Published in final edited form as:
Alcohol Clin Exp Res. 2008 August ; 32(8): 1502–1512. doi:10.1111/j.1530-0277.2008.00717.x.

PREDICTION OF SEROTONERGIC TREATMENT EFFICACY USING AGE OF ONSET AND TYPE A/B TYPOLOGIES OF ALCOHOLISM

John D. Roache, Ph.D., **Yanmei Wang, M.S.**, **Nassima Ait-Daoud, M.D.**, and **Bankole A. Johnson, D.Sc., M.D., Ph.D., M.Phil., FRCPsych.**
From the Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio, Texas (JDR, YW), and the Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia (NA-D, BAJ)

Abstract

Background—Previously, we reported that ondansetron was efficacious at treating early-onset (≤25 years old) but not late-onset (≥26 years old) alcoholics in a double-blind, randomized, placebo-controlled clinical trial (n = 321 enrolled patients, 271 of them randomized). Randomized participants underwent 11 weeks of treatment with ondansetron (1, 4, or 16 μg/kg twice daily; n = 67, 77, and 71, respectively) or identical placebo (n = 56), plus weekly standardized group cognitive behavioral therapy.

Methods—For this study, we reanalyzed the original sample to determine whether the Type A/B typological classification predicts ondansetron treatment response. In this comparative analysis, k-means clustering was applied to 19 baseline measures of drinking behavior, psychopathology, and social functioning, similar to those used by Babor in the original typological derivation. A two-factor solution described robustly two groups phenomenologically consistent with Type A/B classification. Subjects were subdivided into early- and late-onset alcoholics.

Results—Seventy-two percent of Type B subjects had early-onset alcoholism; 67% of Type A subjects had late-onset alcoholism. The A/B typology better discriminated two clusters based upon baseline severity of alcoholism. There was a significant effect ($p < 0.05$) for Type B alcoholics to respond to ondansetron (4 μg/kg); however, Type A alcoholics receiving ondansetron showed no beneficial effect. Early-vs. late-onset classification predicted ondansetron response substantially better than Type A/B classification, which did not add to the prediction of treatment outcome. Further analyses showed that ondansetron was effective in the 33% of Type A alcoholics with early-onset alcoholism but ineffective in the 28% of Type B alcoholics with late-onset alcoholism.

Conclusions—Type A/B classification best discriminates alcoholic subtypes based upon baseline severity. Early- vs. late-onset classification is, however, a better predictor of response to ondansetron treatment because it might be more closely related to fundamental neurobiological processes associated with the underlying pathophysiology of alcoholism.

Keywords

Alcoholism; Alcohol dependence; Ondansetron; Serotonin; Typology; Early onset; Late onset; Type A; Type B

Corresponding author: John D. Roache, Ph.D., Department of Psychiatry, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mailstop 7792, San Antonio, Texas 78229. Phone: 210-562-5401. Fax: 210-562-5403. roache@uthscsa.edu.

INTRODUCTION

Since the early description of different types of alcoholism by Bowman and Jellinek (1941), there has been a long-standing interest in subtyping alcoholics based upon phenomenological characteristics. Although a total of five "types" were described by Jellinek (1960), the descriptions of two basic types known as delta and gamma were prominent until Cloninger (1987b) proposed a new classification based upon his family studies of inheritance patterns. This classification described a "milieu-limited" (Type I) subtype where environmental risk factors were largely determinant of alcoholic drinking patterns, as opposed to a "male-limited" (Type II) subtype where family inheritance seemed to determine a biological vulnerability having the characteristics of male sex, psychological vulnerability, and an early age of onset of problem drinking. Subsequently, Babor et al. (1992a,b) used a systematic, multidimensional assessment of 228 male and 85 female alcoholics to derive empirically two subtypes of alcoholism known as Type A and Type B. In that study, alcoholics were clinically and psychometrically assessed on 17 dimensions to characterize family history and age of onset of alcoholism, lifetime patterns of drinking and other drug use, medical health, physical symptoms of withdrawal and motivation for "relief drinking", the extent of psychosocial disruption, and psychometric assessment of personality and childhood and adult psychiatric status. A k-means cluster analysis empirically resolved two groups where, compared with Type A, Type B was "characterized by early onset, a more rapid course, more severe symptoms, greater psychological vulnerability, and poorer prognosis" (Babor et al., 1992b).

