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Directional Effects of Anxiety and Depressive Disorders with Substance Use: a Review of Recent Prospective Research

Lorra Garey[1] · Hannah Olofsson[1] · Tatyana Garza[1] · Andrew H. Rogers[1] · Brooke Y. Kauffman[1] · Michael J. Zvolensky[1,2,3]

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Abstract

Purpose of Review Anxiety and depressive disorders are highly prevalent, frequently comorbid, and contribute to high rates of disability and death globally. They also commonly co-occur with substance use, including alcohol, cigarettes, and cannabis. Yet, the directionality for the onset and progression of these conditions is not fully understood. The present review highlights key findings from recent longitudinal studies on the prospective associations between anxiety and depressive disorders and the most commonly used substances (alcohol, tobacco, and cannabis). Additionally, this article reviews the potential of each condition to affect the outcome, course, and treatment of the other.

Recent Findings The current literature remains mostly inconclusive on the temporal associations between anxiety and depressive disorders and substance use and reverse causality, with some studies supporting the self-medication hypothesis and other work supporting the substance-induced hypothesis or the shared-vulnerability hypothesis.

Summary Future prospective work that utilizes sophisticated research designs to test proposed causality is crucial to inform treatment of comorbid anxiety/depressive disorders and substance use.

Keywords Comorbidity · Anxiety disorders · Depressive disorders · Tobacco · Cannabis · Alcohol

Anxiety and depressive disorders are the most common psychiatric disorders globally [1]. A staggering 284 million people globally (3.6% of the total population) meet criteria for a past-year anxiety disorder, with an estimated 6.3% of adults in the USA experiencing a current anxiety disorder [1]. Equally high, the past-year prevalence rate for a depressive disorder is 4.4% globally (exceeding 300 million people), and as high as 5.9% in the USA [1]. These disorders are frequently chronic, highly comorbid, and associated with substantial individual and societal costs [1–3]. Notably, anxiety and depressive disorders often co-occur with substance use at high rates [4–7]. According to the Anxiety and Depression Association of America [8], 20% of Americans with an anxiety or depressive disorder have a substance use disorder, and about 20% of those with a substance use disorder also have an anxiety or depressive disorder. Indeed, high rates of co-occurrence have been consistently demonstrated across populations, study designs, methods of analysis, and definitions of disorders or substance use [9, 10••, 11, 12].

Although the co-occurrence of anxiety and depressive disorders with the most frequently and widely used substances (alcohol, tobacco, and cannabis) [13, 14] is well-established [15], less is understood about the temporal sequencing of these conditions. Specifically, mixed findings have been reported regarding the directional effect for anxiety or depressive disorders to increase the likelihood of substance use, and vice versa [15–18]. Ultimately, three prevailing theoretical models have been proposed to explain the association between anxiety/depressive disorders and substance use: (1) the self-medication or coping hypothesis [19, 20]; (2) the substance-induced hypothesis [21], and (3) the shared-vulnerability hypothesis [22, 23]. The self-medication or coping hypothesis

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✉ Lorra Garey
llgarey@uh.edu

[1] Department of Psychology, University of Houston, 3695 Cullen Blvd., Room 126 Heyne Building, Houston, TX 77204, USA

[2] Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3] HEALTH Institute, University of Houston, Houston, TX 77204, USA

postulates that individuals use substances to self-regulate and mitigate negative mental health symptoms, such as anxiety and depressive symptoms, due to a lack of adaptive coping skills [19]. Thus, these symptoms precede the onset of substance use. Alternatively, the substance-induced hypothesis posits that prolonged substance use will lead to a toxic effect and neurological changes that prompt or exacerbate the severity of anxiety and depressive symptoms, particularly during periods of acute or prolonged withdrawal [6, 24]. Finally, the shared-vulnerability hypothesis argues that there are common, shared, third-variable risk factors (including genetic, behavioral, and environmental factors) that predispose individuals to both anxiety and depressive disorders and substance use [25]. Unlike the shared-vulnerability hypothesis, which offers a non-causal explanation for the high rates of co-occurrence, both the self-medication/coping and substance-induced hypotheses propose directionality for the onset of anxiety/depressive disorders and substance use, albeit from different perspectives, and offer complementary theoretical rationales for potential bidirectional causal relations.

