Published in final edited form as:

Child Adolesc Psychiatr Clin N Am. 2016 July ; 25(3): 533–548. doi:10.1016/j.chc.2016.02.006.

MEDICAL COMORBIDITY AND COMPLICATIONS

Scott E. Hadland, MD, MPH^{1,2,3} and Leslie R. Walker, MD^{4,5}

¹Boston Children's Hospital, Division of Adolescent / Young Adult Medicine, Department of Medicine, 300 Longwood Avenue, Boston, MA, USA, 02115

²Harvard T. H. Chan School of Public Health, Department of Health Policy and Management, Kresge Building, 677 Huntington Avenue, Boston, MA, USA, 02115

³Harvard Medical School, Department of Pediatrics, 25 Shattuck St., Boston, MA, USA, 02115

⁴Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA, USA, 98105

⁵University of Washington, Department of Pediatrics, 1959 NE Pacific St., Box 356320, Seattle, WA, USA, 98195

Abstract

Like their peers in the general youth population, YCMC are at risk of experimentation and regular substance use, including non-medical use of prescription medications. However, given dangerous disease-substance interactions, the stakes for detecting and intervening on substance use are perhaps even higher for YCMC. Given risk for non-adherence with chronic disease management among substance-using youth, it is incumbent on primary care providers, specialty providers, and behavioral health specialists to be vigilant in asking about substance and providing brief counseling and referral to formal substance use treatment when appropriate. Doing so is not only likely to prevent the direct harm of alcohol and drug use, but also to simultaneously improve chronic disease treatment outcomes.

Keywords

adolescents; chronic disease; substance-related disorders; ethanol; street drugs; tobacco products; electronic cigarettes

To date, the wealth of observational studies on youth substance use have focused on the general adolescent population, which is comprised predominantly of healthy youth. As established in previous chapters, alcohol and drug use are associated with a wide range of adverse health effects and neurocognitive changes for all adolescents. Less studied, however,

Send correspondence to: Scott E. Hadland, MD, MPH, Division of Adolescent / Young Adult Medicine, Department of Medicine, 300 Longwood Avenue, Boston, MA, USA, 02115, **Phone:** 857-218-3236, **Fax:** 617-730-0185, scott.hadland@childrens.harvard.edu.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

are the *additional* potential consequences for youth with chronic medical conditions (YCMC) who use substances. There has been almost no systematic epidemiologic examination of substance use among YCMC, thus constituting an enormous knowledge gap. Since alcohol and drugs have widespread and potentially harmful physiologic effects throughout the body, the potential for organ systems to sustain a ‘double hit’, both from chronic illness and from substance use, is high.

Here, we review (1) the epidemiology of substance use among YCMC, (2) mechanisms whereby substances might alter the course of illness for YCMC, and (3) recommendations for routine health care and medical screening for all adolescents who use substances, with special consideration for YCMC. Using case examples, we also present some special considerations for YCMC with regard to the substances they use and potential disease-specific concerns (see Boxes 1-3).

Epidemiology of substance use among YCMC

Despite readily available information on drug and alcohol use among the general adolescent population (e.g., [1-3]), there have been no similarly rigorous, large-scale, systematic epidemiologic studies of substance use among YCMC. Since at least 1 in 10 of adolescents live with identified chronic conditions, there is urgent need for further study [4-5]. Data on substance use are available from smaller samples of YCMC, but data are increasingly outdated and do not capture more recent trends (e.g., the emergence of e-cigarette use and of synthetic cannabinoids [1]).

Fortunately, data from small studies are available from multiple settings worldwide, but findings from one country do not necessarily generalize to other locations. Additionally, there has been no systematic comparison across different illnesses – for example, comparing youth with asthma to youth with type 1 diabetes mellitus (T1DM) or to youth with inflammatory bowel disease – to help understand the interplay between different illness experiences and substance use. Finally, most samples are clinic-based, which exclude YCMC who are not actively receiving medical care and may have poorer disease control; although this has not been studied, these same youth may be more likely to use substances and experience related harm.

Many studies conducted to date have demonstrated comparable or even slightly *lower* prevalence of lifetime or recent drug, alcohol or tobacco use among YCMC [6-9]. However, as outlined below, there have also been documented notable exceptions to this, particularly among adolescents with asthma [10-12], suggesting that there may be critical differences among different chronic medical conditions. Additionally, what is clear from studies to date is that even when the prevalence of substance use is lower among YCMC, there remains a substantial number of youth who do use substances, thus necessitating careful screening by all health care providers for alcohol, tobacco and drug use, and their associated harms.

Asthma

No large-scale epidemiologic studies provide stable estimates of the proportion of youth with asthma who smoke cigarettes or use alcohol or other drugs, though several studies have

suggested that cigarette smoking and other substance use may be higher among youth with asthma than without [10-12]. Reasons for why this is remain unclear. One national survey of adolescents recruited from schools (rather than from clinics) demonstrated that adolescents with asthma were significantly more likely to smoke cigarettes daily and smoked more cigarettes per day on average [11]. However, the authors also found that adolescents with asthma were more likely to have started smoking at a younger age, which raises the question of whether their initiating smoking may have precipitated an asthma diagnosis in the first place. Regardless of whether a diagnosis of asthma precedes smoking or vice versa, from the health care provider's perspective, it is critical to recognize that tobacco use has clear deleterious effects on disease management and symptom control [13]. Alcohol use and marijuana use are clearly prevalent among youth with asthma, and youth who smoke cigarettes are themselves even more likely to use other substances [9,10,14-16].

Type I diabetes mellitus

For adolescents with T1DM, several studies have identified lower prevalence of alcohol and other substance use compared to the general adolescent population [7,8,17], but a more recent survey highlighted that in one clinic-based sample, more than 1 in 3 adolescents with T1DM reported past-year alcohol use and nearly 1 in 2 reported lifetime binge drinking [9]. In this same study, nearly 1 in 5 adolescents with T1DM reported past-month marijuana use. The lower prevalence of substance use reported in some studies may be due to sampling young adolescents; some data suggests that adolescents with T1DM may have lower prevalence of substance use in their early teen years but have similar prevalence to the general youth population by the end of adolescence [17]. Data from Australia highlight a high prevalence of street drug use among adolescents with T1DM, which is concerning given the appetite-altering effects of many substances with resultant effects on blood glucose levels [18,19].

