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Comparison of Alcoholism Subtypes as Moderators of the Response to Sertraline Treatment

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Abstract

Background—A variety of typologies have been used to categorize alcoholism's diverse manifestations. Although the most widely studied typologies are dichotomous ones based on genetic epidemiologic findings or using cluster analytic methods, recent efforts have utilized a single item or the onset of a diagnosis of alcohol dependence to subtype individuals based on the age of alcoholism onset. We compared three different methods to subtype alcoholics.

Methods—This secondary analysis used data from 134 alcohol-dependent participants in a placebo-controlled trial of sertraline (Kranzler et al. 2011). We compared cluster analysis to distinguish two risk/severity subtypes (Babor et al. 1992) with two age-of-onset subtypes (i.e., based on the age of onset of problem drinking or the age at which alcohol dependence criteria were first met).

Results—Each method yielded subgroups that differed significantly from one another on demographic and clinical measures. Although concordance was high between the two age-of-onset methods, it was poor between the age-of-onset methods and the cluster analysis-derived approach. All three subtyping approaches significantly moderated the effects of sertraline or placebo, but only in the L′L′ genotype group, as originally reported (Kranzler et al. 2011). In all cases, sertraline treatment was superior to placebo in later-onset individuals and inferior to placebo in the earlier-onset groups.

Conclusions—Because age-of-onset subtypes can be defined retrospectively on an individual basis, they may be more clinically useful than cluster-derived subtypes, which require group data. Because the two age-of-onset measures we examined appear to have comparable validity, a single item is easier to use as a measure of the age of onset of problem drinking.

Keywords

Age of onset; Alcohol Dependence; Cluster Analysis; Sertraline

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INTRODUCTION

Alcoholism is a complex, multidimensional disorder. A variety of typologic approaches have been used to categorize its diverse manifestations (Babor & Lauerman 1986, Hesselbrock & Hesselbrock 2006, Leggio et al. 2009). Although more complex typologies have been proposed, the dichotomous typologies of Cloninger (1987) and Babor et al. (1992) have received considerable research attention, perhaps in part because they can readily be considered as moderators of treatment response. Cloninger (1987) differentiated Type 1 and Type 2 alcoholics using family data from a Swedish adoption study in which the prevalence and characteristics of alcoholism were compared in offspring of biological and adoptive parents with alcoholism. Babor and colleagues (1992) applied an empirical clustering technique to data obtained from alcoholics in treatment to differentiate two homogeneous subtypes: Type A and Type B. Cloninger's Type 1 alcoholic shares with Babor's Type A alcoholic a later onset of alcohol-related problems and the absence of antisocial characteristics. Cloninger's Type 2 alcoholic shares with Babor's Type B alcoholic an early onset of alcohol-related problems and the presence of antisocial characteristics, particularly when the individual is intoxicated.

Biological features have also been used to differentiate alcoholic subtypes. Buydens-Branchey et al. (1989a) distinguished early-onset alcoholics (EOAs) from late-onset alcoholics (LOAs) admitted to a rehabilitation program. Among EOAs (who reported more frequent incarceration for violent crimes, more suicide attempts, and more frequent depression than LOAs), central serotonergic activity (i.e., measured as the ratio of plasma tryptophan to other amino acids competing for brain entry) was inversely related to depression and aggression. Swann et al. (1999) found that individuals with low activity on this measure of serotonergic function were more anxious and had antisocial personality characteristics and an early age of onset of alcoholism. In another sample of recently abstinent alcoholics, EOAs also had a more severe course of alcoholism and a lower mean cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid, the major serotonin metabolite, than LOAs (Fils-Aime et al. 1996).

Considered together, these studies provide substantial empirical evidence for a dichotomous typology of alcoholism, a key dimension of which is age of alcoholism onset. Further, the pathologic mood and behavioral dimensions that distinguish EOAs from LOAs may reflect abnormalities in serotonergic neurotransmission. These differences may help explain why later-onset/lower vulnerability alcoholics show different responses than earlier-onset/higher vulnerability alcoholics to treatment with serotonergic medications (see Kenna 2010 for a comprehensive review), including selective serotonin reuptake inhibitors (Kranzler et al. 1996, Pettinati et al. 2000, Chick et al. 2004) and the serotonin-3 receptor antagonist ondansetron (Johnson et al. 2000a, Kranzler et al. 2003).