Schuckit et al. (1995) applied the k-means clustering approach to 1539 alcohol-dependent participants in the Collaborative Study on the Genetics of Alcoholism and replicated Babor's Type A/B classification. While that study described the Type B subgroup as having an earlier age of onset and more severe disease, it also demonstrated that the Type A/B dichotomy holds up even in a sample that had emergence of symptoms after the age of 25 years. However, a look at the primary characteristics loading onto the Type A/B cluster classification reveals that it is primarily a measure of disease severity that includes: 1) amount of drinking, 2) withdrawal avoidance, and 3) negative medical, physical, and social consequences. Hence, it makes sense that even within the later-age-of-onset group, it is possible to cluster subjects based upon severity and consequences. Carpenter and Hasin (2001) compared Cloninger's Type I/II classification and Babor's Type A/B classification of non-severe "problem drinkers" from a general population sample (n = 8643) and a selected community sample (n = 664) and found a dichotomous classification resembling Babor's Type A/B. The authors further stated that clustering techniques were "stronger for subtype models that incorporate dimensions of alcohol use and/or the frequency of negative consequences". Thus, the multidimensional, *post hoc* sorting of problem drinkers into dichotomous categories has reproducibly verified a schema to identify a Type B cluster known by an earlier onset of illness, more severe dependence symptoms, and, overall, a worse prognosis.

Several studies have shown that subgroups of alcoholics may respond differently to treatment with serotonergic medication. Our group reported that age of onset of alcohol-related problems is an effective predictor of response to treatment with the 5-HT_3 antagonist ondansetron (Johnson et al., 2000c). In that study, age of onset ($\leq$25 years vs. $\geq$26 years) was used as a means of *a priori* classification of two alcoholism subtypes known as early-onset alcoholism (EOA) vs. late-onset alcoholism (LOA), respectively, prior to randomized treatment with placebo or one of three doses (1, 4, or 16 μg/kg twice daily) of ondansetron. Ondansetron was superior to placebo among EOA but not LOA subjects. The optimal dose in that study was determined to be 4 μg/kg of ondansetron although some positive results also were obtained with lower (1 μg/kg) and higher (16 μg/kg) doses. This finding was extended to show that the combination of ondansetron (4 μg/kg) and naltrexone (25 mg) was effective in the treatment of EOA subjects (Johnson et al., 2000a). In a subsequent open-label trial with ondansetron (4

μg/kg), Kranzler et al. (2003) replicated our finding that EOA subjects responded better than LOA subjects to treatment. These studies clearly establish that alcoholics with an early age of onset can be treated effectively with the 5-HT_3 antagonist, ondansetron, and further indicate that age of onset is a strong predictor of response to treatment with ondansetron.

Importantly, response to treatment with selective serotonin reuptake inhibitors (SSRIs) also appears to be predicted by alcoholism subtype. Whereas experimental studies among problem drinkers have reported that SSRIs including zimelidine, citalopram, viqualine, and fluoxetine each reduced alcohol intake in comparison with placebo (Naranjo et al., 1984, 1987, 1989, 1990), SSRIs including fluvoxamine and fluoxetine were not found to be efficacious for the treatment of a heterogeneous group of alcohol-dependent outpatients (Kranzler et al., 1993, 1995). In the latter of these studies (Kranzler et al., 1995), fluoxetine was superior to placebo at improving depressive symptoms in a subgroup of patients with comorbid depression even though this was not associated with a reduction in alcohol consumption. Subsequently, these investigators reanalyzed their data (Kranzler et al., 1996) using a cluster analysis to divide subjects into Babor's Type A/B groupings. They found that fluoxetine was not better than placebo at improving drinking outcomes among Type A alcoholics (n = 60); in contrast, fluoxetine treatment, compared with placebo, was associated with significantly worse drinking outcomes among Type B alcoholics (n = 35). Subsequently, Pettinati et al. (2001) compared the effects of sertraline (200 mg/day) vs. placebo in 53 alcohol-dependent patients with lifetime histories of depression and 47 patients without histories of depression. They failed to detect an antidepressant effect of sertraline; however, they did observe that sertraline reduced the drinking of subjects who had no lifetime history of depression. To understand this paradoxical finding, their data were reanalyzed by cluster analyses (Pettinati et al., 2000), after which sertraline treatment was shown to be substantially superior to placebo at reducing drinking in Type A alcoholics (n = 55) but not in Type B alcoholics (n = 45). At 6-month longitudinal follow-up (Dundon et al., 2004), the Type A alcoholics previously treated with sertraline continued to do better than those treated with placebo. In contrast, among the Type B alcoholics, those previously treated with sertraline drank significantly more over the follow-up period than did those treated with placebo. Also, Chick et al. (2004) published a reanalysis of a large sample of alcohol-dependent patients that originally was not published because fluvoxamine treatment was poorly tolerated, was associated with high dropout rates, and did not improve drinking outcomes compared with placebo. The reanalysis of those data divided subjects into Type I and Type II subgroups based upon Cloninger's tridimensional personality inventory (Cloninger, 1987a) and into EOA and LOA groupings based upon age of onset of regular drinking. Placebo-treated subjects showed no differences among subgroups divided as Type I vs. Type II or divided as LOA vs. EOA. In contrast, among subjects treated with fluvoxamine, the subgroups classified as Type II or EOA did worse than the subjects classified as Type I or LOA. Thus, data from three independent studies of three different SSRIs, published in six different analyses, have all uniformly demonstrated that the classification of alcoholism subtype is critical to predicting treatment response with SSRIs (Pettinati, 2001). All three studies have shown that SSRI treatment can worsen the prognosis and increase drinking relative to placebo in the Type B-, Type II-, or EOA-classified subgroup of alcoholics whose disease is characterized as more severe and, perhaps, more determined by innate biological dysregulation.