Other chronic medical conditions

Data on substance use among adolescents with other chronic medical conditions are lacking. However, in light of findings from one sample of youth from subspecialty clinics serving adolescents with asthma/cystic fibrosis, T1DM, arthritis, or inflammatory bowel disease (IBD) showing that there may be disease-specific differences in prevalence of alcohol and marijuana use [9], further studies are merited to understand the epidemiology of substance use across a wide array of chronic medical conditions.

How substances may alter the course of illness among YCMC

Clinically significant harm can result from the use of substances in the setting of a chronic medical condition. Potential mechanisms include the direct physiologic effects of alcohol and drugs, toxic effects, interaction with medications used for chronic disease management, effects resulting from the route of administration of substances, and behavior changes resulting from substance use. Table 1 reviews these mechanisms and provides some examples documented in the medical literature.

The first of these mechanisms, physiologic or metabolic changes exerted by substances, may involve direct action of the substance at the cellular level and/or indirect effects mediated by the central nervous system (CNS). For example, stimulants act directly on the cardiovascular system by enhancing transmission at sympathetic nerve terminals that innervate myocardium and the peripheral vasculature, and also enhance CNS-mediated increases in heart rate, blood pressure, and systemic vascular resistance [20-21]. Although poorly studied, it is probable such physiologic changes acutely place adolescents with chronic hypertension, structural heart disease, or cardiac conduction abnormalities at even higher risk of morbidity or mortality. Additionally, a newer body of evidence reveals that cannabinoids such as Δ^9 -tetrahydrocannabinol (THC) have a direct effect on cannabinoid receptors in the gastrointestinal tract [22]. Resulting physiologic effects may include decreased intestinal motility, secretion, and inflammation, all of which may theoretically be favorable for patients with inflammatory bowel disease, although it should be noted that in patients with Crohn's disease who use marijuana regularly, long-term outcomes may actually be worse [23].

The second of these mechanisms is the direct, toxic effect of substances on cells and tissues of the body. One of the most thoroughly described examples is the hepatotoxic effect of ethanol [24]. Oxidation of ethanol in the liver produces excess reduced nicotinamide adenine dinucleotide (NADH), which inhibits fatty acid oxidation, ultimately leading to hepatic steatosis [25]. Ethanol metabolism in the liver also produces reactive oxygen species, which are directly cytotoxic to hepatocytes [26-27]. These processes are likely deleterious for young people with preexisting liver disease who drink alcohol, and compounding this, hepatotoxicity may be further exacerbated by medications commonly prescribed for YCMC, such as methotrexate and acetaminophen [28-29].

The third mechanism is interaction of drugs and alcohol with medications used for chronic disease management. A full review of all possible substance-medication interactions is beyond the scope of this article, but such processes are best understood for alcohol, and ethanol-medication interactions are briefly reviewed here. Ethanol first affects the metabolism of medications by decreasing gastric emptying [30]. This delay in gastric emptying occurs even after one-time consumption of alcohol (*i.e.*, it does not require regular alcohol consumption), and alters the normal first-pass metabolism of medications. First-pass metabolism significantly alters plasma levels of propranolol, morphine, meperidine, diazepam, midazolam, lidocaine, and cimetidine. Thus, levels of these medications could be significantly altered among YCMC who ingest alcohol, although extensive studies have not been conducted [30-32]. Alcohol also induces cytochrome P450 2C9, potentially affecting the metabolism of medications metabolized by this enzyme (*e.g.*, warfarin, phenytoin) [30]. Other interactions of ethanol with medications include disulfiram-like reactions (*e.g.*, from metronidazole, griseofulvin, procarbazine, some cephalosporins) [33-34], and enhancement of the depressive effects of certain medications on the CNS and on respiratory drive [30-35-36].

The fourth mechanism involves complications specific to the route of administration of the substance being used (*e.g.*, inhaled, ingestion, injected, or other routes). Smoking marijuana, for example, is associated with increased wheeze, cough, and airway inflammation [37],

which may have critical implications for youth with asthma and for YCMC undergoing surgical procedures requiring general anesthesia with airway intubation [38-39]. Drug injection places users at risk of abscesses, blood-borne bacterial and viral infections, which may have particularly dangerous for youth with immunodeficiency or who are on immunosuppressive medications [40-42]. Similarly, the risk for endocarditis as a result of drug injection could be particularly acute for youth with preexisting structural or valvular heart disease [40].

The fourth and final mechanism relates to inferior medication adherence or other disease management among YCMC who use alcohol or drugs. In one recent sample of adolescents with asthma, cystic fibrosis, T1DM, arthritis or IBD, youth who drank were nearly 80% more likely to report regularly missing medications [9]. Poor medication adherence among young adult heavy drinkers is well described [43], and is further complicated by co-occurring marijuana use [44]. Since adolescence represents a transition period of increasing autonomy and independence, the influence of substance use on self-care and disease management should be critical area for future study.

Although the mechanisms above highlight how substances may be harmful to YCMC, there is also the possibility that some substances, or compounds within them, have therapeutic benefits. For no substance is this more passionately debated currently than for marijuana, which in the United States and elsewhere has been legally approved in many jurisdictions for medicinal use [45-51]. Major professional bodies, including the American Academy of Pediatrics, remain opposed to use of marijuana for medicinal purposes outside the usual drug approval regulatory processes (*e.g.*, by the US Food and Drug Administration) [48]. This is in part in response to the lack of strong empirical evidence that marijuana has medicinal benefits in conditions that manifest during adolescence.

