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AN IMPORTANT NEW PHENOTYPE AND SOME NEXT-STEP QUESTIONS: COMMENTARY ON SARTOR *ET AL.* (2007)

The paper by Sartor *et al.* [1] is an important extension to the work by Wagner & Anthony [2], the Minnesota group [3] and others in the articulation of the early architecture of drug involvement as a multi-stage process. It replicates a considerable amount of work demonstrating greater risk for eventual alcohol dependence (AD) among earlier first drinkers [4,5]. It also replicates findings that risk factors in the behavioral dysregulation/undercontrol domain [conduct disorder (CD), attention deficit hyperactivity disorder (ADHD)], [3,6,7], as well as family disorganization/conflict (parent divorce, maternal AD) known to sustain such undercontrolled behavior [8,9], predict earlier drinking onset. What is new is the elaboration of a two-stage model of progression, involving (a) risk for onset of use and (b) rapidity of progression into dependence. The Sartor *et al.* [1] data indicate that these are differentiated processes, with mostly different factors predicting speed of progression into disorder. For the latter, it remains important to clarify order of precedence of the other drug comorbidity and generalized anxiety disorder (GAD) *vis-à-vis* the onset of AD. At least for cannabis comorbidity precedence is likely [2], but the issue needs to be addressed. It also would be useful to know whether those factors which predict rapidity of progression into AD also predict whether or not dependence occurs. Although the issue is not highlighted in this report, the two are not the same phenotype. Their Table 2 data on differences in the probability of meeting AD criteria suggest that this may be related more to those factors which predict onset.

While it is true that the association between GAD and progression into AD has not often been reported, there is in fact precedence for this finding in the developmental high risk literature. A recent review I conducted identifies three studies in the internalizing domain that predict AD risk with anxious rather than purely social inhibitory content. [10]

The dissection of the developmental progression process provided by Sartor *et al.* [1], like all good work, also encourages us to ask what are the next-step questions, particularly for the speed of progression findings where little earlier work exists. The most obvious ones are about process. What mechanistic model might account for rapidity of AD onset, especially as these predictors, with the exception of CD, are different from predictors of onset? The authors suggest a mediational model through genetic and environmental mechanisms, with the common genetic liability showing in their data via the proximal factors of CD and nicotine dependence, and with the environmental risk probably involving greater association with delinquent and/or drug-using peers and its concomitants of greater drug availability and more frequent cueing for use. This is a plausible explanation, but still leaves a gap. The movement from beginning to drink into the symptomatic complex that is AD does not occur without moving into heavy consumption and sustaining that for some time. Drug availability is not sufficient to explain this. Next-step work will need to probe this domain, perhaps including a measure of differences in alcohol sensitivity [11] or, at the least, proxy markers of such process by way of maximum consumption indicators.

Acknowledgements

Preparation of this article was supported in part by Grant R37 AA07065 to the author from the National Institute on Alcohol Abuse and Alcoholism.

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EARLY DRINKING AND THE DEVELOPMENT OF ALCOHOLISM: A COMMENTARY ON SARTOR *ET AL.* (2007)

Researchers have increasingly adopted developmental approaches to the study of alcoholism. As a consequence, we know that individuals who develop alcoholism differ from those who do not in, for example, early manifestations of personality [1]; risk of experiencing abuse [2]; and the attainment of developmental milestones [3]. They also differ in the age at which they first tried alcohol, the focus of research reported by Sartor *et al.* [4] in this issue of *Addiction*. In a highly influential paper, Grant & Dawson [5] reported a strong association between age at first drink (AFD) and risk of alcoholism. Individuals who reported an AFD of less than 15 years were four times more likely to have been alcoholic as an adult than those reporting an AFD of greater than 20 years.

Sartor *et al.* begin by replicating the Grant & Dawson association: in their sample, individuals who first drank alcohol prior to age 14 were more than two times more likely to be alcoholic than those trying alcohol after age 16. Importantly, they go on to show that an early AFD does not occur in isolation, but rather is associated with numerous other markers of alcoholism risk. Individuals with an early AFD were more likely to have a diagnosis of conduct disorder or attention deficit/hyperactivity disorder, a family history of alcoholism, and come from a divorced family. None the less, they report that an early AFD is not associated with a rapid progression from the initial stages of drinking to alcohol dependence.

This study provides several key insights into the nature of the association first reported a decade ago. First, the finding that AFD is part of a spectrum of risk supports one of the major hypotheses about the source of the association of AFD with alcoholism; namely, that it owes, at least in part, to the existence of a generalized vulnerability that can express as an early AFD, alcoholism and a wide range of disinhibited behaviors [6]. Secondly, the finding that AFD is not predictive of the rate of progression to alcoholism implies the existence of distinct processes underlying drinking transitions, and underscores the need for prospective developmental approaches to explicate the nature of these transitions. This latter finding may also have implications for another of the major hypotheses on the source of the AFD–alcoholism association. It has been speculated that an early AFD increases alcoholism risk because young adolescents are especially vulnerable to the toxic neurological and social effects of alcohol [7]. However, increased vulnerability might be expected to result in rapid progression to problem drinking, an expectation at odds with Sartor *et al.*'s failure to find differences in time to onset of alcohol dependence between those with versus without an early AFD.

The Grant & Dawson finding has legitimately drawn widespread attention because it has obvious implications for alcoholism prevention. If an early AFD predicts a substantially elevated risk of alcoholism, then prevention must be delivered early if it hopes to be successful; but success will also require understanding the nature of the mechanisms that underlie the AFD–alcoholism association. The paper by Sartor and colleagues has brought us closer to achieving that understanding.

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