

# POLYSUBSTANCE USE AMONG PEOPLE WHO USE OPIOIDS OR OTHER DRUGS NONMEDICALLY

## A LITERATURE REVIEW

### INTRODUCTION

Drug policy and addiction medicine experts have, for years, warned that there is no such thing as a single-drug epidemic. The medical literature supports this reality; the “opioid crisis” was the beginning of a polysubstance crisis. Polysubstance use is the co-occurring nonmedical use of two or more substances within a certain time period, and is common among people with substance use disorders (SUDs).<sup>1</sup> Polysubstance use can be concurrent, sequential, or combination use.<sup>2</sup> As such, when developing strategies to prevent opioid or other substance misuse, stakeholders should bear in mind that individuals often do not use a singular substance.

Problematic use of any substance on its own can carry significant health risks, including overdose and death (see Table 1 for examples).

| Table 1: Health Risks of Substance Misuse* |   |
|--|---|
| Substance                                  | Health Risk   |
| Opioids                                    | Respiratory depression, physical dependence, gastrointestinal issues, hormonal effects, sedation, immunosuppression, and depression and anxiety <sup>3</sup>                          |
| Benzodiazepines                            | Memory problems and confusion, motor skill impairment, and over-sedation <sup>4</sup>   |
| Cocaine                                    | Elevated heart rate, heart attack, seizures, or stroke <sup>5</sup>   |
| Marijuana                                  | Increased heart rate and lung irritation; impairments of memory, attention, sensory perception, reaction time, and psychomotor control; <sup>6</sup> and declines in IQ. <sup>7</sup> |
| Alcohol                                    | Liver disease, heart disease, high blood pressure, digestive problems; certain cancers; depression and anxiety; learning and memory problems; and dependence <sup>8</sup>             |
| Nicotine                                   | Certain cancers, heart and lung diseases, gum and other mouth diseases, stroke, diabetes, and chronic obstructive pulmonary disease <sup>9</sup>                                      |
| *Not an exhaustive list                    |   |

At the same time, those who use substances for nonmedical reasons commonly use more than one substance.<sup>10</sup> As such, these individuals not only face the health risks posed by each substance used, but also face additional health risks posed by co-occurring use. Polysubstance use can result in harmful drug-drug interactions and may increase the risk of other adverse events, including overdose and death. For instance, combining an opioid with other central nervous system (CNS) depressants (e.g., benzodiazepines, other opioids, or alcohol) can increase the risk of fatal respiratory depression.<sup>11</sup> Therefore, if prevention, intervention, treatment, or harm reduction efforts are narrowly focused on one class of substances, such as opioids, opportunities may be missed to lower the risks of dangerous drug-drug interactions, overdose, and other adverse health events.

Additionally, a comprehensive strategy may also help prevent problematic substance use from progressing into an SUD. This is especially important when targeting adolescents and young adults. An important risk factor for SUDs is age at first use. The earlier in life individuals use a substance, the more likely they are to develop an SUD.<sup>12</sup> According to the U.S. Surgeon General's Report on Alcohol, Drugs, and Health, nearly 70 percent of adolescents who try an illicit drug before age 13 will develop an SUD within seven years, compared to 27 percent for those who first try an illicit drug after the age of 17.<sup>13</sup>

## MEDICAL LITERATURE ON POLYSUBSTANCE USE

The medical literature indicates that certain substances tend to be used concurrently, sequentially, or in combination.<sup>14</sup> This section contains several examples of polysubstance use that are discussed in medical journals and government-supported articles. The following information is not intended to be an exhaustive review, but rather a guide for stakeholders as they develop their prevention, intervention, treatment, and harm reduction strategies.

### A. Opioids and Polysubstance Use

A study published in January 2020 sought to understand trends in polysubstance use among individuals with opioid use disorder (OUD).<sup>15</sup> The study, which looked at survey data of past-one month use of nearly 16,000 individuals entering treatment for OUD, found that at least one nonopioid drug use was reported in nearly all participants (>90 percent).<sup>16</sup> The study concluded that “[v]iewing opioid trends in a “silo” ignores the fact not only that polysubstance use is ubiquitous among those with opioid use disorder but also that significant changes in polysubstance use should be monitored alongside opioid trends.”<sup>17</sup> The authors further stated that the “study also reinforces the conclusion that polysubstance use is common in those with an OUD; indeed, our results indicate that polysubstance abuse is the norm, not the exception . . .”<sup>18</sup> Specific examples of substances that are used in conjunction with opioids include benzodiazepines, stimulants, alcohol, marijuana, and nicotine.