Each model has received varying levels of empirical support in recent years [10, 26••, 27, 28]. As this work continues to mount and evolve, efforts are needed to synthesize novel research that explains the propensity for anxiety and depressive disorders and substance use to mutually influence each other. Such work is key to inform "next generation" research that integrates and builds upon knowledge gained from current advancements in conducting psychological research (i.e., data access, analysis, and design). To address this objective, the current review offers a narrative overview of the most impactful, significant, and recent (primarily data published between 2015 and 2019) research on longitudinal associations between anxiety and depressive disorders and the most frequently and widely used substances (alcohol, tobacco, and cannabis) [13, 14]. We review prospective work that has evaluated substance use as an indicator or consequent of anxiety and depressive disorders, and the reverse, as well as the potential for each condition to impact the course and treatment of the other.

Anxiety Disorders and Alcohol Use

Alcohol is the most widely used substance in the world and contributes to approximately 3 million deaths annually [14]. Seminal work posits that alcohol use and anxiety disorders demonstrate a reciprocal causal relation, with anxiety disorders leading to alcohol dependence and vice versa [18, 29–32]. Yet, recent data have been discrepant and suggest directional pathways may vary across specific anxiety disorders and alcohol use intensity. For example, Torvik et al. [33••] concluded that social anxiety disorder (SAD) prospectively predicted alcohol use disorder (AUD) and anxiety disorders other than SAD were unrelated to later AUD onset, suggesting a unique directionality specific to SAD and AUD. The directional association between SAD and AUD is further substantiated by work that has suggested AUD predicts the later onset of anxiety disorders except for SAD [33••]. The robustness of these findings, however, should be considered in the context of recent epidemiological data that has failed to find a relation between current (past 12 months) SAD diagnosis and later incidence of AUD [34]. Similar findings were reported by Farmer et al. [35•] who found no association between childhood or adolescent anxiety disorder diagnosis and later onset of AUD, which has been replicated in independent samples [36] and across specific disorders, including specific phobia [37] and generalized anxiety disorder [27, 38]. As this area of work continues to evolve, additional research is needed to explicate the directional effects between specific anxiety disorders and AUD.

Relative to AUD, research on alcohol use more broadly defined has suggested that regular (weekly) alcohol use is associated with a *reduced* risk of developing any anxiety disorder over time [39••]. Indeed, relative to abstainers, moderate drinking protects against incidence of generalized anxiety disorder (GAD) [40]. Among men, excessive drinking increases the likelihood of incidence of GAD [40]. Thus, the pattern for men is somewhat consistent with the J-shape hypothesis regarding alcohol use and mental health which suggests that non-drinkers and heavy drinkers are at the highest risk for negative mental health consequences [41], which has received mixed empirical support recently [42] particularly given that some work has reported comparable rates of anxiety onset across those who have and have not used alcohol [36]. Regarding reverse directionality, Dyer et al. [43•] observed that GAD served as a risk factor for later onset of harmful drinking, but not other indicators of drinking severity, such as frequency. Importantly, the strength of this predictive association varied across covariate-adjusted models, particularly when sociodemographic (e.g., gender), parental (e.g., psychiatric and substance use history), and adolescent confounders (e.g., alcohol and drug use) were modeled, and was dependent on data analytic modeling decisions, such as handling of missing data, which raises some concerns about the robustness of these findings [44]. Nevertheless, other independent work has reported that presence of an anxiety disorder does not prospectively predict alcohol use [36].

Limited recent data have examined the effect of anxiety on alcohol treatment outcomes and vice versa. Within this area of research, Bahorik et al. [45] reported that among patients with depression receiving substance use treatment, reductions in hazardous drinking resulted in greater and faster improvement of anxiety symptoms across the follow-up period, while continued hazardous drinking slowed symptom recovery; no evidence for the reverse effect emerged. By extension, Schellekens et al. [46•] found that history of an anxiety

disorder at baseline significantly predicted early (defined as less than 12 weeks following admission) alcohol relapse relative to maintained abstinence or late relapse in a sample of male, alcohol-dependent inpatients. Specificity analyses identified agoraphobia, SAD, and panic disorder as more prevalent among early relapse stages relative to abstainers or late relapse. Additionally, those who suffer from both anxiety and alcohol dependence may also experience more intense symptoms of withdrawal, which would further complicate treatment. A study conducted in Denmark, however, found no differences in drinking behavior following treatment among those with or without an anxiety or depressive disorder at baseline [47••]. Dropout rates were high among patients with anxiety disorders, which may have affected outcomes. Importantly, the implications of recent findings should consider variability in treatment method and duration, sample, and timing of follow-up assessments when drawing conclusions.