Although both the subtyping approaches of Babor et al. (1992) and Cloninger (1987) are of theoretical interest, neither can be applied easily to patient care, as the cluster analytic approach demands a moderately large sample and is applied *post hoc* and Cloninger's approach does not categorize all patients (Lamparski et al. 1991). However, age of onset alone may be a clinically meaningful approach to categorizing alcoholic subtypes (Irwin et al. 1990; Johnson et al. 2000b). Roache et al. (2008) used a similar approach in a sample of patients participating in a placebo-controlled trial of ondansetron (Johnson et al. 2000a) and obtained a 2-cluster solution similar to that obtained by Babor et al. (2002). The same patients were grouped into EOAs (onset at ≤ 25 years of age) or LOAs (onset at > 25 years of age) using a single question about the age at which drinking problems began. Seventy-two percent of high-risk/vulnerability (Type B) patients were EOAs and 67% of low-risk/vulnerability (Type A) patients were LOAs. Although Type B alcoholics had a better

response to treatment with ondansetron than placebo, age of onset was a substantially better moderator of this response than the cluster-derived subtypes.

In a clinical trial of sertraline for alcohol dependence, Kranzler et al. (2011) used the Structured Clinical Interview for DSM-IV (SCID, First et al. 2001) to ascertain age of onset (early ≤ 25 years vs. late > 25 years) of alcohol dependence. This study showed differential effects of sertraline that were dependent upon the combination of age of onset and genotype (5-HTTLPR, S′ carriers vs. L′ homozygotes). They found that age of onset of alcohol dependence moderated the response to sertraline in L′ homozygotes, but not in S′ allele carriers. Among L′ homozygotes LOAs reported fewer drinking and heavy drinking days when treated with sertraline than placebo and EOAs showed the opposite effect.

In this study, we compared two additional alcoholic subtype categorization methods to the method employed by Kranzler et al. (2011). Specifically, we examined a cluster analytic classification (Babor et al. 2002) with one based on the age of onset of alcohol problems, which was determined using a single item. Based on the findings that the interaction of subtype by medication was significant only when conditioned on variation in the serotonin-transporter-linked promoter region (5-HTTLPR) (Kranzler et al. 2011), we included genotype as a variable in the comparisons involving treatment outcome. Because in that prior study, the effect was limited to individuals with the L′L′ genotype, we anticipated that any differences would be limited to that genotype group.

METHODS

Detailed characteristics of participants in the placebo-controlled trial of sertraline for the treatment of alcohol dependence are presented elsewhere (Kranzler et al. 2011). Briefly, this was a 12-week, placebo-controlled trial in which we examined main and interaction effects of medication group, age of onset of alcohol dependence (≤ 25 years vs. > 25 years), and the tri-allelic 5-HTTLPR genotype (S′ carriers vs. L′ homozygotes) on drinking outcomes. A total of 134 patients (80.6% male; 34.3% EOAs) with DSM-IV alcohol dependence were treated with sertraline 200 mg/day (N=63) or matching placebo (N=71). A diagnosis of current (but not lifetime) major depressive disorder was exclusionary. All patients also received coping skills training, a structured, manual-guided, individual intervention.

Measures

At screening, all patients underwent a demographic interview. We used the Timeline Follow-back procedure (Sobell & Sobell 1992) to estimate drinking during the 90 days prior to study enrollment. The SCID (First et al. 2001) was used to obtain current and lifetime diagnoses of substance use, mood, anxiety, and antisocial personality disorders.

Alcohol Cluster Typology—To subtype patients using a multivariate approach, 15 variables from assessments conducted during the screening period were chosen to match as closely as possible those used by Babor et al. (1992).

