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Co-use of alcohol and opioids

Edwards, K. A., Vowles, K. E., & Witkiewitz, K. (2017). Co-use of alcohol and opioids. *Current Addiction Reports*, 4(2), 194-199. <https://doi.org/10.1007/s40429-017-0147-x>

Published in:
Current Addiction Reports

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

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Co-Use of Alcohol and Opioids

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Abstract

Purpose of Review: This paper provides a narrative review of the co-use of alcohol and opioids, and its impact on biological, neurocognitive, and behavioral systems. In addition, data addressing co-use among patients receiving opioid-replacement therapy and those who have chronic pain are discussed. *Recent Findings:* Alcohol and opioids are among the most commonly used substances, and co-use has contributed to a growing number of accidental poisonings, emergency room visits, and overdose deaths. Prevalence of co-use is high among multiple populations, and severely impacts treatment outcomes. *Summary:* Substance abuse treatment for those that co-use alcohol and opioids is inadequate. Future research should further investigate salient influences on co-use and successful areas for intervention to address this treatment need.

Co-Use of Alcohol and Opioids

Alcohol and prescribed opioids represent two of the most commonly used substances in the United States. Among individuals aged 12 or older, more than 50% reported current alcohol use in 2015 (Substance Abuse and Mental Health Services Administration, 2016). ~~Opioids and re currently are the most frequently used prescription medication (Hughes et al., 2015) with~~ approximately 20% of individuals with pain-related diagnoses ~~were~~ prescribed opioids in 2010 (Daubresse et al., 2013). ~~At present, opioids are the most frequently used prescription medication (Hughes et al., 2015).~~ Given that both substances are commonly used, are both central nervous system depressants (Kreek, 1984), and have synergistic effects (White et al., 1999), their co-use presents a substantial risk factor for morbidity (i.e., overdose) and mortality. Unfortunately, co-use appears to be relatively common in some settings with recent data indicating that 19% of emergency department visits and 22% of overdose deaths involved both opioids and alcohol (Jones, Paulozzi, & Mack, 2014). Further, prescription opioids and alcohol are the most common substances found in accidental poisonings (Calcaterra, Glanz, & Binswanger, 2013).

The purpose of the present review is to synthesize the ~~current~~ literature ~~focused~~ ~~concerning on~~ the co-use of alcohol and opioids. ~~Following an overview of the , specifically including a summary of the key biological mechanisms that are shared by the two substances, findings regarding the prevalence, involved, nvolved, as well as prevalence rates, neurocognitive and behavioral impacts, behavioral impacts and effects, and importantsalient risk factors in relation to co-use will be discussed.~~ In addition, ~~the available data concerning~~ co-use of alcohol and opioids in two special clinical populations will be ~~reviewed~~ reviewed, ~~including , those receiving opioid-substitution therapy (e.g., methadone maintenance) and those with chronic pain who are prescribed opioids as part of their treatment regimen.~~

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Biological Mechanisms ~~of Co-Use~~ Shared by Alcohol and Opioids

When discussing the use of two or more substances, *simultaneous use* refers to the co-ingestion of substances at the same time (e.g. within two hours of one another), while *concurrent use* refers to co-use within a broader time period (e.g. 12 months; Earleywine & Newcomb, 1997; McCabe et al., 2006). ~~Most commonly, individuals use alcohol and opioids simultaneously in order to metabolize the substances faster and enhance their euphoric effects, a process known as ‘dose dumping’ (Cushman, 1987; Jobski et al., 2012; Kreek, 1984).~~ At a biological level, ~~when used together, alcohol and opioids interact in two ways the effects of alcohol and opioids can interact in two ways dose-dumping manifests through two interactions.~~ First, they can interact through pharmacokinetic interactions, in which alcohol and opioids interfere with the metabolization of one another. Second, alcohol and opioids can interact through pharmacodynamic interactions, in which they each enhance the effect of one another (see Kreek, 1984 and Weathermon & Crabb, 1999 for detailed reviews).

These interactions arise as both alcohol and opioids require, and therefore compete for, liver enzymes in order to be metabolized. The competition for enzymes result in the pharmacokinetic interactions (i.e. an increase in metabolism speed) to account for the amplified load on the body and the increase in metabolism speed then produces many of the additive effects through the pharmacodynamic interactions (Weathermon & Crabb, 1999). The primary concern with co-use is that both opioids and alcohol act as central nervous system (CNS) depressants and use of both substances at the same time can produce significant respiratory depression and sedation, common contributors to fatal overdoses (White et al., 1999). ~~Research also suggests that alcohol can affect the binding properties of opioid receptors, leading to a decreased effect of exogenous opioids (Herz, 1997). This not only puts the co-user at risk for experiencing increased pain, but~~

could contribute to additional use of opioids to achieve adequate pain reduction and thereby increase risk of overdose. Some Risk for overdose is also increased with certain prescription opioid formulations, specifically high dose, prolonged release, and once daily formulations, significantly increase risk of overdose when combined with alcohol (Jobski et al., 2012).