Nonetheless, small observational studies and anecdotal reports have shown that for some young people with intractable epilepsy [52-53], severe autism [54], inflammatory bowel disease [23-55], and arthritis [56], certain cannabinoids present in marijuana may have a beneficial effect. Additionally, a recent placebo-controlled trial of 21 adults with Crohn's disease showed improvement in symptoms with cannabis use when other therapies had failed [57]. This study did not include adolescents, and it is possible adolescents' pathophysiological profile may differ and that they are at greater risk for long-term harms of chronic marijuana use [58-62]. Other proposed clinical applications for cannabis include symptomatic management of nausea, poor appetite, and pain, as well as treatment of multiple sclerosis, spinal cord injury, and glaucoma [63]. Nonetheless, owing to its status as an illegal, controlled substance in the United States and elsewhere, high-quality randomized-controlled trials of cannabinoids are lacking. Until careful studies demonstrate the safety, tolerability, efficacy, and proper dosing of cannabinoids for chronic disease, practitioners should continue to exercise caution given the well-established long-term health and adverse neurocognitive effects of marijuana for adolescents and young adults [58-62].

Finally, in addition to substances affecting the course of chronic medical conditions, certain disease processes can in turn affect the metabolism of drugs of misuse. A commonly cited example is that benzodiazepines require oxidation by the liver for their metabolism and

elimination, and therefore the misuse of benzodiazepines by adolescents with liver disease may be especially hazardous (with the exception of lorazepam, oxazepam, and temazepam, which do not require extensive modification by the liver) [29-64].

Routine health care and screening

During adolescent periodic and routine preventive health care visits, screening for drug use including non-medical use of prescription medications is recommended [65], and should also be conducted at behavioral health visits and specialty clinic visits. Research has shown that the health provider is a trusted source of information that adolescents and their families look to for advice on drug use, even more so than the internet or social media sources [66-67].

Preventive messages to YCMC are critical. YCMC may not visit the primary care provider's office often and therefore may not have the opportunity to learn about the risks posed by substance use and non-medical use of prescription drugs. Similarly, owing to school absences for medical visits, they may be less likely to receive substance use prevention education. Even if they do, universal prevention messages may not apply as readily to YCMC and the additional risks they may have as someone managing a chronic medical condition.

There is much literature on the need for adolescents to have private health conversations with their provider, and when confidentiality is explained at the beginning of the visit, adolescents are often open to disclosing substance use, as well as other sensitive information pertaining to mental health and sexual health. Conversely, they are unlikely to disclose this information when their parent or guardian is present [68-69]. When adolescents and young adults are given private time one-on-one with the provider, they often disclose information on substance use and non-medical use of prescription medications that can be helpful in optimizing the care and well being of the adolescents and young adults.

At specialty clinic appointments for chronic disease management, providers may be more likely to focus on illness treatment and may be less likely to ask about substance use or to inform YCMC of the risks of substance use, particularly as it pertains to their specific condition. Specialty providers may be less likely to realize that YCMC are in need of this information or lack sufficient time to discuss these concerns if disease management concerns prevail [9].

Routine screening and brief intervention can be obtained effectively either during face-to-face encounters or using computer or phone assisted applications [70-71]. These tools not only screen but also can deliver personalized preventive messages in real time to the adolescent. Some adolescents are even more likely to disclose sensitive information during computerized screening than during face-to-face interview with a provider. This is beneficial for providers who must manage significant clinical time constraints; once the adolescent is with the provider the screening information is available to guide the encounter and any needed intervention.

There are readily available, free screening forms that have been validated in this age group. The CRAFFT screen and S2BI questionnaires are valid and reliable for screening adolescent substance use and are fast to administer in the busy clinical setting [72-74]. Such screens are recommended as a routine component of Screening, Brief Intervention, and Referral to Treatment (SBIRT), which is universally recommended by the American Academy of Pediatrics [75].

Summary

Like their peers in the general youth population, YCMC are at risk of experimentation and regular substance use, including non-medical use of prescription medications. However, given dangerous disease-substance interactions, the stakes for detecting and intervening on substance use are perhaps even higher for YCMC. Given risk for non-adherence with chronic disease management among substance-using youth, it is incumbent on primary care providers, specialty providers, and behavioral health specialists to be vigilant in asking about substance and providing brief counseling and referral to formal substance use treatment when appropriate. Doing so is not only likely to prevent the direct harm of alcohol and drug use, but also to simultaneously improve chronic disease treatment outcomes.

Acknowledgments

Dr. Hadland is supported by the Division of Adolescent and Young Adult Medicine at Boston Children's Hospital and the Leadership Education in Adolescent Health Training Program T71 MC00009 (MCH/HRSA) and by a National Research Service Award 1T32 HD075727 (NIH/NICHHD).

References

1. Johnston, LD.; O'Malley, PM.; Miech, RA., et al. [February 24, 2015] Monitoring the Future National Results on Drug Use: 2014 Overview, Key Findings on Adolescent Drug Use. Available at: <http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2014.pdf>
2. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48. Rockville, MD: 2014. HHS Publication No. (SMA) 14-4863
3. Johnson NB, Hayes LD, Brown K, et al. CDC National Health Report: Leading Causes of Morbidity and Mortality and Associated Behavioral Risk and Protective Factors-United States, 2005-2013. MMWR Surveill Summ. 2014; 63:3-27.
4. Sawyer SM, Drew S, Yeo MS, et al. Adolescents with a chronic condition: challenges living, challenges treating. Lancet (London, England). 2007; 369:1481-9.
5. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA. 2010; 303:623-30. [PubMed: 20159870]
6. Britto MT, Garrett JM, Dugliss MA, et al. Risky behavior in teens with cystic fibrosis or sickle cell disease: a multicenter study. Pediatrics. 1998; 101:250-6. [PubMed: 9445499]
7. Jacobson AM, Hauser ST, Willett JB, et al. Psychological adjustment to IDDM: 10-year follow-up of an onset cohort of child and adolescent patients. Diabetes Care. 1997; 20:811-8. [PubMed: 9135947]
8. Glasgow AM, Tynan D, Schwartz R, et al. Alcohol and drug use in teenagers with diabetes mellitus. J Adolesc Health. 1991; 12:11-4. [PubMed: 2007146]
9. Weitzman ER, Ziemnik RE, Huang Q, et al. Alcohol and Marijuana Use and Treatment Nonadherence Among Medically Vulnerable Youth. Pediatrics. 2015
10. Forero R, Bauman A, Young L, et al. Asthma, health behaviors, social adjustment, and psychosomatic symptoms in adolescence. J Asthma. 1996; 33:157-64. [PubMed: 8675494]

