White Paper

P.O. Box 2102
Lenox, MA 01240
833-SAFERX0 (723-3790)
info@saferxpharmaceuticals.com
https://saferxpharmaceuticals.com

The U.S. Opioid Epidemic is Fueled by Alcohol

SafeRx Pharmaceuticals is pursuing FDA approval of our patented platform of products designed to solve a critical but previously unaddressed dimension of the U.S. opioid crisis- the combination of opioids with alcohol.

When taken together, opioids and alcohol interact in the body in a very dangerous way, increasing the risk of overdose. And according to the CDC, nearly one-in-four prescription opioid-related deaths is associated with concurrent alcohol consumption. But although patients are routinely warned about the danger of drinking with their medication, more than one-third of long-term opioid users admit to doing so. And yet, prescribers currently have no effective means of preventing their patients from making this all-too-often deadly mistake. SafeRx Pharmaceutical's new class of Alcohol-Resistant Opioids (AROs), therefore, address a major unmet medical need.

This paper is intended to provide scientific background on:

- *the role of opioid-alcohol interaction in the U.S. opioid crisis*, and
- *the rationale for and premise behind the SafeRx ARO platform*

Importance of the Problem

Opioids have killed more than half a million people in the United States over the last two decades, where the opioid epidemic has been recognized as a national public health emergency since 2017.[1-3] Although most of these fatalities have been caused by illicit substances such as heroin and illegally manufactured fentanyl, an alarming number have been associated with prescription medications, such as methadone and oxycodone.[4-7] And a significant but previously unaddressed dimension of the crisis involves the combination of prescription opioids with alcohol.[8-11]

Concurrent consumption of alcohol with opioids increases the risk of overdose and death primarily by causing synergistic inhibition of brainstem and peripheral GABA receptors, which are involved in the involuntary control of breathing. That is, while opioids are known to suppress the respiratory drive independently in the absence of alcohol (an effect known as opioid-induced respiratory depression, OIRD), significant worsening of OIRD occurs at even low blood alcohol concentrations (i.e., BAC of 0.05–0.10%).[12,13] Research also suggests that alcohol consumption may reverse the limited degree of tolerance that develops to the respiratory depressant effects of chronic opioid administration.[14] Finally, alcohol consumption can induce the pharmacokinetic effects of "dose dumping" in long-acting opioids, significantly increasing peak plasma concentrations of the drug and thereby elevating both their potential physiologic hazard and their abuse liability.[15]

In addition to conveying an increased risk of overdose, alcohol misuse among individuals receiving opioid agonist therapy for opioid use disorder (OUD) has been associated with a host of other adverse clinical outcomes. Negative clinical endpoints in such patients include poor compliance with pharmacotherapy, increased risk of relapse into illicit drug use, and increased likelihood of discharge from treatment.[16-18]

Despite these well-known risks and related warnings from prescribers to abstain from alcohol with their prescribed opioid, such co-consumption remains prevalent, especially in patients receiving opioid agonist maintenance therapy (e.g., methadone) to treat OUD. Clinical studies in such patients suggest that over three-quarters admit to at least occasional drinking with their medication, one-third exhibit problematic alcohol use, and approximately one-quarter meet diagnostic criteria for alcohol use disorder (AUD).[19-23]

Another dimension of particular timely importance relates to the exacerbating influence of the ongoing COVID-19 pandemic on both alcohol and opioid misuse and abuse. Specifically, since the onset of the COVID pandemic in the U.S., opioid overdose rates have increased sharply, reaching an all-time high of over 70,000 in 2020.[24-28] Similarly, during this period domestic alcohol sales and consumption have also increased significantly.[29]

The findings outlined above emphasize the need for novel abuse-deterrent formulations that mitigate the risk of alcohol-mediated prescription opioid overdose. And yet, prescribers currently have no effective means of preventing their patients from making the all-too-common mistake of consuming alcohol with their prescribed opioid. The CDC has therefore determined that novel interventions to reduce this dangerous form of polysubstance abuse are needed.[8]