~~In in regards to concurrent use, consumption of opioids and alcohol within a broader time frame can also be associated with adverse effects. Zaeny and Drum (2010) examined the effect of a single opioid dose among individuals who identified as light or moderate drinkers. Specifically, the pharmacological effects of taking Oxycodone among light drinkers (< 4 drinks/month) and moderate drinkers (> 7 drinks/week). Results indicated that both groups experienced adverse effects, such as vomiting, lightheadedness, dizziness, drowsiness, dry mouth, headaches, and nausea, with no difference in severity based on drinking status. Further, women were found to report significantly more dysphoric effects as compared to men, indicating that women may be prone to experiencing more harmful effects. Research also suggests that alcohol can affect the binding properties of opioid receptors, leading to a decreased effect of exogenous opioids (Herz, 1997). This not only puts the co-user at risk for experiencing increased pain, but could contribute to additional use of opioids to achieve adequate pain reduction and thereby increase risk of overdose. In addition, consistent with respiratory depression findings, short term decreases in oxygen saturation are often present, which can heighten risk long term effects of co-use also include an increased risk for liver disease and degradation of brain tissue over the longer term (Cushman, 1987; Zaeny & Drum, 2010).~~

Prevalence **Rates of Co-Use**

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When discussing use of two or more substances, *simultaneous use* refers to the co-ingestion of substances at the same time (e.g. within two hours of one another), while *concurrent use* refers to use within a broader time period (e.g. 12 months; Earleywine & Newcomb, 1997; McCabe et al., 2006). Overall, the extant literature does not always specify the exact type of use being measured, but it does appear that co-use of opioids and alcohol appears to be ~~is~~ relatively common. For example, Peacock and colleagues (2016) found that upwards of 20% of individuals prescribed opioids consume alcohol and opioids in the same day, with a median of 4.6 drinks. A similar proportion of co-use was reported in a sample of just over 1500 individuals in Australia who were daily users of prescribed opioids with 16% classified as “occasional” and 8% as “regular” risky drinkers, defined as the consumption of more than four standard drinks, on an at least yearly or weekly basis, respectively (Larance et al., 2016). In a prevalence study of simultaneous use specifically, 1 in 8 patients receiving chronic opioid therapy reported the ingestion of two or more drinks within two hours of taking an opioid dose (Saunders et al., 2012).

In those who use opioids non-medically, prevalence rates of co-use appear even higher, with 50% - 70% reporting simultaneous ingestion in the past year (McCabe et al., 2006; McCabe et al., 2012). Data also suggested that individuals who meet criteria for Alcohol Use Disorder (AUD) are 18 times more likely to report a prescription drug use disorder and non-medical use of prescription medications than those who did not meet criteria for AUD (McCabe, Cranford, & West, 2008). Conversely, prevalence of AUD was found to be significantly higher among individuals on a high potency opioid regimen than the general population (Jobski et al., 2012).

Consumption of opioids with even small amounts of alcohol can be associated with adverse effects. Zaeny and Drum (2010) studied pharmacological effects among light drinkers (<

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4 drinks/month) and moderate drinkers (> 7 drinks/week) taking Oxycodone. Results indicated that both groups experienced adverse effects, such as vomiting, lightheadedness, dizziness, drowsiness, dry mouth, headaches, and nausea, with no difference in severity based on drinking status. Further, women were found to report significantly more dysphoric effects as compared to men, indicating that women may be prone to experiencing more harmful effects.

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Neurocognitive and Behavioral Impacts of Co- Use

Substantive neurocognitive effects have been found both when using these substances simultaneously and concurrently. Consistent with respiratory depression findings, simultaneous use is associated with short-term decreases in oxygen saturation, which individuals can use alcohol and opioids simultaneously in order to metabolize the substances faster and enhance their euphoric effects, a process known as 'dose-dumping' (Cushman, 1987; Jobski et al., 2012; Kreek, 1984). In addition to heightened risk of overdose, co-use has been linked with often precedes impairments in hand-eye coordination as well as short- and long-term memory recall (Cushman, 1987). In addition, consistent with respiratory depression findings, short-term decreases in oxygen saturation are often present, which can heighten risk for liver disease and degradation of brain tissue over the longer term (Cushman, 1987; Zaeny & Drum, 2010). Research examining chronic long-term co-use of alcohol and opioid use has identified multiple neurocognitive deficits, however these findings should be interpreted with caution, as temporal precedent has not yet been fully addressed in the current neurocognitive literature. Generally, concurrent use has been associated with impairment in executive functioning, attentional focus, working memory tasks, and motor functioning (Arias et al., 2016). A meta-analysis by Baldacchino et al. (2012) compared neurocognitive functioning among individuals with chronic opioid use (excluding those with alcohol dependence) to healthy controls and found

that individuals exhibited deficiencies in verbal working memory, cognitive impulsivity, and cognitive flexibility. Although individuals with alcohol dependence were excluded from the Baldacchino et al (2012) study, previous research shows that with the addition of alcohol, these impairments become worse (Gudin et al., 2013; Khalili-mahani et al., 2012). ~~While temporal precedent is often unclear with these studies,~~In addition, to help address issues of temporal precedence, Baldacchino et al. (2012) compared these deficits to long term heroin users (> 6 months) and ~~concluded~~determined that core deficits were found in verbal fluency and working memory, and opiate specific effects in divided attention, reasoning, and decision making. ~~Although not conclusive,~~These findings have broad implications suggest that when discussing medical and psychological treatments aimed at reducing substance use, as individuals may have fewer cognitive resources that could impede adherence and engagement with medical and psychological treatments as a result of co-use.