Collectively, recent research has documented mixed findings regarding the temporal association between anxiety disorder and alcohol use with regard to onset and course of treatment outcomes and suggests variability across specific anxiety disorder and degree of alcohol use behavior. Indeed, support was observed for the self-medication/coping and substance-induced hypotheses but varied considerably across disorders and defined alcohol use. Moreover, several studies reported no association between anxiety disorders and alcohol. In part, this suggests a shared-vulnerability model may best explain the common co-occurrence of these conditions. Ultimately, the inconsistencies across studies are likely due to a combination of a variety of diagnostic assessments employed, other substance use, differences in drinking-related definitions, and varying length of follow-up sessions [47••]. Continued prospective work is needed to explicate these relations using more controlled designs that utilized consistent assessments and data analytic procedures across independent studies.

Anxiety Disorders and Cigarette Smoking

Smoking is the leading preventable cause of disability and death globally [48]. The association between smoking and anxiety is robust and has been replicated across populations [49, 50]. The application of this work to inform treatment development, however, is limited by the cross-sectional designs commonly employed to examine the anxiety-smoking associations [50]. To more directly inform treatment and prevention efforts, epidemiological data have been used recently to explicate directional effects for smoking and anxiety disorder onset. In recent research, after controlling for covariates (e.g., age, income, marital status, gender, and psychiatric comorbidity), regular (weekly) nicotine use was associated with an increased likelihood of developing any anxiety disorder [39••]. Specificity tests revealed that the odds of developing panic disorder (with or without agoraphobia), social anxiety, specific phobia, and GAD were higher among individuals who regularly used nicotine. Among adolescents, however, work has suggested that any crude associations between cigarette use in adolescence and onset of later anxiety are modest and largely confounded by third variables that significantly attenuate associations [36, 51]. Few other recent works have explored the longitudinal relation between smoking onset/smoking status and later anxiety, yet systematic reviews have reported mixed findings across earlier work with the most robust associations present for panic disorder and GAD [50, 52, 53]. To clarify the directional impact of smoking initiation and maintenance on the subsequent development of anxiety, future research that capitalizes on current advancements in data analysis and study methodology (i.e., multi-level modeling and/or ecological momentary assessment) is critically needed to confirm the robustness of published findings.

Regarding the reverse associations, a recent review found evidence that baseline anxiety was significantly related to smoking onset [52]. Indeed, 80% of the papers reviewed concluded a positive relation between anxiety and later smoking onset. Given the small study size ($n = 5$), the implications of this work should be interpreted with caution. Moreover, empirical data recently suggested that these relations may not be present across all anxiety disorders [36]. For example, Lieb et al. [37] found no association between lifetime history of specific phobia and onset of nicotine use disorder over a 10-year follow-up period. Such inconsistent findings parallel those reported by an earlier review of established epidemiological longitudinal studies, which presented inconsistent evidence for anxiety as a risk factor for the onset of smoking [50]. In part, the authors attributed the discrepancies to variability in population characteristics, length of follow-up, diagnostic tool employed, and smoking definition.

Specific to the course of smoking and anxiety following treatment, among a sample of smokers with attention deficit hyperactivity disorder (ADHD) enrolled in a specialized smoking cessation treatment, baseline anxiety did not influence abstinence status at the 1- and 6-week post-quit date [54]. Contrary to this work, Piper et al. [55] documented significant differences in abstinence at 8 weeks post-quit across those with a current or lifetime anxiety disorder relative to those without; differences were maintained at the 6-month follow-up among those with a lifetime anxiety disorder. The nuanced effect of specific anxiety disorders on abstinence, however, varied with the most robust associations observed for history of panic attacks and a history of meeting diagnostic criteria for more than one anxiety disorder [56]. Moreover, smoking cessation treatment, although effective among those without an anxiety disorder, tend to be equally effective as a placebo among those with an anxiety disorder [56]. In part, these findings have motivated work to develop specialized treatments

for smokers with anxiety. Indeed, in the event that specialized, integrated treatments for smokers with anxiety can be effective, robust evidence has indicated that the subsequent quit success will support greater reductions in anxiety-related symptoms [54, 57] that may then lead to prolonged abstinence.

