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The natural history of substance use disorders

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Abstract

Purpose of review—Illicit drugs, alcohol, and tobacco use disorders contribute substantially to the global burden of disease. Knowledge about the major elements of the natural history of substance use disorders (incidence, remission, persistence, and relapse) is crucial to a broader understanding of the course and outcomes of substance use disorders.

Recent findings—Prospective cohort studies in nonclinical samples indicate that externalizing psychopathology in earlier life, including early disordered substance use, delinquency, and personality disorders, are related to substance use disorders later in life and chronic course. Externalizing psychopathology may be initiated by early adverse experiences, for example, childhood maltreatment and stressful life events. After controlling for confounders, ‘age at first use’ as a causal factor for alcohol use disorder later in life and the ‘drug substitution’ hypothesis are not supported in general population data.

Summary—Future research should focus on elaborating the causal framework that leads to the development and persistence of severe substance use disorders, with an emphasis on identifying modifiable factors for intervention by policy makers or health professionals. More research is needed on the natural history of substance use disorders in low-income and middle-income countries.

Keywords

incidence; persistence; relapse; remission; substance use disorder

INTRODUCTION

Of the world population aged 14–65, between 162 000 000 and 329 000 000 individuals (3.4–7%) used an illicit drug in 2013 [1], and ~9% of all years of life lost to death and disability are attributable to illicit drug, alcohol, and tobacco use [2], with most of this disease burden concentrated among those with substance use disorders. Individuals with the

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Conflicts of interest

There are no conflicts of interest.

most severe, persistent, or chronically relapsing substance use disorders are at increased risk for poor health outcomes, for example, liver disease, pancreatitis, and cardiomyopathy for those with alcoholism [3,4], and chronic obstructive pulmonary disease, cancer, cardiovascular disease, and other chronic health conditions for those addicted to tobacco [5,6]. Understanding the natural history of substance use disorders, including their course, causes, and the modifiable individual and environmental characteristics that influence them, is essential for developing medical and public health interventions to reduce this burden of disease. This study reviews recently published work on substance use disorder incidence, remission, persistence, relapse, and special issues concerning the field, with an emphasis on how this work extends active research areas and suggests future directions.

A systematic literature search was conducted in three steps (Fig. 1). First, we searched PubMed using prospectively designed search algorithms to identify studies reporting findings from data on the course of substance use disorders. Second, we conducted targeted searches of PubMed to locate reports of studies identified in the first step. Third, we identified further studies by searching the references of previously located reports, after which the second and third steps were repeated until no new reports were included. To be included, studies must have utilized an observational prospective cohort design and followed participants for ≥ 36 months. Publications must have reported on the incidence or course of a substance use disorder, not been re-analyzed, and not exclusively reported on a highly selected subpopulation (e.g., only those with attention-deficit/hyperactivity disorder). We summarize the studies in five sections: incidence, remission, persistence, relapse, and special issues. Table 1 summarizes methodological features of the studies.

INCIDENCE

Incidence is the onset of disease in a newly affected individual. Prospective studies of the incidence of substance use disorders are rare because of the expense and challenges of the needed sample sizes, retention, and long follow-up times. Early studies varied widely in design, generated widely varying incidence rates, and presented limited or no examinations of sociodemographic variables (e.g., sex, age) or psychiatric conditions as risk factors for incidence [26–30]. The first incidence rate estimates of various Diagnostic and Statistical Manual of Mental Disorders (DSM) - IV psychiatric disease in a large general population sample were reported from the National Epidemiologic Study of Alcohol and Related Conditions (NESARC), a US nationally representative study of adults that included two waves 3 years apart, as well as a broad range of predictors [31]. One-year incidence rates of 1.65 and 0.31% were found for alcohol use disorders and drug use disorders, respectively. Those with wave 2 incident alcohol and drug use disorders were more likely to be male, younger, and separated/divorced/widowed. Incident drug abuse was predicted by wave 1 bipolar I disorder, and borderline, schizotypal, and narcissistic personality disorders; incident alcohol dependence by borderline personality disorder; incident drug dependence by wave 1 panic disorder, and schizotypal and narcissistic personality disorders; alcohol abuse, protectively, by bipolar II disorder and dependent personality disorder, after controlling for other psychiatric conditions and sociodemographic variables. It is important to note, however, that not all substance users go on to develop use disorders, and that risk

factors for incident drug use disorders in the general population may differ from risk factors for incident substance use per se.

