Substance Abuse & Naltrexone Hydrochloride

Executive Summary

Prolonged use of prescription opioids for pain can often cause enhanced pain sensitivity and dependence, potentially leading to a substance use disorder. Opioid-related overdoses and deaths have been on the rise in recent years in the U.S. and early medication-assisted treatment strategies for dependent users may help mitigate these fatal effects and reduce overall dependence. Two bills (HB 2603 and SB 1037) have been introduced to allow the distribution of the addiction-mitigation drug naltrexone hydrochloride (Revia) by physicians and pharmacists upon approval of the Department of Health and Senior Services, and to allow anyone to possess naltrexone.

Highlights

- In 2018, 1 in 56 deaths in Missouri were attributable to opioid overdoses; various drugs can help rescue an overdose victim or help mitigate addiction long term.
- Naltrexone hydrochloride is an approved drug for the mitigation of alcohol and opioid use disorder which can reduce drug cravings and prevent relapse. Naloxone hydrochloride is a drug meant to rescue a patient experiencing an opioid overdose, and can be as high as 75–100% effective at reversing mortality.
- All states have some form of coverage under the Medicaid program for naltrexone as an approved oral medication-assisted treatment strategy for opioid dependence.

Limitations

- Extensive data on the efficacy of naltrexone is limited given the low adoption of the drug in addiction mitigation programs.

Research Background

Substance Abuse and Overdosing

Roughly 1 in 5 adults worldwide suffer some sort of chronic pain, which individuals may often choose to treat with alcohol or prescription opioids for their pain-numbing effects. Extended use of these substances can lead to enhanced pain sensitivity and continued need for using these substances, potentially leading to dependence and a substance use disorder (SUD).[1]

The National Institutes for Drug Abuse report that depressants (such as sleep and anxiety medications), stimulants (such as Adderall), and opioids are some of the most commonly abused prescription drugs.[3] Roughly 9.7 million people in 2019 were estimated to have misused prescription pain relievers. Nationwide, roughly 1 in every 300 people had an opioid-related

hospitalization, and opioid emergency room visits increased by 30% between the years 2016-2017 alone.[2] As many as 1 in 8 patients on opioids eventually develop an opioid use disorder, and 1 in 20 eventually transition to abusing heroin as an alternative to legally prescribed opioids.[4]

Since 1999, nearly 800,000 people have died in the U.S. from a drug overdose, of which roughly two-thirds was caused by an opioid overdose.[2] As of 2018, 1 in every 56 Missouri deaths were attributed to opioid overdoses, with deaths reported in all age groups, races, and geographic areas, and with estimated emergency room charges totaling $116 million dollars.[5]

Opioid Mechanism of Action and Addiction Mitigation

Opioids function via a "lock-and-key" mechanism, with drugs like oxycodone or heroin (keys) binding to opioid receptors (locks) in the brain and throughout the body. Opioids in particular stay wedged in these receptors, consistently producing the effects from the drug (such as pain reduction and euphoria). Tolerance can build up over time, requiring additional amounts of drug to achieve the same effect, which can lead to life-threatening overdoses.[6]

To overcome this, different types of rescue and addiction mitigation drugs exist to counteract dependence and overdosing. *Agonists* (such as methadone) are slow-acting drugs that kick off toxic opioids from receptors and take their place, while generating the same euphoric effects and can be used for individuals who need that stimulation to function. *Partial agonists* (such as buprenorphine) activate the receptor like an agonist, but to a lesser effect, which allows patients to taper off opioid use by providing some stimulation while reducing the chances and severity of withdrawal symptoms. *Antagonists* (such as naloxone and naltrexone) are drugs that bind to receptors and produce no euphoric sensation, thus are useful in drug mitigation protocols where patients can be administered the drug to stay opioid-free and are no longer opioid-dependent, given the increased chances for withdrawal and drug relapse.[7]

Substance abuse, and particularly injection drug use, increased as a result of the COVID-19 pandemic. For more information, please see our Science Notes on COVID-19, Mental Health & Substance Abuse, and Syringe Access Programs.

Terminology and Pharmacology of Naltrexone Hydrochloride

Naltrexone Hydrochloride is a non-addictive, non-opioid based medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of both alcohol use (AUD) and opioid-use disorders (OUD).[8] While naltrexone itself as an antagonist has no potential for abuse, it helps to block the euphoric and sedative effect of opioids, while also reducing and suppressing opioid cravings.[8] Naltrexone differs from naloxone (Narcan) in that while naloxone is used as a rescue drug in emergency overdoses and can be as high as 75-100% effective at reversing mortality, naltrexone is meant for long-term addiction-mitigation.[9,10]

Efficacy of Naltrexone Hydrochloride

Naltrexone can be administered orally or through long-release muscular injectables, which may result in fewer missed doses than oral administration. Apart from notable withdrawal symptoms, naltrexone side effects can include diarrhea, abdominal cramps, and increased blood pressure. Naltrexone combined with behavioral therapy is consistently listed by researchers as a component of best clinical practice for reducing relapses.[9]

Because of the non-euphoric nature of naltrexone, patient interest to initiate treatment can also be low, and lead to lower levels of patient use without peer or behavioral health support. For example, a comparative study of methadone, buprenorphine, and naltrexone found that only methadone and buprenorphine were associated with reduced opioid-related medical care after 3-months.[11] However, a study on naltrexone alone found that injectable naltrexone showed a 37% efficacy for preventing relapse in chronic heroin users (as measured by negative heroin tests), compared to 23% for oral naltrexone.[12] Another study found that naltrexone was up to 61% effective at preventing relapse for opioids, with injectable naltrexone being the most effective at reducing self-reported heroin-cravings for patients.[13] Further, it has been shown that while an injectable naltrexone regimen is harder for patients to initiate than a buprenorphine regimen and can affect early chances of relapse, 6-month follow-up of patients in both groups showed similar efficacies longer term.[14]

Lack of familiarity among medical personnel, limited insurance coverage, and zoning restrictions for outpatient clinics have all been cited as barriers towards effective use of addiction mitigation medications.[15] As such, extensive data on the efficacy of naltrexone is limited given the low adoption of the drug in addiction mitigation programs.