Since alcoholics' response to treatment with serotonergic agents appears to depend upon alcoholism subtype, it is important to identify an individual patient's alcoholism subtype before treatment is initiated. This appears to be especially true when using SSRIs, because the drinking of Type B/Type II patients may be increased by SSRI treatment. Unfortunately, Type A vs. B classification requires a *post hoc* multidimensional clustering approach, and there is no validated way to classify an alcoholic as Type B using *a priori* methods. However, a recent small-sample pilot study (Kampman et al., 2007) did attempt such a classification and found

that quetiapine was superior to placebo in subjects classified *a priori* as Type B but not in subjects classified as Type A. In that study, 28 subjects were classified as Type B if they drank ≥12 drinks/drinking day and had 1) onset of alcohol dependence before the age of 25 years (i.e., EOA), 2) elevated Hamilton Rating Scale for Depression scores, or 3) three or more childhood symptoms of antisocial personality disorder. The small sample size of the study prevents conclusions regarding the validity of the *a priori* classification scheme or the selectivity of differential effects of quetiapine in Type B patients. Notably, an early age of onset of alcohol dependence was a cardinal discriminating factor in Type B classification such that 18 of the Type B subjects had EOA while only 2 of the Type A subjects had EOA. Clearly, early age of onset of alcohol dependence can identify individual patients on an *a priori* basis. Hence, EOA/LOA classification is well suited to *a priori* identification of alcoholism subtype prior to treatment.

Herein, we report a comparative analysis of the two classification schemes using data from our previous study on the effects of ondansetron in the outpatient treatment of 321 alcoholics (Johnson et al., 2000c). In that study, age of onset was used *a priori* to subdivide subjects into EOA/LOA strata prior to randomization. For the present analysis, we sought to compare the EOA/LOA classification and Type A/B clustering schemes with respect to their phenomenological distinctions, and to determine which scheme worked better as a predictor of ondansetron treatment response. We hypothesized that ondansetron would be effective in Type B but not Type A alcoholics but wanted to know whether the Type A/B classification would be superior to the age-of-onset classification to predict ondansetron response. Like the approach taken by others who conducted a reanalysis of a previously completed study (Chick et al., 2004; Kranzler et al., 1996; Pettinati et al., 2000), the Type A/B classification employed a *post hoc* clustering approach to derive Type A and Type B alcoholic subgroups using multiple dimensional measures of baseline demographics, drinking, and addiction severity characteristics related to those dimensions used by Babor et al. (1992a,b). Thus, this analysis provides an opportunity to compare and contrast the value of *post hoc* derived Type A/B clustering techniques with the *a priori* EOA/LOA subgrouping to distinguish alcoholism subtypes in terms of phenomenological characteristics and to predict treatment response to serotonergic agents such as ondansetron.

MATERIALS AND METHODS

Study Design

The current study is a comparative analysis of two typological classification schemes using baseline and treatment outcome data from a previous outpatient treatment trial, which showed that ondansetron benefited the treatment of EOA but not LOA subjects (Johnson et al., 2000c). In that study, 321 alcohol-dependent male and female subjects were classified *a priori* by age of onset (n = 161 with EOA vs. n = 160 with LOA) before randomization to placebo or one of three doses (1, 4, or 16 μg/kg twice daily) of ondansetron. As described previously (Johnson et al., 2000c), the age of onset for each subject was determined during a clinical interview with the Comprehensive Drinker Profile (Miller and Marlatt, 1984), which assessed drinking-related problems in multiple domains of psychosocial dysfunction (i.e., employment problems, legal problems, marital problems, etc.) and asked the question (item #28), "…at what age did drinking become a problem for you?" For alcohol-dependent patients, this age of the first symptoms of problem drinking constitutes the initial onset of the symptoms of dependence. The final age of onset for each subject was confirmed during clinical interviews using the Addiction Severity Index (ASI) (McLellan et al., 1980) and the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, Revised Third Edition (DSM-III-R) (Spitzer et al., 1992; Williams et al., 1992), which also query ages for the onset of symptoms of dependence. Because the Type I/II classification of Cloninger (1987b)