A self-report questionnaire was used to evaluate lifetime drinking history, drug use, and alcoholism treatment history (Hesselbrock et al. 1983). Specifically, the following 7 variables represented these domains: (1) *Childhood behavior problems* were reported on a 26-item self-report questionnaire; (2) A *drinking milestones* composite was formed by taking the mean of three “milestone” events: age of the initiation of regular drinking, age of first getting intoxicated regularly, and age of onset of the period of heaviest drinking; (3) *Alcohol dependence symptoms* were assessed with 28 items concerning experiences in the preceding 3 months that were related to drinking; (4) *Benzodiazepine use* was assessed with a single question on the use of these drugs during the preceding 3 months (or during a recent

period of heavy use); (5) *Other drug use* was assessed with 8 items pertaining to the use of amphetamines, barbiturates, marijuana, heroin, synthetic narcotics, other narcotics, cocaine/crack, hallucinogens, and PCP; (6) *Self-medication reasons for drinking* was assessed by asking participants to rate the importance (1 = "not at all," 2 = "fairly important," 3 = "very important") of 9 statements regarding their drinking in the preceding 3 months. We formed a composite to calculate the mean response of the 9 items; and (7) *Chronicity of alcohol-related medical problems* was assessed with 26 items. Patients were asked to indicate the frequency of such problems using a 3-point scale (1 = never, 2 = sometimes, 3 = frequently). We formed a composite by taking the mean of the 26 items.

The remaining eight variables reflected substance use and comorbid psychopathology and were based on standardized assessments: (1) *Family alcoholism vulnerability* was assessed with the FHAM (Rice et al. 1995), which yields a proportion of all first-degree relatives, excluding offspring, reported by the patient to be alcoholic; (2) *Physical and social consequences of drinking* were assessed with the Short Index of Problems (SIP; Miller et al. 1995, Feinn et al. 2003); (3) *Alcohol dependence liability* was assessed with 49 items from the 51-item MacAndrew alcoholism scale derived from the MMPI. To obtain an uncontaminated measure of dependence risk, we did not include 2 items that asked about alcohol use; (4) *Lifetime depression severity* was assessed using a count of the number of lifetime major depressive symptoms on the SCID; (5) *Intensity of drinking* was assessed using the Timeline Follow-back. Participants reported the number of drinking days and the total amount of standard drinks consumed in the preceding 90 days; drinks per drinking day was determined by dividing the total number of standard drinks by the number of drinking days; (6) *Lifetime alcoholism severity* was assessed with the 24-item MAST (Selzer et al. 1971); (7) *Sociopathy* was assessed with 7 items adapted from the antisocial personality disorder section of the SCID. Patients were rated on a 3-point scale (1 = absent or false, 2 = sub-threshold, 3 = threshold or true). We formed a continuous measure by taking the mean of the 7 items; and (8) An *anxiety severity* index was created by calculating the proportion of lifetime symptoms participants reported in the panic disorder, agoraphobia, social phobia, specific phobia, and obsessive-compulsive and generalized anxiety disorder sections of the SCID.

Age of onset of alcohol dependence was obtained using the SCID at screening to determine the age at which patients met at least 3 of 7 criteria for the disorder during a 12-month period. Individuals who met criteria at age 25 or younger were categorized as EOAs and those who were older than 25 years when first meeting criteria were identified as LOAs.

Age of onset of problem drinking was determined using a single item (i.e., item B28 of the Comprehensive Drinker Profile, CDP), which was a significant moderator of the response to ondansetron treatment of alcohol dependence (Johnson et al. 2000a, Roache et al. 2008).

Genotyping—We used the tri-allelic 5-HTTLPR genotype, the methods for which are described in detail in Kranzler et al. (2011). Briefly, we first differentiated the S and L alleles. Then, L_A vs. L_G allele-specific probes were used to characterize the A→G SNP in the L allele. The L_G and S alleles were grouped together and designated as S′ (the lower expression allele) and the L_A allele was designated as L′ (the higher expression allele). As reported in Kranzler et al. (2011), genotype frequencies did not differ from Hardy-Weinberg equilibrium expectations. We limited the analysis to two genotype groups because of the small sample sizes.