Current and Previous Solutions

To combat the nation's opioid crisis, the FDA has encouraged the development of prescription opioids with abuse-deterrent properties that make it either more difficult or less rewarding to use the medication inappropriately. To date, 10 such abuse-deterrent formulation (ADF) products have been approved in the U.S., however, only three remain commercially available. Although these ADFs employ different individual technologies to convey their deterrent properties, they are all designed to achieve essentially the same goal- make it harder

and/or less rewarding to crush, chew, or grind and then snort, swallow, or inject the opioid.[30-33]

But whereas SafeRx's new class of alcohol-resistant products target misuse known to be involved with approximately 22% of fatal prescription opioid overdoses in North America[8,34], existing ADFs all target routes of misuse for which no sound epidemiologic data to support a disproportionate increase in overdose risk has ever existed. And although post-marketing studies designed to evaluate the impact of approved ADF medications on overdose risk are required by the FDA (not to mention the enormous market advantage to be gleaned from demonstrating an enhanced safety profile), no such findings have been published. Why? Because none of the approved abuse-deterrent opioid formulations significantly mitigate real world overdose risk.

Looking beyond the approved ADF options, there are currently no commercially available products capable of effectively preventing patients from consuming alcohol with their prescription opioid analgesic. Of course, disulfiram has been proven effective at deterring alcohol consumption when the medication is administered in a regular, monitored manner, such as in a clinical trial[35-40], and it has been similarly effective at reducing concurrent alcohol consumption in patients on chronic methadone therapy when administered under such conditions.[41] But in clinical practice, the efficacy of outpatient, unsupervised disulfiram therapy is only modestly effective at preventing alcohol consumption, because it depends on voluntary patient compliance.[42-44] And other measures, such as patient counseling and random blood/breath alcohol testing- as evidenced from the data reviewed above- have proven woefully ineffective. ***A novel method to deter or prevent concurrent alcohol consumption in patients taking prescription opioids is critically needed to reduce the death, morbidity, and other immense costs associated with this form of medication misuse.***

Our Solution

SafeRx is developing a proprietary platform of products[45-47] to reduce the risk of overdose, death, or other injury associated with the inappropriate consumption of alcohol with prescription opioid medications. This paradigm-shifting new class of products represent fixed-dose combination medications that include, along with an opioid analgesic of choice (e.g., methadone, buprenorphine, oxycodone, morphine, or hydrocodone), an aldehyde dehydrogenase inhibitor (ALDI; i.e., disulfiram), a pharmaceutical enzyme inhibitor of an intermediary step in alcohol metabolism[48] (Figure 1), which is already FDA-approved to treat AUD. By including both active moieties in a single, matrix-based tablet that prevents their separation, the combination products are expected to provide effective analgesia or opioid maintenance treatment while also effectively deterring concurrent alcohol consumption.

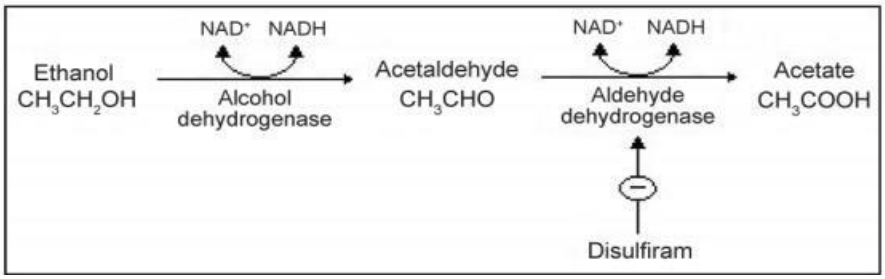

Figure 1: Disulfiram mechanism of alcohol metabolism inhibition.

Scientific Premise

The expected efficacy of SafeRx's new class of AROs derives from a straightforward premise. If the medication is taken as directed and the patient abstains from concurrent alcohol consumption, the opioid induces its typical effect profile and the ALDI (i.e., disulfiram) remains chemically inert and goes unnoticed by the patient. But if, against medical advice, the patient consumes alcohol with the ARO, the added disulfiram inhibits aldehyde dehydrogenase-mediated oxidation of acetaldehyde (see Figure 1), leading to a rapid accumulation of this toxic intermediate byproduct of alcohol metabolism. The

consequent elevation of serum acetaldehyde concentration then induces a noxious physiologic response, characterized by flushing, dizziness, headache, and nausea/vomiting[48,49], referred to as the disulfiram-alcohol reaction, which effectively prevents additional alcohol consumption in the acute context and deters future attempts of inappropriate alcohol-opioid co-consumption. This new class of AROs, therefore, compels patients to choose between taking their prescription opioid and consuming alcohol, for they cannot (agreeably) do both.