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Behavioral Impacts of Co-Use

In addition to the harmful ~~neurophysical~~neurophysiological and cognitive effects, simultaneous co-use is also associated with increased substance use and a number of other poor health outcomes. For example, among college students, it was found that simultaneous users consumed alcohol more frequently and in higher amounts than those who used only alcohol (Garnier et al., 2009). It has also been found that those who had co-ingested in the past had significantly more substance use related problems than those who did not co-ingest, even after controlling for frequency of alcohol and drug use (McCabe et al., 2012). Simultaneous users exhibited much more aberrant drug behaviors, such as requesting early refills, motor vehicle accidents, and hoarding medication, as well as lower treatment completion rates than single substance users (Fleming et

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al., 2007; Gossop et al., 2002). Data suggests that any use of alcohol and opioids can increase risk for substance use disorders and recurrence of depressive, anxiety, and bipolar episodes (Earleywine & Newcomb, 1997; McCabe et al., 2006; Schepis & Hakes, 2013).

—A study done by Hedden et al. (2010) found that among the general population, past year concurrent alcohol and opioid use was associated with poorer mental health outcomes, unemployment, and incarceration. Findings also indicated that alcohol dependence was associated with other comorbid substance dependence 64% of the time, with prescription opioids being the second most common substance behind marijuana (Hedden et al., 2010). Another national survey found that 60% of individuals with a past year prescription opioid use disorder met criteria for another past year substance use disorder, with alcohol being the most common substance (McCabe et al., 2008).

In experimental settings, concurrent use of alcohol and opioids has been associated with a diversity of adverse effects, including vomiting, lightheadedness, dizziness, drowsiness, dry mouth, headaches, and nausea (Zacny and Drum, 2010), with significantly more pronounced dysphoric effects in women. Repeated or prolonged co-use has also been examined as a risk factor for long-term complications. In addition to increased risk for liver disease and degradation of brain tissue (Cushman, 1987; Zacny & Drum, 2010), alcohol can negatively affect the binding properties of opioid receptors, leading to a decreased effect of exogenous opioids (Herz, 1997). This effect not only puts the co-user at risk for experiencing increased pain, but could contribute to additional use of opioids to achieve adequate pain reduction and thereby increase risk of overdose.

~~Those same data also suggested that individuals who met criteria for Alcohol Use Disorder (AUD) were 18 times more likely to report a prescription drug use disorder and non-~~

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medical use of prescription medications than those who did not meet criteria for AUD (McCabe et al., 2008). Conversely, prevalence of AUD was found to be significantly higher among individuals on a high-potency opioid regimen than the general population (Jobski et al., 2012). These trends have also been replicated among college students, with data showing that young adults were at a much higher risk for reporting binge drinking, AUD's, and non-medical use of prescription opioids than older adults. Of those young adults who met criteria for AUD, 3 in 10 reported significant non-medical use of opioids (McCabe, Cranford, & Boyd, 2006).

Risk Factors and Patterns of Co-Use

Given the sparse literature on co-use, there is currently only limited information with regard to risk factors for co-use.~~there have been limited risk factors identified.~~ The data does indicate that those meeting criteria for Major Depression Disorder, Generalized Anxiety Disorder, and chronic pain report higher rates of concurrent use in the past year (Fleming et al., 2007; Hedden et al., 2010; Schepis & Hakes, 2013; Witkiewitz et al., 2016). Engaging in deviant behaviors (e.g., ???), initiating alcohol use at an earlier age, and reporting a sexually transmitted infection were also associated with concurrent use (Hedden et al., 2010; McCabe et al., 2006). In addition, individuals identifying as White, male, and younger age are 2-5 times more likely to report non-medical prescription drug use in the past year (McCabe, Cranford, & Boyd, 2006). Particularly, Individuals identifying as White, male, and younger age are 2-5 times more likely to report non-medical prescription drug use in the past year (McCabe, Cranford, & Boyd, 2006). research examining substance use in young adults have found they are at a much higher risk for reporting binge drinking, AUD's, and non-medical use of prescription opioids than older adults. Moreover, of those young adults who met criteria for AUD, 3 in 10 reported significant non-medical use of opioids (McCabe, Cranford, & Boyd, 2006). ~~These findings further highlight the~~

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~~strong cyclical and extremely risky relationship between alcohol and opioid use. Those meeting criteria for Major Depression Disorder and Generalized Anxiety Disorder also report higher rates of concurrent use in the past year (Fleming et al., 2007; Hedden et al., 2010; Sehep & Hakes, 2013). In addition, engaging in deviant behaviors, initiating alcohol at an earlier age, and reporting a sexually transmitted infection were also associated with concurrent use (Hedden et al., 2010; McCabe et al., 2006).~~