The most robust evidence emerged for smoking as a risk factor for later onset of panic, thereby supporting the substance-induced hypothesis. Such findings are consistent with seminal epidemiological work on the causal relation between smoking and panic [58]. This established and currently validated pattern may be related to the physiological effects of smoking (i.e., increased heart rate and blood pressure) [59], and/or internal perturbations associated with nicotine withdrawal (i.e., increased stress and alteration in brain chemistry) [59, 60]. Relations across other disorders and models of reverse causality were largely inconsistent and bring to question the validity of reported findings. As this work continues to become more specialized and focused, accumulating evidence suggests that smokers may be at risk for developing panic attacks. Future work would benefit from evaluating moderators of this relation to identify smokers at greatest risk for the onset of panic as panic symptoms perpetuate smoking maintenance [61].

Anxiety Disorders and Cannabis Use

Cannabis is one of the most widely used substances in the USA, with an estimated 22.2 million adults endorsing current use [62]. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive compound in cannabis and places users into a mind-altered ("high") state [63, 64] that is characterized by changes in mood (including anxiety and depression), difficulty with cognitive functioning, and, at times, psychotic symptoms [64, 65]. Indeed, extensive cross-sectional, clinical, and epidemiological data highlight a robust, positive association between cannabis use and anxiety disorders and symptomatology [10••, 26••, 66]. The propensity for each condition to influence the onset and progression of the other, however, remains unclear with some data supporting an effect of cannabis use on the development of anxiety disorders (i.e., substance-induced hypothesis) [26••], anxiety disorders exerting an effect on cannabis use initiation (i.e., self-medication hypothesis) [26••, 67], and some research reporting no directional pathways [68••, 69]. Notably, any evidence in support of directional effects has not typically been robust to covariate-adjusted modeling (e.g., type of nicotine replacement therapy, age, sex, substance use) and has suggested a shared propensity for the co-occurrence and influence of each condition on the other [70]. Importantly, the effect of cannabis use on anxiety disorder onset varies across specific anxiety disorders, with some directional relations maintained even after controlling for confounds. For example, recent epidemiological work among adults reported that past-year, regular (weekly) cannabis use predicted the onset of SAD and panic disorder with (but not without) agoraphobia in covariate-adjusted models [39••]. Research focused on the influence of cannabis use frequency has indicated that daily or almost daily cannabis use marginally predicted the onset of SAD in covariate-adjusted analyses, which adjusted for sociodemographic variables and comorbid psychiatric disorders [71••]. Additionally, among adolescents and young adults, data have suggested that regular and non-regular cannabis use did not predict SAD in an unadjusted model, but rather was related to more severe symptoms of GAD later in life in unadjusted and adjusted models [72]. It is important to note, however, some of the findings reviewed have not been replicated when considering other potential confounds [70]. Thus, continued work is needed to clarify the role of cannabis use on the subsequent onset of an anxiety disorder and the contribution of putative shared vulnerability factors in observed relations.

Regarding the reverse model (i.e., that anxiety contributes to cannabis use initiation), extant work has suggested that the presence of any anxiety disorder does not increase the likelihood of cannabis use initiation or CUD onset [69, 71••, 73•]. Specificity tests, however, have indicated that panic disorder appears to be a unique risk factor for the onset of cannabis use, suggesting possible self-medication or coping hypotheses [71••]. This directional pattern is only marginally significant among adolescents, as evidence has suggested a more robust causal relation between generalized anxiety and cannabis use onset among this group [67]. The cultural context (i.e., Chilean adolescents) of this work should be considered when interpreting findings. Other work with adolescents has found results to the contrary, such that social anxiety protects against cannabis use initiation, a relation largely explained by cannabis use expectancies [74]. Further work is needed to determine the directionality and test the robustness of these findings. Additionally, disorder- and population-specific research is required to verify directional pathways for unique associations they may present.