Improvements in Clinical Practice

Given the enhanced safety profile described above, AROs have the potential to positively influence clinical practice across multiple dimensions. Foremost, these products help prescribing physicians meet their most solemn fiduciary duty- to limit the risk of harm to their patients (i.e., "primum non nocere"). Because as outlined above, despite all warnings patients receive about the potential hazards of alcohol-opioid interaction, more than a third still drink with their medication, and roughly one-quarter engage in excessive/immoderate alcohol consumption (i.e., "binge drinking"), which has been shown to double the risk of opioid misuse.[11,50] Even more concerning are reports suggesting that patients with a prior history of alcohol abuse or dependence exhibit 5 times the rate of opioid overdose, 2.3 times the rate of accidents, and 1.2 times the rate of injury, as well as higher all-cause health care costs.[19] And although "high-risk" patients (including those with an established history of alcohol use disorder, opioid use disorder, substance abuse of any type, or overdose) can often be readily identified based on medical history, prescribing physicians still have no effective means of preventing them from engaging in this dangerous form of polysubstance abuse. These physicians therefore routinely encounter conundrum wherein they are forced to either prescribe medication known to convey a disproportionately high risk of harm to some of their patients, or to withhold it and allow those patients to suffer.

Decreased Diversion Risk

Another expected, albeit indirect, benefit of alcohol-resistant opioids relates to their reduced anticipated likelihood of drug diversion, which refers to the illicit transfer of a legally prescribed controlled substance from the individual for whom it was prescribed to another person, often for recreational use. Because recreational opioid abusers using diverted prescription opioid pain medication often prefer to take the opioid with alcohol, formulations that deter such co-consumption will presumably be much less attractive to such users. Thus, as has been previously reported with an abuse-deterrent formulation of oxycodone[51], the new ARO products are expected to show reduced rates of drug diversion as compared to other opioid formulations.

References

1. Holly Hedegaard, Arialdi M. Miniño, and Margaret Warner. *Drug Overdose Deaths in the United States, 1999–2018*. https://www.cdc.gov/nchs/data/databriefs/db356-h.pdf.
2. FACING ADDICTION IN AMERICA: The Surgeon General's Spotlight on Opioids; 2018. https://addiction.surgeongeneral.gov/sites/default/files/OC_SpotlightOnOpioids.pdf.
3. News Division. HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis. https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html. Accessed September 8, 2020.
4. Peppin JF, Coleman JJ. CDC's Efforts to Quantify Prescription Opioid Overdose Deaths Fall Short. Pain Ther. 2021 Jun;10(1):25-38.
5. Lovegrove MC, Dowell D, Geller AI, Goring SK, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Acute Harms From Prescription Opioid Use, 2016-2017. Am J Public Health. 2019 May;109(5):784-791.
6. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2020. Available at http://wonder.cdc.gov.
7. Jones CM, Baldwin GT, Manocchio T, White JO, Mack KA. Trends in Methadone Distribution for Pain Treatment, Methadone Diversion, and Overdose Deaths - United States, 2002-2014. MMWR Morb Mortal Wkly Rep. 2016 Jul 8;65(26):667-71.