11. Precht DH, Keiding L, Madsen M. Smoking patterns among adolescents with asthma attending upper secondary schools: a community-based study. *Pediatrics*. 2003; 111:e562–8. [PubMed: 12728110]
12. Mo F, Robinson C, Choi BC, et al. Analysis of prevalence, triggers, risk factors and the related socio-economic effects of childhood asthma in the Student Lung Health Survey (SLHS) database, Canada 1996. *Int J Adolesc Med Health*. 15:349–58. [PubMed: 14719417]
13. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*. 1996; 312:1195–9. [PubMed: 8634562]
14. Weekes JC, Cotton S, McGrady ME. Predictors of substance use among black urban adolescents with asthma: a longitudinal assessment. *J Natl Med Assoc*. 2011; 103:392–8. [PubMed: 21809788]
15. Guo S-E, Ratner PA, Johnson JL, et al. Correlates of smoking among adolescents with asthma. *J Clin Nurs*. 2010; 19:701–11. [PubMed: 20500312]
16. Hublet A, De Bacquer D, Boyce W, et al. Smoking in young people with asthma. *J Public Health (Oxf)*. 2007; 29:343–9. [PubMed: 17675644]
17. Martínez-Aguayo A, Araneda JC, Fernandez D, et al. Tobacco, alcohol, and illicit drug use in adolescents with diabetes mellitus. *Pediatr Diabetes*. 2007; 8:265–71. [PubMed: 17850469]
18. Lee P, Greenfield JR, Gilbert K, et al. Recreational drug use in type 1 diabetes: an invisible accomplice to poor glycaemic control? *Intern Med J*. 2012; 42:198–202. [PubMed: 22356493]
19. Ng RSH, Darko DA, Hillson RM. Street drug use among young patients with Type 1 diabetes in the UK. *Diabet Med*. 2004; 21:295–6. [PubMed: 15008844]
20. Gorelick, DA.; Baumann, MA. The Pharmacology of Cocaine, Amphetamines, and Other Stimulants. In: Ries, RK.; Fiellin, DA.; Miller, SC., et al., editors. *ASAM Princ Addict Med*. 5. Philadelphia, PA: LWW; 2014.
21. Afonso L, Mohammad T, Thatai D. Crack whips the heart: a review of the cardiovascular toxicity of cocaine. *Am J Cardiol*. 2007; 100:1040–3. [PubMed: 17826394]
22. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. *Gut*. 2008; 57:1140–55. [PubMed: 18397936]
23. Storr M, Devlin S, Kaplan GG, et al. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. *Inflamm Bowel Dis*. 2014; 20:472–80. [PubMed: 24407485]
24. O'Shea RS, Dasarthy S, McCullough AJ. Alcoholic liver disease. *Am J Gastroenterol*. 2010; 105:14–32. quiz 33. [PubMed: 19904248]
25. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology*. 2008; 134:1655–69. [PubMed: 18471545]
26. Albano E. Oxidative mechanisms in the pathogenesis of alcoholic liver disease. *Mol Aspects Med*. 2008; 29:9–16. [PubMed: 18045675]
27. Dey A, Cederbaum AI. Alcohol and oxidative liver injury. *Hepatology*. 2006; 43:S63–74. [PubMed: 16447273]
28. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med*. 2006; 354:731–9. [PubMed: 16481640]
29. Kim JW, Phongsamran PV. Drug-induced liver disease and drug use considerations in liver disease. *J Pharm Pract*. 2009
30. Chan L-N, Anderson GD. Pharmacokinetic and pharmacodynamic drug interactions with ethanol (alcohol). *Clin Pharmacokinet*. 2014; 53:1115–36. [PubMed: 25267448]
31. Pond SM, Tozer TN. First-pass elimination basic concepts and clinical consequences. *Clin Pharmacokinet*. 1984; 9:1–25. [PubMed: 6362950]
32. Parlesak A, Billinger MH-U, Bode C, et al. Gastric alcohol dehydrogenase activity in man: influence of gender, age, alcohol consumption and smoking in a Caucasian population. *Alcohol Alcohol*. 2002; 37:388–93. [PubMed: 12107043]
33. Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet*. 1997; 33:79–90. [PubMed: 9260032]

