

The natural history of adolescent alcohol use disorders

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ABSTRACT

Aim To examine clinically relevant research on the development, course and outcomes of adolescence alcohol use disorders (AUDs).

Methods Observational studies with adolescent samples were selected for inclusion based on systematic assessment of AUDs and clinical relevance. The literature was searched using Medline and Psychinfo. Articles on childhood predictors, characteristics, course, complications and adult outcomes of adolescent AUDs were reviewed.

Results The developmental trajectory toward adolescent AUDs begins with the emergence of childhood mental disorders. These problems are transmitted from parent to child in a developmentally specific fashion, reflect psychological dysregulation dimensions and predict adolescent AUDs. While most DSM-IV AUD diagnostic criterion items are valid for adolescents, tolerance and impaired control items are problematic, and some adolescents with significant alcohol problems are not identified by this diagnostic system. Understanding the psychosocial and biomedical complications that accompany AUDs requires attention to factors other than alcohol involvement itself, including childhood maltreatment and comorbid psychopathology. While some adolescents with AUDs manifest chronic alcohol dependence in adulthood, a substantial proportion overcome alcohol problems and transition to abstinence or normative drinking.

Conclusions Developmentally specific phenotypic characteristics define the natural history of adolescent AUDs, inform clinical assessment and provide the developmental context for treatment research. While alcohol consumption may be the primary treatment focus, other important consequences, comorbidities and complications need to be addressed for successful developmental outcomes to result.

KEYWORDS Adolescents, alcohol, psychopathology.

INTRODUCTION

Alcohol involvement in adolescence plays a pivotal role in development. The initiation of alcohol consumption occurs typically by middle adolescence. Among affected adolescents, problematic alcohol involvement soon follows. Despite the long-acknowledged importance of the adolescent developmental period in understanding alcohol involvement, adolescents with alcohol use disorders (AUDs) have been a focus of substantial systematic study for only the past decade. Prior to recent years, studies on

adolescent alcohol involvement typically did not systematically assess for AUDs, or reports were limited to descriptions of small samples (e.g. Famularo *et al.* 1985; Keller *et al.* 1992). This paper will summarize clinically relevant findings from the empirical literature on adolescence and AUDs, focusing on risks, course and outcomes viewed from a developmental perspective.

Adolescent-onset AUDs are not synonymous with 'early onset alcoholism'. Adults with AUDs have been hypothesized to be divisible into subtypes defined by onset age, characterized as 'early-onset' and 'late-onset'

alcoholism (Tarter *et al.* 1977; Morey, Skinner & Blashfield 1984; Cloninger 1987; Buydens-Branchey, Branchey & Noumair 1989; Irwin, Schuckit & Smith 1990; Babor *et al.* 1992; McGue *et al.* 1997). By design, these studies focus primarily on adults with chronic alcohol dependence and have defined 'early' by varying criteria including adolescent and adult ages (e.g. up to 25 years old: Cloninger 1987; up to 30 years old: Schuckit *et al.* 1993). Further dividing the 'early onset' years into adolescent and early adult periods may yield distinct groups. For example, among males with substance use disorders, Clark, Kirisci & Tarter (1999) found that adolescents and adolescent-onset adults, compared with early adult and late-adult-onset groups, had more childhood psychopathology, more rapid transitions from first alcohol use to alcohol dependence and shorter times from first to second substance dependence. Adolescents with AUDs have characteristics distinct from their adult counterparts and warrant separate consideration.

The empirical literature on adolescent AUDs confirms some and contradicts other traditional assumptions about this important problem. Thus, adolescents with AUDs typically have childhood characteristics predicting later alcohol problems, yet the adolescent course of alcohol problems is highly variable. Treatment rarely results in prolonged abstinence, yet many adolescents with AUDs show an absence of alcohol-related problems after treatment. Adolescents with AUDs have evidence of health problems, yet most of these health problems may be attributable to problems other than alcohol involvement. Most adolescents with AUDs do not fit the pattern described by 'early onset alcoholism', and recent studies indicate that only a minority of adolescents with AUDs are embarking on a course of severe and chronic alcohol dependence.

The objective of this review is to describe the natural history of adolescent AUDs in the context of related developmental characteristics. The emphasis is on clinically relevant features, and the review is intended to provide information pertinent to clinical treatment and related research. Given these broad goals, several constraints should be acknowledged. Although a conceptual framework is provided, theoretical concepts have been consigned to providing general organizing principles. Furthermore, only a few predominant dimensions are discussed in detail. Many other important psychological, social and biological characteristics could legitimately have been included, and some will be considered in other articles in this special issue.

This review of the natural history of adolescent AUDs intends to offer a developmentally informed guide to some of the clinical characteristics pertinent to treatment research. The developmental psychopathology

perspective emphasizes the insights gleaned from contrasting normal and atypical development (Cicchetti & Cohen 1995; Zucker, Fitzgerald & Moses 1995; Clark & Winters 2002), as illustrated by many of the studies discussed below. Development is characterized by stages, and the resulting phenotypes may be qualitatively distinct from one stage to the next. For example, psychological dysregulation may be reflected in childhood mental disorders, and become manifest as AUDs in adolescence when the context provides drinking opportunities. As with other substances (e.g. nicotine: Mayhew *et al.* 2000), alcohol involvement may be considered more precisely in a continuous rather than a stage fashion. Practical limitations in measurement, however, may preclude such an approach in empirical studies.

Translating the implications of the developmental psychopathology framework into clinical interventions and research paradigms presents methodological and conceptual challenges (Richters 1997). A principal foundation for collecting adequate information is the institution of systematic, comprehensive and developmentally informed assessment protocols in clinical practice and research (Clark & Winters 2002). Substantial progress has been made in methods characterizing qualitatively distinct but related phenotypic structures over developmental stages (Gottlieb 1998; Clark *et al.* 2001a) and statistically modeling the measured developmental trajectories (Muthen & Muthen 2000).

Research on the predictors, course and outcomes of adolescent AUDs has primarily utilized observational methods. Observational studies identify efficiently characteristics important for understanding etiology, course, complications and outcomes, complementing research using alternative designs (Rosenbaum 1995). The multifaceted and interactive natural history of risk and outcome variables complicate causal interpretation in research on adolescent AUDs, particularly in observational study designs. Traditional statistical thought has held that observational data are highly problematic for creating causal models. With observational data, the elements needed for causal interpretation, in ascending hierarchy, are association, time order and causal direction, with the latter being the most difficult condition to satisfy. While observational studies may not support definitive causal interpretations, such studies may be sufficiently informative so as to constrain plausible causal models and thereby provide causal information (Susser 1991; Clogg & Haritou 1997; Cooper 1999; Clark & Winters 2002).

From the perspective of the multi-factorial model of complex diseases (Lander & Schork 1994), AUDs occur when an initial genetic liability is influenced by environmental factors to produce a phenotype that is above a

diagnostic threshold for alcohol problem characteristics (Tarter *et al.* 1999). The conceptual framework utilized here proposes that the developmental pathways defining adolescent AUD phenotypes and related adult outcomes can be described by paths defined by childhood characteristics, patterns of alcohol consumption over developmental stages, alcohol-related problems and complications and adulthood outcomes.

BEFORE THE FIRST DRINK—CHILDHOOD MENTAL DISORDERS

Among childhood characteristics predicting adolescent AUDs, the most clinically relevant are the childhood mental disorders, including conduct disorder (CD), attention deficit hyperactivity disorder (ADHD), major depressive disorder (MDD) and anxiety disorders (Clark & Winters 2002). Children of parents with substance use disorders are at elevated risk for these disorders (Clark *et al.* 1997c). The extent to which these offspring disorders are a consequence of parental substance use disorders or more specific corresponding parental psychopathology has recently been studied with statistical consideration of the nested data structure in a sample of 1167 children ages 6–14 from 613 families (Clark *et al.* 2004). For CD, ADHD, MDD and anxiety disorder, a history of the specific disorders in mothers and fathers predicted similar disorders in their children. After taking corresponding parental psychopathology and socio-demographic characteristics into consideration, parental substance use disorders did not contribute significantly to explaining offspring psychopathology. These findings illustrate the developmental specificity of phenotypic manifestations emphasized by the developmental psychopathology perspective.

Several lines of evidence indicate that childhood psychopathology predicts adolescent AUDs. Childhood mental disorders are among the most distinguishing features of children at high risk for AUDs (Earls *et al.* 1988; Clark *et al.* 1997c), and are common among adolescents with AUDs and other substance use disorders (Brown *et al.* 1996; Clark *et al.* 1997b). Childhood psychopathology predicts regular alcohol use in early adolescence, the adolescent onset of alcohol-related problems (Clark *et al.* 1999b) and the development of alcohol use disorders (Rydelius 1981; Boyle *et al.* 1992; Manuzza *et al.* 1993; Lynskey & Fergusson 1995; Thompson *et al.* 1996; Biederman *et al.* 1997; Clark *et al.* 1998a, 1999b; White *et al.* 2001). Childhood disruptive behavior disorders and later AUDs appear to have a common diathesis (Cadoret *et al.* 1995; Grove *et al.* 1990). The relationships among childhood mental disorders and the later development of AUDs may be due to common genetic and environmental influ-

ences (Eaves *et al.* 2000; Waldman & Slutske 2000). Furthermore, CD, ADHD, MDD and anxiety are not independent characteristics, and their overlap may have considerable significance.

Psychological dysregulation may be a useful organizing concept for understanding the general liability for AUDs, other SUDs, psychopathology and risky behaviors observed in these problematic adolescents. Among children at risk for AUDs, antisocial behavior, attentional difficulties and depression are highly coincidental. Rather than considering each of these characteristics as distinct disorders, a more parsimonious conceptualization may be that these mental disorders are manifestations of a liability trait termed psychological dysregulation. Psychological dysregulation has been found to have significant heritability, to account for associations among disruptive behavior disorders and to contribute significantly to substance use behavior (Tarter *et al.* 1999, 2003; Young *et al.* 2000).

A general propensity toward psychological dysregulation may underlie specific forms of childhood psychopathology, and may predict AUDs. Tarter *et al.* (2003) constructed an index termed 'neurobehavioral disinhibition' from indicators of behavioral, affective and cognitive dysregulation. Drawn from variables assessed at ages 10–12 years, indicators included disruptive disorders symptoms, difficult temperament items and performance on tests of executive cognitive functioning. Neurobehavioral disinhibition was unidimensional, discriminated high- from low-risk boys and predicted substance use disorders at age 19.

Common environmental influences may also be at work causing psychological dysregulation, as reflected in childhood mental disorders and adolescent AUDs. Indicators of problematic family functioning, which have been implicated in the development of childhood antisocial behaviors and AUDs, include low level of parental monitoring and inconsistent disciplinary practices (Clark *et al.* 1998b, 2004b) and childhood maltreatment (Clark *et al.* 1997a, 2003). Specific environmental factors may be particularly influential in critical developmental periods (Moss *et al.* 1997). Parental AUDs and other mental disorders may act as barriers to adequate mental health treatment for their offspring, which may in turn further increase their offsprings' likelihood of developing AUDs (Cornelius *et al.* 2001a).

Since the developmental timing of emergent behavioral, affective and cognitive regulation in adolescence parallels maturation of the prefrontal cortex, a neurobiological basis for psychological dysregulation has been postulated (Spear 2000; Chambers, Taylor & Potenza 2003). Neuroimaging findings also indicate that morphological deviation in the prefrontal cortex, the hypothesized anatomical site of emotional and behavioral

regulation, is associated with severe antisocial behavior (Raine *et al.* 2000). The rate of maturation of frontal-limbic circuits may be an important mechanism through which genetic factors operate to produce psychopathology (Todd *et al.* 1995). Childhood mental disorders may thus be an early indicator of a dysregulation syndrome characterizing a pathway to adolescent AUDs.