Treatment Outcome Measures—Interactive voice response technology, which uses the telephone to administer survey questions, was used to measure drinking behavior through daily reports (Kranzler et al. 2004). The number of standard drinks of beer, wine, and liquor

that patients consumed were summed to create a total number of standard drinks per day. The Timeline Follow-back was administered every two weeks during treatment to augment daily drinking data. Days for which data were missing either because the patient failed to provide data that day despite remaining in the study or after having discontinued study participation prematurely were coded as heavy drinking days. This conservative approach included all patients in the analysis and yielded 12 weekly values for the drinking outcomes (Kranzler et al. 2011).

Statistical Analysis—A k-means cluster analysis of the 15 standardized variables was used to differentiate Type A and Type B alcoholics. Agreement among the three classification methods was calculated by Cohen's kappa. The subtypes derived using each of the three approaches [Type A vs. Type B for Babor et al. (1992) or early onset vs. late onset for the two age-of-onset typologies] were compared on baseline characteristics with independent samples t-tests for continuous variables and chi-square [or Fisher's Exact Test (FET) when cell frequencies were small] for categorical variables.

We used linear mixed models in SPSS v17 to test for main effects of classification method, time, medication group, 5-HTTLPR genotype, and their interactions on the number of drinking days and the number of heavy drinking days (defined as days on which men drank ≥ 5 standard drinks and women drank ≥ 4 standard drinks) per week during the 12-week study period. These are the same outcomes that were examined by Kranzler et al. (2011) in the initial analysis of the clinical trial of sertraline for AD, with subtyping based on age of onset of alcohol dependence as determined using the SCID. Hence, we present outcome data here only for the other two typologies (i.e., the cluster analytic and single item age-of-onset methods).

RESULTS

Cluster analysis (with k=2) resulted in 40 patients being classified as higher risk/severity (Type B) alcoholics and 94 patients being classified as lower risk/severity (Type A) alcoholics. The SCID-derived age of onset of alcohol dependence yielded 46 EOAs and 88 LOAs. Although 80% of the patients classified as LOAs were classified as Type A alcoholics, fewer than half (48%) of the EOAs were classified as Type B alcoholics, resulting in a modest rate of concordance ($\kappa = 0.28$), which was significantly lower ($p<0.01$) than the concordance ($\kappa = 0.72$) that was reported by Roache et al. (2008).

Application of the age of onset of problem drinking based on a single item from the CDP classified 47 patients as EOAs and 87 patients as LOAs. Cross-tabulation of the SCID-derived age of onset and the CDP-derived age of onset resulted in 95% agreement ($\kappa = 0.89$) in the classification of EOAs and LOAs. Of the 7 patients (5%) classified differently by the two methods, 3 were classified as EOAs with the SCID and as LOAs with the CDP and 4 patients were classified as LOAs with the SCID and as EOAs with the CDP. Subtypes derived from the single-item age of onset and those obtained using the k-means clustering method showed modest concordance ($\kappa = 0.27$), similar to that seen between the SCID age of onset and the k-means cluster subtypes.

Table 1 shows the baseline characteristics for the 134 patients subtyped using each of the three approaches. Each method yielded subgroups that differed significantly from one another on age, income, SIP total score, and the prevalence of lifetime cannabis dependence and ASPD. Type B individuals and EOAs (based on either age-of-onset approach) were younger and had higher SIP scores and a higher lifetime prevalence of cannabis dependence and ASPD than Type A individuals and LOAs, respectively. Type B alcoholics also had a higher lifetime prevalence of both cocaine dependence and conduct disorder than Type A

alcoholics. None of the subtyping approaches yielded groups that differed from one another on the prevalence of a lifetime diagnosis of major depressive disorder, which could be relevant given that the study evaluated the effects of sertraline, an antidepressant medication.

Drinking days

There was a significant four-way interaction of cluster type, medication group, genotype, and week on this outcome measure ($t = 2.38$, $p = 0.019$). Examination of the interaction revealed a three-way interaction of cluster type, medication group, and week among L′ homozygotes ($t = 2.48$, $p = 0.022$), but not S′ carriers ($t = 1.07$, $p = 0.29$). Figure 1 shows that, among L′ homozygotes, Type B subjects drank less frequently when treated with placebo than sertraline, while Type A subjects drank less frequently when treated with sertraline than placebo. The effects in S′ carriers were not statistically significant.