discriminated between groups based upon an age of onset of >25 years or <25 years, respectively, and because EOA subjects having an onset of ≤25 years were reported to demonstrate biological abnormalities in serotonin function (Fils-Aime et al., 1996; George et al., 1999), we also used an age of ≤25 years for EOA vs. ≥26 years for LOA as the criterion to divide dichotomous groups. Previously (Johnson et al., 2000b), we reported that using an age-of-onset cutoff of <20 years resulted in a more narrowly defined, more severely affected group of EOA subjects, but that the 20- to 25-year group was still more severe and like EOA subjects than the LOA >25-year group. The current analysis used baseline assessment data from the original 321 EOA/LOA study subjects and subjected them to a k-means cluster analysis as used by others (Babor et al., 1992a,b; Schuckit et al., 1995) to conduct a *post hoc*, multidimensional classification of subjects into two dichotomous groups (i.e., Type A and Type B). Then, we used parallel analysis of covariance regression models to compare the effectiveness of ondansetron vs. placebo in subjects classified both by the A/B typology and by the EOA/LOA typology. Finally, we further divided subjects into four subgroups based upon the 2 × 2 factorial combination of the two typologies (Type A-EOA, Type A-LOA, Type B-EOA, and Type B-LOA) and examined, within each of those subgroups, the ondansetron dose effects (four levels).

Subjects and Baseline Measures

Subjects were 321 individuals (70% male) who met DSM-III-R (American Psychiatric Association, 1987) criteria for alcohol dependence and did not have other significant psychiatric or medical conditions, as described previously (Johnson et al., 2000c). These subjects were seeking treatment and participated in a 13-week outpatient treatment program involving cognitive behavioral therapy plus randomized treatment with placebo or one of three doses of ondansetron. Subjects were randomized to one of these four dose levels after stratification into EOA/LOA age-of-onset subgroups, resulting in relatively similar sample sizes across dosage groups.

We collected basic demographic information (age, sex, race, education, etc.) and identified 19 assessments, collected during the screening of subjects for study eligibility (Table 1), that measured dimensions related to the characteristics used by Babor et al. (1992a,b) in their original classification of the Type A/B subtypes of alcoholism. The first seven of these items were the same as those originally used and included: the Michigan Alcoholism Screening Test (MAST) (Selzer, 1971); the Child Behavior Checklist (Achenbach and Edelbrock, 1981); the MacAndrew Alcoholism Scale (MacAndrew, 1965); age of onset (Johnson et al., 2000b,c); years of drinking; drinks per day, and occurrence of familial alcoholism. We used the tension-anxiety and depression ratings from the Profile of Mood States (POMS) (McNair et al., 1971) instead of the Diagnostic Interview Schedule and Minnesota Multiphasic Personality Inventory, and used the ASI (McLellan et al., 1980) and Social Functioning Questionnaire (Tyrer, 1990) to code for the medical, social, and physical consequences similar to those listed by Babor et al. (1992a,b). Additionally, we coded the presence or absence of an antisocial personality disorder diagnosis (as defined by DSM-III-R) instead of using the Diagnostic Interview Schedule symptoms, and added self-report measures of aggression from the Buss-Durkee Inventory (Buss and Durkee, 1957).

Data Analysis

Drinking Outcomes—In the original analysis of ondansetron treatment outcome (Johnson et al., 2000c), mean drinking measures post-randomization were examined using a PROC GLM (SAS® Release 8.2; SAS Institute, Cary, NC) analysis of covariance model accounting for ondansetron dose and age-of-onset classification, adjusted by the covariate of pre-randomization baseline drinking. The present study analysis used a similar approach including ondansetron dose and subgroup classification, with the baseline drinking measure as a covariate

in the model. Because this is a reanalysis of previously published data, and for systematic replication purposes, we employed a different drinking outcome — mean drinking during the last 14 days of study participation — as the endpoint measure. All drinking measures, which included mean drinks per drinking day, percent days abstinent, and mean drinks per day, were collected as "standard drinks" that were self-reported each day by the calendar-based timeline follow-back (TLFB) method (Sobell and Sobell, 1992). Drinking over the 90 days preceding the study was ascertained by TLFB during a Form 90 interview (Miller and Del Boca, 1994) at initial study intake, and baseline drinking during the first study week was collected by TLFB prior to dosing with double-blind medication. All data analyses were conducted using SAS® Release 8.2.

Cluster Analysis—The 19 items listed in Table 1 were used to derive the Type A/B clusters. Data were subjected to a k-means clustering approach using PROC FASTCLUS (SAS® Release 8.2). A two-factor solution was determined to be a good fit to the data by examining the cluster discriminates of external and internal clustering variables, the discriminant validity of varying item/factor solutions (Fleiss, 1981), and individual factor contribution to the cluster assignment. The two-cluster solution using all 19 baseline item measures identified 141 Type B-like and 180 Type A-like subjects and had a model $R^2 = 0.27$. A stepwise removal of individual items with the least individual R^2 contribution demonstrated that the items "family history", "ASI-medical", and "ASI-treatment" could be removed, generating a 16-item cluster with 100% agreement and good convergence validity. Thus, two clusters of subjects, described herein as Type A and Type B clusters, were robustly classified by 16 of our 19 baseline items.

