RESEARCH REPORT

Are there empirically supported and clinically useful subtypes of alcohol dependence?

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ABSTRACT

Aims This paper provides an overview of several multidimensional empirically derived typologies of alcohol use disorders that have been derived primarily for research purposes in relation to their clinical utility. **Methods** Studies using multivariate statistical methods for identifying homogeneous groups of subjects were selected for inclusion. Theoretically based typologies were not included in this review. **Results** While formal diagnostic criteria typically identify separate categories of alcohol abuse and dependence, several studies using different statistical methods consistently suggest as many as four homogeneous types of alcoholism: a chronic/severe type, a depressed/anxious type, a mildly affected type and an antisocial type. **Conclusions** Even though the longitudinal outcomes of few empirically derived subtypes have been examined, alcoholism typologies remain a viable and potentially valuable tool for investigating etiological pathways, the effectiveness of treatments and the long-term course of alcohol use disorders.

Keywords Alcohol dependence, classification, diagnosis, subtypes.

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INTRODUCTION

Drinking, as an example of drug use behavior in the general population, varies considerably from severe alcohol dependence through simple abuse, to low-risk drinking patterns, to abstinence. Further, alcohol abuse and dependence often co-occur with other Axis I and Axis II disorders. These additional phenomena create problems in defining the nature of alcoholism, separating it from normal drinking and in identifying distinct boundaries between alcohol use disorders and other psychiatric disorders. These problems are common when examining most substances of abuse and illustrate the critical role and importance of properly defined criteria in clinical assessment.

Although many drug dependencies are often defined in clinical studies as a single diagnostic entity, their clinical expression is likely to be heterogeneous. Indeed, people with alcohol or other drug dependencies are heterogeneous in terms of their history and patterns of substance use, demography and other co-occurring psychiatric conditions. Further, different family backgrounds and rearing patterns and a variety of biological, social and psychiatric problems have been associated with chronic drug use. These factors may influence treatment-seeking behavior, treatment outcomes and the life-course of substance abuse or dependence by moderating or mediating its clinical expression [1]. Because most of the published efforts in identifying 'subtypes' of substance abuse or dependence have focused on 'alcoholism', a term that often encompasses both alcohol dependence and alcohol abuse, this review will focus on that literature.

MULTIVARIATE TYPOLOGIES OF ALCOHOLISM

A variety of multivariate, multi-dimensional typologies of alcoholism have been proposed [2,3], but seldom developed and examined in well-characterized samples. A well-known example of a multi-dimensional classification of alcoholism was proposed by Cloninger and colleagues [4], who identified two separate forms of alcoholism based on differences in alcohol-related symptoms, patterns of transmission and personality characteristics using data derived from a cross-fostering study of Swedish adoptees. Type 1 is characterized by either mild or severe alcohol abuse in the probands and no criminality in the fathers. Type 1 alcoholics came from relatively

high socio-economic backgrounds and alcohol abuse in the biological mothers was frequent. Type 1 alcoholics are hypothesized to be responsive to environmental influence, to have relatively mild alcohol-related problems with few hospitalizations, and to have an age of onset of alcoholism after the age of 25 years. These individuals are thought to be dependent on social approval (high reward dependence), cautious (high harm avoidance) and prefer non-risk-taking situations (low novelty-seeking). On the other hand, type 2 alcoholism is characterized as being associated with familial alcoholism, having severe and violence-related alcohol problems, other drug use, and as having an onset of alcohol problems before 25 years of age. Low reward dependence, low harm avoidance and high novelty-seeking characterize these individuals. Although multivariate statistical methods were used to identify subtypes, Cloninger's types of alcoholism have been criticized due to the small sample size of both males ($n = 151$) and females ($n = 31$), sample selection methods, indirect assessment of family variables and other methodological limitations [5].

The heritability of the type 1/type 2 forms of alcoholism has been examined in twins [6] and among the family members of alcohol-dependent patients [7]. In both cases the more severe, type 2 form was found to have a higher heritability than the type 1 form.

TYPES A AND B SUBTYPES OF ALCOHOLISM

A second multi-dimensional classification of alcoholism was proposed by Babor *et al.* [8] based upon a sample of 321 male and female in-patient alcoholics. Seventeen defining characteristics covering the areas of pre-morbid risk factors, the pathological use of alcohol and other substances, and the chronicity and consequences of drinking were used to identify homogeneous groups of alcoholics. Type A, resembling Cloninger's type 1, was characterized by a later onset of the disorder, fewer childhood behavior problems and less psychopathology. Type B resembled type 2 alcoholism and was defined by a high prevalence of childhood behavior problems, familial alcoholism, early onset of alcohol problems, a more chronic treatment history, more psychopathology and more life stress. While Cloninger *et al.*'s type 2 male-limited alcohol abuse was associated with moderate alcohol abuse, Babor *et al.*'s type B was associated with severe alcoholism and its more chronic consequences. Further, the Babor *et al.* subtypes of alcoholism were found in both male and female patients.