A current area of research concerns the long-debated nature of the relationship of depressed mood to the incidence of substance use disorders [32]. In a ‘precipitation’ model, substance use disorders cause depressive disorders through neurotoxic substance effects [33–36]. The ‘self-medication’ model posits that substance use, initiated and maintained as a maladaptive coping mechanism for depressive mood/symptoms [37–46], leads to substance use disorders. A third model posits common genetic and/or environmental factors underlying substance and depressive disorders. Some studies suggest that ‘precipitation’ and ‘self-medication’ are both important and that their relevance may vary between people, and across the life-course [47–50]. In the Oregon Adolescent Depression Project (OADP), alcohol use disorder in adolescence predicted major depressive disorder (MDD) in early adulthood, but that this relationship was reversed in later stages of the life-course, with early adult MDD predicting later adult alcohol use disorder [17[■]]. The Harlem Longitudinal Development Study (HLDS) utilized a similar design. A recent report identified four distinct trajectories of depressive symptoms and delinquent behavior over 20 years in African-American and Puerto Rican individuals initially assessed in adolescence. Two trajectories, one characterized by persistently high depressive symptoms, and the other by high delinquent symptoms, predicted adult substance use disorders, suggesting that both depressive symptoms and delinquent behavior can independently be risk factors for substance disorders [22[■]]. In a third recent study, participants were followed for over 21 years in a birth cohort from the Mater Misericordiae Hospital and University of Queensland Study of Pregnancy. Investigators found that age 14 happiness and life satisfaction was inversely related to subsequent onset of alcohol use disorders [24[■]].

Other risk factors for incident substance use disorders were also examined. The Christchurch Health and Development Study (CHDS) tested exposure to stressful life events as a cause of alcohol use disorders [15[■]], following a New Zealand birth cohort of 1265 individuals for over 30 years. Repeated measurements over the early life-course allowed development of a causal model that controlled for time-varying confounders and unobserved fixed confounders. Distress from stressful life events predicted alcohol use disorder incidence, an effect that did not vary by age of stress exposure, and that was stronger in females than males.

Age at first drinking has long been posited as a causal factor for alcohol use disorders [51], although current evidence is mixed [52–56]. The CHDS study showed that age at first drinking is associated with alcohol use disorders in crude models, but that this association does not remain after controlling for differences in demographic variables, childhood experiences, family history, and environmental variables [16[■]]. Although delaying age at first drink may prevent proximal adverse adolescent outcomes, the CHDS results raise questions about delaying age at first drink as a prevention strategy for later alcohol use disorders.

Externalizing behaviors and comorbidity have been proposed as risk factors for substance disorder incidence, supported by past work in the CHDS [57,58]. A recent analysis of

NESARC data examined cannabis use as a predictor of several substance use disorders [7[■]]. Multiple regression analyses used propensity score matching to control for several confounders, including life-course phases (childhood, early adolescence, late adolescence, adulthood, and past year) and demographic variables. Results showed that cannabis use at baseline predicted incident noncannabis drug use disorders, nicotine dependence, and alcohol use disorders 3 years later. OADP findings indicated that having one or more disorder in the externalizing domain (e.g., a substance use disorder, antisocial personality disorder) predicted cannabis use disorder onset [20[■]].

REMISSION

Remission is a highly important component of the natural history of substance use disorders. Remission is variously defined as no longer meeting full criteria for a substance use disorder, no longer experiencing any symptoms, and also as no longer using the substance (i.e., abstinent; commonly used in treatment studies). Predictors of abstinent and nonabstinent remission can vary, at least for alcohol [59]. Most community-based and general population studies of remission of substance use disorders have reported on alcohol [60–62], with early studies indicating that alcohol dependence has a chronic course, whereas alcohol abuse is likely to remit [63]. Less is known about remission from cannabis use disorders in the general population. A meta-analysis estimated a 1-year remission rate for cannabis use disorders of 17% [64], although this included data from treatment studies. Community studies of cannabis use disorder remission found high rates of remission over variable time periods; those who remit are more likely to be female, employed, have cannabis-induced symptoms, and have self-competence [21[■],65–67].

Data from the NESARC provide a unique opportunity to study remission from cannabis use disorders in a large national sample. In one analysis, 42.4% of individuals with a cannabis use disorder during the year prior to wave 1 reached abstinent remission 3 years later, and an additional 24.7% reached nonabstinent remission [11[■]]. Individuals were more likely to remit if they had a past-year medical condition, used other substances (other than alcohol or cannabis), or used cannabis less than daily or almost daily. Among remitters, individuals were more likely to be abstinent if they had cannabis dependence (as opposed to abuse only), used cannabis less than daily or almost daily, or started their first full-time job in the past 3 years. In the OADP, 81.8% of those with cannabis use disorder remitted during the study period [21[■]]. Younger women recovered more quickly than men, although the likelihood of recovery by age 30 did not differ between men and women.

