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The Case for Naloxone Co-Prescription

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Opioid prescribing rates have decreased due to tightened regulations and legislation at both the state and federal levels.[1,2,3] After reviewing over 15 years of data, the Centers for Disease Control (CDC) reported that the Nation's opioid dispensing rate dropped to its lowest point in 2019.[4] Nevertheless, fatal and non-fatal overdoses have not significantly declined. This is especially true in West Virginia, the state with the highest 2018 Drug Overdose Death Rate.[5] The CDC reported a significant increase in West Virginia's rate of all opioid overdoses per 10,000 emergency department visits from January 2019 to January 2020.[6]

Research indicates that co-prescribing naloxone (an opioid overdose reversal drug) with an opioid is effective in decreasing non-fatal and fatal overdoses.[7,8] This white paper will briefly describe naloxone and provide an in-depth analysis on the importance of normalizing and enforcing co-prescribing of the overdose reversal drug when prescribing an opioid. Lastly, this white paper will discuss the legislative trends on naloxone co-prescribing rules and regulations throughout the United States, and compare these legal efforts with the efforts currently underway in West Virginia.

Naloxone

Naloxone is a Food and Drug Administration ("FDA") approved opioid antagonist that rapidly reverses the effects of an opioid overdose.[9] Naloxone can be administered via intermuscular injection, intravenously, or intranasally.[10] The life-saving medication will only work if there are opioids in the recipient's system. There are no adverse reactions if naloxone is administered to a person not experiencing an opioid overdose.

It is perhaps equally important to highlight what naloxone is not. Naloxone is not a medication which can be abused. It is not a controlled substance.[11] It is not addictive. It does not require specialized training to administer. It must be communicated, however, that naloxone is also not a substitute for emergency medical care.[12]

At least one form of naloxone is covered by most insurance providers and available at all major pharmacy chains – most with no prescription required.[13] The CDC reports that the number of prescriptions for naloxone doubled from 2017 to 2018.[14] And, the U.S. Department of Health and Human Services reported a 773% increase in naloxone prescriptions from July 2016 to June 2020.[15]

The Importance of Co-prescribing Naloxone

National research indicates that providers are more comfortable prescribing naloxone when they have been educated about the medication. One study published in 2018 and funded by the National Institutes of Health (NIH) conducted a systematic review of 270 unique articles relating to the acceptability or feasibility of prescribing naloxone in primary care settings (the

"Acceptability and Feasibility Study").[16] Over 17 of those articles were ultimately included in the Acceptability and Feasibility Study.[17] The cited studies provided prescribers with in-person naloxone training and implemented universal prescribing of naloxone.[18] Results of the Acceptability and Feasibility Study indicated that prescribers were more comfortable having difficult conversations with patients regarding opioid prescriptions after receiving naloxone training.[19] At least one article cited in the same study found that when compared to providers who had not received education on naloxone, providers who did receive naloxone education were 11 times more likely to prescribe naloxone to their patients (in comparison to providers who had not received naloxone education).[20]

Additionally, the Acceptability and Feasibility Study reviewed six articles that assessed providers' willingness to prescribe naloxone.[21] The earliest articles (2003-2006) showed a high provider resistance to naloxone prescribing, with 37%-54% of providers reporting that they would not be willing to prescribe naloxone.[22] Later, articles published in 2016 and 2017 reported that 90% and 99% of providers were willing to prescribe naloxone, respectively.[23] One article reviewed in the Acceptability and Feasibility Study quoted a provider as saying:

> "I expected the decreases in death from overdose – but I hadn't thought about how this simple act of prescribing potentially lifesaving treatment has opened up other important conversations that have allowed me to provide better, safer and more compassionate care to my patients."[24]

Research supports the efficacy of training both pharmacists and physicians on co-prescribing and dispensing of naloxone. Additionally, there is a strong case for educating health providers about identifying patients with Opioid Use Disorder ("OUD") and recognizing MAT as a viable treatment pathway for patients seeking long-term recovery. Such training not only significantly impacts providers' attitudes and beliefs regarding naloxone and OUD, but also impacts patients by providing them access to care needed to combat possible overdose and addiction.

Enforcing and Normalizing Naloxone Co-Prescribing

Research shows that naloxone access laws have a beneficial effect on naloxone access. For example, one study published in 2018 reviewed naloxone legislation in all 50 states between 2007 and 2016, then used the Medicaid State Drug Utilization dataset to determine the effects of the naloxone laws on each state by comparing the number of outpatient naloxone prescriptions that were reimbursed by Medicaid during that year range (the "Medicaid Study").[25] Specifically, the Medicaid Study examined four categories of legal provisions found within the naloxone laws. These provisions were: (1) prescriber immunity, (2) third party prescription, (3) standing order, and (4) lay person dispensing.