The Babor *et al.* [8] alcoholism subtypes have been examined by different authors, using either the original data set [9–11] or similar defining characteristics and statistical methods ([12–13], among others). Schuckit

et al. [12], using a clustering algorithm approximating that described by Babor *et al.*, found two similar groups as Babor *et al.* Type 'A' was characterized by a later onset of alcohol symptoms, fewer childhood behavior problems, somewhat fewer alcohol-related symptoms and fewer other psychological/psychiatric problems (e.g. anxiety and depressive symptoms). Type 'B' individuals reported more childhood problems (mainly conduct problems), an earlier onset of alcohol problems, greater severity of alcohol dependence, more physical problems, more polydrug use and greater psychological dysfunction.

Type A/B clusters do occur within different ethnic groups. Using similar methods as Babor *et al.* [8] and Schuckit *et al.* [12], a two-cluster solution similar to type A/B has been found separate analyses of Hispanic ($n = 106$), African American ($n = 351$) and Alaska Native ($n = 442$) alcohol-dependent samples [14].

MORE THAN TWO SUBTYPES?

Most cluster analytical studies of alcoholism indicate that the majority of cases can be classified into one of two clusters. The remaining cases are either dropped from further analyses or cluster solution parameters were changed to include the maximum amount of cases. However, two-group solutions do not fully capture the clinical or general population samples. Further, most data reduction techniques (e.g. cluster analysis, factor analysis) are not governed by proscribed rules, so the final solution may be influenced by a variety of factors including sample characteristics and sample size, the clinical information available and the theory underlying the original analysis. The indeterminate nature of cluster-derived typologies is exemplified by a reanalysis of the Babor *et al.* [8] data by Del Boca & Hesselbrock [11]. Using lifetime alcoholism risk and severity variables as defining characteristics, the resulting four-cluster solution revealed important sex differences, as well as distinctions within the broader types that have etiological and clinical significance. The high-risk/high-severity (HRHS) cluster contained equal proportions of males and females (22% from each group) and included those cases highest in family history of alcoholism loading and the earliest age of onset of alcoholism. HRHS subjects were, on average, the youngest and were characterized by moderate alcohol involvement, a high frequency of other psychiatric symptoms including conduct problems, and other drug use. The low-risk/low-severity cluster (LRLS) contained 31% of the cases (28% of males, 39% of females) and was was characterized by relatively low alcohol involvement, low drug use, low levels of alcohol-related consequences and low rates of other psychiatric symptoms. The 'internalizers' cluster contained 32% of females and only 11% of males in the sample who were characterized by high levels of depressive

and anxiety symptoms. The 'externalizers' cluster was characterized by a high prevalence of childhood behavior problems; this group had the highest rates of alcohol use for self-medication, benzodiazapine use and alcohol dependence and medical/physical consequences. Fewer externalizing subjects had a family history of alcoholism, but subjects had high rates of alcohol use and alcohol-related social consequences and high rates of antisocial personality disorder. This cluster contained 38% of the males and 7% of females in the sample.

Unlike most other multivariate substance dependence subtypes, longitudinal follow-up data are available on the subtypes of alcohol dependence proposed by Del Boca & Hesselbrock [11]. They compared the four clusters described above in relation to their 1- and 3-year post-treatment outcome data. In general, the differences between the four clusters were in the expected direction. At the 1-year follow-up, the HRHS and the externalizing groups reported the most drinking days during the year prior to follow-up. The HRHS group also reported the most total drinking at the 3-year follow-up assessment. The internalizing group reported the fewest total drinking days at both follow-up assessments. Consistent with this finding, the internalizing group and the LRLS groups also reported the most days abstinent/occasional drinking at 1 and 3 years post-treatment, while the externalizing group reported the fewest abstinent days at both intervals. The majority of the sample received additional treatment for alcoholism after the index hospitalization, but the highest rate (85–90%) was found among the externalizer subtype at both follow-up assessments. This is consistent with the group's increased level of alcohol-related consequences at intake. However, the HRHS subtype spent the largest number of number of weeks in treatment, reporting an average of 5 weeks at the 1-year interval and about 7.5 weeks in the year prior to the 3-year follow-up. Internalizers spent the fewest weeks in treatment at both follow-up assessments, with less than 2 weeks at each.