Although a clear link between alcohol and opioid use has been established, the literature has found mixed findings in regards to the relationship between patterns of use with opioids and alcohol. Specifically regarding the validity of the “substitution hypothesis,” which states that opioids and alcohol patterns of use have an inverse relationship (Kreek, 1984; White et al., 1999), ~~m-~~ ~~M-~~ Mixed findings have emerged with some studies supporting this hypothesis (Almog, Anglin, & Fisher, 1993; Gossop et al., 2002) and others finding that opioid use increased with alcohol consumption (Gossop et al., 2000; Gossop, Browne, Stewart, & Marsden, 2003). A recent meta-analysis indicated inconclusive support for the substitution hypothesis, but did find conclusive support that alcohol significantly increased relapse to drug use (Staiger et al., 2012). When taken together, these findings may reflect the poor efficacy of addiction treatments when dealing with dual substance users.

Co-Use Among Special Populations

Patients Receiving Opioid-Substitution Therapy

Due to the rising number of individuals struggling with opioid addiction, there has also been a rise in number of patients seeking opioid-substitution treatment, including methadone and buprenorphine. For a review of efficacy of these opioid-substitution therapies, please see Whelan & Remski (2012). Generally, methadone is a full-agonist treatment, meaning that it most closely

mimics heroin by producing high intrinsic activity among μ opioid receptors, causing similar euphoric effects, but also decreasing withdrawal and craving symptoms. Buprenorphine is a partial-agonist treatment, meaning that it has low intrinsic activity among μ opioid receptors, causing less analgesic and euphoric effect, but still decreasing withdrawal and craving symptoms (Whelan & Remski, 2012). Both treatments also limit the effect of other exogenous opioids (Clark et al., 2006). Due to the strong relationship exhibited between alcohol and opioid use, alcohol is often used among individuals receiving opioid-substitution therapies, with prevalence rates indicating that one-third of patients receiving opioid-substitution treatment also qualify for concurrent alcohol misuse (Nolan, Klimas, & Wood, 2016).

Few studies, however, have examined the effect of alcohol when used concurrently with opioid-agonists among humans. Previous studies done in rat models have provided evidence that acute alcohol consumption increases peak methadone plasma concentration, while chronic alcohol consumption reduces peak methadone plasma levels (Nolan et al., 2016). A study done with humans by Clark, Dietze, Lenné, & Redman (2006) examined the effect of alcohol among 40 patients receiving either methadone or buprenorphine, and assessed the administration of one alcohol dose in two separate sessions (2-3 hours before opioid dose vs 1-2 hours after opioid dose). The interaction between alcohol and opioids was strongest during peak opioid plasma levels, 2-3 hours after receiving their opioid-substitution treatment. Patients reported greater sedation and feelings of euphoria, and those who received methadone reported these symptoms at a greater intensity than those receiving buprenorphine (Clark et al., 2006). The substitution hypothesis among this population has also had mixed findings with most studies finding no change in alcohol consumption once opioid-substitution treatment is started (Srivastava, Kahan, & Ross, 2008).

It is well known that alcohol use is a risk factor for poorer treatment outcomes and compliance with pharmacological treatments, and this still holds true for patients on opioid substitution therapies (Degenhardt & Hall, 2003). In addition, drug-related deaths are also high among this population with one study indicating that 44% of deaths were related to drug and alcohol overdoses, and another study finding that excessive alcohol use was the leading contributor to death among active methadone maintenance patients (Joseph, 1985; Zador & Sunjic, 2000). Previous research also shows that methadone maintenance patients that meet criteria for an AUD were less satisfied on their dose of methadone, even though they had significantly higher doses, than those who did not meet criteria for AUD (Senbanjo, Wolff, & Marshall, 2006). This same study also found that those who met criteria for AUD reported significantly more physical and psychological health problems along with poorer quality of life and social functioning (Senbanjo et al., 2006). Again, these findings highlight the need for more robust and efficacious addiction treatment programs that can better address dual substance users, even among patients receiving opioid-substitution therapies.

Chronic Pain Patients

Individuals engaging in the concurrent use of alcohol and opioids who also have chronic pain have an increased complexity surrounding their use of substances and their treatment needs. For example, chronic pain patients that use opioids and alcohol concurrently have been found to utilize medical treatments more frequently, report significantly more health problems, and have poorer treatment outcomes than those who do not co-use (Caldeiro et al., 2008; Trafton et al., 2004). For example, a 12-month longitudinal study of veterans enrolled in outpatient addiction treatment programs found that those with persistent pain, as compared to intermittent pain, were in treatment for 35 fewer days (indicating lower levels of engagement with treatment and/or

drop-out), less likely to abstain from drugs or alcohol, and more likely to be hospitalized, leading to higher total service costs (Caldeiro et al., 2008). Research has also shown that individuals with persistent pain are at a much higher risk for developing a substance use disorder, relapse during substance abuse treatment, and engagement in aberrant pain management behaviors (Goebel et al., 2016; Larson et al., 2007; Witkiewitz et al., 2016).