There was also a significant four-way interaction between the single-item CDP age of onset with medication group, genotype, and week ($t = 2.33$, $p = 0.022$). Among L′ homozygotes, there was a significant three-way interaction of age of onset, medication group, and week ($t = 3.42$, $p = 0.003$). Among S′ carriers, this interaction effect was not significant ($t = 0.42$, $p = 0.68$). Figure 2 looks very similar to Figure 1 from Kranzler et al. (2011), which also showed an interaction effect using the age of onset of alcoholism based on the SCID diagnosis of alcohol dependence rather than the single item from the CDP. All the parameter estimates for the single-item CDP age of onset were within the standard errors of the parameter estimates found by Kranzler et al. (2011) using the SCID-derived age of onset.

Heavy drinking days

The effects for heavy drinking days were similar to those for DDs, so they are not presented graphically. There was a significant four-way interaction of cluster type, medication group, genotype, and week ($t = 2.89$, $p = 0.005$) on heavy drinking days. Conditioned on genotype, the three-way interaction of cluster type, medication group, and week was significant among L′ homozygotes ($t = 2.77$, $p = 0.014$), but not among S′ carriers ($t = 1.11$, $p = 0.27$). Among L′ homozygotes, Type B alcoholics reported more heavy drinking days when treated with sertraline than placebo, while Type A alcoholics showed the opposite effect.

There was also a significant four-way interaction of the single-item CDP age of onset with medication group, genotype, and week ($t = 2.26$, $p = 0.026$). When analyzed by genotype, there was a significant three-way interaction of age of onset, medication group, and week among L′ homozygotes ($t = 3.16$, $p = 0.007$), but not S′ carriers ($t = 1.03$, $p = 0.31$). Analogous to the findings for drinking days, among L′ homozygotes, EOAs treated with sertraline reported more heavy drinking days than those receiving placebo. The converse was true for LOAs, such that the sertraline group had fewer heavy drinking days than the placebo group. All of the parameter estimates using the CDP-derived age of onset were within the standard errors of the parameter estimates obtained by Kranzler et al. (2011) using the SCID-derived age of onset.

DISCUSSION

A substantial literature supports the concurrent, discriminant, and predictive validity of alcoholism subtypes. Because different methods and criteria for subtyping have been employed and variable results obtained, however, there is no clear consensus on the clinical utility of these subtypes. Using data from a placebo-controlled trial of sertraline in which participants were assessed using three different dichotomous subtyping approaches, we compared the resulting subtypes on pretreatment and treatment-related measures. We found

high concordance between the two age-of-onset approaches, but poor concordance between either of the age-of-onset approaches and the one derived using cluster analysis. The poor concordance between an age-of-onset subtype and a cluster analytic subtyping approach differs from that seen in an analysis of data from a placebo-controlled study of ondansetron for the treatment of alcohol dependence (Roache et al. 2008). This difference may be attributable to the fact that Roache et al. (2008) included three self-report measures of aggression, which were not included in our cluster analysis [nor were they elements in the original cluster analysis conducted by Babor et al. (1992)]. The use of aggression measures to differentiate alcoholism subtypes has important implications for their moderating effects on the response to a serotonergic antidepressant such as sertraline. Buydens-Branchey et al. (1989a) reported that, among EOAs, central serotonergic activity was inversely related to aggression. Thus, inclusion of this behavioral dimension in the derivation of cluster subtypes could increase the utility of the approach.

Although both subtyping approaches had significant moderating effects, inspection of the figures showing weekly drinking measures suggests that the moderator effects were greater for the age-of-onset than for the cluster-derived subtypes. Although Roache et al. (2008) also found that age of onset was a better moderator of treatment response than the cluster-derived subtypes, in that study the differences seen between the two subtyping approaches were more evident than those seen here. This may reflect differences in the effects of the medications used, since sertraline has direct effects on serotonin reuptake via the serotonin transporter with secondary effects on postsynaptic receptors (McRae and Brady 2001), while the primary effects of ondansetron are on serotonin-3 receptors (Wilde and Markham 1996), with other postsynaptic receptors being affected as well (McNulty 2007).