A recent prospective analysis of data from adolescents found that higher levels of cannabis use predicted more stability in anxiety symptoms over time, whereas lower levels of cannabis use were associated with greater improvements in anxiety symptoms over time [75]; anxiety levels did not influence change in cannabis use over time. Further evidence for cannabis use to interfere in the course of anxiety disorders was reported by Feingold et al. [76] who found that among individuals with an anxiety disorder at baseline assessment, remission rates at follow-up were 65.97% among non-users of cannabis, 52.79% among cannabis users, and 46.8% among individuals with a CUD. While potentially clinically significant, these differences were not statistically significant in covariate-adjusted models, suggesting sociodemographic and

contextual factors may help account for these relations. Moreover, among persons receiving CUD treatment, reductions in cannabis use play a critical role in the course of anxiety symptoms such that reduction leads to fewer anxiety symptoms over time [77]. Additionally, among psychiatric outpatients with depression receiving mental health treatment, cannabis use, compared to non-use, predicted less improvement in anxiety symptoms at 6 months [78].

Recent changes in legalization have informed an interest in isolating and evaluating non-psychoactive constituents of cannabis for potential medicinal purposes. One non-psychoactive cannabis constituent that has garnered considerable scientific attention is cannabidiol (CBD) [79]. CBD does not produce the "high" common to cannabis with THC nor do users experience many of the side effects associated with THC given its non-psychoactive composition [80]. Emerging evidence suggests that CBD is an effective treatment for epilepsy and a potential treatment for substance abuse [81–83]. CBD has also recently been studied as a potential anxiolytic [84], and one recent review found that CBD produced acute anti-anxiety effects in subjects with SAD [81]. Similarly, another recent review by Soares et al. [85] found evidence for anxiolytic effects of CBD in humans and anti-panic effects in animal models. Conversely, other findings have yielded mixed results of the efficacy of CBD as a treatment for anxiety [86, 87], with some work reflecting a dose-dependent anxiolytic effect (with efficacy inversely related to CBD dosage) [88]. Considering the novelty of CBD use, future work is crucial to inform physicians and the general community on the effects of CBD and whether or not it has a lasting, positive impact on anxiety treatment.

Collectively, there remains no clear, consistent evidence for the temporal sequencing of anxiety disorders and cannabis use. The mixed findings are likely related to variability in covariates, study methodology, and study length across studies and provide competing evidence for theoretical models of directionality. Thus, it is plausible that shared vulnerabilities, such as age, sex, other substance use, and socioeconomic factors, account for the high rate of comorbidity across these conditions. Additionally, the evidence for CBD acting as a potential anxiolytic remains inconclusive, underscoring the critical need for further research [66].

Depressive Disorders and Alcohol Use

Major depressive disorder (MDD) is the most common co-occurring psychiatric disorder among people with AUD, and AUD is the most common co-occurring substance use disorder among individuals with depression [89, 90]. As for their causal relation, only a few recent studies have explored directionality. Of these, few have found support for the self-medication or the substance-induced hypothesis for depression and alcohol use [36, 38, 40, 91], which has largely been limited to patterns of excessive alcohol consumption or specifically to male populations. Rather, evidence to the contrary of these theoretical models or no directional effect has been reported across most recent research [35•, 92•, 93, 94]. Indeed, the available recent work has largely suggested that regular (weekly) or moderate drinking *protects* against incidence of depression [39••, 40], and has suggested that alcohol abstinence may actually be associated with an increased likelihood of future depression [93, 95]. However, these findings have not been replicated in all samples [36]. Similar to anxiety and alcohol, these findings should be considered in the context of confounds, such as age, health behaviors (diet), and socioeconomic and marital status, which often dilute or attenuate the strength of associations [93].

Regarding reverse causality (i.e., depression influencing drinking behavior), research among nondrinking, elderly Chinese has found that depression protected against drinking initiation and promoted drinking abstinence at a 2-year follow-up relative to those without depression [95]. Other work among delinquent youth has provided only modest effects for depressive disorders to predict later AUD, which are largely not maintained in the covariate-adjusted models [38]. Some evidence has suggested that presence of a depressive disorder increases the likelihood of alcohol use and AUD among Mexican youth [36], but this crude relation may be driven by confounds that contribute to both conditions. The dearth of recent work on the causal effect of depression and alcohol use behaviors and the unique samples studied preclude drawing any firm conclusions regarding this pathway.