Addiction treatment outcomes are poor among chronic pain patients as alcohol is often used to help manage their pain and other related symptoms in addition to using prescription opioids (Caldeiro et al., 2008; Savage, 1993). Thus, it is often unclear whether it is best to treat the substance use first, the pain first, or address both issues concurrently (Goebel et al., 2016; Larson et al., 2007; Morasco et al., 2011). A national survey of 5,692 individuals in the United States with substance use disorder and pain indicated that 58% reported the substance use disorder occurred first, 35% reported the pain occurred first, and 7% indicated they both occurred within the same year (Ilgen, Conner, Valenstein, Austin, & Blow, 2010). Evidence has also shown that pain transmission and alcohol reinforcement often have similar and overlapping neural substrates, therefore further increasing hardship for concurrent users in addiction treatment (Egli, Koob, & Edwards, 2012). However, interestingly, Savage (1993) notes that often after patients have been weaned off both alcohol and opioids and completed addiction treatment, pain often goes unchanged or even decreases, but rarely increases. In addition, a recent study asked treatment-seeking individuals with opioid dependence about their reasons for concurrent use, and found that many initially used concurrently to help manage pain, however at the time of the interview these individuals were only using alcohol and opioids concurrently to avoid withdrawal symptoms (Weiss et al., 2014). Given these data, it seems clear that pain and

substance use exacerbate each other, and that substance use treatment programs may not be adequate to address their needs.

Conclusion

Based on the extant literature, it can be concluded that co-use of alcohol and opioids is a reliable risk factor for a variety of poor health outcomes. Specifically, co-use is consistently associated with increased risk of overdose and death, as well as a diffuse set of cognitive deficits, greater frequency of mental health diagnoses, poorer adherence to treatment, and more frequent discontinuation of treatment. Further, those who co-use these two substances appear to use them with greater frequency and/or in larger amounts in comparison to those who do not co-use. Thus, the risks of co-use are readily identifiable across the broader array of studies, as well as in those who are on opioid-substitution therapy or who are diagnosed with chronic pain.

There is, however, a clear need for guidance regarding effective interventions for such risky co-use. There is no current state-of-the-literature on how best to address the co-use of alcohol and opioids specifically, and there is limited data on the efficacy of treatments for polysubstance use. A somewhat dated meta-analysis done by (Dutra et al., (2008) did examine the efficacy of four substance use treatments among individuals who used one of four substances (cannabis, cocaine, opiate, or polysubstance) does not provide clear empirically-based guidance on appropriate interventions or what the components of effective interventions are likely to be. It was found that polysubstance users were the least responsive to treatment had the lowest responses to treatment (intervention effect size, $d = .24$), followed by opiate users ($d = .39$). By comparison, the effect sizes were larger for cocaine users ($d = .62$), and then cannabis users ($d = .81$). Therefore, findings suggest that current treatment outcomes for co-use of alcohol and opioids are poorly likely to be weak. However, given that the data only spans until 2005, it is

possible that treatment outcomes have improved. For example, one relatively new treatment that has shown promise in polysubstance users is Mindfulness Based Relapse Prevention (MBRP). Studies using MBRP have found decreases through a 12 month follow-up in in-substance use in polysubstance users that sustain up to 12 months after treatment completion (Bowen et al., 2009, 2017; Witkiewitz et al., 2014). Regardless, the current literature does not provide clear empirically-based guidance on appropriate interventions or what the components of effective interventions are likely to be for those who co-use alcohol and opioids. Given the prevalence of co-use and the significant adverse impacts associated with it, there is a clear need for further work in this area to identify appropriate and efficacious interventions.

Furthermore, ~~While~~ while the treatment literature for other polysubstance treatment approaches is likely relevant to alcohol and opioid co-use, there ~~Yet, there may be~~ are likely unique aspects involved in treatments concerning two substances that can be legally obtained or which involve those who are prescribed opioids as part of their use of prescribed opioids, which may be viewed as a necessary part of a pain-pain treatment regimen. These distinctions would appear to require focused efforts to determine the salient influences on co-use, effects that are maintaining this use, and appropriate areas for intervention.