34. Ren S, Cao Y, Zhang X, et al. Cephalosporin induced disulfiram-like reaction: a retrospective review of 78 cases. *Int Surg.* 99:142–6. [PubMed: 24670024]
35. Hesse LM, von Moltke LL, Greenblatt DJ. Clinically important drug interactions with zopiclone, zolpidem and zaleplon. *CNS Drugs.* 2003; 17:513–32. [PubMed: 12751920]
36. Fiske WD, Jobes J, Xiang Q, et al. The effects of ethanol on the bioavailability of oxymorphone extended-release tablets and oxymorphone crush-resistant extended-release tablets. *J Pain.* 2012; 13:90–9. [PubMed: 22208805]
37. Tetrault JM, Crothers K, Moore BA, et al. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med.* 2007; 167:221–8. [PubMed: 17296876]
38. Mallat A, Roberson J, Brock-Utne JG. Preoperative marijuana inhalation--an airway concern. *Can J Anaesth.* 1996; 43:691–3. [PubMed: 8807175]
39. Mills PM, Penfold N. Cannabis abuse and anaesthesia. *Anaesthesia.* 2003; 58:1125. [PubMed: 14616609]
40. Gordon RJ, Lowy FD. Bacterial infections in drug users. *N Engl J Med.* 2005; 353:1945–54. [PubMed: 16267325]
41. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet.* 2012; 379:55–70. [PubMed: 22225671]
42. Lloyd-Smith E, Kerr T, Hogg RS, et al. Prevalence and correlates of abscesses among a cohort of injection drug users. *Harm Reduct J.* 2005; 2:24. [PubMed: 16281979]
43. Grodensky CA, Golin CE, Ochtera RD, et al. Systematic review: effect of alcohol intake on adherence to outpatient medication regimens for chronic diseases. *J Stud Alcohol Drugs.* 2012; 73:899–910. [PubMed: 23036207]
44. Peters EN, Leeman RF, Fucito LM, et al. Co-occurring marijuana use is associated with medication nonadherence and nonplanning impulsivity in young adult heavy drinkers. *Addict Behav.* 2012; 37:420–6. [PubMed: 22189052]
45. D'Souza D, Ranganathan M. Medical marijuana: Is the cart before the horse? *JAMA.* 2015; 313:2431–2. [PubMed: 26103026]
46. Choo EK, Benz M, Zaller N, et al. The Impact of State Medical Marijuana Legislation on Adolescent Marijuana Use. *J Adolesc Health.* 2014
47. Wall MM, Poh E, Cerda M, et al. Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear. *Ann Epidemiol.* 2011; 21:714–6. [PubMed: 21820632]
48. Ammerman S, Ryan S, Adelman WP. The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update. *Pediatrics.* 2015; 135:584–7. [PubMed: 25624383]
49. Harper S, Strumpf EC, Kaufman JS. Do medical marijuana laws increase marijuana use? Replication study and extension. *Ann Epidemiol.* 2012; 22:207–12. [PubMed: 22285867]
50. Hasin DS, Wall M, Keyes KM, et al. Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys. *The Lancet Psychiatry.* 2015; 0366
51. Lynne-Landsman SD, Livingston MD, Wagenaar AC. Effects of state medical marijuana laws on adolescent marijuana use. *Am J Public Heal.* 2013; 103:1500–6.
52. Vogelstein, F. [August 3, 2015] One Man's Desperate Quest to Cure His Son's Epilepsy - With Weed. Available at: <http://www.wired.com/2015/07/medical-marijuana-epilepsy/>
53. Gonzalez, D. [August 3, 2015] For Children's Seizures, Turning to Medical Marijuana. Available at: <http://lens.blogs.nytimes.com/2015/03/26/medical-marijuana-eases-childhood-seizures/>
54. Borchardt, D. [August 3, 2015] Desperate Parents Of Autistic Children Trying Cannabis Despite Lack Of Studies. Available at: <http://www.forbes.com/sites/debraborchardt/2015/06/10/desperate-parents-of-autistic-children-trying-cannabis-despite-lack-of-studies/>
55. Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. *Digestion.* 2012; 85:1–8. [PubMed: 22095142]

56. Fitzcharles M-A, Clauw DJ, Ste-Marie PA, et al. The dilemma of medical marijuana use by rheumatology patients. *Arthritis Care Res (Hoboken)*. 2014; 66:797–801. [PubMed: 24591442]
57. Naftali T, Bar-Lev Schleider L, Dotan I, et al. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol*. 2013; 11:1276–80.e1. [PubMed: 23648372]
58. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009; 374:1383–91. [PubMed: 19837255]
59. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012; 109:E2657–64. [PubMed: 22927402]
60. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007; 370:319–28. [PubMed: 17662880]
61. Hadland SE, Knight JR, Harris SK. Medical marijuana: review of the science and implications for developmental-behavioral pediatric practice. *J Dev Behav Pediatr*. 36:115–23. [PubMed: 25650954]
62. Hadland SE, Harris SK. Youth marijuana use: state of the science for the practicing clinician. *Curr Opin Pediatr*. 2014; 26:420–7. [PubMed: 24914878]
63. Ben, Amar M. Cannabinoids in medicine: A review of their therapeutic potential. *J Ethnopharmacol*. 2006; 105:1–25. [PubMed: 16540272]
64. Witek MW, Rojas V, Alonso C, et al. Review of benzodiazepine use in children and adolescents. *Psychiatr Q*. 2005; 76:283–96. [PubMed: 16080423]
65. Hagan, JF.; Shaw, JS.; Duncan, PM. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents. 3 Available at: http://brightfutures.aap.org/3rd_Edition_Guidelines_and_Pocket_Guide.html
66. Kim SU, Syn SY. Research trends in teens' health information behaviour: a review of the literature. *Heal Inf Libr J*. 2014; 31:4–19.
67. Selkie EM, Benson M, Moreno M. Adolescents' Views Regarding Uses of Social Networking Websites and Text Messaging for Adolescent Sexual Health Education. *Am J Health Educ*. 2011; 42:205–12. [PubMed: 22229150]
68. Britto MT, Tivorsak TL, Slap GB. Adolescents' needs for health care privacy. *Pediatrics*. 2010 peds – 2010.
69. Ford C, English A, Sigman G. Confidential Health Care for Adolescents: Position Paper for the Society for Adolescent Medicine. *J Adolesc Heal*. 2004; 35:160–7.
70. Harris SK, Csemy L, Sherritt L, et al. Computer-facilitated substance use screening and brief advice for teens in primary care: an international trial. *Pediatrics*. 2012; 129:1072–82. [PubMed: 22566420]
71. Chisolm DJ, Gardner W, Julian T, et al. Adolescent Satisfaction with Computer-Assisted Behavioural Risk Screening in Primary Care. *Child Adolesc Ment Health*. 2008; 13:163–8. [PubMed: 19779573]
72. Levy S, Weiss R, Sherritt L, et al. An electronic screen for triaging adolescent substance use by risk levels. *JAMA Pediatr*. 2014; 168:822–8. [PubMed: 25070067]
73. Knight JR, Sherritt L, Shrier LA, et al. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. *Arch Pediatr Adolesc Med*. 2002; 156:607–14. [PubMed: 12038895]
74. Knight JR, Shrier LA, Bravender TD, et al. A new brief screen for adolescent substance abuse. *Arch Pediatr Adolesc Med*. 1999; 153:591–6. [PubMed: 10357299]
75. Levy SJ, Kokotailo PK. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics*. 2011; 128:e1330–40. [PubMed: 22042818]
76. Silverman RA, Boudreaux ED, Woodruff PG, et al. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest*. 2003; 123:1472–9. [PubMed: 12740263]
77. Leuenberger P, Schwartz J, Ackermann-Liebrich U, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am J Respir Crit Care Med*. 1994; 150:1222–8. [PubMed: 7952544]