The Medicaid Study found a dramatic increase in the number of states with naloxone laws after 2013, jumping from 16 total states in 2013 to 47 states total in 2016. [26] The number of outpatient naloxone prescriptions that were reimbursed by Medicaid rose by approximately 400 to 1,300 per year between 2007 and 2011, then began to rapidly increase in 2014, jumping from 7,788 prescriptions in 2014 to 47,264 prescriptions in 2016. [27] Evidence obtained in the Medicaid

Study supports the conclusion that the presence of any naloxone law is significantly associated with increases in naloxone reimbursed through Medicaid. [28] The Medicaid Study further found that no specific legal provision – other than standing orders – was consistently significantly associated with prescription reimbursements across model specifications. [29] Ultimately, the Medicaid Study concluded that the "[p]resence of a naloxone law is associated with increased Medicaid-reimbursed naloxone prescriptions." [30]

Naloxone access laws such as standing order and third-party provider provisions are not enough to substantially expand availability of naloxone and reduce opioid overdose deaths. Evidence of this is found in a study published in 2019 (the "Co-Prescription Study") that assessed the association between naloxone co-prescription legal mandates in Vermont and Virginia and naloxone dispensing in retail pharmacies in those states.[31] The Co-Prescription Study assessed IQVIA's national prescription audit, which represents 90% of all retail pharmacies in the nation, between January 1, 2011, to December 31, 2017. [32] The data also included information on payment type. The Co-Prescription Study took into consideration covariates such as: the passing of naloxone access laws which aimed to increase the availability of naloxone to laypersons, retail prescription opioid distribution variations, opioid-involved overdose deaths, and percentage of naloxone prescriptions that were paid for by third-party payers because even if the naloxone was co-prescribed, the patient retained the right to choose not to fill the naloxone prescription if it was not covered by a third-party payer. [33] Additionally, populations were adjusted to better compare the outcomes between Virginia and Vermont.

In an unadjusted analysis, the rate of naloxone dispensed per 100,000 people increased significantly after the implementation of legal requirements for naloxone co-prescription. [34] The

Co-Prescription Study found that during the first full month that the legal requirement was effective, 88 naloxone prescriptions per 100,000 were dispensed in Virginia and 111 naloxone prescriptions per 100,000 were dispensed in Vermont. [35] These numbers were compared to the number of naloxone prescriptions dispensed in the top 10 states with opioid related overdose deaths (WV, NH, OH, DC, MA, MD, RI, ME, CN, and KY) which averaged 16 naloxone prescriptions per 100,000 during July 2017. [36] It should be noted, however, that the naloxone prescription numbers decreased in December 2017 for both Vermont and Virginia, but the Co-Prescription Study anticipated this trend as legal mandates are "at the patient level and not the prescription level," thus "it would be expected that once an initial naloxone co-prescription was written and documented in the medical record, a prescriber would not issue a second naloxone prescription until such time the patient indicated that they no longer had a valid prescription or were no longer in possession of naloxone." [37] Ultimately, the Co-Prescription Study concluded that its findings "suggest that legally mandated naloxone prescription for persons at risk for [opioid overdose death] may increase naloxone dispensing and further reduce harm and save lives." [38]

Arguments Against Co-prescribing Naloxone

One argument against the co-prescribing of naloxone is the potential in increased liability risk, but this argument has been demonstrated to be unjustified. An editorial published by the Substance Abuse journal in 2016 considered the legal concerns that medical providers have regarding risks associated with naloxone prescribing to pain patients.[39] The authors found that "[t]he legal risk associated with prescribing or dispensing naloxone is no higher than that associated with any other medication and is lower than many." [40] An additional concern is that

co-prescribing naloxone may be seen by a court as an admission that the underlying opioid prescription was inappropriate. [41] Research finds that there is no credible legal basis for this conclusion. [42] Accordingly, co-prescribing naloxone is a reasonable and prudent clinic and legal decision. [43]