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References

- Almog, Y. J., Anglin, M. D., & Fisher, D. G. (1993). Alcohol and heroin use patterns of narcotics addicts: gender and ethnic differences. *The American Journal of Drug and Alcohol Abuse*, 19(2), 219–38. <http://doi.org/10.3109/00952999309002682>
- Arias, F., Arnsten, J. H., Cunningham, C. O., Coulehan, K., Batchelder, A., Brisbane, M., ... Rivera-Mindt, M. (2016). Neurocognitive, psychiatric, and substance use characteristics in opioid dependent adults. *Addictive Behaviors*, 60, 137–143. <http://doi.org/10.1016/j.addbeh.2016.03.018>
- Baldacchino, A., Balfour, D. J. K., Pasetti, F., Humphris, G., & Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 36(9), 2056–2068. <http://doi.org/10.1016/j.neubiorev.2012.06.006>
- Bowen, S., Collins, S. E., Witkiewitz, K., Hsu, S., Grow, J., Garner, M., ... Marlatt, A. (2009). Mindfulness-Based Relapse Prevention for Substance Use Disorders: A Pilot Efficacy Trial. *Substance Abuse*, 30, 295–305. <http://doi.org/10.1080/08897070903250084>
- Bowen, S., Witkiewitz, K., Clifasefi, S. L., Grow, J., Chawla, N., Hsu, S. H., ... Larimer, M. E. (2017). Relative Efficacy of Mindfulness-Based Relapse Prevention, Standard Relapse Prevention, and Treatment as Usual for Substance Use Disorders A Randomized Clinical Trial. *JAMA Psychiatry*, 98105(5), 547–556. <http://doi.org/10.1001/jamapsychiatry.2013.4546>
- Calcaterra, S., Glanz, J., & Binswanger, I. A. (2013). National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. *Drug and Alcohol Dependence*, 131(3), 263–270. <http://doi.org/10.1016/j.drugalcdep.2012.11.018>
- Caldeiro, R. M., Malte, C. A., Calsyn, D. A., Baer, J. S., Nichol, P., Kivlahan, D. R., & Saxon, A. J. (2008). The association of persistent pain with out-patient addiction treatment outcomes and service utilization. *Addiction*, 103, 1996–2005. <http://doi.org/10.1111/j.1360-0443.2008.02358.x>
- Clark, N. C., Dietze, P., Lenné, M. G., & Redman, J. R. (2006). Effect of opioid substitution therapy on alcohol metabolism. *Journal of Substance Abuse Treatment*, 30(3), 191–196. <http://doi.org/10.1016/j.jsat.2005.11.010>
- Cushman, P. (1987). Alcohol and Opioids: Possible Interactions of Clinical Importance. *Advances in Alcohol and Substance Abuse*, 6(3), 33–46.
- Daubresse, M., Chang, H., Yu, Y., Viswanathan, S., Shah, N. D., Stafford, R. S., ... Alexander, G. C. (2013). Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Medical Care*, 51, 870–878.
- Degenhardt, L., & Hall, W. (2003). Patterns of co-morbidity between alcohol use and other substance use in the Australian population. *Drug and Alcohol Review*, 22, 7–13. <http://doi.org/10.1080/0959523021000059776>
- Dutra, L., Stathopoulou, G., Basden, S. L., Leyro, T. M., Powers, M. B., & Otto, M. W. (2008). A Meta-Analytic Review of Psychosocial Interventions for Substance Use Disorders. *Am J Psychiatry*, 165, 179–187.
- Earleywine, M., & Newcomb, M. D. (1997). Concurrent Versus Simultaneous Polydrug Use: Prevalence, Correlates, Discriminant Validity, and Prospective Effects on Health Outcomes. *Experimental and Clinical Psychopharmacology*, 5(4), 353–364.

- Egli, M., Koob, G. F., & Edwards, S. (2012). Neuroscience and Biobehavioral Reviews Alcohol dependence as a chronic pain disorder. *Neuroscience and Biobehavioral Reviews*, 36(10), 2179–2192. <http://doi.org/10.1016/j.neubiorev.2012.07.010>
- Fleming, M. F., Balousek, S. L., Klessig, C. L., Mundt, M. P., & Brown, D. D. (2007). Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *The Journal of Pain*, 8(7), 573–582. <http://doi.org/10.1016/j.jpain.2007.02.432>
- Garnier, L. M., Arria, Amelia, M., Caldeira, Kimberly, M., Vincent, K. B., Grady, K. E., & Wish, E. D. (2009). Nonmedical Prescription Analgesic Use and Concurrent Alcohol Consumption among College Students. *The American Journal of Drug and Alcohol Abuse*, 35(5), 334–338. <http://doi.org/10.1080/00952990903075059>
- Goebel, J. R., Compton, P., Zubkoff, L., Lanto, A., Asch, S. M., Sherbourne, C. D., ... Lorenz, K. A. (2016). Prescription Sharing , Alcohol Use , and Street Drug Use to Manage Pain Among Veterans. *Journal of Pain and Symptom Management*, 41(5), 848–858. <http://doi.org/10.1016/j.jpainsymman.2010.07.009>
- Gossop, M., Browne, N., Stewart, D., & Marsden, J. (2003). Alcohol use outcomes and heavy drinking at 4-5 years among a treatment sample of drug misusers. *Journal of Substance Abuse Treatment*, 25(3), 135–143. [http://doi.org/10.1016/S0740-5472\(03\)00129-6](http://doi.org/10.1016/S0740-5472(03)00129-6)
- Gossop, M., Marsden, J., & Stewart, D. (2002). Dual dependence: Assessment of dependence upon alcohol and illicit drugs, and the relationship of alcohol dependence among drug misusers to patterns of drinking, illicit drug use and health problems. *Addiction*, 97(2), 169–178. <http://doi.org/10.1046/j.1360-0443.2002.00028.x>
- Gossop, M., Ph, D., Marsden, J., Ph, D., Stewart, D., Rolfe, A., & Sc, B. (2000). Patterns of drinking and drinking outcomes among drug misusers 1-year follow-up results. *Journal of Substance Abuse Treatment*, 19, 45–50.
- Gudin, J. A., Mogali, S., Jones, J. D., & Comer, S. D. (2013). Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgraduate Medicine*, 125(4), 115–130. <http://doi.org/10.3810/pgm.2013.07.2684.Risks>
- Hedden, S. L., Martins, S. S., Malcolm, R. J., Floyd, L., Cavanaugh, C. E., & Latimer, W. W. (2010). Patterns of illegal drug use among an adult alcohol dependent population: Results from the National Survey on Drug Use and Health. *Drug and Alcohol Dependence*, 106(2–3), 119–125. <http://doi.org/10.1016/j.drugalcdep.2009.08.002>
- Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology*, 129, 99–111.
- Hughes, A., Williams, M. R., Lipari, R. N., Bose, J., Copello, E., & Krout, L. A. (2015). Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. Retrieved from <http://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm>
- Ilgen, M. a, Conner, K. R., Valenstein, M., Austin, K., & Blow, F. C. (2010). Violent and nonviolent suicide in veterans with substance-use disorders. *Journal of Studies on Alcohol and Drugs*, 71(4), 473–9. <http://doi.org/N/A>
- Jobski, K., Schmid, U., Behr, S., Andersohn, F., & Garbe, E. (2012). 3-year prevalence of alcohol-related disorders in German patients treated with high-potency opioids. *Pharmacoepidemiology and Drug Safety*, 21(April), 1125–1129. <http://doi.org/10.1002/pds>
- Jones, C. M., Paulozzi, L. J., & Mack, K. A. (2014). Alcohol Involvement in Opioid Pain Reliever and Benzodiazepine Drug Abuse – Related Emergency Department Visits and