The two different methods of determining age of onset (i.e., a single self-report item or responses to a semi-structured interview) showed comparable validity. A recent systematic review of factors affecting the implementation of information technologies in clinical settings (Gagnon et al. 2010) showed ease of use to be an important factor promoting the adoption of new technology. Thus, given the greater simplicity of the single-item measure, we would anticipate that it would be the better approach to use clinically (and, possibly, in treatment guidelines). However, other considerations, such as the psychometric properties of the measure should be included in this determination. Thus, research on the temporal stability of the age-of-onset measure is needed.

The present study is limited by the sample size of the clinical trial, which particularly affected some of the subgroups (Kranzler et al. 2011). Further, this report is based on a secondary analysis using data collected in a clinical trial in which age of onset was defined *a priori* using DSM-IV criteria for AD. Because the effects that we observed were limited to L′-allele homozygotes, additional pharmacogenetic studies are needed to validate these findings.

Although the similarity of our findings to those reported by Roache et al. (2008), which was also a secondary analysis, supports the validity of the age-f-onset subtypes, prospective replication in larger samples is needed to validate this approach to subtyping individuals in treatment trials of serotonergic medications. A key point, though, is that irrespective of which typologic approach one uses, a substantial subgroup of alcohol-dependent individuals benefit from treatment with sertraline. Equally important, however, is that a substantial number of individuals also appear either to derive no benefit (S′-allele carriers) or to be harmed (earlier-onset L′ homozygotes) by such treatment.

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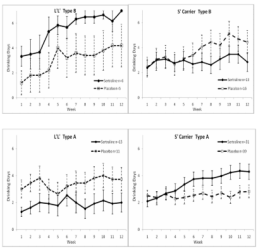

Figure 1.

Drinking Days by Genotype and Cluster

Number of drinking days by Study Week, A/B Cluster Subtype, Medication Group, and 5-HTTLPR Genotype. Values are mean (±SEM) and reflect drinking behavior during the week identified on the x-axis. The decrease in drinking days from baseline to week 1 is not shown in the figure

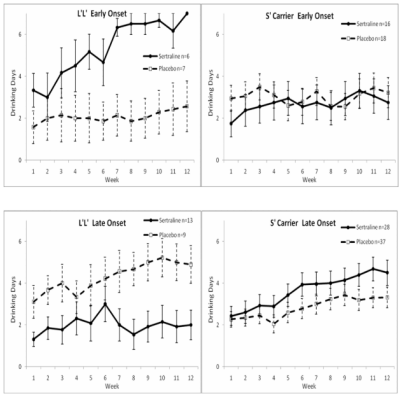

Figure 2.

Drinking Days by Genotype and Age of Onset of Problem Drinking

Number of drinking days by Study Week, Age of Onset of Alcohol Dependence (based on a single item), Medication Group, and 5-HTTLPR Genotype. Values are mean (±SEM) and reflect drinking behavior during the week identified on the x-axis. The decrease in drinking days from baseline to week 1 is not shown in the figure

Table 1

Demographic and Clinical Features of Subtypes Derived Using Three Different Approaches