78. Gilliland FD, Islam T, Berhane K, et al. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med*. 2006; 174:1094–100. [PubMed: 16973983]
79. Primack BA, Soneji S, Stoolmiller M, et al. Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. *JAMA Pediatr*. 2015;1–7.
80. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA*. 2015; 314:700. [PubMed: 26284721]
81. Kalkhoran S, Glantz SA. Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis. *JAMA Intern Med*. 2015
82. Collaco JM, Drummond MB, McGrath-Morrow SA. Electronic cigarette use and exposure in the pediatric population. *JAMA Pediatr*. 2015; 169:177–82. [PubMed: 25546699]
83. Bae J. Influence of asthma on the longitudinal trajectories of cigarette use behaviors from adolescence to adulthood using latent growth curve models. *J Prev Med Public Health*. 2015; 48:111–7. [PubMed: 25857649]
84. Wolpert, H.; Anderson, B.; Harris, M. Transitions in care: Meeting the challenges of type 1 diabetes in young adults. Alexandria, VA: American Diabetes Association; 2009.
85. Peters A, Laffel L. Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems A position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the Am. Diabetes Care. 2011; 34:2477–85. [PubMed: 22025785]
86. Lee P, Greenfield JR, Campbell LV. Managing young people with Type 1 diabetes in a “rave” new world: metabolic complications of substance abuse in Type 1 diabetes. *Diabet Med*. 2009; 26:328–33. [PubMed: 19388960]
87. Seymour HR, Gilman D, Quin JD. Severe ketoacidosis complicated by “ecstasy” ingestion and prolonged exercise. *Diabet Med*. 1996; 13:908–9. [PubMed: 8911787]
88. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999; 16:466–71. [PubMed: 10391393]
89. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999; 16:466–71. [PubMed: 10391393]
90. Laing SP, Jones ME, Swerdlow AJ, et al. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care*. 2005; 28:1618–23. [PubMed: 15983310]
91. Wen H, Hockenberry JM, Cummings JR. The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. *J Health Econ*. 2015; 42:64–80. [PubMed: 25863001]
92. Hill K. Medical marijuana does not increase adolescent marijuana use. *The Lancet Psychiatry*. 2015; 2:572–3. [PubMed: 26303534]
93. Leung Y, Heyman MB, Mahadevan U. Transitioning the adolescent inflammatory bowel disease patient: guidelines for the adult and pediatric gastroenterologist. *Inflamm Bowel Dis*. 2011; 17:2169–73. [PubMed: 21910179]
94. Lu Y, Markowitz J. Inflammatory bowel disease in adolescents: what problems does it pose? *World J Gastroenterol*. 2011; 17:2691–5. [PubMed: 21734775]
95. Philpott JR. Transitional care in inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2011; 7:26–32. [PubMed: 21346849]
96. Naftali T, Mechulam R, Lev LB, et al. Cannabis for inflammatory bowel disease. *Dig Dis*. 2014; 32:468–74. [PubMed: 24969296]
97. Turner BC, Jenkins E, Kerr D, et al. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care*. 2001; 24:1888–93. [PubMed: 11679452]
98. Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. *Circulation*. 2010; 122:2558–69. [PubMed: 21156654]
99. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med*. 2001; 345:351–8. [PubMed: 11484693]

100. Blowey DL. Nephrotoxicity of over-the-counter analgesics, natural medicines, and illicit drugs. *Adolesc Med Clin*. 2005; 16:31–43. x. [PubMed: 15844382]
101. Joffe HV, Xu R, Johnson FB, et al. Warfarin dosing and cytochrome P450 2C9 polymorphisms. *Thromb Haemost*. 2004; 91:1123–8. [PubMed: 15175798]
102. Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenet Genomics*. 2002; 12:251–63.
103. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014; 46:86–95. [PubMed: 24160757]
104. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol*. 2003; 2:347–56. [PubMed: 12849151]

BOX 1**Case Example 1 – Asthma**

JV is a 15-year-old adolescent male with moderate persistent asthma and near-daily use cigarettes and marijuana. In the last two years, JV has been hospitalized three times for status asthmaticus, including a recent admission to the intensive care unit (ICU) requiring intravenous magnesium sulfate and continuous albuterol.

A careful history by the ICU clinician reveals that JV began smoking e-cigarettes (*i.e.*, “vaping”) with friends when he was 14 years-old, and then shortly after began smoking combustible (*i.e.*, traditional) cigarettes. JV currently smokes 3-4 cigarettes per day with friends before and after school, and occasionally vapes at home in the evenings. He also has been smoking marijuana blunts more days than not, sometimes with friends, and sometimes alone in his backyard. He does not drink alcohol. Although JV’s mother, with whom he lives, wants him to quit marijuana and cigarettes, JV reports that he is not interested in cutting back or quitting. In fact, JV feels as though smoking marijuana actually helps him breathe easier, but his mother has noted that he seems to cough more when she has caught him using it.