8. Jones CM, Paulozzi LJ, Mack KA, Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug- related deaths - United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(40):881-885.
9. Witkiewitz K, Vowles KE. Alcohol and Opioid Use, Co-Use, and Chronic Pain in the Context of the Opioid Epidemic: A Critical Review. Alcohol Clin Exp Res. 2018;42(3):478-488.
10. Tori ME, Larochelle MR, Naimi TS. Alcohol or Benzodiazepine Co-involvement With Opioid Overdose Deaths in the United States, 1999-2017. JAMA Netw Open. 2020 Apr 1;3(4):e202361
11. Esser MB, Guy GP Jr, Zhang K, Brewer RD. Binge Drinking and Prescription Opioid Misuse in the U.S., 2012-2014. Am J Prev Med. 2019 Aug;57(2):197-208.
12. Koski A, Ojanperä I, Vuori E. Interaction of alcohol and drugs in fatal poisonings. Hum Exp Toxicol. 2003;22(5):281-287.
13. van der Schrier R, Roozekrans M, Olofsen E, Aarts L, van Velzen M, de Jong M, Dahan A, Niesters M. Influence of Ethanol on Oxycodone-induced Respiratory Depression: A Dose-escalating Study in Young and Elderly Individuals. Anesthesiology. 2017 Mar;126(3):534-542.
14. Hill, Rob; Lyndon, Abi; Withey, Sarah; Roberts, Joanne; Kershaw, Yvonne; MacLachlan, John et al. (2016): Ethanol Reversal of Tolerance to the Respiratory Depressant Effects of Morphine. In *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 41 (3), pp. 762–773.
15. Gudin, Jeffrey A.; Mogali, Shanthi; Jones, Jermaine D.; Comer, Sandra D. (2013): Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. In *Postgraduate medicine* 125 (4), pp. 115–130.
16. Hser YI, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. Chronic pain among patients with opioid use disorder: Results from electronic health records data. J Subst Abuse Treat. 2017;77:26-30.
17. Hartzler B, Donovan DM, Huang Z. Comparison of opiate-primary treatment seekers with and without alcohol use disorder. J Subst Abuse Treat. 2010 Sep;39(2):114-23.
18. Degenhardt L, Hall W. Patterns of co-morbidity between alcohol use and other substance use in the Australian population. Drug Alcohol Rev. 2003 Mar;22(1):7-13.
19. Landsman-Blumberg PB, Katz N, Gajria K, Coutinho AD, Yeung PP, White R. Burden of alcohol abuse or dependence among long-term opioid users with chronic noncancer pain. J Manag Care Spec Pharm. 2017;23(7):718-724.
20. Dobler-Mikola A, Hättenschwiler J, Meili D, Beck T, Böni E, Modestin J. Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment. J Subst Abuse Treat. 2005;29(4):259- 265.
21. Hillebrand J, Marsden J, Finch E, Strang J. Excessive alcohol consumption and drinking expectations among clients in methadone maintenance. J Subst Abuse Treat. 2001;21(3):155-160.

22. Soyka M. Alcohol use disorders in opioid maintenance therapy: prevalence, clinical correlates and treatment. Eur Addict Res. 2015;21(2):78-87.
23. Rowan-Szal GA, Chatham LR, Simpson DD. Importance of identifying cocaine and alcohol dependent methadone clients. Am J Addict. 2000 Winter;9(1):38-50.
24. Bacher R. Help Needed as Alcohol, Opioid Use Rise During Coronavirus. https://www.aarp.org/health/conditions-treatments/info-2020/alcohol-opioid-addiction-rise- coronavirus.html. Published August 24, 2020. Accessed September 3, 2020.
25. McGreal C. "Opioid overdoses are skyrocketing": as Covid-19 sweeps across US an old epidemic returns. *The Guardian*. http://www.theguardian.com/us-news/2020/jul/09/coronavirus-pandemic-us-opioids-crisis. Published July 9, 2020. Accessed August 31, 2020.
26. Mann B. U.S. Sees Deadly Drug Overdose Spike During Pandemic. *NPR*. https://www.npr.org/sections/coronavirus-live-updates/2020/08/13/901627189/u-s-sees-deadly-drug-overdose-spike-during-pandemic. Published August 13, 2020. Accessed August 31, 2020.
27. Kaur H. The opioid epidemic was already a national crisis. Covid-19 could be making things worse. *CNN*. May 2020. https://www.cnn.com/2020/05/07/health/opioid-epidemic-covid19-pandemic- trnd/index.html. Accessed August 31, 2020.
28. COVID-19 may be worsening opioid crisis, but states can take action. https://www.ama-assn.org/delivering-care/opioids/covid-19-may-be-worsening-opioid-crisis-states-can-take-action. Accessed August 31, 2020.
29. Pandemic drives alcohol sales — and raises concerns about substance abuse. https://news.usc.edu/168549/covid-19-alcohol-sales-abuse-stress-relapse-usc-experts/. Published April 14, 2020. Accessed September 3, 2020.
30. Center for Drug Evaluation Research. Abuse-Deterrent Opioid Analgesics. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics. Accessed September 8, 2020.
31. Becker WC, Fiellin DA. Abuse-Deterrent Opioid Formulations - Putting the Potential Benefits into Perspective. N Engl J Med. 2017;376(22):2103-2105.
32. Fleming AB, Carlson DR, Varanasi RK, et al. Evaluation of an Extended-Release, Abuse-Deterrent, Microsphere-in-Capsule Analgesic for the Management of Patients with Chronic Pain With Dysphagia (CPD). Pain Pract. 2016;16(3):334-344.
33. Litman RS, Pagán OH, Cicero TJ. Abuse-deterrent opioid formulations. Anesthesiology. 2018;128(5):1015- 1026.
34. Gomes T, Juurlink DN, Mamdani MM, Paterson JM, van den Brink W. Prevalence and characteristics of opioid-related deaths involving alcohol in Ontario, Canada. Drug Alcohol Depend. 2017;179:416-423.
35. Levy MS, Livingstone BL, Collins DM. A clinical comparison of disulfiram and calcium carbimide. *Am J Psychiatry*. 1967;123(8):1018-1022.
36. Peachey JE, Brien JF, Roach CA, Loomis CW. A comparative review of the pharmacological