In summary, the conceptual framework described here postulates that psychological dysregulation is caused by interacting genetic liability and environmental influences. While estimates of the degree of heritability vary substantially, genetic variation clearly plays an important role in the development of childhood mental disorders and subsequent adolescent AUDs, with a substantial proportion of such variance shared among childhood mental disorders indicating dysregulation, AUDs and other drug use disorders (Vanyukov *et al.* 2003; Dick *et al.* 2004). Environmental factors interact with genetic liability to produce phenotypic variations that change over the course of development, including childhood psychopathology and adolescent AUDs (Tarter *et al.* 1999). Environmental influences may be conceptualized as nested systems, from the family and peers to the larger community (Sameroff 1995; Tarter *et al.* 1999). While predictors of adolescent AUDs are evident in childhood, the environmental context in adolescents provide the opportunities for risk to be manifested as alcohol involvement.

ALCOHOL CONSUMPTION—INITIATION AND PROGRESSION

Alcohol consumption changes dramatically from ages 12 to 18. Community survey data (i.e. *Monitoring the Future*: Johnston, O'Malley & Bachman 2001) indicate that most adolescents have tried alcohol (e.g. 51.7% in 8th grade, 80.3% in 12th grade). Binge drinking, defined as five or more drinks in one episode, is reported by over 30% of 12th-graders in any 2-week period. These statistics have been stable for several years, indicating that alcohol experimentation is normative and binge drinking common among adolescents. While alcohol involvement in the adolescent years is influenced by genetic predispositions and predicted by childhood mental disorders, the availability of drinking opportunities in adolescence fundamentally changes the phenotypic manifestations of the risk for AUDs.

Drinking opportunities during adolescence vary as a function of parental supervision, peer characteristics and community context. Ideally, parents foster increasing independence, encourage positive outside influences and opportunities and simultaneously promote socialization and behavioral regulation (Silk *et al.* 2003).

Variability in the parent–child relationship increases from early to middle adolescence (Granic *et al.* 2003). In adolescence, inadequate parental supervision and support are associated strongly with the earlier initiation of alcohol use, higher levels of alcohol involvement and AUDs (Johnson & Pandina 1991; Barnes *et al.* 1995; Clark *et al.* 1998b).

Diminished parental involvement tends to be accompanied by an increased association with drinking peers (Barnow *et al.* 2002). While influenced by parent behaviors, the adolescent plays an active role in the selection of peers and responses to peer behaviors. Alcohol use and shared propensities toward risky behaviors influence peer selection, discrepancies between perceived and actual peer alcohol use occur and reciprocal influences among adolescents transpire (Clark & Winters 2002). The influence of drinking peers may be mitigated by increased psychosocial maturity and assertiveness (Adalbjarnardottir 2002; Donovan 2004).

While increased psychosocial maturity may act to reduce early alcohol involvement, early sexual maturation may accelerate alcohol involvement. Variations in psychosexual development have been shown to influence substance involvement trajectories (Dawes *et al.* 2000). Early maturing girls, compared with on-time or late maturing girls, have been found to be significantly more advanced in their alcohol involvement trajectories, including the initiation of alcohol use and binge drinking (Lanza & Collins 2002; Kaltiala-Heino *et al.* 2003). Similar results have been noted for boys (Kaltiala-Heino *et al.* 2003). Accelerated alcohol involvement may occur as a result of early maturing adolescents affiliating with more deviant or older peers, increased parent–adolescent conflict, increased negative affect or interactions among these factors (Ge *et al.* 1996; Dawes *et al.* 2000).

Socio-demographic characteristics influencing adolescent alcohol involvement include family structure, socio-economic status (SES), race and gender. Adolescents from intact families, compared to those from single-parent or step-parent households, tend to have less alcohol involvement (Flewelling & Bauman 1990; Kung & Farrell 2000). While lower family SES is associated with higher levels of alcohol involvement among adolescents, this relationship is probably explained by related factors. Families with lower SES are less likely to be intact and more likely to include parents with alcohol problems (Flewelling & Bauman 1990; Droomers *et al.* 2003). Ethnic group differences in adolescent alcohol involvement have been noted. Compared with African American and Asian American adolescents, European American and Hispanic American adolescents show higher levels of alcohol involvement (Johnston *et al.* 2001). In the majority of studies examining gender,

males and females have not been found to have significantly different ages of alcohol initiation (Donovan 2004). Nevertheless, the relationships among these socio-demographic factors and other risks, such as the relationships among gender, sexual victimization and comorbid psychopathology discussed below, need to be considered in order to understand fully their influences on adolescent AUDs.

Community efforts to limit the availability of alcohol to adolescents have met with modest success. Federal legislation was enacted in 1984 and implemented throughout the United States in 1989, establishing age 21 as the national minimum legal drinking age (Voas *et al.* 2003). Increases in the minimum drinking age have been associated with reduced alcohol involvement and related consequences among adolescents (Johnston *et al.* 2001; Voas *et al.* 2003). Nevertheless, underage drinking laws are not vigorously enforced, as evidenced by the relative ease of alcohol purchasing by adolescents (Wagenaar *et al.* 1996; Wolfson *et al.* 1996). Given the ubiquitous availability of alcohol in our society, clinical efforts to curtail adolescent alcohol involvement rely on interventions at the individual and family levels.

Defining the distinction between normative and deviant alcohol consumption is complicated by the observation that experimentation with alcohol is part of the normal developmental trajectory for adolescents (Shedler & Block 1990; Johnston *et al.* 2001). In examining alcohol consumption initiation, the age of first experience with alcohol may not be a particularly important landmark. Rather, the age of first whole 'standard drink', regular drinking of significant quantities and binge drinking predict later outcomes and therefore have more solid standing as landmarks. In a study comparing pre-adolescent boys with and without fathers with substance use disorders (i.e. high risk and low risk, respectively), the majority of boys in both high- and low-risk groups had tried alcohol (67% versus 63%; Clark *et al.* 1998a). In contrast, only one of 102 high-risk boys and none of 164 low-risk boys had ever experienced a phase with consumption of a full standard drink at least once per month (i.e. 'regular drinking'). When these boys were assessed 2 years later in early adolescence (i.e. ages 12–14), a similar pattern was noted with any interim alcohol consumption, which was no different for high-risk boys (43%) and low-risk boys (43%). By the higher standard of regular drinking, however, high-risk boys were significantly more likely than low-risk boys to have had a drinking phase [12% versus 3%, adjusted odds ratio (OR) = 4.1, $P = 0.005$]. Childhood conduct disorder predicted early adolescent regular drinking. By early adolescence, then, the majority of individuals have consumed some alcohol; few have a pattern of regular drinking.

The extent to which significant drinking in early adolescence is influenced by heritable or environmental factors remains under investigation. Rose *et al.* (2001) reported that environmental factors shared by twin siblings accounted for most of the variance in regular drinking by age 14. In a retrospective study with adults, McGue *et al.* (2001a,b) found that a reported age of first drink before age 15 was associated with adult alcohol dependence and attributable more to heritable than environmental factors, particularly in males. In any case, an early adolescent age of first 'drink' and regular alcohol use may be conceptualized as important predictive phenotypes.

By late adolescence, binge drinking and drinking to intoxication becomes relatively common. Binge drinking, defined by five or more drinks per episode, is reported by 14% of 8th graders, 26% of 10th graders and 30% of 12th graders (Johnston *et al.* 2001). A life-time history of having 'been drunk' is reported by the majority of adolescents by 12th grade (62%; Johnston *et al.* 2001). Among adolescents with binge drinking, many do not meet the criteria established for AUDs. Nevertheless, binge drinking is potentially hazardous and is therefore inherently problematic. Binge drinking leads to driving while intoxicated, a significant source of preventable morbidity and mortality among adolescents (Duncan 1997; Voas *et al.* 2003). Acute alcohol poisoning is another consequence of binge drinking, with the potential for death from respiratory depression (Poikolainen *et al.* 2002). The high rates of binge drinking among adolescents suggest that acute alcohol poisoning may occur more than might be suggested by the lack of formal reports on this topic. Furthermore, the trajectory of binge drinking in adolescence is an important characteristic, predicting adult developmental outcomes (Hill *et al.* 2000). Using binge drinking patterns from ages 13–18 to predict outcomes at age 21, a trajectory characterized by little binge drinking in early adolescence and high levels of binge drinking in late adolescence (i.e. 'increasers') predicted a high rate of AUDs at age 21 (43%).

ADOLESCENT ALCOHOL ABUSE AND DEPENDENCE

Rare in early adolescence, AUD rates approach those in adults by late adolescence. As with alcohol consumption, rates of alcohol problems and AUDs are influenced by the ages of participants within the adolescent age span. AUDs among children and adolescents under the age of 14 are rare. Among 541 children aged 10–13 years, Cohen *et al.* (1993) found no AUD cases. Among 1167 children aged 6–14 years, about half from high-risk families, no cases of AUDs were noted (Clark *et al.* 2004). Rates increase at age

14 years, corresponding typically to 9th grade. Among 9th- and 12th-grade high school students, 7% of 9th-graders and 15% of 12th-graders indicated the presence of at least one *Diagnostic and Statistical Manual*, 4th edition (DSM-IV; American Psychiatric Association) SUD symptom (Harrison, Fulkerson & Beebe 1998). In another community sample of 1507 students aged 14–18, 23% had had at least one DSM-IV alcohol abuse or dependence symptom (Lewinsohn, Rohde & Seeley 1996). Lewinsohn and colleagues (Lewinsohn *et al.* 1996; Rohde, Lewinsohn & Seeley 1996) found that 94 of 1507 (6%) subjects aged 14–18 years met life-time criteria for AUDs; the MECA study (Kandel *et al.* 1999) found 16 of 401 (4%) with AUDs for ages 14–17 years. A recent study with the largest community sample to date ($n=4023$; Kilpatrick *et al.* 2000) reported rates in this range, with alcohol abuse at 3.6% and alcohol dependence at 0.8%. Other studies with community-recruited adolescent samples (see Chung *et al.* 2002 for review) have reported AUD rates ranging from 1% (Costello *et al.* 1996) to over 10% (Kessler *et al.* 1994; Martin *et al.* 1995). Higher rates occur typically in older adolescent samples (Cohen *et al.* 1993; Giaconia *et al.* 1994). However, as the DSM-IV diagnostic criteria were developed from clinical observations and research with adults (Nathan 1991), consideration of the unique features of adolescent alcohol problems may be needed to place these rates in proper perspective.

Alcohol abuse

The DSM-IV alcohol abuse symptoms reflect risk for or manifestations of negative health and social consequences. Alcohol abuse indicators include role impairment, physically hazardous use (e.g. intoxicated driving), recurrent alcohol-related legal problems and alcohol-related social and interpersonal difficulties. Among alcohol abuse symptoms, the most common are hazardous use and interpersonal problems (Chung *et al.* 2002). The reported prevalence of alcohol abuse in community samples ranged from 0.4% to 4.3%.

Optimally, adolescents categorized as having alcohol abuse would represent a homogeneous group clearly distinct from those with no diagnosis and less severe than those with alcohol dependence. Heterogeneity among adolescents with alcohol abuse is suggested by inconsistent assignments across diagnostic systems (Pollock, Martin & Langenbucher 2000). Concordance among DSM-III, DSM-III-R, DSM-IV and *International Classification of Diseases*, 10th edition (ICD-10) systems for alcohol diagnoses has been found to be relatively poor among adolescents, particularly for alcohol abuse diagnoses (Pollock *et al.* 2000). These inconsistencies make comparisons across studies using

different diagnostic systems problematic. More fundamentally, this observation suggests fundamental problems with the definitions of alcohol abuse as applied to adolescents.

The DSM-IV diagnostic criteria result in some adolescents with clinically significant alcohol problems failing to qualify for an AUD diagnosis. Adolescents with one or two dependence symptoms without abuse symptoms do not meet DSM-IV diagnostic criteria for AUDs. Pollock & Martin (1999) coined the term 'diagnostic orphans' for these individuals and reported that 'diagnostic orphans' were similar to adolescents with DSM-IV alcohol abuse in their level of alcohol consumption. A latent class analysis (Chung & Martin 2001) has indicated that 'diagnostic orphans' are similar in alcohol problem severity to adolescents with alcohol abuse. Among adolescents, diagnostic orphans may be about as common as adolescents meeting abuse criteria (Lewinsohn *et al.* 1996; Harrison *et al.* 1998; Chung *et al.* 2002).