Considerations

- The prevalence of cigarette smoking is elevated among youth who present to clinical attention with an asthma exacerbation [76], so all patients with asthma should be screened to assess for history of smoking.
- Cigarette smoke (both firsthand and secondhand) is a well-established trigger for asthma [13,77], and indeed, may be a risk factor for development of a new diagnosis of asthma [78].
- Similarly, although smoking marijuana may cause bronchorelaxation [37], it is also associated with worsened airway inflammation, mucous production, cough and wheeze [37], and youth with asthma should be counseled regarding the possibility for worsening asthma symptoms with marijuana use.
- E-cigarette use is an increasingly recognized risk factor for transition to smoking combustible cigarettes [79,80], and their role as a cessation aid (*i.e.*, using nicotine-containing e-cigarettes as a replacement for combustible cigarettes among cigarette smokers) is not well established [81].
- Furthermore, the potential harms of e-cigarette use among youth (including those with asthma) are not well studied [82], so all adolescents should be counseled regarding their as-yet unknown potential harms.
- Adolescents with asthma who use substances are less likely to adhere to their medications than those who do not use substances [9,11]; medication adherence should be carefully assessment among youth with asthma who use substances.

- The prevalence of cigarette smoking may actually naturally decrease among adolescents with asthma as they progress to young adulthood [83]; providers should provide assistance in helping youth with asthma quit.

Conclusion

JV was counseled regarding the potential health risks of his cigarette and marijuana smoking, but he was not interested initially in cutting back or quitting. An initial harm reduction approach was used, ensuring his safety when he was using marijuana, including ensuring he never rode in a car with youth who were using substances. With frequent follow-up and motivational enhancement techniques, JV ultimately cut back on his marijuana use and requested assistance in quitting cigarettes. Nicotine replacement therapy (a patch and chewing gum) was prescribed, and he set a quit date. With the close supervision of his mother as well as close clinical follow-up, he was successful in quitting. Nonetheless, he continues to smoke marijuana on weekends with friends, and his provider continues to encourage him to cease marijuana use altogether for his health.

BOX 2**Case Example 2 – Type 1 Diabetes Mellitus**

TB is a 16-year-old female with type I diabetes mellitus (T1DM) diagnosed at age 7 who reports use of alcohol in social settings on two or three weekend nights per month. She previously had generally good glycemic control with her hemoglobin (Hgb) A1c between 7.0% and 7.5%, but at her most recent visit, her Hgb A1c was 8.2%. She is on a basal-bolus regimen with insulin glargine administered every night and insulin aspart with meals.

Careful screening by her endocrinologist reveals that TB first began drinking alcohol this year with friends. She denies current use of other substances, noting that she does not like the idea of inhaling anything, and although she tried ‘molly’ on a single occasion at a party, she is afraid of getting in trouble with the law and plans to avoid illicit drugs moving forward. She receives excellent grades in school, and this has not changed with her substance use. TB would like to attend a competitive college.

She denies drinking alone, reporting that she only ever consumes alcohol in social situations. TB never drives while drinking and always ensures a ride from another friend who has a safe plan to get home. She reports “drinking to get drunk”, and usually consumes four or five beers with one or two occasional shots on a typical night with her friends. Recently, however, she had to be picked up by her parents after she was found vomiting at a house party, and TB disclosed shortly after that on another occasion, she blacked out after drinking on an empty stomach.

Considerations

- Binge drinking is common among adolescents with T1DM [9], and alcohol consumption is associated with risk for hypoglycemia [8,84]. Consistent with recommendations from the American Diabetes Association [85] and the American Academy of Pediatrics [75], clinicians should carefully screen adolescents with T1DM to ascertain their substance use intensity and frequency.
- Hypoglycemia can be delayed by several hours after drinking, which can be particularly hazardous to adolescents who drink and then fall asleep. Compounding this, glucagon for treatment of hypoglycemia may be less effective when youth have been drinking. Clinicians should determine whether youth with T1DM have ever drank to the extent of vomiting or blacking out, which can have hazardous consequences for blood glucose levels.
- On the long-term, alcohol and other substance use is associated with poor glycemic control in adolescents with T1DM [8,18]. Clinicians might consider whether an adolescent with poor glycemic control may have an underlying substance use disorder, and should consider more carefully monitoring for hyperglycemia among adolescents who use alcohol.

- Misuse of stimulants and other recreational club drugs such as ecstasy may place adolescents with T1DM for excess risk for diabetic ketoacidosis [18•86•87]. When screening for substance use among adolescents with T1DM, clinicians should be certain to ask about use of stimulants and other club drugs.
- Mortality is greatly elevated among youth with T1DM, largely owing to hypoglycemia and ketoacidosis [88•89]. Psychiatric comorbidity and substance use are associated with this increase in mortality [90]. Clinicians should be aware that the consequences of alcohol and substance use among patients with T1DM can be life-threatening.

Conclusion

TB was initially reluctant to cut back on her drinking, stating that she did not believe she had a drinking problem. As a harm reduction approach, her endocrinologist helped her understand the importance of wearing a medical alert bracelet at all times, and counseled her to talk to her friends about the criticality of seeking immediate medical attention if she loses consciousness. Her endocrinologist also helped her understand the criticality of vigilantly checking blood glucose levels around the times of her drinking. TB returned for multiple follow-up visits in which she participated in motivational enhancement, and increasingly acknowledged the potential risks that alcohol use posed to her ongoing success in school. In her senior year, TB continued to drink but in smaller quantities, specifically recognizing the hazards of binge drinking given her T1DM diagnosis.

BOX 3**Case Example 3 – Inflammatory Bowel Disease**

CQ is a 17-year-old male with Crohn's disease diagnosed six years earlier who currently uses marijuana daily. He has had multiple exacerbations of his inflammatory bowel disease that have required long-term hospitalizations for intravenous corticosteroid administration. He has been on methotrexate previously and is currently taking 6-mercaptopurine. CQ is concurrently being followed for generalized anxiety disorder diagnosed at age 13 years for which he takes fluoxetine and receives ongoing psychotherapy.