Concerns regarding the cost of naloxone have also been raised. Unfortunately, as the number of nationwide opioid overdoses soared, so did the price of naloxone. For example, the cost of a two-injector kit of Evzio rose 680% from 2014 to 2018.[44] Efforts made by the FDA in 2019 attempted to combat the higher prices by streamlining the labeling thus allowing drug makers to produce over-the-counter versions of the medication.[45] Both the American Medical Association and the American Bar Association advocate that "any settlement of judgment stemming from opioid-related litigation be used for treatment or other related activities to mitigate the harm resulting from the opioid epidemic."[46] Thus, such abatement plans could fund and expand naloxone distribution. [47]

Naloxone Co-prescribing Mandates

The CDC reports that if each person with a high-dose opioid prescription was offered naloxone, nearly 9 million naloxone prescriptions could have been dispensed in 2018 alone.[48] In its guideline for prescribing opioids for chronic pain, the CDC urges clinicians to offer naloxone if there are factors that increase the risk of opioid overdose such as a history of overdose or substance use disorder, a dosage exceeding 50 morphine milligram equivalents ("MME") per day, or a concurrent benzodiazepine use.[49] Similarly, the Substance Abuse and Mental Health Services Administration ("SAMHSA") recommends naloxone co-prescribing for individuals with a history

of overdose or substance use disorder, those who are taking benzodiazepines with opioids, those taking higher dosages of opioids (more than 50 MME/day), and those at risk for returning to a high dose to which they are no longer tolerant (for example, former inmates recently released from prison or patients leaving detoxification facilities).[50]

In a 2018 press release, the United States Department of Health & Human Services recommends prescribing or co-prescribing naloxone to patients at high risk for an opioid overdose.[51] In 2016, the United States House of Representatives passed the Co-Prescribing to Reduce Opioid Overdoses Act which was ultimately included in the Comprehensive Addiction and Recovery Act of 2016. The bill, however, was never funded and thus $5 million dollars in federal grant support was never provided for co-prescribing naloxone. Additionally, in 2018, an advisory panel to the FDA voted 12-11 in favor of labeling changes that recommended prescribing naloxone along with addictive painkillers.[52] In 2020, the FDA officially announced its requirement that opioid pain medicines and medicines to treat opioid use disorder must be updated to recommend that as a routine part of prescribing these medicines, health care professionals should discuss the availability of naloxone with patients and caregivers, both when beginning and renewing treatment.[53]

By fall of 2018, five states had implemented laws mandating co-prescription of naloxone for certain patients (the patient characteristics vary by state). A study published in June 2020 (the "Impact Study") examined the early impacts of the co-prescribing laws by using data from CVS Pharmacy between the years of 2014 and 2018.[54] The Impact Study looked at the naloxone prescriptions 90 days before and 90 days after the co-prescribing mandates took effect in the five states that had mandates: Arizona, Florida, Rhode Island, Vermont, and Virginia.[55] The Impact

Study looked at the number of naloxone doses initiated by prescribers and by pharmacy standing order, prescriber specialty, pharmacies dispensing, and payor type (both public and private).

The Impact Study yielded incredibly interesting yet unsurprising results. "Across the 5 states with mandated naloxone prescription laws, the total number of naloxone doses dispensed in the 90 days after implementation of the co-prescribing mandate grew 255%, from 6,208 to 22,067 compared with the 90 days before adoption of the mandate."[56] Before the mandates took effect, the medical specialties that prescribed naloxone most frequently were nurse practitioners, anesthesiology and pain medicine physicians, other providers, and family and general practice physicians.[57] After the mandates, a significant shift in medical specialty was observed. There was a decrease in the number of prescriptions issued by nurse practitioner, anesthesiology and pain medicine physicians, infectious disease physicians, emergency medicine physicians, pediatric adolescent specialists, and pharmacists.[58] There were significant increases, however, in the proportion of naloxone prescriptions issued by other providers, family and general practice physicians, physician assistants, internal medicine physicians, obstetrician/gynecologists, and surgeons.[59]

Ultimately, the Impact Study concluded that "[m]andating that naloxone be co-prescribed to individuals at increased risk of overdose quickly and effectively expands the reach of naloxone to those individuals and addresses some economic and geographic disparities in naloxone provision."[60]

States Currently Mandating Naloxone Co-prescriptions

There are nine states currently enforcing some kind of co-prescribing rule: Rhode Island, New Mexico, Florida, Vermont, Virginia, Washington, Ohio, California, and Arizona. Additionally, one state, New Jersey, has adopted an Administrative Order and Temporary Rule regarding naloxone co-prescribing, and Tennessee has incorporated co-prescribing recommendations into the appendix of the state's Chronic Pain Guidelines.