PERSISTENCE

Persistent substance use disorders have the most severe health and social consequences [3–6]. Understanding the nature of persistent course and the factors that underlie persistence is critical. At wave 1, NESARC included a large number of individuals with substance use disorders at various points in their course. This feature differentiates NESARC from smaller birth or otherwise temporally defined cohort studies (e.g., OADP or CHDS) that may not follow individuals long enough or have enough participants to study variation within those with substance use disorders.

An active area of research concerns identification of a ‘common liability’ to externalizing psychopathology (genetic or environmental factors), which predisposes individuals to chronic substance use disorders. Previous work with the two waves of NESARC showed that personality disorders (particularly antisocial, borderline, and schizotypal personality disorder), significantly predicted substance use disorder persistence, even after controlling for sociodemographic variables and other psychiatric comorbidity [68–70]. Antisocial personality disorder has been considered an externalizing disorder for decades [71,72], and recent evidence has linked borderline personality disorder to the externalizing domain because of its shared variance with other externalizing disorders [73]. Recent NESARC studies extended this work and connected it with early childhood environmental exposures. For example, several childhood maltreatment types, especially sexual abuse, predicted alcohol and nicotine dependence persistence, even controlling for confounders and other types of childhood maltreatment including emotional and physical neglect [10[■]], a result consistent with findings in the CHDS [58]. More recently, structural equation models showed that personality disorders mediated 61–67% of the effect of childhood maltreatment on nicotine and alcohol dependence persistence [9[■]]; only the indirect effects through antisocial and borderline personality disorders were statistically significant. Other recent work includes data from the CanDep Study, a Dutch community sample of frequent cannabis users. ‘Role impairment’ due to cannabis, and number of lifetime cannabis abuse or dependence symptoms significantly predicted 3-year cannabis dependence persistence [23[■]].

Two OADP studies found that psychopathology in a previous time period did not predict cannabis use disorder duration, but that co-morbid psychopathology did [19[■]]. Furthermore, alcohol and cannabis disorder diagnoses were more stable from young adulthood to adulthood than from youth to young adulthood [18[■]].

Finally, in NESARC, substance dependence in general, and dependence on either tranquilizers or opioids in particular, predicted 3-year nicotine dependence persistence after controlling for demographic and psychiatric variables [12[■]]. Also, in older NESARC adults, no physical or mental health variables significantly predicted persistent substance use dependence, but younger participants (age 55–64) were more likely to have persistent disorders than older participants (age 65+) [13[■]].

RELAPSE

Understanding the patterns and predictors of substance use disorder relapse is important for efforts to prevent such relapse. Previous analysis of NESARC participants in remission from alcohol disorders at baseline examined rates and correlates of relapse. Those in abstinent recovery at baseline were least likely to relapse over the 3-year follow-up period, compared with low risk drinkers and asymptomatic risk drinkers, but the majority of even asymptomatic risk drinkers (60%) remained in remission over the 3-year period [74]. Some of these results were replicated in the Netherlands Mental Health and Incidence Study–2 (NEMESIS-2), a Dutch general population study with a sample design similar to NESARC. This analysis found that at-risk drinking at baseline, a lifetime history of severe alcohol use disorder, and experiencing the symptom ‘impaired control over use’, all predicted alcohol use disorder relapse by 3-year follow-up [25[■]]. Another NESARC study found that

compared with nonsmokers, smokers at wave 1 were more likely to relapse to alcohol abuse and dependence by wave 2, after controlling for demographic, psychiatric, and severity of alcohol use prior to wave 1 [14].

Finally, recent work explored predictors of relapse for cannabis use disorders, for which there is little information in general population samples (earlier research only examined cannabis use relapse in treated samples [75–78]). The first prospective study of cannabis use disorder relapse in a general population found that after controlling for sociodemographic and psychiatric variables, relapse was predicted by shorter time in remission and major depressive disorder [79]. In OADP, relapse was significantly more likely during the first 36 months of remission from a cannabis use disorder [21[■]].

SPECIAL ISSUES

An important issue in the study of substance disorder remission is the comorbidity of multiple substance use disorders throughout the life-course. Current evidence for the brain disease model of addiction [80] and evidence of the transdiagnostic metastructure of psychopathology [72] supports the notion that individuals may be vulnerable to substance use disorders in general, not just those for a particular substance. This has fueled speculation that individuals who remit from a disorder involving a particular substance may then go on to develop a disorder involving a different substance. Thus, studies of the course and outcomes of a particular substance use disorder might be misleading if they ignore the possibility of ‘substance substitution’. When this hypothesis was recently tested in NESARC, individuals in remission were actually less likely to have a new onset substance use disorder involving a different substance than those without a remission, after adjusting for socio-demographic covariates, and number of substance use disorders at baseline [8[■]]. This does not support ‘substitution’ as a critical component of the course and outcome of substance use disorders in the general population, although findings in treated samples may differ.