In general, alcohol abuse is a less severe syndrome than alcohol dependence (Chung & Martin 2001). For individual abuse and dependence symptoms, however, this severity scaling characteristic does not hold for all specific items (Martin & Winters 1998). Furthermore, symptoms of abuse do not always precede symptoms of dependence, as would be expected if abuse were consistently prodromal to dependence (Martin *et al.* 1996b).

Alcohol dependence

Alcohol dependence rates in adolescent community samples are typically below 5%, ranging from 0.6% to 4.3% (Chung *et al.* 2002). Data from community adolescent samples have indicated that the DSM-IV items 'tolerance' and 'drinking larger amounts or for a longer period than intended' were the most common alcohol dependence symptoms (Chung *et al.* 2002). Compared with adults, adolescents developing AUDs tend to have a more rapid transition from alcohol use to dependence, are less likely to experience blackouts and have alcohol withdrawal less frequently (Clark *et al.* 1999a; Deas *et al.* 2000; Langenbucher *et al.* 2000).

Among adolescents, the dependence symptoms of tolerance and impaired control (i.e. 'using more or longer than intended') tend to occur early in the course of alcohol involvement and are more frequent than several abuse symptoms (Martin *et al.* 1996b). Furthermore, these two alcohol dependence symptoms may have poor validity in adolescence for developmental reasons (Martin in Hasin *et al.* 2003).

The development of tolerance to alcohol is, to an extent, a normal developmental phenomenon (Chung *et al.* 2001). Among adolescents, alcohol tolerance has

been found to be a less severe indicator than some abuse symptoms (Martin *et al.* 1995; Bailey *et al.* 1999; Chung *et al.* 2001). Also, adolescents often lack the element of anticipated alcohol consumption amount or time period needed to meet the criterion for impaired control (Chung & Martin 2002). Variability in the operationalization of these diagnostic criteria leads to important variability in their rates among clinical and community samples (Chung *et al.* 2002; Martin & Hasin *et al.* 2003).

DSM-IV defines alcohol withdrawal as manifested by either (1) the characteristic withdrawal syndrome for alcohol, or (2) alcohol or a closely related substance is taken to relieve or avoid withdrawal symptoms. Unlike tolerance, a history of alcohol withdrawal may effectively identify the most severely dependent adolescents (Langenbucher *et al.* 2000). However, withdrawal develops late in the course of adolescent AUDs and is a relatively infrequent symptom among adolescents (Martin *et al.* 1995, 1996b; Winters, Latimer & Stinchfield 1999; Chung *et al.* 2002; Clark & Winters 2002).

The conceptual distinction between alcohol abuse and alcohol dependence is based in part on the assumption that abuse symptoms, compared with dependence symptoms, occur earlier in the course of alcohol involvement and represent milder syndrome indicators. Data from adolescents indicate problems with these assumptions. These findings indicate four areas in which changes in the DSM diagnostic system for AUDs would improve validity and clinical applicability for adolescents. First, some symptoms need revised definitions to improve their validity for adolescents. The definition of tolerance needs to take into consideration physical development during adolescence, standardize the identification of the initial drinking period and set a minimum alcohol consumption quantity and frequency (Chung *et al.* 2001). Impaired control criteria need to take into consideration social context and the extent to which adolescents perceive the need for limiting alcohol consumption, because clear intentions are a required element for identifying the breaches of anticipated drinking parameters (Caetano 1999; Chung & Martin 2002). Secondly, revised diagnostic criteria are needed to eliminate diagnostic orphans. The similarities between adolescents meeting DSM criteria for alcohol abuse and those with one or two dependence symptoms argue for affording these groups similar status in the diagnostic system. Thirdly, alcohol use disorder severity classes are not well represented by the current abuse and dependence distinction, and may be better based on an overall symptom counts (Chung & Martin 2001). Fourthly, physiological dependence may be best defined by withdrawal only, rather than a combination of tolerance and withdrawal (Langenbucher *et al.* 2000).

ALCOHOL USE DISORDER COMPLICATIONS

Adolescents with AUDs often have a surfeit of psychosocial and biomedical problems distinct from AUD symptoms. These problems are difficult to characterize definitively as consequences of AUDs, and are therefore described here as 'complications'. Complications particularly relevant to clinical evaluation and treatment include substance use disorders involving illicit drugs, comorbid psychopathology, social and role functioning, suicidal behavior, risky sexual behavior and STDs, health impairments and neurobiological abnormalities.

Substance use disorders involving illicit drugs

Initiation rates for illicit drugs peak during adolescence (Kandel & Yamaguchi 1999; O'Malley, Johnston & Bachman 1999; Johnston *et al.* 2001). Most adolescents with AUDs engage in illicit drug use, with cannabis abuse and dependence being common in this group (Winters & Henly 1993; Myers, Brown & Mott 1995; Sussman, Dent & Galaif 1997; Crowley *et al.* 1998). Many adolescents with AUDs engage in simultaneous polydrug use, the practice of ingesting one, two or more drugs in combination with alcohol (Martin *et al.* 1996a). Adolescents with significant cannabis involvement are at high risk for drug dependence involving other illicit drugs (Fergusson & Horwood 2000). While AUDs during adolescence may facilitate the development of other SUDs, common etiologies for both AUDs and other SUDs probably contribute to their association.

The conceptualization emphasizing common liabilities for alcohol and other drug problems has been termed the Common Risk Model, and is contrasted with the Gateway Theory. The Gateway Hypothesis posits that there is a sequence of initiation characterized by drug class, and that use of the drug lower in the sequence increases the risk of using drugs higher in the sequence (Kandel 2002). In other words, 'use of gateway drugs causes youths to have an increased risk of progressing to other, more serious drugs' (Morrall *et al.* 2002). An alternative model proposes that a general propensity toward substance use causes an increased probability of alcohol and drug involvement, and the sequence involved is a function of opportunity (Tarter *et al.* 1999; Vanyukov *et al.* 2003). Results from several recent studies support the common risk model for relationships among alcohol and drug problems (Lynskey, Fergusson & Horwood 1998; Tarter *et al.* 2003). Using a simulation approach with a frailty model to construct conditional survival functions, Morrall *et al.* (2002) demonstrated the plausibility of the common risk model for AUDs and other SUDs.

Comorbid psychopathology

Although childhood mental disorders often precede and predict adolescent AUDs, alcohol and other substance use probably exacerbates these problems (Clark & Bukstein 1998). In adolescent samples, antisocial behaviors have been found to correlate with AUD severity and worsen alcohol outcomes (Brown *et al.* 1996; Bucholz, Heath & Madden 2000; Chung & Martin 2001). Major depressive disorder has also been found to be common among adolescents with AUDs, more so in females than in males, and to accelerate relapse (Clark *et al.* 1997b; Cornelius *et al.* 2004b). Childhood physical and sexual abuse are important contributors to depression among adolescents with AUDs (Clark *et al.* 2003). Depression and anxiety symptoms may be produced by alcohol consumption and withdrawal (Clark & Sayette 1993; Schuckit & Hesselbrock 1994). While several models suggest that SUD individuals with antisocial disorders and those with negative affect disorders represent distinct types (Zucker *et al.* 1995), data from adolescents with SUD indicate that conduct disorder and major depression cluster (Clark *et al.* 1997b).

The importance of specific treatment for comorbid psychopathology among adolescents with AUDs remains controversial (Clark *et al.* 2002b). The use of pharmacotherapy for comorbid depression and AUDs among adolescents is in a preliminary stage (Cornelius *et al.* 2004), and empirical support for other comorbid conditions is lacking. Despite this lack of empirical support, clinical use of pharmacological treatments for adolescents with comorbid AUDs and mental disorders is apparently increasing. An examination of clinical practices from 1991 to 2000 in a sample of adolescents with AUDs included 110 adolescents with comorbid MDD and AUDs (Clark *et al.* 2003). Among these comorbid adolescents, antidepressant medication use increased significantly from 18% to 55% over the decade studies. The increasing use of pharmacotherapy for adolescents with comorbid mental disorders and AUDs highlights the need for research on this topic.

Social and role functioning

The psychosocial difficulties of adolescents with SUDs extend beyond psychopathological characteristics to social and role functioning. In this context, consideration of the effects of comorbid disorders is important for determining the psychosocial problems that may be specifically attributable to AUDs. Clark & Kirisci (1996) reported differential effects of adolescent AUDs, MDD and post-traumatic stress disorder (PTSD) on social competence, social anxiety, academic achievement, school adjustment and overall functioning by DSM Axis V.

Whereas social competence was affected most adversely by depression, AUDs had a pronounced effect on academic achievement, school adjustment and overall psychosocial functioning.

Sexual behavior, sexual victimization and sexually transmitted disease

Adolescents with AUDs have elevated rates of risky sexual behaviors (Bailey *et al.* 1999). Adolescent females with AUDs, compared to those without AUDs, are more likely to have sexually transmitted diseases (Cook *et al.* 2002) and to become pregnant as teens (Clark, Lesnick & Hegeudus 1997a). In addition to voluntary engagement in risky sexual behaviors, sexual victimization is more common among adolescent girls with high alcohol involvement (Pedersen & Skrondal 1996). Sexual victimization experiences are much more common among females than males, and this difference may partly explain gender differences in comorbid psychopathology among adolescents with AUDs (Clark *et al.* 2003a).

Suicidal behavior

Among adolescents, AUDs is a risk factor for suicide attempts (Kelly *et al.* 2001, 2004). AUDs and MDD interact to elevate risk for suicidal behavior above what would be expected by an additive effect, particularly among females (Kelly *et al.* 2004). Serotonin markers, such as serum tryptophan ratio, may improve the prediction of suicidal behavior, although the status of such research is too preliminary to be relied upon for clinical decisions (Clark 2003).

Health status

Adolescent alcohol involvement has been reported to be associated with self-reported health problems (Farrow, Rees & Worthington-Roberts 1987; Newcomb & Bentler 1987; Hansell & White 1991; Clark *et al.* 2001b). Self-reported health problems have been interpreted as reflecting organic pathology induced by toxic alcohol effects (Arria *et al.* 1995) or nutritional deficiencies (Farrow *et al.* 1987). Given the comorbidity between depression and AUDs in adolescents, however, the extent to which health problems are attributable to alcohol-induced organ pathology or to somatic manifestations of anxiety and depression needs to be examined. In addition, tobacco involvement has also been shown to be associated with adolescent AUDs (Cornelius *et al.* 2001b) and to have a substantial effect on health outcomes in analogous adult populations (Hurt *et al.* 1996). Following a review of studies examining self-reported health problems and adolescent alcohol involvement, this paper

will discuss analogous studies measuring health findings by objective indicators.

Self-reported health problems

Self-reported health problems are clearly associated with alcohol involvement in adolescents. In a household adolescent sample (Hansell, White & Vali 1999), alcohol consumption contributed to increases in self-reported health problems over time. Aarons *et al.* (1997) found that self-reported health problems were more common in adolescents treated for SUDs than in a community reference group over a 6-year follow-up period. Among adolescents generally, medically unexplained self-reported health problems have been found to be associated with anxiety and depression (Ferdinand & Verhulst 1995; Egger, Angold & Costello 1998; Campo *et al.* 1999; Zwaigenbaum *et al.* 1999). Hansell & White (1991) found that while general substance use contributed to both physical and psychological symptoms, physical and psychological symptoms were correlated independently of substance use.

Negative emotionality, the disposition to anxiety and depression (Watson & Clark 1984), has been found to be associated with adolescent AUDs (Martin *et al.* 2000). Clark *et al.* (2001b) compared adolescents with AUDs and a community reference group on self-reported health problems, and investigated the relevance of negative emotionality to understanding these health complaints. While adolescents with AUDs reported more health problems than the reference group, negative emotionality mediated the relationship between AUDs and self-reported health problems. Exceptions were sleep disturbances, which retained a significant association with AUDs despite a strong correlation with negative emotionality, and cardiopulmonary complaints, which were attributable to cigarette smoking.