State	Age-Adjusted Rate of Drug Overdose Deaths in 2018[61]	Statute	Effective Date
Arizona	23.8	32-3248.01. Schedule II controlled substances; dosage limit; exceptions; morphine; opioid antagonist	April 25, 2018
California	12.8	2018 California Code Business and Professions Code - BPC DIVISION 2 - HEALING ARTS CHAPTER 1 - General Provisions ARTICLE 10.7 - Opioid Medication Section 741.	January 1, 2019
Florida	22.8	Chapter 456.44 Controlled substance prescribing.	July 1, 2018
New Jersey	33.1	Administrative Order from Division of Consumer Affairs Requires NJ Practitioners to Co-Prescribe Naloxone to Certain At-Risk Opioid	May 21, 2020

		Patients During COVID-19 Emergency	
New Mexico	26.7	SB 221 Require Certain Overdose Counselings	March 28, 2019
Ohio	35.9	Chapter 4731-11 of the Ohio Administrative Code	October 31, 2020
Rhode Island	30.1	216-RICR-20-20-4.4 Pain Management and Prescribing	July 2, 2018
Tennessee	27.5	Commissioner's Committee on Chronic Pain Guidelines Appendix	Last revised January 2020
Vermont	26.6	Chapter 2 – Alcohol and Drug Abuse Subchapter 3	July 1, 2017
Virginia	17.1	Treatment of acute pain with opioids. 18 Va. Admin. Code §85-21-40	March 15, 2017
Washington	35.4	WAC 246-919-980 Coprescribing of naloxone	January 1, 2019

Legislation in West Virginia

Of the 11 states that currently enforce a co-prescribing rule or recommendation, Ohio yields the highest Age-Adjusted Rate of Drug Overdose Deaths in 2018, reporting a rate of 35.9. West Virginia's Age-Adjusted Rate of Drug Overdose Deaths in 2018 was a staggering 51.5.[62] Although research suggests that co-prescribing laws are a significant and beneficial method of increasing naloxone availability, laws and policies regarding the oversight of opioid

prescribing and monitoring of opioid use in West Virginia do not currently include any provisions for such co-prescribing mandates.

West Virginia uses the Medicaid 115 Substance Use Disorder Waiver to expand Medicaid benefits while also providing a strategy to address drug misuse and substance use disorders. Phase 1 of the Medicaid 115 Substance Use Disorder Waiver began in January 2018 and included "implementing the Naloxone Distribution initiative to make the opioid antagonist naloxone widely available and increase awareness of its benefits in reversing the effects of an overdose."[63] The Naloxone Distribution Initiative in West Virginia states that it will reimburse providers for not only the cost of naloxone, but also the administrative costs associated with administering naloxone to Medicaid beneficiaries as well as the cost of providing Medicaid beneficiaries with information about and referrals to addiction treatment programs.[64]

Senate Bill 335, made effective in 2015, added code sections 16-46-1 through 16-46-6, which states that permitting licensed health care providers with the ability to prescribe opioid antagonists to first responders, individuals at risk of overdose, and relatives, friends, or caregivers of individuals at risk of overdose could prevent accidental opioid-related deaths.[65] One year later, Senate Bill 431 added code section 16-46-3a which authorized pharmacists to dispense an opioid antagonist without a prescription in accordance to an established protocol.[66]

Two years later, in 2018, Senate Bill 272 amended section 16-46-4 to require local and State government agencies to require first responders to carry opioid antagonists – subject to certain conditions and so long as sufficient supplies and funding were available.[67] Additionally, Senate Bill 272 added section 16-46-7, which provided the State health officer with the ability to

use standing orders to prescribe an opioid antagonist on a State-wide basis to certain recipients.[68] To date, West Virginia has no law requiring co-prescription of naloxone.

Conclusion

It is abundantly clear that naloxone saves lives. Equally as clear is the positive effect of educating health-care providers on the benefits of co-prescribing naloxone. It is regrettable that so many states still lack co-prescribing laws, regulations, and/or protocols.

The overdose epidemic shows no signs of ending. In fact, overdose rates are climbing nationwide as the country weathers the global pandemic. This is especially true in West Virginia, as the State continues to struggle with substance use disorders – a battle made harder to fight due to a rural landscape and the lack of many medical resources. The co-prescribing of naloxone is an effective tool in preventing fatal and non-fatal overdoses. Through advocation, normalization, and the enforcement of laws mandating the co-prescribing of naloxone, many more lives can be saved.

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