A 2-year post-treatment follow-up of this sample was made through a search of Social Security Death Index records and death certificates, crude death rates and average age at death varied between the four types of alcoholism. The rate of death was 21.4% among HRHS, 34% among internalizers, 37.2% among externalizers and 46.9% among the LRLS subjects. The youngest age at death was found among the HRHS (39.9 years), followed by the internalizers (51.1 years), the externalizers (54.6 years) and the LRLS (59.1 years) [13].

Windle & Scheidt [15] studied 481 male and 321 female alcohol-dependent in-patients using defining characteristics similar to those of Babor *et al*. They identified four subtypes of alcohol dependence: mild course, polydrug, negative affect and chronic/antisocial personality disorder (ASPD). The mild course subtype had a later onset of alcohol dependence, fewer years of drinking, tended to drink less than the other groups, reported impairment and withdrawal symptoms and few childhood conduct symptoms. The polydrug users subtype had the highest level of drug use, including benzodiazeipines. The negative affect cluster reported the highest number of symptoms of affective and anxiety symptoms, along with the greatest number of characteristics. The chronic/ASPD cluster had the highest levels of alcohol consumption and alcohol impairment, and the most years drinking at high levels of consumption. The four types did differ by gender, but not by ethnicity. A higher percentage of the women than the men were found in the mild course, the polydrug and negative affect clusters. Males were over-represented in the chronic alcohol use/ ASPD cluster. The clusters did not vary in relation to socio-economic status, including educational level. In general, these clusters are consistent with those identified by Zucker & Gomberg [16], Schuckit *et al*. [12], Del Boca & Hesselbrock [11] and Hesselbrock *et al*. [17].

LATENT CLASS-DERIVED SUBTYPES OF ALCOHOL DEPENDENCE

Bucholz *et al*. [18] used latent class analysis to fit 37 life-time symptoms of alcohol dependence with data from 1360 female and 1191 male relatives of alcoholic probands. Separate solutions were identified for males and females. A four-class solution was selected as the best fitting among those examined; individuals were assigned to their most probable class. The four classes included: non-problem drinkers (37.8% males, 50% females); mild alcoholics (persistent desire to stop, tolerance and blackouts) (31.1% males, 28.8% females); moderate alcoholics (social health, and emotional problems) (19.9% males, 14.6% females); and severely affected alcoholics (withdrawal, inability to stop drinking, craving, health and emotional problems) (11.2% males, 6.7% females). There was little evidence for the construct of alcohol abuse. Endorsement probabilities for abuse symptoms [e.g. arrests, driving while intoxicated (DWIs)] were very low for all classes, while hazardous use was common among non-problem drinking men. In this high risk for alcohol dependence sample, latent classes did not differ qualitatively with distinct symptom profiles. Rather, they appeared to lie, for the most part, on a continuum of severity. One exception was 'withdrawal' which characterized only severely affected individuals.

GENETIC ANALYSIS OF LATENT CLASSES OF ALCOHOL DEPENDENCE

Foroud *et al*. [19], based upon a sample of male and female alcoholic probands ($n = 830$), used persistent

desire/being unable to quit or cut down on drinking, morning drinking, craving for alcohol, one or more episodes of binge drinking (defined as drinking for 2 or more days without sobering up), spending a great deal of time drinking or recovering from the effects of alcohol, narrowing of the drinking repertoire, giving up activities in order to drink, having 12 or more blackouts with five or more co-occurring withdrawal symptoms, having any health problems from drinking and having any psychological problems from drinking as defining characteristics. A four-class solution was selected: an unaffected group with very low symptom endorsement probabilities for most items and containing 47% of the individuals in the sample, a mildly problematic group accounting for 23% of the sample, a moderately affected group including 17% of individuals and a severely affected group containing 13% of the sample. *Post hoc* analyses indicated that classes 3 and 4 defined an affected group of individuals with more severe alcohol dependence, and these two classes were combined to conduct an exploratory series of affected sib-pair analyses. Evidence for a locus on chromosome 16, near the marker D16D675, for classes reflecting alcohol dependence was found with a maximum multipoint lod score of 4.0.