Regarding treatment outcomes, as with anxiety, patients receiving mental health treatment for depression who reduced hazardous drinking exhibited greater improvement in post-treatment depression symptoms; no evidence for the reverse effect was evident [45]. By extension, work has indicated that AUD complicates treatment responsiveness among depressed patients receiving pharmacological treatment for depression [96]. Yet, Mellentin et al. [47••] found that those with and without depression evinced similar drinking outcomes following outpatient alcohol treatment. Further, authors argued that other third variables, such as the variability in treatment methods and other substance use/psychiatric disorders, may be more relevant to drinking behavior during treatment. Thus, comorbid AUD interferes with depression outcomes following treatment, but comorbid depression may not impact the effect of alcohol specific treatment in terms of drinking outcomes.

Recent work *largely* supports that moderate drinking protects against depression. Still, mixed and inconsistent results for the temporal order of depression and alcohol use suggest that a shared-vulnerability model for the co-occurrence of depression and alcohol use is apt to be present. Indeed, this has been substantiated by research that has found common genetic links between AUD and depression [97, 98]. Differences in

study methodology, including analysis and definitions used to define depression and/or alcohol use [44], also may contribute to variability or confound directional associations. Continued work is needed to explicate how these conditions influence one another throughout the lifespan and to determine potential causal relations across gradients of alcohol use to guide tailored intervention efforts.

Depressive Disorders and Cigarette Smoking

The comorbidity of depression and smoking has also been well-established [49, 99]. With regard to recent prospective data, findings from epidemiological research have revealed that, after controlling for covariates, regular nicotine use at baseline was associated with an increased risk of onset of a depressive disorder at follow-up among adults [39••]. Other national data indicate that cigarette smoking significantly predicted the onset and persistence of MDD over a 10-year follow-up [100•]. These findings are consistent with a recently published review [52] and other empirical work among adults [95]. Findings may be sample specific as smoking is not a risk factor for later depression among veterans [94]. Similarly, among adolescents, any crude associations between cigarette use in adolescence and onset of later depression are largely confounded by third variables that significantly attenuate associations, including sociodemographic (e.g., age, sex), social-environmental (e.g., parents who smoke), psychological (e.g., stress/worry), and lifestyle-related factors (e.g., alcohol use) [36, 44, 51, 101]. This finding is in line with other work that has indicated sustained cigarette use does not impact the severity of depressive symptoms over time among adolescents [102]. Additionally, if smoking impacts depression onset among adolescents, this pattern may be gender specific (i.e., stronger associations for males) [101].

Relative to smoking influencing depression, greater depression experienced in adolescents appears to be related to increased likelihood of smoking [91, 102]. Again, third-variable confounds may help explain these relations [44]. As this area of research continues to develop and evolve, it is imperative that research focuses on patterns unique to different populations with varying backgrounds that may confound findings given emerging evidence for differential patterns across sociodemographic variables.

It is generally accepted that depression complicates smoking cessation success [103]. This association, however, is only modest when smokers receive formal smoking cessation treatment [104]. Indeed, recent work among smokers with ADHD enrolled in a specialized smoking cessation treatment reported no differences in 1- and 6-week post-quit abstinence across those with and without depression [54]. This is largely consistent with a recent review on the efficacy of smoking treatments across smokers with depression [105]. Yet, other recent empirical work has found significant differences in smoking outcomes across those with and without depression [70, 106]. Moreover, depression appears to place former smokers and those attempting to quit at increased risk for relapse [107, 108]. In the event of cessation success, however, reductions in depression are often observed [100•, 106]. Yet, this effect may be modulated by treatment variability (i.e., pharmacotherapy, behavioral, combined approaches) [109]. Nevertheless, depression severity and likelihood of onset are equivalent across former smokers and lifetime non-smokers [100•], with the likelihood of depression significantly reducing among former smokers who remain abstinent for 10 years [100•].