#### 1. Benzodiazepines

Patients with OUD commonly misuse benzodiazepines.<sup>19</sup> A 2011 study found that nearly 40 percent of individuals receiving treatment with medications for OUD had a history of benzodiazepine misuse.<sup>20</sup> Similarly, a study of individuals prescribed buprenorphine for OUD found a lifetime prevalence of benzodiazepine use of 67 percent and a 30-day prevalence of 46 percent.<sup>21</sup>

Combining opioids and benzodiazepines is dangerous and can be fatal. The Substance Abuse and Mental Health Services Administration (SAMHSA) estimates that between 2005 and 2011, nearly 250,000 emergency department visits involved combinations of opioid analgesics and benzodiazepines.<sup>22</sup> Additionally, several studies have found that benzodiazepines may contribute to up to 80 percent of opioid-involved accidental drug-poisoning deaths.<sup>23</sup> According to other studies, benzodiazepines have been identified in 40 to 80 percent of methadone-related deaths and in 50 to 80 percent of heroin-related deaths.<sup>24</sup>

#### 2. Stimulants

Stimulants (e.g., cocaine and amphetamines) are frequently used with opioids. Treatment Improvement Protocol 43 (TIP 43), published by the Center for Substance Abuse Treatment (CSAT), explains that the following combinations are common among

individuals in treatment for OUD: heroin plus cocaine (i.e., “speedballs”); heroin followed by cocaine; cocaine followed by heroin; methadone plus cocaine; and any opioid plus amphetamines.<sup>25</sup>

A study of the urine drug test results of patients at 11 methadone maintenance treatment programs found that 15.7 percent of patients tested positive for cocaine during the month previous to the study, with rates ranging between 5.9 and 33 percent among each of the 11 programs.<sup>26</sup> Another study examining patterns of cocaine use among patients admitted for treatment with methadone for OUD found that 20 percent of patients ceased cocaine use at 18 – 24 months after starting treatment, while 20 percent started using cocaine at 18 – 24 months after intake.<sup>27</sup>

Opioids and stimulants may be combined for a variety of reasons, including to create greater euphoria than either the opioid or stimulant drug alone, to reduce side effects of the other drug, or to produce unique subjective effects desired by the user.<sup>28</sup> For example, some individuals have reported misusing methamphetamine to counteract the depressant effects of prescription opioids or, alternatively, misusing opioids to heighten the effects of methamphetamine.<sup>29</sup>

Co-occurring opioid and stimulant use is dangerous. A study examining opioid-involved accidental drug-poisoning deaths in San Francisco between 2010 and 2012 found that over one-third of all such deaths also involved cocaine.<sup>30</sup> When using speedballs, for instance, cocaine’s stimulant effects can offset heroin’s sedative effects. As a result, combination users may use higher doses of heroin, which can lead to drug poisoning.<sup>31</sup>

### **3. Alcohol**

A 2019 study by Centers for Disease Control and Prevention (CDC) examining individuals who misused prescription opioids found that more than half of those individuals also engaged in binge drinking alcohol.<sup>32</sup>

### **4. Marijuana**

A study of individuals with chronic pain who were prescribed opioid analgesics found prevalent marijuana use among the study population. The study also found that marijuana use was associated with prescription opioid misuse.<sup>33</sup>

### **5. Nicotine**

Finally, as discussed in section F below, nicotine use is also associated with nonmedical use of opioids.<sup>34</sup>

## **B. Benzodiazepines and Polysubstance Use**

Substances used concurrently with benzodiazepines may include opioids, alcohol, stimulants, and nicotine.

Benzodiazepine-related drug-poisoning mortality has risen dramatically over the last decade.<sup>35</sup> One study looking at benzodiazepine use and misuse among adults in the United States found that approximately 17 percent of benzodiazepine users misused their medications.<sup>36</sup> Benzodiazepines are also involved in many emergency department visits, as well as falls and fractures and motor vehicle crashes.<sup>37</sup>

A 2019 study of national trends in child and adolescent benzodiazepine exposure and poisoning found that poisonings caused by benzodiazepine drugs increased by 54 percent between 2000 and 2015.<sup>38</sup> The researchers attributed this in part to the fact that adolescents often take benzodiazepines with other substances, such as alcohol or opioids. The researchers found that of over 250 benzodiazepine-related overdose deaths, all but two involved both benzodiazepines and other substances.<sup>39</sup>

Alcohol and opioids are the two substances most commonly misused in combination with benzodiazepines.<sup>40</sup> As explained in section C below, benzodiazepines also are known to be misused by individuals who use cocaine or crack-cocaine,<sup>41</sup> and are known to be misused by those who use methamphetamine.<sup>42</sup> As explained in section F below, benzodiazepine misuse has been associated with nicotine use.

### C. Stimulants and Polysubstance Use

Stimulants include cocaine and amphetamines. Amphetamines consist of amphetamine, dextroamphetamine, and methamphetamine.<sup>43</sup> Substances known to be co-used with stimulants include alcohol, marijuana, opioids, benzodiazepines, and nicotine.