Group Comparisons—Table 2 lists the baseline and demographic characteristics of four groups of subjects broken down by Type A/B cluster and by EOA/LOA classification. Groups were compared by Pearson's chi-square test for categorical items and by *t*-tests among group means for continuous variables. PROC GLM (SAS®) was used in regression analyses of ondansetron-related drinking outcomes during the last 14 days of study participation (i.e., endpoint). The model included baseline drinking as a covariate and between-groups factors of ondansetron dose level (placebo or 1, 4, or 16 μg/kg) and subgroup classification (i.e., Type A/B and/or EOA/LOA). Also, the analysis of variance models included the subgroup × ondansetron dose interaction, and significant findings were followed up by Dunnett's *t*-test contrasts of ondansetron dose vs. placebo, which helps to protect against type 1 statistical errors while preserving power. Although statistical power was limited by small sample size in some of the ondansetron dosage groups after subgroup classification, statistical errors were minimized by conducting only planned comparisons of ondansetron dose with placebo within each subgroup. Except for our use of 14-day endpoint drinking rather than the previously reported overall study mean drinking, this approach is the same as previously described (Johnson et al., 2000c).

RESULTS

As previously reported (Johnson et al., 2000c), classification of subjects by age of onset included 161 EOA subjects with an age of onset of ≤25 years and 160 LOA subjects with an age of onset of ≥26 years. The *post hoc* cluster analysis resolved subjects into two groups referred to as Type A (n = 180) and Type B (n = 141). We examined the R^2 contribution of each of the individual items used to generate the A/B clusters and entered into a stepwise elimination of the least significant contributor to the cluster. We found that three assessments were eliminated (genetic family history, ASI-treatment, and ASI-medical) without any change whatsoever to the identity of members in the cluster (i.e., kappa = 1.0). Further decomposition of the individual items showed excellent cluster integrity such that, with only six items remaining (MAST, Child Behavior Checklist, MacAndrew Alcoholism Scale, POMS-depression, POMS-tension-anxiety, and age of onset), cluster identity was essentially

unchanged (kappa = 0.95), with only two subjects switching cluster identity. Age of onset was significantly correlated with each of the five other core items except for the MacAndrew Alcoholism Scale (r = −0.09) and was most highly correlated with the MAST score (r = −0.53). As Babor had argued for the multidimensional assessment of cluster membership using a 17-item cluster, we elected to retain the final Type A/B clusters defined by our 16-item solution (i.e., three were eliminated with no change of membership). Although age of onset was one of the dimensions used both by Babor et al. (1992a,b) and in the current study cluster analysis, the individual item R^2 contribution of age of onset to the cluster was only 18%. Nonetheless, there was about 70% homology (kappa = 0.72) between classification membership based upon the two methods of subgrouping (i.e., EOA/LOA vs. Type A/B).

Table 2 lists the baseline assessment characteristics of the Type A/B clusters, further subdivided by age-of-onset classification, resulting in four subgroups of subjects. The table includes all 16 assessments used in the cluster analysis, as well as other baseline characteristics important to a description of the subjects. There were no significant group differences in racial distribution or the probability of having an alcoholic father/parent, but substantial group differences were seen in all other measures. Compared with subjects classified as having LOA, EOA subjects within each Type A/B cluster were currently younger, had a younger age of onset (by definition), and had been drinking for several years longer. There were only a few other differences between the EOA and LOA subjects, including a greater likelihood of being male (significant within the Type A cluster) or having more family/social or psychiatric problems (as evidenced by ASI scores within the Type B cluster). In contrast to minor differences between the age-of-onset classification groups, the Type B cluster of subjects frequently showed large differences from the Type A cluster regardless of age-of-onset classification. Within both the EOA and LOA classification groups, the Type B cluster showed higher scores than Type A subjects on the MAST, MacAndrew Alcoholism Scale, Buss-Durkee Inventory (i.e., aggression), POMS (i.e., mood disturbance), and Temperament and Character Inventory (TCI)-harm avoidance. They also had younger ages of onset, poorer social functioning, and lower TCI-self-directedness than Type A subjects. Within the subject group classified as having EOA, the Type B cluster was of lower social class, had greater addiction severity as measured on the ASI, and more frequently had a diagnosis of antisocial personality disorder than did the Type A cluster. Within the LOA classification group, Type B subjects drank more, drank for more years, and had higher TCI-novelty seeking than did Type A subjects.