Liver injury

Of liver enzyme assays, γ -glutamyl transferase (also known as γ -glutamyl transpeptidase, or GGT) has been noted to be the most sensitive correlate of alcohol consumption (Anton & Moak 1994; Allen *et al.* 1997; Daepfen *et al.* 1999). Two studies with relatively small samples measuring GGT in adolescents with AUDs have reported positive (Arria *et al.* 1995) and negative (Farrow *et al.* 1987) results. With substantially larger samples, Clark *et al.* (2001b) compared adolescents with AUDs and community adolescents on serum liver enzyme assays including GGT. While adolescents with AUDs compared with reference adolescents had significantly elevated GGT, few had clinically abnormal findings and none had 'very high' GGT by adult standards (Daepfen *et al.* 1999).

The low rate of clinically significant liver injury was due probably to the less frequent drinking episodes and shorter alcohol involvement periods seen in adolescents with AUDs compared with adults with AUDs in analogous studies (Daepfen *et al.* 1999; Deas *et al.* 2000; Clark *et al.* 2001b). These modest elevations of serum liver enzymes were nevertheless of concern, because these changes may preface the development of the more serious liver pathology in some individuals.

Physical examination findings

Characteristic physical examination findings do not occur typically until the late stages of severe and chronic alcohol dependence (Alterman, Gelfand & Sweeney 1992; Goodwin & Gabrielli 1997). In adolescents with AUDs, Clark *et al.* (2001b) noted no physical examination findings attributable to the toxic effects of alcohol on organ systems. As a more general health status indicator, however, dental caries and periodontal diseases may be early and sensitive measures (Crowson 1974), and have been shown to be associated with risk for substance use disorders in children (Cornelius *et al.* 2004a) and AUDs in adults (King & Tucker 1973). Clark *et al.* (2001b) found adolescents with AUDs compared to reference adolescents had a higher rate of abnormal findings on the corresponding oral component of the physical examination.

In summary, the health status of adolescents with AUDs is clearly compromised. Self-reported health symptoms are substantially elevated in adolescents with AUDs compared with reference adolescents. Among adolescents with AUDs, self-reported health problems primarily reflect negative emotionality rather than organ pathology. Modest elevations in serum liver enzymes have been demonstrated, indicating subclinical liver injury. Physical examination findings suggest generally poor health maintenance behavior without the signs of alcohol-induced organ injury evident in adults with chronic alcohol dependence.

Neuropsychological, neuroanatomical and neurochemical changes

A worrying possibility is that alcohol involvement during adolescence adversely affects central nervous system development, manifested by changes in neurocognitive function, brain structure and neurochemistry. A few studies have assessed the neuropsychological functioning of adolescents with AUDs. Moss *et al.* (1994) reported that adolescents with AUDs, compared with reference adolescents, had lower verbal and full-scale IQ scores but were not impaired in learning and memory tasks. Brown *et al.* (2000) compared

adolescents with alcohol dependence and matched controls on tests of verbal and non-verbal learning and memory, visuospatial functioning, language skills, attention and problem-solving skills. Adolescents with alcohol dependence showed poorer verbal and non-verbal retention on some tests, and were unimpaired on other learning and memory tasks. Modest, albeit statistically significant, correlations were noted between alcohol withdrawal symptoms and neuropsychological impairment. These findings suggest that adolescents with AUDs, overall, manifest only relatively mild neurocognitive impairment.

With continued alcohol dependence, however, adolescents with AUDs risk deteriorating neuropsychological functioning. For adolescents completing alcohol and drug treatment, Tapert & Brown (1999) reported performance on a neuropsychological battery 4 years after discharge. Alcohol withdrawal symptoms in the interim period predicted poorer performance on tests of visuospatial skills, attention and working memory.

While the neuroanatomical characteristics of adolescents with AUDs have not been determined definitively, the available data are of concern. The hippocampus undergoes significant change during adolescence and is known to be sensitive to toxic alcohol effects (Sullivan *et al.* 1995; De Bellis *et al.* 1999). If hippocampal development is adversely affected by alcohol involvement during adolescence, one might expect to see smaller hippocampal volumes in individuals with adolescent-onset AUDs. De Bellis *et al.* (2000) used magnetic resonance imaging (MRI) to measure the hippocampal volumes and comparison brain regions in 12 subjects with adolescent-onset AUDs and 24 matched controls. Both left and right hippocampi were significantly smaller in AUD subjects compared to controls, and other brain regions did not differ between groups. In contrast to the more global brain changes seen in adults with chronic alcohol dependence, these findings suggest that the adolescent hippocampus may be specifically susceptible to toxic alcohol effects.

Positron emission tomography (PET) studies examining middle-aged or older adults with AUDs have suggested that AUDs may result in downregulation of benzodiazepine receptors, particularly in the anterior cingulate cortex (Gilman *et al.* 1996). Clark *et al.* (2000) have reported similar findings in young adults with adolescent-onset AUDs. Because the anterior cingulate cortex is involved in affect regulation, response selection and motivation for goal-directed behavior (Spear 2000), neurochemical changes in this brain area may be relevant to understanding the neurobiological mechanism of alcohol dependence.

These findings indicate that the early course of adolescent AUDs is marked by mild neuropsychological

impairment. In the foreseeable future, increasingly sensitive neuroimaging capabilities may result in the detection of adverse neurobiological effects from alcohol prior to functional changes. Among adolescents progressing to more severe alcohol dependence, neuropsychological abnormalities have been demonstrated. Further information on the neurobiological and functional effects of alcohol involvement on the developing brain during adolescents is urgently needed.

Adolescent AUD outcomes

Treatment outcomes over 1-year follow-up

Treatment programs for adolescents with AUDs typically aspire to produce alcohol abstinence. While this desirable goal is rarely achieved for extended periods, substantial improvement over a 1-year follow-up period is the mode (Lewinsohn *et al.* 1996; Nelson & Wittchen 1998). Maisto *et al.* (2001, 2002) have reported outcomes over a 1-year period for adolescents with AUDs. While 51% of the sample no longer met criteria for AUDs, only one-fifth (19%) were alcohol abstinent. Chung & Martin (2001) constructed latent classes of AUD symptoms and investigated transition probabilities at 1-year follow-up among adolescents in addictions treatment. Among adolescents in the mild AUD class at baseline, the most common outcome was a transition to the asymptomatic class, with fewer subjects remaining in the mild class and transition to the severe class least probable. For those in the severe class at baseline, transitioning to the mild class or asymptomatic class were both more common than remaining in the severe class. Other adolescent studies have also indicated that short-term outcomes are influenced by AUD severity, with alcohol abuse (i.e. abuse without dependence) typically a transient phenomenon (Lewinsohn *et al.* 1996; Nelson & Wittchen 1998). Such findings suggest that, for many adolescents, AUDs have a developmentally limited course.

Among adolescents with AUDs, continued alcohol involvement without reported problems is a common outcome. Maisto *et al.* (2002) reported that, among 150 adolescents in treatment for AUDs, 23% were drinking but had no AUD symptoms at a 1-year outcome assessment. At 1-year follow-up, non-problem drinkers had psychosocial functioning similar to abstainers and better than problem drinkers. Longer-term follow-up assessments will be needed to determine whether the non-problem drinkers sustain the improvements noted.

Adulthood outcomes

Generalizing from the literature on 'early onset alcoholism', adolescents with AUDs might be predicted to have

a chronic course culminating in severe alcohol dependence in adulthood. On the other hand, 1-year follow-up studies indicate that many adolescents with AUDs have substantial short-term improvement. Prospective studies of the adult outcomes of adolescents with AUDs are therefore critically important in understanding the range of adult outcomes manifested by these adolescents.

Among adolescents with alcohol consumption in the normal range, the level of alcohol involvement may not be a strong predictor of later alcohol involvement characteristics. Most studies with community samples have found that the level of adolescent alcohol consumption has little or no relationship with adult alcohol involvement (Donovan, Jessor & Jessor 1983; Kandel *et al.* 1986; Newcomb, Scheier & Bentler 1993; Stacy, Newcomb & Bentler 1993), although there have been some exceptions (e.g. Guy, Smith & Bentler 1993). Adolescent alcohol involvement over time has better predictive validity and has been found to be related to adulthood alcohol problems (Duncan *et al.* 1997). Nevertheless, qualitatively distinct results may be found for adolescent alcohol involvement resulting in AUDs.

Studies to date examining the young adulthood outcomes of adolescents with AUDs indicate reduced alcohol involvement over time, with about half no longer meeting criteria for AUD diagnoses (Clark *et al.* 2003). Rohde *et al.* (2001) reported data on 82 adolescents (14–18 years) with AUD ascertained from a total sample of 908 recruited in high schools and followed to adulthood (age 24 years). Among adolescents with AUD, 55% had AUDs at the adult assessment. While the slight majority had adulthood AUDs, the obverse of this coin is worth emphasizing—nearly half did not qualify for an adulthood AUD diagnosis. Adolescents with AUD were much more likely than other adolescents to have adulthood AUDs (OR = 3.6), other substance use disorders (42%, OR = 4.6), depressive disorder (53%, OR = 2.3), antisocial personality disorder (31%, OR = 5.8) and borderline personality disorder (31%, OR = 5.8).

On average, adolescents participating in addictions treatment show improvement in adulthood. Brown *et al.* (2001) followed adolescents recruited from in-patient addictions treatment to adulthood, and reported reduced alcohol and drug involvement. For adolescents in treatment for substance use disorders, long-term outcomes have been found to be predicted by alcohol and drug involvement severity, interpersonal and family problems, legal problems and negative affect (Stewart & Brown 1993; Myers, Stewart & Brown 1998). Participation in aftercare treatment interventions has been found to be associated with better outcomes (Alford, Koehler & Leonard 1991; Ralph & McMenamy 1996; Kelly, Myers & Brown 2000).

CONCLUSIONS

Developmentally informed treatment of adolescents with AUDs is founded on an understanding of alcohol involvement trajectories from childhood to adulthood. The manifestations of this trajectory proceed according to developmental stages. Occurring prior to significant alcohol involvement, childhood mental behaviors presage adolescent alcohol problems, are associated with the persistence of alcohol problems in adolescence and predict adult AUD outcomes. The initiation of alcohol involvement occurs typically in early adolescence, with age at initiation predicted by both childhood characteristics reflecting psychological dysregulation and low parental supervision. Rapid progression to alcohol problems then occurs among the relatively small proportion of adolescents developing AUDs. More commonly, binge drinking occurs in later adolescence with the potential for related adverse outcomes despite the lack of diagnosis. For adolescents with AUDs, psychosocial problems are much more common than dependence signaled by withdrawal symptoms. Data on short-term outcomes indicates that adolescents with AUDs have heterogeneous responses to treatment, including abstinence, non-problem drinking and chronic problem drinking. Adolescent alcohol abuse and subthreshold dependence are typically developmentally limited. Adolescents with alcohol dependence, compared to those with abuse, tend to have more persistent alcohol problems, although they also show short-term improvement on average. While few studies of adult outcomes have been completed, data available to date similarly suggest that about half manifest AUDs as adults.

The heterogeneity evident in the long-term outcomes of adolescents with AUDs is also evident in their complications. The biomedical consequences seen in adults with chronic alcohol dependence are rare in adolescents with AUDs. Self-reported health symptoms are generally attributable to negative affect, liver injury when present is usually subclinical and neuropsychological abnormalities are generally mild. When severe and persistent, however, adolescents with AUDs show alcohol-related complications similar to those in their adult counterparts, illicit drug abuse and dependence, persistent comorbid psychopathology and worrying neurobiological changes that may indicate significant adverse effects on central nervous system development. The highly variable adulthood outcomes for adolescents with AUDs suggest that adolescence is a pivotal time in the life-course of alcohol involvement.