- Drug-Related Deaths — United States , 2010. *Morbidity and Mortality Weekly Report*, 63(40).
- Joseph, H. (1985). Alcoholism and methadone treatment: Consequences for the patient and program. *The American Journal of Drug and Alcohol Abuse*, 11(1–2), 37–53.
- Khalili-mahani, N., Zoethout, R. M. W., Beckmann, C. F., Baerends, E., Kam, M. L. De, Soeter, R. P., ... Rombouts, S. A. R. B. (2012). Effects of Morphine and Alcohol on Functional Brain Connectivity During “ Resting State ”: A Placebo-Controlled Crossover Study in Healthy Young Men. *Human Brain Mapping*, 33(December 2010), 1003–1018. <http://doi.org/10.1002/hbm.21265>
- Kreek, M. J. (1984). Opioid Interactions with Alcohol. *Advances in Alcohol and Substance Abuse*, 3(4), 35–46.
- Larance, B., Campbell, G., Peacock, A., Nielsen, S., Bruno, R., Hall, W., ... Degenhardt, L. (2016). Pain , alcohol use disorders and risky patterns of drinking among people with chronic non-cancer pain receiving long-term opioid therapy. *Drug and Alcohol Dependence*, 162, 79–87. <http://doi.org/10.1016/j.drugalcdep.2016.02.048>
- Larson, M. J., Paasche-orlow, M., Cheng, D. M., Lloyd-travaglini, C., Saitz, R., & Samet, J. H. (2007). Persistent pain is associated with substance use after detoxification : a prospective cohort analysis. *Addiction*, 102, 752–760. <http://doi.org/10.1111/j.1360-0443.2007.01759.x>
- McCabe, S. E., Cranford, J. A., & Boyd, C. J. (2006). The relationship between past-year drinking behaviors and nonmedical use of prescription drugs: Prevalence of co-occurrence in a national sample. *Drug and Alcohol Dependence*, 84, 281–288. <http://doi.org/10.1016/j.drugalcdep.2006.03.006>
- McCabe, S. E., Cranford, J. A., Morales, M., & Young, A. (2006). Simultaneous and Concurrent Polydrug Use of Alcohol and Prescription Drugs: Prevalence, Correlates, and Consequences. *Journal of Studies on Alcohol*, 67, 529–537.
- McCabe, S. E., Cranford, J. A., & West, B. T. (2008). Trends in prescription drug abuse and dependence, co-occurrence with other substance use disorders, and treatment utilization: Results from two national surveys. *Addictive Behaviors*, 33, 1297–1305. <http://doi.org/10.1016/j.addbeh.2008.06.005>
- McCabe, S. E., West, B. T., Teter, C. J., & Boyd, C. J. (2012). Co-ingestion of prescription opioids and other drugs among high school seniors : Results from a national study. *Drug and Alcohol Dependence*, 126, 65–70. <http://doi.org/10.1016/j.drugalcdep.2012.04.017>
- Morasco, B. J., Gritzner, S., Lewis, L., Oldham, R., Turk, D. C., & Dobscha, S. K. (2011). Systematic review of prevalence , correlates , and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain*, 152(3), 488–497. <http://doi.org/10.1016/j.pain.2010.10.009>
- Nolan, S., Klimas, J., & Wood, E. (2016). Alcohol use in opioid agonist treatment. *Addiction Science & Clinical Practice*, 11(17), 1–7. <http://doi.org/10.1186/s13722-016-0065-6>
- Peacock, A., Bruno, R., Larance, B., Lintzeris, N., Nielsen, S., Ali, R., ... Degenhardt, L. (2016). Same-day use of opioids and other central nervous system depressants amongst people who tamper with pharmaceutical opioids: A retrospective 7-day diary study. *Drug and Alcohol Dependence*, 166, 125–133. <http://doi.org/10.1016/j.drugalcdep.2016.07.003>
- Saunders, K. W., Von Korff, M., Campbell, C. I., Banta-Green, C. J., Sullivan, M. D., Merrill, J. O., & Weisner, C. (2012). Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors. *Journal of Pain*, 13(3), 266–275. <http://doi.org/10.1016/j.jpain.2011.11.004>