State-Level Legislation

Missouri law (RSMo 195.206) exclusively permits the dispensation of the rescue drug naloxone by pharmacists during an emergency standing order. Introduced in the 2022 Missouri Legislative Session, two bills (HB 2603 and SB 1037) would allow the director of the Department of Health and Senior Services to issue a statewide standing order for licensed physicians and pharmacists to dispense an addiction mitigation medication or opioid-antagonist, such as naltrexone hydrochloride, if it has been approved by the FDA. The bills further allow anyone to possess naltrexone legally..

Several states (including KY, OK, and TN) have limited the amount of drug or length of time by which opioid medications can be prescribed at one time in an effort to reduce the chance of patients becoming chronically addicted, ranging from 3–14 days.[16] As of 2020, 47 states (including MO, AR, IL, KY, NE, OK, TN) and the District of Columbia have also passed "Good Samaritan" laws for individuals who have administered an approved *rescue drug*, meant to counteract the effects of a life-threatening overdose, if the individual acted in good faith and immediately contacts emergency authorities (Figure 1).[17] These laws can vary on the specific drug that retains these protections, and can also extend to the overdose victim. A study by the U.S. Government Accountability Office found that states with Good Samaritan laws were linked

to lower rates of overdose deaths by opioids. However public awareness of these laws varied by population.[18]

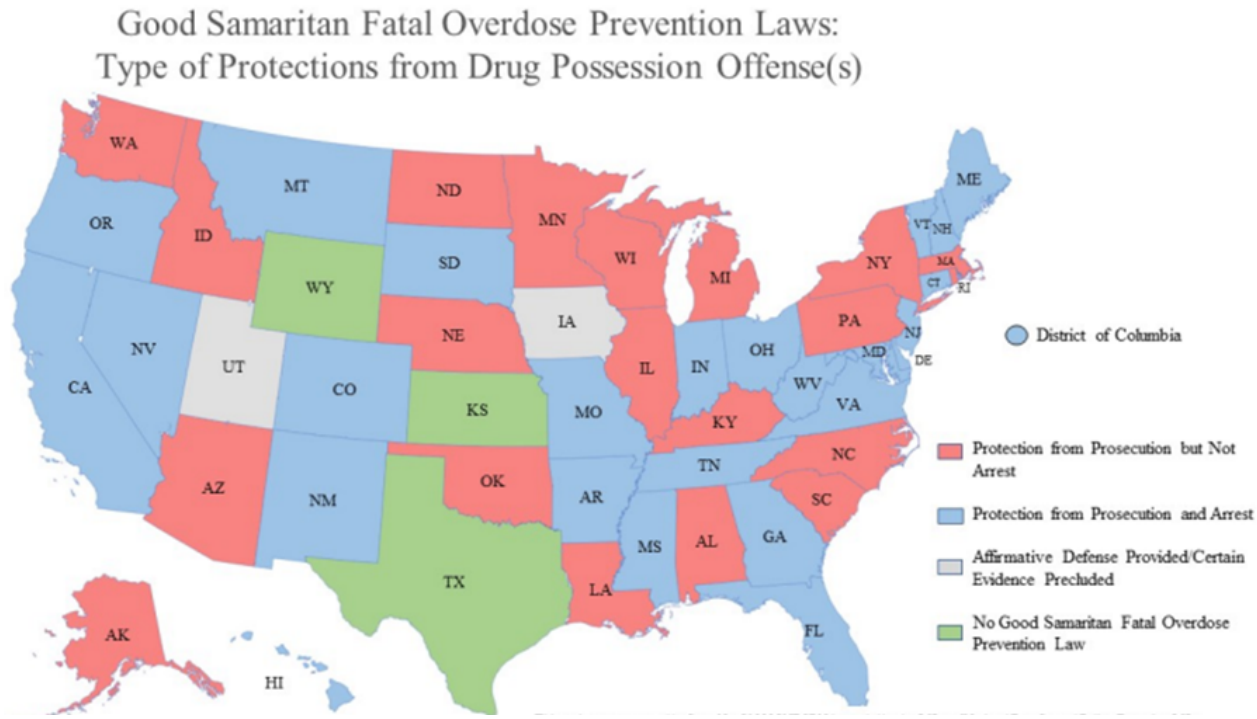

Figure 1: Map of states with laws protecting bystanders from civil liabilities for administering addiction-mitigation medications. Blue states have laws that protect "Good Samaritans" from prosecution and arrest, red states protect from prosecution, gray states prevent certain types of evidence from being used in a case, and green states have no laws that protect the bystander or the overdose victim. Map reproduced from the Legislative Analysis and Public Policy Association.[17]

Since 2018, all states have maintained Medicaid coverage for naltrexone as an approved oral medication-assisted treatment strategy for opioid dependence.[19] The American College of Emergency Physicians also reported in 2017 that 43 states maintained a standing order for distribution of the rescue drug naloxone by physicians and pharmacists for immediate overdoses.[20] States with opioid response programs that had the most success in reducing overdose deaths and addiction have focused on 1) authorizing first responders, pharmacists, and bystanders to administer rescue drugs, 2) reduce barriers to obtaining addiction mitigation drugs, 3) have robust telehealth infrastructure, 4) covered substance use disorder care, and 5) focused on enrolling rural populations in Medicaid.[21]

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