While studies to date have depicted the range of outcomes manifested by a few samples of adolescents with AUDs, the extent to which these studies generalize to the population of adolescents with AUDs is unknown. Adolescents with AUDs are difficult to identify and assess

through community sampling methods. Several factors contribute to the difficulties in studying 'hard-to-reach' or 'hidden' populations through traditional sampling strategies (Faugier & Sargent 1997), including: (1) the low base rate in the population necessitates the study of very large samples; (2) potential legal and social sanctions deter respondents from cooperating; and (3) affected subjects are more difficult to contact than unaffected subjects. Estimates from community samples indicating that approximately 5% of adolescents meet DSM criteria for alcohol use disorders (Chung *et al.* 2002) suggest that samples with several thousand adolescents would be required to provide sufficient samples for studying adolescent AUD variants. Another alternative to random community sampling is the use of medical record databases. While large medical record databases with these variables may be available, variation in the typically unstructured clinical assessment leads to inaccurate diagnostic formulations, as has been demonstrated for adolescents with AUDs (Clark *et al.* 1995). While the possibility of selection bias is never entirely eliminated in clinically oriented research (Ellenberg 1994), a high degree of selection bias leads to problems in interpreting comorbidity (Kraemer 1995), including potential problems with the generalizability of models. Consideration of selection bias in this context thus involves an evaluation of the degree of bias and the probable influence on generalizability of findings. Selection bias can be conceptualized as a missing data problem and methods to correct sampling bias have been developed (Stolzenberg & Relles 1997). However informative, the characterization of the course and outcomes of adolescents with AUDs depicted at this time must be considered a preliminary estimate.

There may also be a bias toward the publication of studies showing adverse alcohol effects on adolescent development. Studies showing significant differences between adolescents with AUDs and control adolescents (i.e. positive results) may be more likely to be presented and published than studies of equal methodological merit not showing significant differences between groups (i.e. negative results). The dissemination of negative studies, particularly where the results are contrary to expected or other published studies, is as important as the publication of studies showing adverse effects of alcohol on adolescent development.

Thorough clinical assessment is the foundation for effective treatment planning in programs for adolescents with AUDs. Characterization of the alcohol involvement history includes identification of relevant beverages, determination of the age of important alcohol consumption landmarks and description of alcohol-specific problems (Martin & Winters 1998; Clark & Winters 2002). Ideally, the initial alcohol involvement assessment takes a diachronic approach, depicting changes in beverage

choice, quantity, frequency and patterns of alcohol consumption and alcohol-related problems over time (Clark *et al.* 2001). Because an unstructured clinical assessment may lead to inaccurate diagnostic formulations, systematically planned assessment protocols using structured interviews for diagnostic formulations are needed to provide accurate profiles (Clark *et al.* 1995; Clark 1999). In clinical practice, as in treatment research, ongoing assessment in the course of treatment is intended to determine intervention effects. The presence or absence of AUD is a crude outcome indicator, and a multi-faceted approach applying the principle of diachronic assessment provides more useful data. Characterization of the course of adolescents with AUDs is enhanced by non-categorical measures, including the empirical identification of developmental alcohol involvement trajectories. In addition to DSM-IV AUDs, other substance use disorders, comorbid mental disorders, health status and neuropsychological functioning, social relationships and school functioning are also important assessment domains. Assessment strategies and instruments validated for the adolescent period are available (Clark & Winters 2002). Comprehensive, diachronic and developmentally informed evaluation optimizes treatment evaluation.

Problems with the application of DSM-IV definitions of alcohol abuse and dependence to adolescence have important clinical implications. Perhaps the most serious dilemma is the identification of diagnostic orphans. These adolescents have alcohol-related problems similar in severity to those with alcohol abuse, yet do not meet the defined threshold for a diagnosis. Without a diagnosis, such adolescents may not qualify for participation in treatment programs. Health service delivery to such adolescents may be jeopardized as a result. In addition to the need to eliminate diagnostic orphans, changes are needed to define specific AUD symptoms in such a way as to more validly apply to adolescents. An improved AUD classification method for adolescents would yield more appropriate health services delivery (Aylsworth 1998).

In most treatment programs, the goal of abstinence from alcohol is promoted. While indisputably a successful treatment outcome for adolescents with AUDs, long-term abstinence is atypical. Treatment programs for adolescent AUDs also need to consider other outcome indicators. For many adolescents, a reduction in alcohol use to normative levels and elimination of alcohol-related problems may be an achievable goal with acceptable developmental outcomes (Maisto *et al.* 2002). Furthermore, the elimination of other substance use, the reduction of anti-social behavior and resolution of depression need to be integrated into the intervention goals.

Particularly when AUDs are comorbid with mental disorders, psychosocial treatments may be more effective when problems manifested in multiple levels of

psychosocial organization are addressed. Multidimensional treatment programs (e.g. Multisystemic Treatment: Henggeler *et al.* 1998) represent an ideal solution and are a necessary approach for some adolescents with AUDs. Although the use of medications for alcohol-related problems and comorbid mental disorders is not guided by a substantial empirical literature at this time, pharmacological interventions may also need to receive due consideration (Clark, Bukstein & Cornelius 2002b). Although the high cost of comprehensive programs may limit their application, the societal costs of neglecting the most problematic adolescents is greater than the cost of the most extensive intervention (Scott *et al.* 2001). While some adolescents may require intensive interventions, others, particularly those with alcohol abuse, may fare well with conventional, more limited treatment. A more extensive empirical basis for specific treatment matching recommendations is needed to provide the basis for offering more comprehensive services to the adolescents most likely to benefit from the more costly intervention. Clinical assessment and treatment taking full advantage of available approaches are critical in assuring the best possible adult outcomes for these adolescents.

The burgeoning research on adolescents with AUDs promises further advances in coming years. Considerably more research is needed to optimize the delivery of psychosocial and pharmacological treatment to adolescents with AUDs. The natural history of adolescent AUDs provides guideposts relevant for clinical evaluation and treatment. Information on normative and pathological developmental trajectories and their relationship with adolescent AUDs and adult outcomes provides a needed perspective. The initiation and evaluation of treatment may be guided by the severity of childhood mental disorders, the extent to which early adolescent alcohol involvement represents deviant or normative behavior and the relationships among childhood, adolescent and adulthood characteristics. By expanding the focus of treatment to an array of developmentally and clinically relevant risks and outcomes, treatment research will be more influential in guiding clinical practice.

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References

- Aarons, G. A., Brown, S. A., Coe, M. T., Myers, M. G., Garland, A. F., Ezzet-Lofstrom, R., Hazen, A. L. & Hough, R. L. (1997) Adolescent alcohol and drug abuse and health. *Journal of Adolescent Health*, **24**, 412–421.
- Adalbjarnardottir, S. (2002) Adolescent psychosocial maturity

- and alcohol use: quantitative and qualitative analysis of longitudinal data. *Adolescence*, **37**, 19–53.
- Alford, G. S., Koehler, R. A. & Leonard, J. (1991) Alcoholics Anonymous–Narcotics Anonymous Model inpatient treatment of chemically dependent adolescents: a 2-year outcome study. *Journal of Studies on Alcohol*, **52**, 118–126.
- Allen, J. P., Fertig, J. B., Litten, R. Z., Sillanaukee, P. & Anton, R. F. (1997) Proposed recommendations for research on biochemical markers for problematic drinking. *Alcoholism: Clinical and Experimental Research*, **21**, 244–247.
- Alterman, A. I., Gelfand, L. A. & Sweeney, K. K. (1992) The Alcohol Clinical Index in lower socioeconomic alcohol-dependent men. *Alcoholism: Clinical and Experimental Research*, **16**, 960–963.
- American Psychiatric Association (APA) (1994) *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th edn. Washington, DC: American Psychiatric Association.
- Anton, R. F. & Moak, D. H. (1994) Carbohydrate-deficient transferrin and gamma-glutamyltransferase as markers of heavy alcohol consumption. *Alcoholism: Clinical and Experimental Research*, **18**, 747–754.
- Arria, A. M., Dohey, M. A., Mezzich, A. C., Bukstein, O. G. & Van Thiel, D. H. (1995) Self-reported health problems and physical symptomatology in adolescent alcohol abusers. *Journal of Adolescent Health*, **16**, 226–231.
- Aylsworth, A. S. (1998) Defining disease phenotypes. In: Haines, J. L. & Pericak-Cance, M. A., eds. *Approaches to Gene Mapping in Complex Human Diseases*, pp. 53–76. New York: Wiley-Liss.
- Babor, T. F., De Hofman, M. I., Boca, F. K., Hesselbrock, V., Meyer, R. E., Dolinsky, Z. S. & Rounsaville, B. (1992) Types of alcoholics. I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*, **49**, 599–608.
- Bailey, S. L., Pollock, N. K., Martin, C. S. & Lynch, K. G. (1999) Risky sexual behaviors among adolescents with alcohol use disorders. *Journal of Adolescent Health*, **25**, 179–181.
- Barnes, G. M., Farrell, M. P. & Banerjee, S. (1995) Family influences on alcohol abuse and other problem behaviors among black and white adolescents in a general population sample. In: Boyd, G. M., Howard, J. & Zucker, R. A., eds. *Alcohol Problems Among Adolescents: Current Directions in Prevention Research*, pp. 13–31. Hillsdale, NJ: Erlbaum.
- Barnow, S., Schuckit, M. A., Lucht, M., John, U. & Freyberger, H. J. (2002) The importance of a positive family history of alcoholism, parental rejection and emotional warmth, behavioral problems and peer substance use for alcohol problems in teenagers: a path analysis. *Journal of Studies on Alcohol*, **63**, 305–315.
- Biederman, J., Wilens, T., Mick, E., Farone, S. V., Weber, W., Curtis, S., Thornell, A., Pfister, K., Jetton, J. G. & Soriano, J. (1997) Is ADHD a risk factor for psychoactive substance use disorders: findings from a four-year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **36**, 21–29.
- Boyle, M. H., Offord, D. R., Racine, Y. A., Szatmari, P., Fleming, J. E. & Links, P. (1992) Predicting substance use in late adolescence: results of the Ontario Child Health Study Follow-up. *American Journal of Psychiatry*, **149**, 761–767.
- Brown, S. A., D'Amico, E. J., McCarthy, D. M. & Tapert, S. F. (2001) Four-year outcomes from adolescent alcohol and drug treatment. *Journal of Studies on Alcohol*, **62**, 381–388.
- Brown, S. A., Gleghorn, A., Schuckit, M. A., Myers, M. G. & Mott, M. A. (1996) Conduct disorder among adolescent