Figure 1 shows drinking outcome results of the study as a function of ondansetron dose when subjects are classified by age of onset (Fig. 1A) or, alternatively, when they are divided into the Type A/B clusters (Fig. 1B). Significant ondansetron-dose-by-age-of-onset interactions (Fig. 1A) indicated differential effects of ondansetron in the two age-of-onset groups for drinks per day ($F = 4.27$, $p < 0.006$), drinks per drinking day ($F = 4.12$, $p < 0.008$), and, marginally, percent days abstinent ($F = 2.54$, $p < 0.06$). Compared with placebo, all ondansetron doses significantly reduced drinking (both drinks per day and drinks per drinking day) and the 4- and 16-μg/kg doses increased days of abstinence among EOA subjects. However, no ondansetron dose reduced the drinking of LOA subjects, and there was evidence for increased drinking relative to placebo (for 16 μg/kg ondansetron on drinks per day) and reduced abstinence (for 1 μg/kg ondansetron on percent days abstinent) among the LOA group. When subjects were divided by their membership in the Type A/B clusters (Fig. 1B), overall ondansetron dose effects and interactions with the clustering factor were not significant (all $F < 2$, $p < 0.20$). However, planned comparisons did show that the 4-μg/kg dose of ondansetron significantly reduced drinking (both drinks per day and drinks per drinking day) among the Type B subjects only.

Figure 2 shows the same drinking outcomes, but now subdividing subjects into the four groups characterized by their age of onset × Type A/B cluster. Among subjects classified as having

EOA (Fig. 2A), main effects of ondansetron without any interactions with A/B cluster were observed for drinks per day ($F = 3.44$, $p < 0.02$), drinks per drinking day ($F = 3.42$, $p < 0.02$), and percent days abstinent ($F = 2.58$, $p < 0.06$). Planned comparisons with placebo showed that 4 μg/kg significantly reduced drinking (both drinks per day and drinks per drinking day) and increased percent days abstinent in the majority of the EOA subjects who were members of the Type B cluster and that the 16-μg/kg dose increased abstinence as well. The minority of EOA subjects who were in the Type A cluster showed the very same effects of ondansetron as those in the Type B cluster; however, due to the limited statistical power of the small sample size, only the 4-μg/kg dose achieved significance for only the drinks per day measure. In contrast, among the LOA subjects (Fig. 2B), there were no main effects of ondansetron dose (all $F < 1$) for any of the drinking measures. However, there was a significant main effect ($F = 3.94$, $p < 0.05$) of Type A/B cluster on percent days abstinent and a marginal effect ($F = 3.28$, $p < 0.08$) on drinks per day, indicating that overall, the LOA-Type B subjects drank more and were abstinent less than the LOA-Type A subjects. Planned comparisons showed that 1 μg/kg ondansetron tended to increase drinking (both drinks per day and drinks per drinking day) in the LOA-Type A subjects. Among the LOA subjects, there was no evidence for ondansetron to decrease drinking at any dose within the majority of subjects comprising the Type A cluster. This also was true among the minority of LOA subjects within the Type B cluster, except for the reduced drinks per drinking day seen with 1 μg/kg ondansetron, where a dose-by-cluster interaction was observed ($F = 3.28$, $p < 0.08$), indicating differential effects of ondansetron dose in the LOA-Type A/B subgroups. However, this may be a spurious finding of an unusually low mean value heavily influenced by one subject among the small-sample-size (n = 7) LOA-Type B subgroup.

DISCUSSION

A multidimensional cluster analysis of 16 baseline assessments of 321 alcohol-dependent outpatients identified two subgroups easily characterized as Type A and Type B alcoholics who had clinical characteristics replicating the original work of Babor et al. (1992a,b). Compared with the Type A subgroup, Type B subjects were more severe on several clinical dimensions including a younger age of onset of alcoholism, greater amount and years of drinking, and greater psychopathology and psychosocial impairment. This dichotomization of participants into more vs. less severe groups is entirely consistent with the large-scale analyses of the A/B typology of alcohol-dependent samples from the Collaborative Study on the Genetics of Alcoholism cohort (Schuckit et al., 1995) as well as the Apollonian/Dionysian dichotomy of a general U.S. population sample (Carpenter and Hasin, 2001). Our approach of examining the treatment outcomes based upon a *post hoc* Type A/B dichotomy also replicates the findings of other investigators (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 1993, 1995, 1996; Pettinati et al., 2000, 2001), who reanalyzed previously published clinical trial data after their initial planned analysis of the trial and found Type A/B-related differences in response to treatment with SSRIs. However, the current study extends these findings by comparing the baseline characteristics and treatment outcome data for two typological classification schemes — namely age of onset and Type A/B. Interestingly, we found reasonably good homology (approximately 70%) between the multidimensional Type A/B clusters and an EOA/LOA classification based solely upon the age of onset of problem drinking. As reported previously by others (Babor et al., 1992a,b; Schuckit et al., 1995), we found that the Type B cluster included predominately a majority of subjects having an early age of onset (≤25 years; i.e., EOA subjects) and the Type A cluster included a majority of those with a later age of onset (≥26 years; i.e., LOA subjects).