- Savage, S. R. (1993). Addiction in the treatment of pain: Significance, recognition, and management. *Journal of Pain and Symptom Management*, 8(5), 265–278.
- Schepis, T. S., & Hakes, J. K. (2013). Dose-Related Effects for the Precipitation of Psychopathology by Opioid or Tranquilizer/Sedative Nonmedical Prescription Use. *Journal of Addiction Medicine*, 7(1), 39–44. <http://doi.org/10.1097/ADM.0b013e318277e9e5>
- Senbanjo, R., Wolff, K., & Marshall, J. (2006). Excessive alcohol consumption is associated with reduced quality of life among methadone patients. *Addiction*, 102, 257–263. <http://doi.org/10.1111/j.1360-0443.2006.01683.x>
- Srivastava, A., Kahan, M., & Ross, S. (2008). The effect of methadone maintenance treatment on alcohol consumption: A systematic review. *Journal of Substance Abuse Treatment*, 34, 215–223. <http://doi.org/10.1016/j.jsat.2007.04.001>
- Staiger, P. K., Richardson, B., Long, C. M., Carr, V., & Marlatt, G. A. (2012). Overlooked and underestimated? Problematic alcohol use in clients recovering from drug dependence. *Addiction*, 108, 1188–1193. <http://doi.org/10.1111/j.1360-0443.2012.04075.x>
- Substance Abuse and Mental Health Services Administration. (2016). 2015 National Survey on Drug Use and Health.
- Trafton, J. A., Oliva, E. M., Horst, D. A., Minkel, J. D., & Humphreys, K. (2004). Treatment needs associated with pain in substance use disorder patients: Implications for concurrent treatment. *Drug and Alcohol Dependence*, 73(1), 23–31. <http://doi.org/10.1016/j.drugalcdep.2003.08.007>
- Weathermon, R., & Crabb, D. W. (1999). Alcohol and Medication Interactions. *Alcohol Research and Health*, 23(1), 40–54. <http://doi.org/10.1086/250095>
- Weiss, R. D., Potter, J. S., Griffin, M. L., McHugh, R. K., Haller, D., Jacobs, P., ... Rosen, K. D. (2014). Reasons for opioid use among patients with dependence on prescription opioids: The role of chronic pain. *Journal of Substance Abuse Treatment*, 47, 140–145. <http://doi.org/10.1016/j.jsat.2014.03.004>
- Whelan, P. J., & Remski, K. (2012). Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *Journal of Neurosciences in Rural Practice*, 3(1), 45–52. <http://doi.org/10.4103/0976-3147.91934>
- White, J. M., Irvine, R. J., White, J. M., & Irvine, R. J. (1999). Mechanisms of fatal opioid overdose. *Addiction*, 94(7), 961–972.
- Witkiewitz, K., Vowles, K. E., McCallion, E., Frohe, T., Kirouac, M., & Maisto, S. A. (2016). Pain as a Predictor of Heavy Drinking and Any Drinking Lapses in the COMBINE Study and the United Kingdom Alcohol Treatment Trial. *Addiction*, 110(8), 1262–1271. <http://doi.org/10.1111/add.12964>
- Witkiewitz, K., Warner, K., Sully, B., Barricks, A., Stauffer, C., Thompson, L., & Luoma, J. B. (2014). Randomized Trial Comparing Mindfulness-Based Relapse Prevention Addiction Treatment Center. *Substance Use & Misuse*, 49, 536–546. <http://doi.org/10.3109/10826084.2013.856922>
- Zacny, J. P., & Drum, M. (2010). Psychopharmacological effects of oxycodone in healthy volunteers: Roles of alcohol-drinking status and sex. *Drug and Alcohol Dependence*, 107(2–3), 209–214. <http://doi.org/10.1016/j.drugalcdep.2009.10.012>
- Zador, D., & Sunjic, S. (2000). Deaths in methadone maintenance treatment in New South Wales, Australia 1990–1995. *Addiction*, 95(1), 77–84.