]. Media reporting of drug use in urbanized areas was found to be reported in stories that emphasized violence and arrests [16]. In contrast stories regarding rural drug use emphasized the unexpectedness of the problem and highlighted personal stories that humanized the individual [16].

In addition to race, social network was one of the considered variables in rural opioid use. One study reported that rural residents who have used drugs associated with network characteristics, such as having trust above the average in one's network, had lower odds of being diagnosed with ASPD [21]. Those non-medical prescription opioid users with HCV tended to cluster together, which suggests the need for the development of a network-based intervention to prevent the spread of HCV [23]. Still another suggested the utilization of school nurses, technology and social media in opioid management [17].

Opioid use was associated with individuals with low income and manual labor jobs in a at least two studies [12,20]. Results of one study showed that lower income and manual labor were associated with an increase in the hospital discharge diagnosis of prescription opioid poisoning [12]. Another, also found those working in manual labor had higher rates of prescription opioid misuse [20].

An intersection between other demographic variables and the opioid use or misuse emerged in this review of the literature. A study by Rigg and Monnat [19] found misuse of prescription opioids were associated with other factors such as age (young), marital status (unmarried), difficult financial status and less religiosity. Unsurprisingly, these findings were similar to the findings in another national analysis of the NSDUH data set [28]. These findings indicate opioid use and misuse are influenced by different demographic variables and no one set of variables can explain an opioid problem.

Physician waivers for buprenorphine prescriptions were discussed in several articles [8,13,14,20,24]. A possible rationale for the lack of research in the published literature on waiver practices beyond that of physicians is the newness of the extension of CARA [29]. Two studies that went beyond the numbers of physicians with prescription waivers, found that there were barriers for obtaining the waiver of buprenorphine maintenance treatment [8,24]. These barriers included time, finances, clients' needs and worries about violating patient confidentiality. After examining the Drug Enforcement Administration (DEA) list questionnaire, a different study found that family physicians were five times more likely to prescribe buprenorphine than other physicians, a statistically significant finding [24]. Only 28% of trained physicians reported prescribing buprenorphine. Abstaining from prescribing buprenorphine was associated with lack of institutional support [24].

A study in Washington state including American Indian and non-American Indian, rural and urban sites offering Opioid Assisted Treatment (OAT) found that "the number of clinics offering OAT in rural versus urban regions was significantly lower, indicating that difficulties may remain for rural residents in terms of accessing most OAT services offered in these facilities" (p. 105) [14]. One study found that the number of physicians with waivers increased in shortage counties between 2002-2011; however, opioid treatment program access remained the lowest in counties with populations less than 2,500 individuals [13].

Around 90% of physicians with waivers are located in urban areas and only about 1.3% practiced in the most rural areas [20]. These authors concluded rural residency was associated with lack of access to buprenorphine prescriptions [20].

Rural practitioners, researchers, and policy makers often consult rural specific journals. As part of the review, an analysis was conducted of which journals published research on opioid issues and rural populations. Only two journals emerged having published more than one study within this review (Table 5). Of the 22 articles reviewed, only four were in rural specific journals. One limitation to this finding is that not all rural specific journals were indexed in the search engines used for this systematic review.

Table 5. Publishing journals.

Journal Name	Number of Opioid Articles per Journal
Annals of Family Medicine	3
The Journal of Rural Health	4
Remaining 16 journals, none rural specific	1 each

LITERATURE LIMITATIONS

Authors routinely discussed possible limitations of their research. One limitation pertinent to research on sensitive topics included recognition that participants may be reluctant to disclose opioid use or misuse due to stigma and possible legal ramifications. Lack of anonymity is often considered inherent in rural research (particularly with small sample sizes) and clinical practice in rural areas. Although appropriate to the design, at least one article reported data collected from twenty years ago [15].

CONCLUSION

Although there is no doubt about the spread of negative effects and side-effects of opioid use and misuse, past perceptions of drug use as primarily an urban problem, were not supported in this review. The research was inconclusive on the question of where opioid abuse is worse, in rural or urban environments. How rural was operationalized differed from one study to another, adding to the lack of clarity regarding exactly how severe an opioid problem exists in rural areas. In addition to the geographical factors that may be associated with opioid use and misuse; physical, psychological, social, financial, occupational and religious factors were reported.

Although buprenorphine prescribing was studied in a sub-set of the articles, more interventional studies about opioid management are needed. More than half of the reviewed articles were descriptive and based on secondary data analysis. Interventional studies for opioid misuse prevention and management is suggested. These types of interventional studies are needed to provide evidence on how to best decrease the opioid crisis. The literature reviewed failed to produce data on implementation of solutions, beyond measuring the number of and location of physicians with MAT prescribing waivers. As interventions are developed and tested, healthcare providers, public health officials and policy makers need to expect that transcribing potential urban solutions into rural settings will be difficult given the many differences in lifestyle and circumstances among rural and urban residents. Further study is needed to develop rural-specific solutions.

The literature reviewed did not provide evidence of prescribing factors of Nurse Practitioners, Certified Nurse Midwives and Physician Assistants and how this may influence the accessibility to drug treatment in rural areas. As more data is collected on the prescribing practices of waived healthcare providers beyond physicians, it will be critical to conduct research to see if these types of prescribers will help meet the needs for MAT in rural areas. Policy makers should ensure that all qualified healthcare providers, not only physicians, are able to provide MAT in order to improve treatment access to people in rural areas. Reports continue to come forth regarding the work being

done to overcome barriers to providing MAT, particularly buprenorphine, in rural areas [29].

Strengths of this systematic review include the wide search for peer-reviewed literature on the chosen topic. This review establishes baseline data with which to compare future research. The review also establishes the current state of knowledge and identifies gaps in the literature to date. The topic of opioid use and misuse is crucially important and has been identified as a public health crisis. Exploring the trend of opioid addiction in rural areas along with approaches for prevention and treatment progress are needed to meet the goals of public health.

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