CONCLUSION

The course and outcome of substance use disorders is an active area of research of high importance to the fields of medicine and public health. General population studies have been particularly fruitful in identifying psychiatric risk factors for substance disorder persistence. These may be targeted as a way to reduce the burden of disease due to the most severe subtypes of substance use disorders, although additional careful study is needed to identify the particular aspects, whether behavioral or biological, of these risk factors that cause use disorders to persist. Studies of biological mechanisms are also needed, for example, brain imaging studies that follow individuals over time, as well as studies that explain why some substance users go on to develop use disorders while others do not. Furthermore, there is a dearth of prospective research on substance use disorders in populations other than those of the wealthiest countries. Basic descriptive epidemiologic research on substance use disorder course and outcome is needed in these areas.

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KEY POINTS

- Incidence of alcohol and drug disorders is predicted by early depressive symptomatology, although this relationship likely varies throughout the life-course.
- Cannabis use disorder (abuse or dependence) is highly remitting in the US general population (42.4% over 3 years) and is predicted by lower frequency of use, abuse rather than dependence, and presence of other medical conditions.
- Adverse childhood experiences are implicated in substance use disorder persistence and this mechanism may be mediated by personality disorder.
- Risk drinking, smoking, and a history of severe alcohol use disorder are risk factors for relapse among those in remission from alcohol use disorder.
- General population prospective studies avoid selection and other biases inherent to treatment studies, and are necessary despite high costs and participant retention challenges. No general population follow-up studies in low-income and middle-income countries exist, leaving the natural history of substance use disorders in these countries unknown. Future studies should also address potential differences in the sets of risk factors for incident substance use disorders and incident substance use per se.

FIGURE 1.
 Search algorithms.

Table 1

Key methodological features of included studies

Study	Population	Sample size at baseline	Age at baseline (mean)	Baseline year	Follow-up time points	Included studies
National Epidemiologic Study of Alcohol and Related Conditions (NESARC)	Noninstitutionalized adults in the United States	43093	18+ (46.4)	2001–2002	3 years	Blanco <i>et al.</i> (2016) [7 [■]]; Blanco <i>et al.</i> (2014) [8 [■]]; Elliott <i>et al.</i> (2015) [9 [■]]; Elliott <i>et al.</i> (2014) [10 [■]]; Feingold <i>et al.</i> (2015) [11 [■]]; Goodwin <i>et al.</i> (2014) [12 [■]]; Mackenzie <i>et al.</i> (2014) [13 [■]]; Weinberger <i>et al.</i> (2015) [14]
Christchurch Health and Development Study (CHDS)	Children born in the Christchurch urban region of New Zealand	1265	0 (0)	1977	Birth, 4 months, 1 year, annually to 16 years, 21 years, 25 years, 30 years	Boden <i>et al.</i> (2014) [15 [■]]; Newton-Howes <i>et al.</i> (2016) [16 [■]]
Oregon Adolescent Depression Project (OADP)	High school adolescents of Western Oregon, USA	1709	14–18 (16.6)	1987–1989	1 year, at age 24, at age 30	Briere <i>et al.</i> (2014) [17 [■]]; Duncan <i>et al.</i> (2015) [18 [■]]; Farmer <i>et al.</i> (2016) [19 [■]]; Farmer <i>et al.</i> (2015) [20 [■]]; Farmer <i>et al.</i> (2015) [21 [■]]
Harlem Longitudinal Development Study (HLDS)	High school adolescent African-Americans and Puerto Ricans from East Harlem, New York, USA	1332	12–16 (14.1)	1990	5 years, 10–11 years, 11–12 years, 17–20 years	Brook <i>et al.</i> (2015) [22 [■]]
The Dutch cannabis dependence (CanDep) study	Dutch frequent cannabis users (via chain referral initiated in cannabis outlets)	600	18–30 (22.1)	2008–2009	1.5 years, 3 years	van der Pol <i>et al.</i> (2015) [23 [■]]
Mater Misericordiae Hospital and University of Queensland Study of Pregnancy	Singleton children born at the Mater Misericordiae Hospital in Brisbane, Australia	7223	0 (0)	1981–1983	3–5 days, 6 months, 5 years, 14 years, 21 years	Fischer <i>et al.</i> (2015) [24 [■]]
Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2)	Dutch adult general population	6646	18–64 (44.3)	2007–2009	3 years	Tuithof <i>et al.</i> (2014) [25 [■]]