- alcohol and drug abusers. *Journal of Studies on Alcohol*, *57*, 314–324.
- Brown, S. A., Tapert, S. F., Tate, S. R. & Abrantes, A. M. (2000) The role of alcohol in adolescent relapse and outcome. *Journal of Psychoactive Drugs*, *32*, 107–115.
- Bucholz, K. K., Heath, A. C. & Madden, P. A. F. (2000) Transitions in drinking in adolescent females: evidence from the Missouri Adolescent Female Twin Study. *Alcoholism: Clinical and Experimental Research*, *24*, 914–923.
- Buydens-Branchey, L., Branchey, M. H. & Noumair, D. (1989) Age of alcoholism onset. I. Relationship to psychopathology. *Archives of General Psychiatry*, *46*, 225–230.
- Cadoret, R. J., Troughton, E., Bagford, J., Woodward, G. & Steward, M. A. (1995) Adoption study demonstrating two genetic pathways to drug abuse. *Archives of General Psychiatry*, *52*, 42–52.
- Caetano, R. (1999) The identification of alcohol dependence criteria in the general population. *Addiction*, *94*, 255–267.
- Campo, J. V., Jansen-McWilliams, L., Comer, D. M. & Kelleher, K. J. (1999) Somatization in pediatric primary care: association with psychopathology, functional impairment, and use of services. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*, 1093–1101.
- Chambers, R. A., Taylor, J. R. & Potenza, M. N. (2003) Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *American Journal of Psychiatry*, *160*, 1041–1052.
- Chung, T. & Martin, C. S. (2001) Classification and course of alcohol problems among adolescents in addictions treatment programs. *Alcoholism: Clinical and Experimental Research*, *25*, 1734–1742.
- Chung, T. & Martin, C. S. (2002) Concurrent and discriminant validity of DSM-IV symptoms of impaired control over alcohol consumption in adolescents. *Alcoholism: Clinical and Experimental Research*, *26*, 485–492.
- Chung, T., Martin, C. S., Armstrong, T. D. & Labouvie, E. W. (2002) Prevalence of DSM-IV alcohol diagnoses and symptoms in adolescent community and clinical samples. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*, 546–554.
- Chung, T., Martin, C. S., Winters, K. C. & Langenbucher, J. (2001) Assessment of alcohol tolerance in adolescents. *Journal of Studies on Alcohol*, *62*, 687–695.
- Cicchetti, D. & Cohen, D. J. (1995) Perspectives on developmental psychopathology. In: Cicchetti, D. & Cohen, D. J., eds. *Developmental Psychopathology: Theory and Methods*, pp. 3–20. New York: Wiley.
- Clark, D. B. (1999) Psychiatric assessment. In: Ott, P. J., Tarter, R. E. & Ammerman, A. T., eds. *Sourcebook on Substance Abuse: Etiology, Methodology, and Intervention*, pp. 197–211. Needham Heights, MA: Allyn & Bacon.
- Clark, D. B. (2003) Serum tryptophan ratio and suicidal behavior in adolescents: A prospective study. *Psychiatry Research*, *119*, 199–204.
- Clark, D. B. & Bukstein, O. G. (1998) Psychopathology in adolescent alcohol abuse and dependence. *Alcohol Health and Research World*, *22*, 117–126.
- Clark, D. B., Bukstein, O. G. & Cornelius, J. R. (2002b) Alcohol use disorders in adolescents: epidemiology, diagnosis and management. *Pediatric Drugs*, *4*, 493–502.
- Clark, D. B., Bukstein, O. G., Smith, M. G., Kaczynski, N. A., Mezzich, A. & Donovan, J. E. (1995) Identifying anxiety disorders in adolescents hospitalized for alcohol abuse or dependence. *Psychiatric Services*, *46*, 618–620.
- Clark, D. B., Cornelius, J. R., Wood, D. S. & Vanyukov, M. (2004) Psychopathology risk transmission in children of parents with substance use disorders. *American Journal of Psychiatry*, *161*, 685–691.
- Clark, D. B., DeBellis, M. D., Lynch, K. G., Cornelius, J. R. & Martin, C. S. (2003) Physical and sexual abuse, depression and alcohol use disorders in adolescents: onsets and outcomes. *Drug and Alcohol Dependence*, *69*, 51–60.
- Clark, D. B. & Kirisci, L. (1996) PTSD, depression, alcohol use disorders, and quality of life in adolescents. *Anxiety*, *2*, 226–233.
- Clark, D. B., Kirisci, L. & Moss, H. B. (1998a) Early adolescent gateway drug use in sons of fathers with substance use disorders. *Addictive Behaviors*, *23*, 561–566.
- Clark, D. B., Kirisci, L. & Tarter, R. E. (1999a) Adolescent versus adult onset and the development of substance use disorders in males. *Drug and Alcohol Dependence*, *49*, 115–121.
- Clark, D. B., Lesnick, L. & Hegeudus, A. (1997a) Trauma and other stressors in adolescent alcohol dependence and abuse. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 1744–1751.
- Clark, D. B., Lynch, K. G., Donovan, J. E. & Block, G. E. (2001b) Health problems in adolescents with alcohol use disorders: self-report, liver injury and physical examination findings and correlates. *Alcoholism: Clinical and Experimental Research*, *25*, 1350–1359.
- Clark, D. B., Moss, H., Kirisci, L., Mezzich, A. C., Miles, R. & Ott, P. (1997c) Psychopathology in preadolescent sons of substance abusers. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 495–502.
- Clark, D. B., Neighbors, B. D., Lesnick, L. A., Lynch, K. G. & Donovan, J. E. (1998b) Family functioning and adolescent alcohol use disorders. *Journal of Family Psychology*, *12*, 81–92.
- Clark, D. B., Parker, A. M. & Lynch, K. G. (1999b) Psychopathology, substance use and substance related problems during early adolescence: a survival analysis. *Journal of Child Clinical Psychology*, *28*, 333–341.
- Clark, D. B., Pollock, N., Bukstein, O. G., Mezzich, A. C., Bromberger, J. T. & Donovan, J. E. (1997b) Gender and comorbid psychopathology in adolescents with alcohol dependence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 1195–1203.
- Clark, D. B., Pollock, N. K., Mezzich, A., Cornelius, J. & Martin, C. (2001a) Diachronic assessment and the emergence of substance use disorders. *Journal of Child and Adolescent Substance Abuse*, *10*, 13–22.
- Clark, D. B., Rao, A., Greer, P., Price, J., Smith, G. & Meltzer, C. (2000) A pilot study of anterior cingulate cortex benzodiazepine receptor binding in adolescent-onset alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, *24*, 713A.
- Clark, D. B. & Sayette, M. A. (1993) Anxiety and the development of alcoholism: clinical and scientific issues. *American Journal on Addictions*, *2*, 59–76.
- Clark, D. B., Thatcher, D. & Maisto, S. (2004b) Adolescent neglect and alcohol use disorders in two-parent families. *Child Maltreatment* (in press).
- Clark, D. B., Vanyukov, M. & Cornelius, J. (2002a) Childhood antisocial behavior and adolescent alcohol use disorders. *Alcohol Research and Health*, *26*, 109–115.
- Clark, D. B. & Winters, K. C. (2002) Measuring risks and outcomes in substance use disorders prevention research. *Journal of Consulting and Clinical Psychology*, *70*, 1207–1223.
- Clogg, C. C. & Haritou, A. (1997) The regression method of casual inference and a dilemma confronting this method. In:

- McKim, V. R. & Turner, S. P., eds. *Causality in Crisis?*, pp. 83–112. Notre Dame, Indiana: University of Notre Dame Press.
- Cloninger, C. R. (1987) Neurogenetic adaptive mechanisms in alcoholism. *Science*, **236**, 410–416.
- Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., Rojas, M., Brook, J. & Streuning, E. L. (1993) An epidemiological study of disorders in late childhood and adolescence: age- and gender-specific prevalence. *Journal of Child Psychology and Psychiatry*, **34**, 851–867.
- Cook, R. L., Pollock, N., Rao, A. & Clark, D. B. (2002) Increased prevalence of herpes simplex virus type 2 among adolescent women with alcohol use disorders. *Journal of Adolescent Health*, **30**, 169–174.
- Cooper, G. F. (1999) An overview of the representation and discovery of causal relationships using Bayesian networks. In: Glymour, C. & Cooper, G. F., eds. *Computation, Causation, and Discovery*, pp. 3–62. Menlo Park, CA: AAAI/MIT Press.
- Cornelius, J. R., Bukstein, O. G., Salloum, I. M., Kelly, T. M., Wood, D. S. & Clark, D. B. (2004c) Fluoxetine in depressed AUD adolescents: a one-year follow-up evaluation. *Journal of Child and Adolescent Psychopharmacology*, **14**, 35–40.
- Cornelius, J. R., Clark, D. B., Weyant, R., Bretz, W., Corby, P., Mezzich, A. & Kirisci, L. (2004a) Dental abnormalities in children of fathers with substance use disorders. *Addictive Behaviors*, **29**, 979–982.
- Cornelius, J. R., Lynch, K., Martin, C. S., Cornelius, M. D. & Clark, D. B. (2001b) Clinical correlates of heavy tobacco use among adolescents. *Addictive Behaviors*, **26**, 273–277.
- Cornelius, J. R., Maisto, S. A., Martin, C. S., Bukstein, O. G., Salloum, I. M., Daley, D. C., Wood, D. S. & Clark, D. B. (2004b) Major depression associated with earlier alcohol relapse in treated teens with AUD. *Addictive Behaviors*, **29**, 1035–1038.
- Cornelius, J. R., Pringle, J., Jernigan, J., Kirisci, L. & Clark, D. B. (2001a) Correlates of mental health service utilization and unmet need among a sample of male adolescents. *Addictive Behaviors*, **26**, 11–19.
- Costello, J. E., Angold, A., Burns, B. J., Stangl, D. K., Tweed, D. L., Erkanli, A. & Worthman, C. M. (1996) The Great Smoky Mountains study of youth: goals, design, methods, and the prevalence of DSM-III-R disorders. *Archives of General Psychiatry*, **53**, 1129–1136.
- Crowley, T. J., Macdonald, M. J., Whitmore, E. A. & Mikulich, S. K. (1998) Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug and Alcohol Dependence*, **50**, 27–37.
- Crowson, C. J. (1974) Dental caries: an early indicator of health status. *Journal of the American College of Health*, **23**, 176–180.
- Daepfen, J. B., Schoenfeld-Smith, K., Smith, T. L. & Schuckit, M. A. (1999) Characteristics of alcohol dependent subjects with very elevated levels of gamma-glutamyltransferase (GGT). *Journal of Studies on Alcohol*, **60**, 589–594.
- Dawes, M. A., Antelman, S. M., Vanyukov, M. M., Giancola, P., Tarter, R. E., Susman, E. J., Mezzich, A. & Clark, D. B. (2000) Developmental sources of variation in liability to adolescent substance use disorders. *Drug and Alcohol Dependence*, **61**, 3–14.
- De Bellis, M. D., Clark, D. B., Beers, S. R., Soloff, P., Boring, A. M., Hall, J., Kersh, A. & Keshavan, M. S. (2000) Hippocampal volume in adolescent onset alcohol use disorders. *American Journal of Psychiatry*, **157**, 737–744.
- De Bellis, M. D., Keshavan, M., Clark, D. B., Casey, B. J., Giedd, J., Boring, A. M., Frustaci, K. & Ryan, N. D. (1999) Developmental traumatology: Part II. Brain development. A. E. Bennett Research Award. *Biological Psychiatry*, **45**, 1271–1284.
- Deas, D., Riggs, P., Langenbucher, J., Goldman, M. & Brown, S. (2000) Adolescents are not adults: developmental considerations in alcohol users. *Alcoholism: Clinical and Experimental Research*, **24**, 232–237.
- Dick, D. M., Li, T.-K., Edenberg, H. J., Hesselbrock, V., Kramer, J., Kuperman, S., Porjesz, B., Bucholz, K., Goate, A., Nurnberger, J. & Foroud, T. (2004) A genome-wide screen for genes influencing conduct disorder. *Molecular Psychiatry*, **9**, 81–86.
- Donovan, J. E. (2004) Adolescent alcohol initiation: a review of psychosocial risk factors. *Journal of Adolescent Health*, in press.
- Donovan, J. E., Jessor, R. & Jessor, L. (1983) Problem drinking in adolescence and young adulthood: a follow-up study. *Journal of Studies on Alcohol*, **44**, 109–137.
- Droomers, M., Schrijvers, C. T., Casswell, S. & Mackenbach, J. P. (2003) Occupation level of the father and alcohol consumption during adolescence; patterns and predictors. *Journal of Epidemiology and Community Health*, **57**, 704–710.
- Duncan, D. F. (1997) Chronic drinking, binge drinking and drunk driving. *Psychological Reports*, **80**, 681–682.
- Duncan, T. E., Duncan, S. C., Alpert, A., Hops, H., Stoolmiller, M. & Muthen, B. (1997) Latent variable modeling of longitudinal and multilevel substance data. *Multivariate Behavioral Research*, **32**, 275–318.
- Earls, F., Reich, W., Jung, K. G. & Cloninger, C. R. (1988) Psychopathology in children of alcoholic and antisocial parents. *Alcoholism: Clinical and Experimental Research*, **12**, 481–487.
- Eaves, L., Rutter, M., Silberg, J. L., Shillady, L., Maes, H. & Pickles, A. (2000) Genetic and environmental causes of covariation in interview assessments of disruptive behavior in child and adolescent twins. *Behavior Genetics*, **30**, 321–334.
- Egger, H. L., Angold, A. & Costello, E. J. (1998) Headaches and psychopathology in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, **37**, 951–958.
- Ellenberg, J. H. (1994) Selection bias in observational and experimental studies. *Statistics in Medicine*, **13**, 557–567.
- Famularo, R., Stone, K. & Popper, C. (1985) Preadolescent alcohol abuse and dependence. *American Journal of Psychiatry*, **142**, 1187–1189.
- Farrow, J. A., Rees, J. M. & Worthington-Roberts, B. S. (1987) Health, developmental and nutritional status of adolescent alcohol and marijuana abusers. *Pediatrics*, **79**, 218–223.
- Faugier, J. & Sargent, M. (1997) Sampling hard to reach populations. *Journal of Advanced Nursing Research*, **26**, 790–797.
- Ferdinand, R. F. & Verhulst, F. C. (1995) Psychopathology from adolescence into young adulthood: an 8-year follow-up study. *American Journal of Psychiatry*, **152**, 1586–1594.
- Fergusson, D. M. & Horwood, L. J. (2000) Does cannabis use encourage other forms of illicit drug use? *Addiction*, **95**, 505–520.
- Flewelling, R. L. & Bauman, K. E. (1990) Family structure as a predictor of initial substance use and sexual intercourse in early adolescence. *Journal of Marriage and the Family*, **52**, 171–181.
- Ge, X., Conger, R. D. & Elder, G. H. (1996) Coming of age too early: pubertal influences on girls' vulnerability to psychological distress. *Child Development*, **67**, 3386–3400.
- Giaconia, R. M., Reinherz, H. Z., Silverman, A. B., Pakiz, B., Frost, A. K. & Cohen, E. (1994) Ages of onset of psychiatric disorders in a community population of older adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, **33**, 706–717.