He has smoked marijuana for three years and initially smoked only on weekends, but he has now progressed to the point that he smokes daily. When he is not smoking, he notes that his anxiety is worsened. Additionally, he feels that his Crohn's disease is helped by his marijuana use, and he has even asked his physician for a license for medicinal cannabis, which recently became legal in his state. CQ denies any alcohol use, citing its effects on his gastrointestinal tract. He does not use other substances, stating that marijuana is the only drug that he uses because it helps him relax. CQ believes marijuana has helped his appetite and attributes a recent improvement in his weight to his ongoing use.

Considerations

- Marijuana use is highly prevalent among patients with IBD, with as many as 1 in 3 adolescents reporting past-year use, and 1 in 8 reporting past-month use; nearly one-half report prior binge drinking [9]. The high prevalence of substance use should prompt the clinician to screen all adolescents with IBD, provide brief intervention, and refer to treatment as appropriate.
- Marijuana is legal for medicinal purposes in a number of jurisdictions in the United States and elsewhere. Studies are mixed as to whether states with medical marijuana laws have observed increases in adolescent marijuana use, but several studies suggest that prevalence of use may indeed be increasing [46·47·49·51·91·92].
- Substance use (particularly heavy alcohol use) among patients with IBD can exacerbate hepatotoxicity associated with medications such as methotrexate and 6-MP [28·29]. Adolescents with IBD should be counseled regarding the potential excess risk associated with substance use while taking hepatotoxic medications.
- Adolescents who use substances may be less likely to adhere to their IBD medications [9], possibly placing them at risk for illness exacerbation. Medication adherence should be carefully assessed among adolescents who use substances, and conversely, adolescents with serious or repeat exacerbations should be screened for use [93·95].

- Gastrointestinal motility is altered among patients who use marijuana [22,23,55,57,96]. It is unclear whether these changes are beneficial; some studies report improvement in Crohn's disease outcomes with marijuana use [22,23,57], but one observational study showed risk for poorer long-term outcomes [22].
- No data on cannabis for IBD exists for adolescents, and it is unknown what cannabinoid compound, dose, route, or schedule would be ideal. At this time, particularly in the face of known long-term adverse health and neurocognitive risks of marijuana use among adolescents [58-62], cannabis cannot be recommended for IBD.

Conclusion

CQ so strongly believed that marijuana was helping his inflammatory bowel disease that he was not interested in cutting back or quitting at any time, even despite frequent and ongoing visits for motivational enhancement, which he ultimately stopped attending when he turned 18 years-old. Before this, however, he was carefully counseled about the potential adverse health and neurocognitive harms of long-term heavy marijuana use [58-62], as well as the lack of available evidence for efficacy of marijuana for inflammatory bowel disease. He ultimately chose to enroll in a randomized clinical trial of dronabinol for adults with Crohn's disease.

Key Points

- A substantial proportion of youth with chronic medical conditions (YCMC) use substances, including cigarettes (traditional and smokeless products such as e-cigarettes), alcohol, and illicit drugs, and also may engage in non-medical use of prescription drugs
- Substance use has direct harms for all youth, but YCMC may be at even higher risk for harm owing to clinically significant disease-substance interactions, as well as medication non-adherence and poor disease management in the setting of substance use
- It is incumbent on all clinicians – primary care providers, specialty providers, and behavioral health specialists – to screen for substance use, briefly intervene, and refer to treatment as appropriate

Potential mechanisms for changes in symptoms or course of illness as a result of substances use among youth with chronic medical conditions.

TABLE 1

Mechanism	Examples	Reference(s)
Direct physiologic or metabolic effects of the substance	Cocaine, methamphetamine, and other stimulants with catecholaminergic effects increase blood pressure, potentially worsening control among patients with cardiovascular or renal disease	[97-99]
	Among patients with type 1 diabetes, chronic alcohol use worsens glycemic control, while acute alcohol consumption is associated with hypoglycemia	[8-18;84]
	Stimulants may precipitate ketoacidosis among patients with type 1 diabetes	[18-86;87]
Toxic effects of the substance on cells and tissues	Marijuana use is associated with alterations in gastrointestinal motility among patients with inflammatory bowel disease	[22-23;55-57;96]
	Alcohol causes direct hepatocellular damage, with implications for patients with preexisting liver disease; this damage may be further exacerbated by certain medications such as acetaminophen, methotrexate, 6-mercaptopurine	[28-29]
	Heroin use can cause renal tubular injury and progressive focal segmental glomerular sclerosis, which may further compromise function in patients with chronic kidney disease	[100]
Interaction with medications used for disease management	Alcohol delays gastric emptying, potentially affecting first-pass metabolism of some medications required for chronic disease management (<i>e.g.</i> , propranolol, opioids, benzodiazepines)	[30-33]
	Alcohol induces cytochrome P450 2C9, potentially affecting the metabolism of medications utilizing this enzyme (<i>e.g.</i> , warfarin, phenytoin); THC is also metabolized by cytochrome P450 2C9 (as well as cytochrome P450 3A4) leading to potential medication interactions, particularly with anti-epileptic drugs	[33-101-104]
	Disulfiram-like reactions (marked by nausea and vomiting) may result from drinking alcohol while taking certain medications (<i>e.g.</i> , metronidazole, griseofulvin, procabazine, some cephalosporins) due to inhibition of acetaldehyde dehydrogenase	[33-34]
Effects related to route of substance administration	Alcohol enhances the sedating effect of benzodiazepines, certain anti-epileptic drugs, psychotherapeutic agents, and other sedative-hypnotic medications	[30-35]
	Drinking alcohol while taking opioids (<i>e.g.</i> , for chronic pain) enhances respiratory depression and increases risk of overdose	[30-36]
	Marijuana inhalation is associated with short-term bronchodilation, but on the long-term, with wheezing, cough, and mucus production among patients with chronic respiratory conditions such as asthma	[37]
Consequences of behaviors resulting from use	Drug injection predisposes to abscesses, endocarditis, and other bacterial and blood-borne infections, which may place users with immunodeficiency at especially high risk	[40-42]
	Nicotine, alcohol, and marijuana use are associated with worsened medication adherence for chronic medical conditions	[9-11;43-44]