SUBTYPES OF ALCOHOL DEPENDENCE BASED ON CO-OCCURRING PSYCHOPATHOLOGY

A number of studies have demonstrated that the majority of male and female people with alcohol dependence (both treated and untreated) have associated comorbid psychiatric symptoms/conditions (cf. Hesselbrock *et al.* [20]; Helzer & Pryzbeck [21]). Some of these symptoms may represent pre-existing psychiatric disorders, while others may be related to the chronic use of alcohol. For alcoholic males, the most common pre-existing disorder observed is ASPD, with estimated prevalence rates ranging from 16% to 49%. Female alcoholics are also found to have significant rates of ASPD, possibly approaching 20%. The importance of comorbid ASPD for the course, consequences and treatment outcome of alcoholism among both males and females with alcohol dependence has been shown in a number of studies (e.g. Hesselbrock *et al.* [22,23]). Alcoholic probands with comorbid ASPD have been characterized by an earlier onset of regular drinking, regular drinking to intoxication and problem drinking compared to non-ASPD alcoholics. Further, both alcohol dependent males and females with ASPD have a more severe course of the disorder and are more likely to relapse sooner and at a higher rate following treatment than non-ASPD alcoholics.

CHILDHOOD CONDUCT AND ADULT ANTISOCIAL PERSONALITY DISORDER SYMPTOMS

As mentioned above, the association of ASPD with alcohol dependence has been established in both clinical and general population samples. Further, features of ASPD and conduct disorder have been implicated as important differentiators of subtypes of alcoholics in two well-known alcoholism typologies (Cloninger *et al.* [4]; Babor *et al.* [8]). Because ASPD is a diverse collection of symptoms reflecting patterns of irresponsible and antisocial behaviors that begin in childhood and persist into adulthood, the question arises as to whether certain ASPD symptom patterns might be associated more closely with certain phenotypes of alcohol dependence. To address this question, Bucholz *et al.* [24], using latent class analysis, examined childhood and adult symptoms reflecting lifetime DSM-III-R criteria of ASPD reported by 2834 female and 3504 male relatives of probands and controls. A four-class (A–D) solution for females and a five-class (A–E) solution for males were selected. The classes ranged from unaffected to severely affected in both men and women for both child as well as adult misbehaviors. There was no evidence for a class expressing only childhood conduct problems. Rather, high endorsement of childhood symptoms was associated with high endorsement of adult symptoms as well.

Among women, both childhood conduct disorder and ASPD were found almost exclusively in the most severely affected class. Strong evidence for a linear trend was found for alcohol dependence severity, with each successive ASPD class manifesting a higher prevalence of alcohol dependence than the previous class. Milestones of drinking showed a strong association with class severity, with more severe ASPD classes having an earlier age of first intoxication, of regular drinking, and also a higher maximum of drinks consumed on one occasion. For women, comorbidity with other substance dependence and with panic disorder also increased with ASPD class severity, but neither depression nor social phobia increased with ASPD class severity. Among men, the majority of Class E (74.6%) but only a small percentage of Class D (19.8%) met criteria for ASPD. Class D men had a milder spectrum of childhood misbehaviors, but an adult ASPD profile with other psychiatric comorbidity comparable to their Class E counterparts. Both classes were virtually indistinguishable in terms of lifetime prevalence of alcohol dependence. However, an increased prevalence of dependence on other substances was observed with each successive class. Findings from both men and women did not support the existence of distinct subtypes of ASPD, but rather indicated a disorder distributed on a severity spectrum [24].

ARE THESE MULTIVARIATE TYPOLOGIES OF ALCOHOL DEPENDENCE CLINICALLY USEFUL?