- Gilman, S., Koeppe, R. A., Adams, K., Johnson-Greene, D., Junck, L., Kluin, K. J., Brunberg, J., Martorello, S. & Lohman, M. (1996) Positron emission tomographic studies of cerebral benzodiazepine-receptor binding in chronic alcoholics. *Annals of Neurology*, **40**, 163–171.
- Goodwin, D. W. & Gabrielli, W. F. (1997) Alcohol: Clinical Aspects. In: Lowinson, J. H., Ruiz, P., Millman, R. B. & Langrod, J. D., eds. *Substance Abuse: A Comprehensive Textbook*, 3rd edn, pp. 142–148. Baltimore, MD: Williams & Williams.
- Gottlieb, G. (1998) Normally occurring environmental and behavioral influences on gene activity: from central dogma to probabilistic epigenesis. *Psychological Review*, **105**, 792–802.
- Granic, I., Hollenstein, T., Dishion, T. J. & Patterson, G. R. (2003) Longitudinal analysis of flexibility and reorganization in early adolescence: a dynamic systems study of family interactions. *Developmental Psychology*, **39**, 606–617.
- Grove, W. M., Eckert, E. D., Heston, L., Bouchard, T. J., Segal, N. & Lykken, D. T. (1990) Heritability of substance abuse and antisocial behavior: a study of monozygotic twins reared apart. *Biology Psychiatry*, **27**, 1293–1304.
- Guy, S. M., Smith, G. M. & Bentler, P. M. (1993) Adolescent socialization and use of licit and illicit substances: Impact on adult health. *Psychology and Health*, **8**, 463–487.
- Hansell, S. & White, H. R. (1991) Adolescent drug use, psychological distress, and physical symptoms. *Journal of Health Social Behavior*, **32**, 288–301.
- Hansell, S., White, H. R. & Vali, F. M. (1999) Specific alcoholic beverages and physical and mental health among adolescents. *Journal of Studies on Alcohol*, **60**, 209–218.
- Harrison, P. A., Fulkerson, J. A. & Beebe, T. J. (1998) DSM-IV substance use disorder criteria for adolescents: a critical examination based on a statewide school survey. *American Journal of Psychiatry*, **155**, 486–492.
- Hasin, D. S., Schuckit, M. A., Martin, C. S., Grant, B. F., Bucholz, K. K. & Helzer, J. E. (2003) The validity of DSM-IV alcohol dependence: what do we know and what do we need to know? *Alcoholism: Clinical and Experimental Research*, **27**, 244–252.
- Henggeler, S. W., Schoenwald, S. K., Borduin, C. M., Rowland, M. D. & Cunningham, D. B. (1998) *Multisystemic Treatment of Antisocial Behavior in Children and Adolescents*. New York: Guilford.
- Hill, K. G., White, H. R., Chung, I.-J., Hawkins, J. D. & Catalano, R. F. (2000) Early adult outcomes of adolescent binge drinking: person- and variable-centered analyses of binge drinking trajectories. *Alcoholism: Clinical and Experimental Research*, **24**, 892–901.
- Hurt, R. D., Offord, K. P., Croghan, I. T., Gomez-Dahl, L., Kottke, T. E., Morse, R. M. & Melton, L. J. (1996) Mortality following inpatient addictions treatment: role of tobacco use in community-based cohort. *Journal of the American Medical Association*, **275**, 1097–1103.
- Irwin, M., Schuckit, M. & Smith, T. L. (1990) Clinical importance of age at onset in type 1 and type 2 primary alcoholics. *Archives of General Psychiatry*, **47**, 320–324.
- Johnson, V. & Pandina, R. J. (1991) Effects of the family environment on adolescent substance use, delinquency, and coping styles. *American Journal of Drug and Alcohol Abuse*, **17**, 71–88.
- Johnston, L. D., O'Malley, P. M. & Bachman, J. G. (2001) *National Survey Results on Drug Use from the Monitoring the Future Study, 1975–2000, I: Secondary School Students*. Rockville, MD: US National Institute on Drug Abuse.
- Kaltiala-Heino, R., Marttunen, M., Rantanen, P. & Rimpela, M. (2003) Early puberty is associated with mental health problems in middle adolescence. *Social Science and Medicine*, **57**, 1055–1064.
- Kandel, D. B. (2002) Examining the gateway hypothesis: stages and pathways of drug involvement. In: Kandel, D. B., ed. *Stages and Pathways of Drug Involvement: Examining the Gateway Hypothesis*, pp. 3–15. Cambridge UK: Cambridge University Press.
- Kandel, D. B., Davies, M., Karus, D. & Yamaguchi, K. (1986) The consequences in young adulthood of adolescent drug involvement. *Archives of General Psychiatry*, **43**, 746–754.
- Kandel, D. B., Johnson, J. G., Bird, H. R., Weissman, M. M., Goodman, S. H., Lahey, B. B., Regier, D. A. & Schwab-Stone, M. E. (1999) Psychiatric comorbidity among adolescents with substance use disorders: findings from the MECA Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **38**, 693–699.
- Kandel, D. B. & Yamaguchi, K. (1999) Developmental stages of involvement in substance use. In: Ott, P. J., Tarter, R. E. & Ammerman, R. T., eds. *Sourcebook on Substance Abuse: Etiology, Methodology, and Intervention*, pp. 50–74. Needham Heights, MA: Allyn & Bacon.
- Keller, M. B., Lavori, P. W., Beardslee, W., Wunder, J., Drs, D. L. & Hasin, D. (1992) Clinical course and outcome of substance abuse disorders in adolescents. *Journal of Substance Abuse Treatment*, **9**, 9–14.
- Kelly, T. M., Cornelius, J. R. & Clark, D. B. (2004) Psychiatric disorders and attempted suicide among adolescents with substance use disorders. *Drug and Alcohol Dependence*, **73**, 87–97.
- Kelly, T. M., Lynch, K., Donovan, J. E. & Clark, D. B. (2001) Alcohol use disorders and other risk factors for adolescent suicidal ideation and attempts: a gender specific and interactional analysis. *Suicide and Life-Threatening Behavior*, **31**, 181–190.
- Kelly, J. F., Myers, M. G. & Brown, S. A. (2000) A multivariate process model of adolescent 12-step attendance and substance use outcome following inpatient treatment. *Psychology of Addictive Behaviors*, **4**, 376–389.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H.-U. & Kendler, K. S. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the national comorbidity survey. *Archives of General Psychiatry*, **51**, 8–19.
- Kilpatrick, D. G., Acierno, R., Saunders, B., Resnick, H. S., Best, C. L. & Schnurr, P. P. (2000) Risk factors for adolescent substance abuse and dependence: data from a national sample. *Journal of Consulting and Clinical Psychology*, **68**, 19–30.
- King, W. H. & Tucker, K. M. (1973) Dental problems of alcoholic and nonalcoholic psychiatric patients. *Quarterly Journal of Studies on Alcohol*, **34**, 1208–1211.
- Kraemer, H. C. (1995) Statistical issues in assessing comorbidity. *Statistics in Medicine*, **14**, 721–733.
- Kung, E. M. & Farrell, A. D. (2000) The role of parents and peers in early adolescent substance use: an examination of mediating and moderating effects. *Journal of Children and Family Studies*, **9**, 509–528.
- Lander, E. S. & Schork, N. J. (1994) Genetic dissection of complex traits. *Science*, **265**, 2037–2048.
- Langenbucher, J., Martin, C., Labouvie, E., Sanjuan, P., Bavy, L. & Pollock, N. (2000) Toward the DSM-V: a withdrawal-gate model of alcohol abuse and dependence. *Journal of Consulting Clinical Psychology*, **68**, 799–809.
- Lanza, S. T. & Collins, L. M. (2002) Pubertal timing and the onset of substance use in females during early adolescence. *Prevention Science*, **3**, 69–82.