It is noteworthy that the Type A/B subjects who were discordant with their age-of-onset classification (i.e., EOA/Type A subjects or LOA/Type B subjects) clearly had the clinical characteristics of the A- and B-like clusters to which they were assigned. That is, the minority

of EOA subjects who were classified within the Type A cluster had Type A-like baseline characteristics and did not differ from the majority of LOA subjects within the Type A cluster. Likewise, the minority of LOA subjects who were classified within the Type B cluster exhibited Type B-like baseline characteristics similar to the majority of EOA subjects within that cluster. Thus, Type A/B was a better discriminator of alcohol dependence severity than was age of onset. Although age of onset is correlated with many of the measures used for Type A/B clustering, the multidimensional use of drinking measures, psychosocial disruption, and psychiatric disturbance undoubtedly explain the severity-discriminating power of this typology. Even though age of onset was an important contributing item to the A/B clustering in the current analyses, it was not as strong a contributor as the POMS-depression and POMS-tension-anxiety factors or the MAST scores. Whereas the single dimension of age of onset showed 70% concordance with the A/B clusters, there was discordance such that some EOA subjects did not show the severity of disorder common with the Type B cluster. This is consistent with the findings of Schuckit et al. (1995), who described a minority of more severe (Type B) and a majority of less severe (Type A) cluster groupings within the subgroup of LOA alcohol-dependent subjects, all of whom were selected because of their late age of onset (≥25 years). Although one small pilot study (Kampman et al., 2007) attempted to use only a few items (including age of onset) for Type A/B classification on an *a priori* basis, future research should seek to identify the relative importance of age of onset vs. other severity measures to classify clinically meaningful subtypes of alcoholism.

A key finding of the current study was that beneficial effects of ondansetron as a treatment for alcohol dependence were only observed in subjects classified as having EOA, and we confirmed the hypothesis that ondansetron also was effective in patients classified within the Type B cluster. In contrast, there was no benefit of ondansetron and even evidence of increased drinking among LOA or Type A subjects. Interestingly, the EOA/LOA subgrouping appeared to do a better job of predicting ondansetron treatment response than did the Type A/B classification. This was observed through several findings. First, ondansetron doses were more often detected as superior to placebo at reducing alcohol intake in subjects classified as having EOA than in those classified as Type B. Second, among EOA subjects, Type A/B subgrouping did not appear to alter the ondansetron response. Third, with only one exception (i.e., LOA-Type B for the drinks per drinking day measure), ondansetron was efficacious among Type B subjects only if they had EOA but not if they had LOA. Finally, ondansetron was never found to be superior to placebo in either the LOA or Type A subgroup. Thus, ondansetron was effective in EOA subjects regardless of A/B typology and ondansetron was ineffective in LOA subjects regardless of A/B typology. Therefore, it is reasonable to suggest that the beneficial effects of ondansetron are associated with EOA and that those seen in the Type B subjects were due primarily to the homology between EOA and Type B (i.e., 72% of the Type B subjects had EOA).

The finding of benefits from a 5-HT_3 antagonist among Type B subjects is in stark contrast to previous reports (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 1996) that the drinking among Type B subjects was made worse by treatment with an SSRI. Each of those reports was a reanalysis of clinical trial data that were originally negative as a whole, but the reanalysis showed that Type B typology predicted a poor treatment response with SSRIs. Chick et al. (2004) further showed that while fluvoxamine worsened the condition of subjects classified as Type II, separate classification by age of onset of regular drinking (≤25 years) actually was more predictive of the harmful effects of fluvoxamine than Type I/II typology. Those findings, plus our own, suggest that the differential treatment response to selective serotonergic agents may be predicted better by age of onset of problem drinking than by other multidimensional clustering methods such as Type A/B typologies. Although it has not been replicated, one study suggested that Type A alcoholics may benefit from SSRI treatment (Pettinati et al., 2000). However, in that study, age of onset of regular intoxication did not predict differential sertraline

efficacy as well as Type A/B classification (Pettinati et al., 2000). Overall, these results argue powerfully that there are likely to be differences in serotonin biology among different typological clusters of alcoholics such that the more severe group (i.e., Type B or EOA subjects) may benefit from a 5-HT_3 antagonist but harmed by an SSRI whereas Type A or LOA subjects may benefit from an SSRI but possibly increase drinking with ondansetron relative to placebo.