These data suggest that smoking serves as a risk factor for depression (i.e., substance-induced hypothesis) among adults, but the reverse pattern may be true for adolescents (i.e., self-medicating hypothesis). Moreover, it is possible that any predictive patterns may be better accounted for by shared-vulnerability factors that included the incidence of both conditions. Future work is needed to determine putative causal patterns and directionality of this association using more sophisticated research designs. Additionally, more work is needed to inform clinical protocols to integrate smoking and depression treatments and successfully address the shared-vulnerability factors commonly associated with the smoking/depression relation.

Depressive Disorders and Cannabis Use

The association between cannabis use and depressive disorders also has been well documented in cross-sectional, nationally representative epidemiological work [26••, 110]. Indeed, rates of cannabis use among depressed persons are as high as 40% [111•] and depression among cannabis users is similarly elevated at 24% [112]. Despite strong cross-sectional evidence for the co-occurrence of these conditions, evidence for the directionality is limited and mixed [110]. To help answer fundamental questions regarding causal relations among cannabis use and depression, Feingold et al. [113••] used epidemiological data to study bidirectional relations between cannabis use and depressive disorders. Results revealed no significant differences between past-year cannabis use and non-use at baseline and later onset of MDD diagnosis. Similar findings regarding a lack of association between cannabis use and later depression have been reported by other groups [39••, 68••, 69, 94, 114]. Schoeler et al. [115] examined the putative associations and found evidence that, compared to non-users and those who initiated cannabis use after age 18, cannabis use at age 18 years or earlier was related to an increased likelihood of MDD in both young adulthood and later adulthood as well as shorter time to disorder onset. Beyond the age of cannabis use onset, intensity of cannabis use in

adolescence may be relevant to later depression [51, 72]. Thus, it appears the age of cannabis use initiation and intensity of use are critical when conceptualizing the effect of use on depression.

Among participants without a history of cannabis use, recent (past year) major depressive episode was associated with an increased likelihood of later cannabis use initiation even after controlling for sociodemographic variables and comorbid psychiatric disorders [113••]. These findings, however, have not been observed by other research groups [67, 69]. Extending this work to use frequency, Schoeler et al. [115] found that a diagnosis of MDD between ages 18 and 31 significantly predicted *reduced* frequency of cannabis use in adulthood (age 32–48 years), which is in contrast to self-medication models of substance use. Similar to work with adults, data from adolescents are equally mixed. For example, Farmer et al. [73•] found that childhood depressive disorders were unrelated to CUD in early adulthood, yet Rhew et al. [92•] found evidence that greater depressive symptoms across time in adolescents resulted in an increased likelihood of a CUD in early adulthood. When considered within specific periods versus cumulative depression, however, the relations did not hold. Some work has indicated that depressive symptoms in the 7th grade relate to current cannabis use in the 10th grade [91], but other work has failed to find an association [114].

Questions also remain regarding the impact of cannabis use on the course and severity of depression. Among adults with a past-year diagnosis of MDD, 82.6% of non-users between baseline and follow-up no longer met diagnostic criteria for MDD at follow-up compared to 76.8% of those with a CUD between baseline and follow-up [116••]. Differences in remission rates across these groups did not significantly differ but may carry important clinical implications that warrant further examination. Indeed, this is substantiated by data indicating that relative to non-users, those with CUD may experience greater difficulty with specific symptoms of depression that may contribute to overall worse health outcomes [116••]. Additionally, among psychiatric outpatients with depression receiving mental health treatment, cannabis use, compared to non-use, predicted less improvement in depressive symptoms at 6-month and 1-year follow-up [78, 111•]. Interestingly, this finding appears to be specific to recreational, non-medical use given that medical cannabis use and non-use did not differ on follow-up outcomes of depression [111•]. Moreover, among persons receiving CUD treatment, those who reduced their cannabis use evinced greater or more gradual reductions in their depressive symptoms over time [77, 117]. Such findings, however, may be limited to persons with mild or moderate to severe depression, as depression scores were slightly elevated after cannabis use frequency was reduced among those with minimal depression [117]. These data may be significant in informing clinicians treating cannabis use disorders for those with comorbid depression.

While there is evidence for an effect between cannabis (with THC) and depressive disorders, less is known about the association between CBD and depression. One recent review on CBD found limited and low-grade evidence suggesting CBD may play a role in alleviating depressive symptoms in some individuals [86]. The overall results of the review, however, found no impact of pharmaceutical THC (with or without CBD) on depressive symptoms. Research on this relation is novel, and while there are some animal and small population studies that suggest an association between CBD and depression [86], there is need for future longitudinal work to determine the relation between CBD and depression.