While all the published typologies have demonstrated an ability to identify relatively homogeneous groups of people with alcohol dependence based upon aspects of their clinical features, few of the typological classifications have received rigorous testing to examine their diagnostic validity. Robins & Guze [25] proposed five research activities necessary for establishing a clinically relevant psychiatric diagnosis that are probably still appropriate here. The five activities include: (1) clinical description; (2) laboratory studies; (3) delimitation from other disorders; (4) follow-up studies and (5) family studies. Many of the multivariate typologies of alcohol dependence found in the literature meet the 'clinical description' criterion very well, as Robins & Guze indicated that not only should clinical features be used to form a diagnosis but demographic features, precipitating factors, age at onset, etc. should also be included to define the clinical picture more precisely. The types of alcoholism/alcohol dependence proposed by Knight [26], Jellinek [27], Cloninger *et al*. [4], Babor *et al*. [8], Zucker & Gomberg [16], DelBoca & Hesselbrock [11], Lesch & Walter [28], Windle & Scheidt [15] and others all tend to meet this criterion. The primary limitation of multivariate typologies in the clinical setting is that most typologies contain too many defining characteristics, thus requiring a lengthy clinical assessment. Few treatment facilities are willing to devote additional time or personnel to obtaining the information necessary to permit reliable typological categorization of patients. Consequently, in order to increase their clinical utility, most typologies need to identify a limited number of critical indicators that can be readily identified, even if other features may have some theoretical importance. Further, few subtypes of alcohol or other substance dependence have been subjected to either clinical or basic laboratory investigation, certainly not to the extent proposed by Robins & Guze. In part, this is due to the lack of reliable biological indicators of alcohol or other substance dependence. Some studies have identified differences in MAO-A levels, aspects of the serotonin system, ethanol metabolism rates and brain electrophysiological features in different subtypes of alcohol dependence. However, these biological variables have been examined in other psychiatric conditions as well and the differences found between affected and non-affected individuals are not unique to any specific diagnosis. In the near future, as susceptibility genes are identified for different substances of abuse or dependence, typologies may be identified based upon genotypic differences. While the familial nature and heritability of some of the typologies has been examined using biometrical analyses (cf. van den Bree *et al*. [6]; Gilligan [7]; Hesselbrock [5]), only Foroud *et al*. [19] have looked for genotypic differences in their latent class derived subtypes of alcohol dependence.

For the statistically derived typologies of alcohol dependence, the Robins & Guze criterion of 'delimitation from other disorders' is a problem in at least two respects. First, some of the samples upon which the subtypes were based were heterogeneous in terms of their abuse or dependence upon drugs other than alcohol. Further, many subjects in these samples also had a history of other psychiatric disorders. While these two issues reflect the natural occurrence of alcohol dependence in clinical and general populations, none of the typologies in the literature provide any 'control' for these other comorbid conditions. In fact, several typologies include features of other psychiatric conditions such as conduct disorder, depressive symptoms or other drug use/abuse as defining characteristics. While the presence of symptoms alone does not indicate the presence of another disorder, many typologies of alcohol dependence are not clearly delimited from depressive disorder, antisocial personality disorder or other substance dependencies.

Few subtypes of alcohol dependence have been followed up post-treatment or studied longitudinally to determine the clinical relevance of the subtypes. Follow-up studies are important to determine the stability of the subtype over time, to characterize the subtype's course of illness and to determine the subtype's response to treatment. The lone exception in the current literature is the work of Hesselbrock *et al*. [13], who re-evaluated the four-cluster typology suggested by Del Boca & Hesselbrock [11] at several different points in time. At follow-up differences were found between the four alcohol dependence clusters in relation to drinking behavior, relapse rates and treatment utilization. At 20 years post-treatment, the subtypes differed in terms of their mortality rates [13].

The final criterion suggested by Robins & Guze is the use of family studies to examine more carefully hereditary and environmental causes of an illness leading to a diagnosis. Again, few statistically derived subtypes of alcohol dependence meet this criterion. The heritability of Cloninger's type 1/type 2, particularly type 2, has been established by Gilligan [7] and van den Bree [6], while Hesselbrock *et al*. [17] found moderate heritability for several of his five clusters of alcohol dependence. In the near future other investigators may follow the lead of Foroud *et al*. [19] and begin to examine the genotypic bases of alcohol/substance dependent typologies. Further, none of the typologies examined (other than Cloninger *et al*.) included contextual factors as defining characteristics. Nor have the etiology of the alcohol dependence typologies been examined in relation to environmental factors such as parental home environment,

marital home environment, level of perceived stress, neighborhood variables or treatment history.

In spite of the different theoretical backgrounds of the investigators, the samples examined and the methods used to form the typologies, there is a remarkable similarity across many of the multivariate typologies of alcohol dependence proposed in the literature. Several authors have suggested a chronic/severe type, a depressed/anxious type, a mildly affected type and an antisocial type, although using their own labels. These four types of alcohol dependence are found within both genders and across several different ethnic groups. It is also likely these typologies of alcohol dependence vary in their heritability, although their biological and genotypic bases remain unknown. Also, each multivariate typology in the literature provides a clinical description that identifies homogeneous subgroups. Unfortunately, few have examined outcomes longitudinally to determine their clinical utility in predicting variations in illness course and response to treatment occurring across different subtypes. Thus, typologies still remain a viable and potentially valuable tool for the investigation of etiological pathways into alcohol use disorders, the investigation of both psychological [29,30] and pharmacological [28,31] therapies and studies of the long-term course of alcohol use disorders.

Acknowledgements

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