	Cluster-Derived Subtypes		SCID-Derived Subtypes		Single-Item Subtypes	
	Type B	Type A	EOA	LOA	EOA	LOA
Variables	**n=40**	**n=94**	**n=46**	**n=88**	**n=47**	**n=87**
Gender						
Male	35 (88)	73 (78)	41 (89)	67 (76)	42 (89)	66 (76)
Female	5 (13)	21 (22)	5 (11)	21 (24)	5 (11)	21 (24)
Race/Ethnicity						
White	36 (90)	87 (93)	44 (96)	79 (90)	45 (96)	78 (90)
Other	4 (10)	7 (7)	2 (4)	9 (10)	2 (4)	9 (10)
Age						
Mean ±SD	**43.2 ± 9.9**	**49.4 ± 9.2**	**43.1 ± 10.8**	**50.0 ± 8.4**	**43.0 ± 10.3**	**50.0 ± 8.5**
Years of Education						
Mean ±SD	13.7 ± 2.0	14.8 ± 2.3	14.2 ± 2.3	14.7 ± 2.3	14.4 ± 2.2	14.6 ± 2.3
Income						
< $30,000	**8 (20)**	**7 (7)**	**2 (4)**	**13 (15)**	**2 (4)**	**13 (15)**
$30–49,999	**8 (20)**	**20 (21)**	**10 (22)**	**18 (21)**	**9 (19)**	**19 (22)**
$50–79,999	**15 (38)**	**26 (28)**	**21 (46)**	**20 (23)**	**21 (45)**	**20 (23)**
≥ $80,000	**9 (23)**	**41 (44)**	**13 (28)**	**37 (42)**	**15 (32)**	**35 (40)**
Employment						
Employed	29 (73)	76 (81)	36 (78)	69 (78)	37 (79)	68 (78)
Not employed	11 (28)	18 (19)	10 (22)	19 (22)	10 (21)	19 (22)
Marital Status						
Married	19 (48)	61 (65)	24 (52)	56 (64)	25 (53)	55 (63)
Other	21 (53)	33 (35)	22 (48)	32 (36)	22 (47)	32 (37)
Drinking						
Drinks/day	8.9 ± 5.4	5.4 ± 3.4	7.2 ± 5.0	6.1 ± 4.0	7.1 ± 5.1	6.1 ± 3.9
Drinks/drink day	14.3 ± 7.5	8.0 ± 3.8	11.2 ± 6.9	9.1 ± 5.2	11.0 ± 6.9	9.2 ± 5.3
% DDs	66.3 ± 28	68.6 ± 25	66.1 ± 26	68.8 ± 27	67.4 ± 26	68.2 ± 26
% HDDs	60.3 ± 30	55.0 ± 29	57.3 ± 30	56.2 ± 29	57.3 ± 31	56.1 ± 29
SIP	**29.1 ± 6.7**	**17.9 ± 7.1**	**23.7 ± 7.6**	**20.0 ± 8.9**	**24.6 ± 7.6**	**19.5 ± 8.7**

	Cluster-Derived Subtypes		SCID-Derived Subtypes		Single-Item Subtypes	
	Type B	**Type A**	**EOA**	**LOA**	**EOA**	**LOA**
Variables	**n=40**	**n=94**	**n=46**	**n=88**	**n=47**	**n=87**
Drug Dependence[1]						
Cannabis	**12 (30)**	**11 (12)**	**15 (33)**	**8 (9)**	**15 (32)**	**8 (9)**
Cocaine	**14 (35)**	**12 (13)**	12 (26)	14 (16)	13 (28)	13 (15)
Opioid	2 (5)	0 (0)	1 (2)	1 (1)	1 (2)	1 (1)
Stimulant	1 (3)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)
Hallucinogen	0 (0)	1 (1)	1 (2)	0 (0)	1 (2)	0 (0)
Psychiatric Disorders[1]						
Major depression	12 (30)	16 (17)	11 (24)	17 (19)	10 (21)	18 (21)
Panic disorder	1 (3)	3 (3)	1 (2)	3 (3)	1 (2)	3 (3)
Social phobia	3 (8)	4 (4)	3 (7)	4 (5)	3 (6)	4 (5)
Generalized anxiety	2 (5)	0 (0)	0 (0)	2 (2)	0 (0)	2 (2)
Conduct disorder	**5 (13)**	**3 (3)**	2 (4)	6 (7)	3 (6)	5 (6)
ASPD	**14 (35)**	**4 (4)**	**10 (22)**	**8 (9)**	**10 (21)**	**8 (9)**

SCID, Structured Clinical Interview for DSM-IV; EOA, early-onset alcoholic; LOA, late-onset alcoholic; SD, standard deviation; DDs, drinking days; HDDs, heavy drinking days; SIP, Short Index of Problems; ASPD, Antisocial Personality Disorder

[1]Lifetime Diagnoses Bolded values reflect significant differences between subgroups within an approach.