and toxicological properties of disulfiram and calcium carbimide. *J Clin Psychopharmacol*. 1981;1(1):21-26.
37. Peachey JE, Zilm DH, Robinson GM, Jacob M, Cappell H. A placebo-controlled double-blind comparative clinical study of the disulfiram- and calcium carbimide-acetaldehyde mediated ethanol reactions in social drinkers. *Alcohol Clin Exp Res*. 1983;7(2):180-187.
38. Christensen JK, Møller IW, Rønsted P, Angelo HR, Johansson B. Dose-effect relationship of disulfiram in human volunteers. I: Clinical studies. *Pharmacol Toxicol*. 1991;68(3):163-165.
39. De Sousa AA, De Sousa J, Kapoor H. An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *J Subst Abuse Treat*. 2008;34(4):460-463.
40. Laaksonen E, Koski-Jännes A, Salaspuro M, Ahtinen H, Alho H. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol*. 2008;43(1):53-61.
41. Specka M, Heilmann M, Lieb B, Scherbaum N. Use of disulfiram for alcohol relapse prevention in patients in opioid maintenance treatment. *Clin Neuropharmacol*. 2014;37(6):161-165.
42. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. *J Clin Psychopharmacol*. 2006;26(3):290-302.
43. Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction*. 1997;92(4):381- 395.
44. Neto D, Lambaz R, Tavares JE. Compliance with aftercare treatment, including disulfiram, and effect on outcome in alcohol-dependent patients. *Alcohol Alcohol*. 2007;42(6):604-609.
45. Presti M. US 10478408 B2 - Combination Treatments For Opioid Crisis. *Patent*. November 2019.
46. Presti M. US 10881625 B2 - Combination Treatments For Opioid Crisis. *Patent*. January 2021.
47. Presti M. Combination treatments for opioid crisis, international (PCT: European Union, Canada, Mexico, and India) applications for process and product claims. *Patent application*.
48. Raby K. Relation of blood acetaldehyde level to clinical symptoms in the disulfiram-alcohol reaction. Q J Stud Alcohol. 1954;15(1):21-32.
49. Borja Oliveira CR. Alcohol-medication interactions: The acetaldehyde syndrome. *J Pharmacovigil*. 2014;02(05).
50. Nyamathi A, Cohen A, Marfisee M, et al. Correlates of alcohol use among methadone-maintained adults. *Drug Alcohol Depend*. 2009;101(1-2):124-127.
51. Severtson SG, Ellis MS, Kurtz SP, et al. Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone. Drug Alcohol Depend. 2016;168:219-229.