- Lewinsohn, P. M., Rohde, P. & Seeley, J. R. (1996) Alcohol consumption in high school adolescents: frequency of use and dimensional structure of associated problems. *Addiction*, **91**, 375–390.
- Lynskey, M. T. & Fergusson, D. M. (1995) Childhood conduct problems, attention deficit behaviors, and adolescent alcohol, tobacco, and illicit drug use. *Journal of Abnormal Child Psychology*, **23**, 281–302.
- Lynskey, M. T., Fergusson, D. M. & Horwood, L. J. (1998) The origins of the correlations between tobacco, alcohol, and cannabis use during adolescence. *Journal of Child Psychology and Psychiatry*, **39**, 995–1005.
- Maisto, S. A., Martin, C. S., Pollock, N. K., Cornelius, J. R. & Chung, T. A. (2002) Nonproblem drinking outcomes in adolescents treated for alcohol use disorders. *Experimental and Clinical Psychopharmacology*, **10**, 324–331.
- Maisto, S. A., Pollock, N. K., Lynch, K. G., Martin, C. S. & Ammerman, R. (2001) Course of functioning in adolescents one year following alcohol and other drug treatment. *Psychology of Addictive Behaviors*, **15**, 68–76.
- Manuzza, S., Klein, R. G., Bessler, A., Malloy, P. & LaPadula, M. (1993) Adult outcome of hyperactive boys educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry*, **50**, 565–576.
- Martin, C. S., Kaczynski, N. A., Maisto, S. A., Bukstein, O. G. & Moss, H. B. (1995) Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol*, **56**, 672–680.
- Martin, C. S., Kaczynski, N. A., Maisto, S. A. & Tarter, R. E. (1996a) Polydrug use in adolescent drinkers with and without DSM-IV Alcohol Abuse and Dependence. *Alcoholism: Clinical and Experimental Research*, **20**, 1099–1108.
- Martin, C. S., Langenbucher, J. W., Kaczynski, N. A. & Chung, T. (1996b) Staging in the onset of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol*, **57**, 549–558.
- Martin, C. S., Lynch, K. G., Pollock, N. K. & Clark, D. B. (2000) Gender differences and similarities in the personality correlates of adolescent alcohol problems. *Psychology of Addictive Behaviors*, **14**, 121–133.
- Martin, C. S. & Winters, K. C. (1998) Diagnosis and assessment of alcohol use disorders among adolescents. *Alcohol Health and Research World*, **22**, 95–105.
- Mayhew, K. P., Flay, B. R. & Mott, J. A. (2000) Stages in the development of adolescent smoking. *Drug and Alcohol Dependence*, **59**, S61–S81.
- McGue, M., Iacono, W. G., Legrand, L. N. & Elkins, I. (2001a) Origins and consequences of age at first drink. I. Associations with substance-use disorders, disinhibitory behavior and psychopathology, and p3 amplitude. *Alcoholism: Clinical and Experimental Research*, **25**, 1156–1165.
- McGue, M., Iacono, W. G., Legrand, L. N., Malone, S. & Elkins, I. (2001b) Origins and consequences of age at first drink. II. Familial risk and heritability. *Alcoholism: Clinical and Experimental Research*, **25**, 1166–1173.
- McGue, M., Slutske, W., Taylor, J. & Iacono, W. G. (1997) Personality and substance use disorders. I. Effects of gender and alcoholism subtype. *Alcoholism: Clinical and Experimental Research*, **21**, 513–520.
- Morey, L. C., Skinner, H. A. & Blashfield, R. K. (1984) A typology of alcohol abusers: correlates and implications. *Journal of Abnormal Psychology*, **93**, 408–417.
- Morril, A. R., McCaffrey, D. F. & Paddock, S. M. (2002) Reassessing the marijuana gateway effect. *Addiction*, **97**, 1493–1504.
- Moss, H. B., Clark, D. B. & Kirisci, L. (1997) Developmental timing of paternal substance use disorder offset and the severity of problem behaviors in their prepubertal sons. *American Journal of Addictions*, **6**, 30–37.
- Moss, H. B., Kirisci, L., Gordon, H. W. & Tarter, R. E. (1994) A neuropsychologic profile of adolescent alcoholics. *Alcoholism: Clinical and Experimental Research*, **18**, 159–163.
- Muthen, B. & Muthen, L. K. (2000) Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcoholism: Clinical and Experimental Research*, **24**, 882–891.
- Myers, M. G., Brown, S. A. & Mott, M. A. (1995) Preadolescent conduct disorder and behaviors predict relapse and progression of addiction for adolescent alcohol and drug abusers. *Alcoholism: Clinical and Experimental Research*, **19**, 1528–1536.
- Myers, M. G., Stewart, D. G. & Brown, S. A. (1998) Progression from conduct disorder to antisocial personality disorder following treatment for adolescent substance abuse. *American Journal of Psychiatry*, **155**, 479–485.
- Nathan, P. (1991) Substance use disorders in the DSM-IV. *Journal of Abnormal Psychology*, **100**, 356–361.
- Nelson, C. B. & Wittchen, H. U. (1998) DSM-IV alcohol disorders in a general population sample of adolescents and young adults. *Addiction*, **93**, 1065–1077.
- Newcomb, M. D. & Bentler, P. M. (1987) The impact of late adolescent substance use on young adult health status and utilization of health services: a structural equation model over four years. *Social Sciences and Medicine*, **24**, 71–82.
- Newcomb, M. D., Scheier, L. M. & Bentler, P. M. (1993) Effects of adolescent drug use on adult mental health: a prospective study of a community sample. *Experimental and Clinical Psychopharmacology*, **1**, 215–241.
- O'Malley, P. M., Johnston, L. D. & Bachman, J. G. (1999) Epidemiology of substance abuse in adolescence. In: Ott, P. J., Tarter, R. E. & Ammerman, R. T., eds. *Sourcebook on Substance Abuse: Etiology, Methodology, and Intervention*, pp. 14–31. Needham Heights, MA: Allyn & Bacon.
- Pedersen, W. & Skrandal, A. (1996) Alcohol and sexual victimization: a longitudinal study of Norwegian girls. *Addiction*, **91**, 565–581.
- Poikolainen, K., Leppanen, K. & Vuori, E. (2002) Alcohol sales and fatal alcohol poisonings: a time series analysis. *Addiction*, **97**, 1037–1040.
- Pollock, N. K. & Martin, C. S. (1999) Diagnostic orphans: adolescents with alcohol symptomatology who do not qualify for DSM-IV abuse or dependence diagnoses. *American Journal of Psychiatry*, **156**, 897–901.
- Pollock, N. K., Martin, C. S. & Langenbucher, J. W. (2000) Diagnostic concordance of DSM-III, DSM-III-R, DSM-IV, and ICD-10 alcohol diagnoses in adolescents. *Journal of Studies on Alcohol*, **61**, 439–446.
- Raine, A., Lencz, T., Bihle, S., LaCasse, L. & Colletti, P. (2000) Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry*, **57**, 119–127.
- Ralph, N. & McMenamy, C. (1996) Treatment outcomes in an adolescent chemical dependency program. *Adolescence*, **31**, 91–107.
- Richters, J. E. (1997) The Hubble hypothesis and the developmentalist's dilemma. *Development and Psychopathology*, **9**, 193–229.
- Rohde, P., Lewinsohn, P. M., Kahler, C. W., Seeley, J. R. & Brown, R. A. (2001) Natural course of alcohol use disorders from adolescence to young adulthood. *Journal of the*

- American Academy of Child and Adolescent Psychiatry*, **40**, 83–90.
- Rohde, P., Lewinsohn, P. M. & Seeley, J. R. (1996) Psychiatric comorbidity with problematic alcohol use in high school students. *Journal of the American Academy of Child and Adolescent Psychiatry*, **35**, 101–109.
- Rose, F. J., Dick, D. M., Viken, R. J., Pulkkinen, L. & Kaprio, J. (2001) Drinking or abstaining at age 14? A genetic epidemiological study. *Alcoholism: Clinical and Experimental Research*, **25**, 1594–1604.
- Rosenbaum, P. R. (1995) *Observational Studies*, pp. 1–2. New York: Springer-Verlag.
- Rydellius, P. A. (1981) Children of alcoholic fathers: their social adjustment and their health status over 20 years. *Acta Paediatrica Scandinavica*, **286**, 1–83.
- Sameroff, A. (1995) General systems theory and developmental psychopathology. In: D. Cicchetti & D. J. Cohen, eds. *Developmental Psychopathology: Vol. 1. Theory and Methods*, pp. 659–695. New York: John Wiley & Sons.
- Schuckit, M. A. & Hesselbrock, V. (1994) Alcohol dependence and anxiety disorders: what is the relationship? *American Journal of Psychiatry*, **12**, 1723–1734.
- Schuckit, M. A., Smith, T. L., Anthenelli, R. & Irwin, M. (1993) Clinical course of alcoholism in 636 male inpatients. *American Journal of Psychiatry*, **150**, 786–792.
- Scott, S., Knapp, M., Henderson, J. & Maughan, B. (2001) Financial cost of social exclusion: follow up study of antisocial children into adulthood. *BMJ*, **323**, 1–5.
- Shedler, J. & Block, J. (1990) Adolescent drug use and psychological health. *American Psychologist*, **45**, 612–630.
- Silk, J. S., Morris, A. S., Kanaya, T. & Steinberg, L. (2003) Psychological control and autonomy granting: opposite ends of a continuum or distinct constructs? *Journal of Research on Adolescence*, **13**, 113–128.
- Spear, L. P. (2000) The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, **24**, 417–463.
- Stacy, A. W., Newcomb, M. D. & Bentler, P. M. (1993) Cognitive motivations and sensation seeking as long-term predictors of drinking problems. *Journal of Social and Clinical Psychology*, **12**, 1–24.
- Stewart, M. A. & Brown, S. A. (1993) Family functioning following adolescent substance abuse treatment. *Journal of Substance Abuse*, **5**, 327–339.
- Stolzenberg, R. M. & Relles, D. A. (1997) Tools for intuition about sample selection bias and its correction. *American Sociological Review*, **62**, 494–507.
- Sullivan, E. V., Marsh, L., Mathalon, D. H., Lim, K. O. & Pfefferbaum, A. (1995) Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, **19**, 110–122.
- Susser, M. (1991) What is a cause and how do we know one? A grammar for pragmatic epidemiology. *American Journal of Epidemiology*, **133**, 635–648.
- Sussman, S., Dent, C. W. & Galaif, E. R. (1997) The correlates of substance abuse and dependence among adolescents at high risk for drug abuse. *Journal of Substance Abuse*, **9**, 241–255.
- Tapert, S. F. & Brown, S. A. (1999) Neuropsychological correlates of adolescent substance abuse: four-year outcomes. *Journal of the International Neuropsychological Society*, **5**, 481–493.
- Tarter, R. E., Kirisci, L., Mezzich, A., Cornelius, J. R., Pajer, K., Vanyukov, M., Gardner, W., Blackson, T. & Clark, D. B. (2003) Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry*, **160**, 1078–1085.
- Tarter, R. E., McBride, H., Buonpane, H. & Schneider, D. U. (1977) Differentiation of alcoholics: childhood history of minimal brain dysfunction, family history, and drinking pattern. *Archives of General Psychiatry*, **34**, 761–768.
- Tarter, R. E., Vanyukov, M., Giancola, P., Dawes, M., Blackson, T., Mezzich, A. & Clark, D. B. (1999) Etiology of early age onset substance use disorder: a maturational perspective. *Development and Psychopathology*, **11**, 657–683.
- Thompson, L. L., Riggs, P. D., Mikulich, S. K. & Crowley, T. J. (1996) Contribution of ADHD symptoms to substance problems and delinquency in conduct-disordered adolescents. *Journal of Abnormal Child Psychology*, **24**, 325–347.
- Todd, R., Swarzenski, B., Rossi, P. & Visconti, P. (1995) Structural and functional development of the human brain. In: Cicchetti, D. & Cohen, D., eds. *Developmental Psychopathology*, Vol. 1, pp. 161–194. New York: Wiley.
- Vanyukov, M. M., Tarter, R. E., Kirisci, L., Kirillova, G. P., Maher, B. S. & Clark, D. B. (2003) Liability to substance use disorders: 1. Common mechanisms and manifestations. *Neuroscience and Biobehavioral Reviews*, **27**, 507–515.
- Voas, R. B., Tippetts, A. S. & Fell, J. C. (2003) Assessing the effectiveness of minimum legal drinking age and zero tolerance laws in the United States. *Accident Analysis and Prevention*, **35**, 579–587.
- Wagenaar, A. C., Toomey, T. L., Murray, D. M., Short, B. J., Wolfson, M. & Jones-Webb, R. (1996) Sources of alcohol for underage drinkers. *Journal of Studies on Alcohol*, **57**, 325–333.
- Waldman, I. D. & Slutske, W. S. (2000) Antisocial behavior and alcoholism: a behavioral genetic perspective on comorbidity. *Clinical Psychology Review*, **20**, 255–287.
- Watson, D. & Clark, K. (1984) Negative affectivity: the disposition to experience aversive emotional states. *Psychological Bulletin*, **96**, 465–490.
- White, H. R., Xie, M., Thompson, W., Loeber, R. & Stouthamer-Loeber, M. (2001) Psychopathology as a predictor of adolescent drug use trajectories. *Psychology of Addictive Behaviors*, **15**, 210–218.
- Winters, K. C. & Henly, G. (1993) Measuring alcohol and cannabis use disorders in an adolescent clinical sample. *Psychology of Addictive Behaviors*, **7**, 185–196.
- Winters, K. C., Latimer, W. & Stinchfield, R. D. (1999) The DSM-IV criteria for adolescent alcohol and cannabis disorders. *Journal of Studies on Alcohol*, **60**, 337–344.
- Wolfson, M., Toomey, T. L., Murray, D. M., Forster, J. L., Short, B. J. & Wagenaar, A. C. (1996) Alcohol outlet policies and practices concerning sales to underage people. *Addiction*, **91**, 589–602.
- Young, S. E., Stallings, M. C., Corley, R. P., Krauter, K. S. & Hewitt, J. K. (2000) Genetic and environmental influences on behavioral disinhibition. *American Journal of Medical Genetics*, **96**, 684–695.
- Zucker, R. A., Fitzgerald, H. E. & Moses, H. D. (1995) Emergence of alcohol problems and the several alcoholisms: a developmental perspective on etiologic and life course trajectory. In: Cicchetti, D. & Cohen, D. J., eds. *Developmental Psychopathology: Vol. 2. Risk, Disorder and Adaptation*, pp. 677–711. New York: John Wiley & Sons.
- Zwaigenbaum, L., Szatmari, P., Boyle, M. H. & Offord, D. R. (1999) Highly somatizing young adolescents and the risk of depression. *Pediatrics*, **103**, 1203–1209.