The rate of cocaine use has increased in recent years.<sup>44</sup> According to the CDC, cocaine-related overdoses increased by 34 percent from 2016 to 2017 and another five percent in 2018.<sup>45</sup> Cocaine was involved in nearly one in five overdose deaths in 2017.<sup>46</sup>

Cocaine and alcohol are frequently used together.<sup>47</sup> Both individuals with and without SUDs have reported the use of this combination.<sup>48</sup> Cocaine and marijuana also are frequently used concurrently.<sup>49</sup> Studies have shown that rates of marijuana use range from 59 to 89 percent of cocaine-dependent patients, with prevalence of marijuana dependence estimated between 18 and 53 percent.<sup>50</sup> Cocaine users also commonly misuse amphetamines.<sup>51</sup> Additionally, a study of over 100 users of either cocaine or crack-cocaine found that seven percent of cocaine users and 36 percent of crack-cocaine users engaged in nonmedical use of benzodiazepines.<sup>52</sup>

Like cocaine, nonmedical use of amphetamines is on the rise. Nonmedical use of amphetamines is especially prevalent among teenagers and young adults.<sup>53</sup> According to a 2016 survey funded by the National Institute on Drug Abuse, 6.7 percent of high school seniors reported improper past-year use of amphetamines.<sup>54</sup> Nonmedical use of amphetamines by students is associated with misuse of alcohol and substances in general.<sup>55</sup>

Additionally, a study published in January 2020 looked at over one million routine urine drug tests from 2013 to 2019. The study found that methamphetamine-positive urine samples increased six-fold in that time, with about 1.4 percent of samples testing positive in 2013 and about 8.4 percent in 2019.<sup>56</sup> Alcohol and marijuana use is also common among methamphetamine users.<sup>57</sup> Users of methamphetamine have reported misusing benzodiazepines or opioids to help relieve the uncomfortable come-down effects of falling methamphetamine levels in users' systems, while others reported misusing opioids to increase methamphetamine's effects.<sup>58</sup>

Finally, as described in section F below, stimulant use has been associated with nicotine use.

### D. Marijuana and Polysubstance Use

Marijuana is the most commonly used federally-illicit substance in the United States.<sup>59</sup> In 2018, 43.5 million individuals had used marijuana in the

past year.<sup>60</sup> Alcohol and stimulants are examples of substances commonly used by marijuana users. Opioids also may be used by some marijuana users.

Marijuana is most commonly used with alcohol.<sup>61</sup> While it is common to use marijuana and alcohol at different times, individuals tend to use both substances at the same time (i.e., simultaneously).<sup>62</sup> Simultaneous use has been associated with increased frequency and quantity of alcohol use.<sup>63</sup>

Additionally, a 2017 study of individuals with co-occurring serious mental illness and alcohol use disorders found that those who also used marijuana were 2.5 times more likely to have a positive urine drug test for cocaine versus non-marijuana users.<sup>64</sup> Similarly, a study of chronic pain patients who used marijuana found that such individuals were approximately 4 times as likely to use cocaine and methamphetamine compared to those who did not use marijuana.<sup>65</sup>

At least one study has shown that marijuana use is associated with a risk of return to nonmedical opioid use among patients receiving methadone treatment for OUD.<sup>66</sup> A similar study of individuals receiving medication treatment for OUD found that daily marijuana use was a predictor of nonmedical use of opioids.<sup>67</sup>

Moreover, as described in section II-F below, marijuana use has been associated with nicotine use.

## **E. Alcohol and Polysubstance Use**

Alcohol is the most commonly used drug in the United States. As highlighted throughout this document, several substances are associated with alcohol use, including marijuana, nicotine, opioids, benzodiazepines, and stimulants.

A 2017 study examining the prevalence of marijuana use among adults with serious mental illness who were in outpatient treatment for alcohol use disorder found that those who used marijuana were more than twice as likely to have a positive urine drug test for alcohol at the baseline interview compared to those who did not use marijuana.<sup>68</sup> Individuals who use both marijuana and alcohol may be inherently more susceptible to polysubstance use, in general.<sup>69</sup>

Individuals who drink alcohol are also likely to use nicotine and vice versa compared to nonusers.<sup>70</sup> As explained previously, alcohol use has also been associated with misuse of opioids, benzodiazepines, and stimulants.

## **F. Nicotine and Polysubstance Use**

Use of nicotine-containing products among U.S. youth is increasing.<sup>71</sup> More than 1 in 4 high school students and about 1 in 14 middle school students in 2018 had used a nicotine-containing product in the past 30 days.<sup>72</sup> This increase has been driven by the use of e-cigarettes.<sup>73</sup>

Nicotine is widely considered a catalyst to other substance use.<sup>74</sup> Nicotine users are nearly twice as likely as non-nicotine users to have a marijuana-use disorder.<sup>75</sup> Additionally, as mentioned above, nicotine use is often closely associated with alcohol use. Young adults who reported binge or heavy binge drinking had a nearly three-fold increase in the odds of nicotine dependence relative to non-risky drinkers.<sup>76</sup>

Moreover, early nicotine exposure has been shown to correlate with the development of stimulant use disorder.<sup>77</sup> Statistical analyses have linked

misuse of benzodiazepines to nicotine use,<sup>78</sup> and an animal study published in 2020 has suggested that nicotine use increases the cravings for benzodiazepines.<sup>79</sup> Finally, nicotine use is a strong predictor of nonmedical use of opioids.<sup>80</sup> There is an increased likelihood of developing an OUD in adolescents who use nicotine.<sup>81</sup>

## CONCLUSION

Polysubstance use is common among individuals engaged in substance use. Polysubstance use poses significant health risks, including drug poisoning and death. As such, a comprehensive strategy to address problematic substance use must take into account co-occurring substance use.

## ENDNOTES

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