The current literature on the depression/cannabis use association presents mixed evidence for the self-medicating and substance-induced hypotheses. This suggests that future work is needed to identify causal pathways and the directionality of their association. However, recent findings provide initial evidence for the shared-vulnerability model, evincing factors such as age to be associated with the depression/cannabis use association [51, 72]. Future work could examine potential moderators and mediators which influence the directionality of this relation to shed light on the causal pathways and to determine treatment options. In addition, future research on the association between CBD and depression is needed to find robust evidence for any of the theoretical models associated with depressive disorders and other substance use.

Comorbid Anxiety and Depressive Disorders with Alcohol, Tobacco, and Cannabis

Anxiety and depressive disorders share similar symptomology and are often comorbid [118]. Yet, further research is needed to explore the impact of substance use on the co-occurrence of anxiety and depressive disorders. A study by Bradizza et al. [119] on alcohol and comorbid anxiety and depressive disorders found that individuals with two or more comorbid disorders evinced heavier drinking, higher drinking frequency, and greater severity and intensity of psychological symptoms than those without comorbid anxiety and depressive disorders [119]. Similarly, Karpyak et al. [120] found that comorbid anxiety and depressive disorders increased the propensity for males to drink in negative emotional situations. However, this finding was not observed in females [120]. Another study by Rambau et al. [121] found that individuals with AUD and comorbid SAD were more likely to report current major depression than those without AUD [121]. Regarding smoking relations, a recent review reported mixed findings on whether comorbid anxiety and depressive disorders were likely to influence the onset of smoking or whether smoking would precede comorbid anxiety and depressive disorders [52]. The disparity in findings may be due to variation in study designs and confounders. As to cannabis use, an older study by

Hayatbakhsh et al. [122] found that frequent cannabis users were more likely to experience anxiety and depression at age 21 than those who did not regularly use cannabis [122]. Conversely, a recent Swedish study found no longitudinal relation between cannabis use and comorbid anxiety and depression nor for the reverse association. The variation in findings may be due to the measures utilized to assess cannabis use as well as environmental confounders [69]. There is a paucity of recent work that has studied the relation between cannabis (with or without THC/CBD) on comorbid anxiety and depressive disorders. Future research is crucial to prospectively study the temporal sequencing of anxiety and depressive disorder comorbidity in relation to substance use.

Conclusions

Recent literature depicts varying directional pathways with some evidence endorsing the self-medication or coping hypothesis and other work supporting the substance-induced hypothesis across anxiety/depressive disorders and substance use. These findings should be considered in the context of specific anxiety disorders, as stronger or weaker evidence for putative causal or consequential pathways were observed across specific disorders. Notably, shared-vulnerability and biopsychosocial factors or confounds, particularly sex, genetics, age, cultural variables, and concurrent substance use often contribute to and explain the purported directional effects, suggesting a shared-vulnerability model may best explain high rates of co-occurrence across conditions [33••, 51, 95, 97, 98, 101, 115]. Indeed, environmental, social (e.g., neighborhood or school environment), and genetic factors have been robustly and consistently implicated in the onset and maintenance of anxiety and depressive disorders as well as substance use [33••, 73•, 76]. Thus, such factors may uniquely influence each condition and ultimately increase the likelihood for the development of the other. The occurrence of these conditions in isolation may trigger an increased likelihood for the other, resulting in a positive feedback loop wherein each condition maintains the other. In addition to individual differences, there are numerous methodological considerations that may contribute to the variability in results, such as differences in operationalization and measurement of conditions and use behavior, study design, follow-up period, and analytic strategy [10••, 26••, 52, 123]. Collectively, the literature remains inconclusive on the temporal associations between anxiety and depressive disorders and initiation of substance use and reverse causality, underscoring the need for more prospective work that employs sophisticated research designs to test proposed causality. Efforts to move this work forward would benefit from integrating tests of moderation and mediation as such work is critical to inform effective, process- and person-oriented treatment for mental health conditions such as anxiety/depression and substance use disorders.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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