The neurobiological basis for why 5-HT_3 antagonists may help EOA/Type B subjects but SSRIs may harm this same group is not known. These observations seem paradoxical to conventional thinking that EOA might be associated with a low serotonin syndrome (Johnson, 2000, 2004; Johnson and Ait-Daoud, 2000; LeMarquand et al., 1994). EOA subjects have been reported to have lower cerebrospinal fluid levels of 5-hydroxyindoleacetic acid than LOA subjects, and this effect was particularly clear in those with a family history of alcoholism (Fils-Aime et al., 1996). Reduced plasma ratios of tryptophan to other neutral amino acids also have been related to alcoholism in general (Branchey et al., 1981) and to earlier age of onset more specifically (Buydens-Branchey et al., 1989; Swann et al., 1999). Those studies found that alcoholics with the most reduced tryptophan ratios also had the greatest problems with aggression and depression. This ties together the affect and impulse control problems associated with EOA with a large body of literature on the role of reduced serotonin function in the comorbid symptoms of depression and impulse control problems (Buydens-Branchey et al., 1989; Linnoila, 1997; Linnoila and Virkkunen, 1992, 1994; Linnoila et al., 1993; Virkkunen and Linnoila, 1990). Reduced serotonin function also is associated with impulsive aggression and excessive alcohol intake in monkeys (Heinz et al., 1998). Thus, it is not clear how an SSRI exacerbates, whereas a serotonin antagonist reduces, the drinking of alcohol-dependent patients with low serotonin (i.e., the EOA subjects). Our working hypothesis is that the differential treatment response to selective serotonergic agents among the alcoholism subtypes may be due to differences in the synaptic activity of serotonin, which may be compensatory post-synaptic neuroadaptations in response to alcohol. These differences in synaptic serotonin activity may be related to genetic polymorphisms in the serotonin transporter or related to differences in the way in which alcohol affects or interacts with serotonergic systems. For example, alcohol's effects on brain reward mechanisms are mediated in part by 5-HT_3 receptors (McBride and Li, 1998), whereby ondansetron may block up-regulated post-synaptic 5-HT_3 receptors (Johnson, 2004) while SSRIs could worsen drinking by inducing their rapid desensitization (Johnson, 2000). Also, we have reported recently that down-regulation of the serotonin transporter among alcohol-dependent subjects may be related to years of drinking among subjects carrying the long (L) allelic polymorphism of the serotonin transporter (Johnson et al., 2008).

A significant limitation of our comparative analysis is the *post hoc* nature of subdividing groups into small-sample-size cells (i.e., the 2 × 2 × 4 design illustrated in Fig. 2). However, other investigators have done the same (Chick et al., 2004;Kranzler et al., 1996;Pettinati et al., 2000) and have generated replicable findings with SSRIs. Notably, our results are both internally consistent with respect to ondansetron dose and externally consistent with the hypothesis that EOA/Type B subjects show evidence of a serotonergic abnormality that makes them adversely susceptible to SSRIs but able to gain benefit from treatment with a 5-HT_3 antagonist. While the sample sizes of individual ondansetron dose levels within the four classification subgroups (i.e., the factorial combinations of age of onset × A/B typology) were small, we were fortunate that the stratified randomization of ondansetron into age-of-onset groups coupled with the dichotomization of the Type A/B subgroups resulted in relatively balanced sample sizes. The consistency of ondansetron dose relationships and uniformity of positive findings of ondansetron for three different drinking measures (i.e., drinks per day, drinks per drinking day, and percent days abstinent) only in the EOA subjects are quite remarkable and not likely to be due to either false positive results in the minority of Type A

subjects who had EOA or false negative results in the majority of LOA subjects who were Type A.

In conclusion, our findings add support for the importance of subtyping alcohol-dependent individuals before pharmacotherapy with selective serotonergic agents. Clearly, our findings continue to demonstrate that ondansetron (4 μg/kg twice daily) is an efficacious agent for the treatment of EOA (or Type B alcohol dependence). When combined with previous studies showing that this same group of individuals (i.e., those with EOA, Type B, or Type II) may increase their drinking when given an SSRI (Chick et al., 2004; Dundon et al., 2004; Kranzler et al., 1993, 1995, 1996; Pettinati et al., 2000, 2001), it becomes all the more essential for treatment practitioners to recognize the importance of subtyping alcoholics before treatment. This is important clinically because of the widespread prescription of SSRIs with relatively little evidence for efficacy (Mark et al., 2003) for many mental disorders where alcohol dependence is comorbid. Type A/B classification appears to be an excellent method of classifying subtypes that differ in the severity of alcohol dependence. Although Type B clearly is associated with an early age of onset of alcoholism, our findings lead us to speculate that the early age of onset may be more importantly associated with neurobiological differences in serotonin synaptic activity underlying the differences in subtypes of alcohol-dependent individuals. Obviously, there is much need for additional research into the molecular neurobiology and environmental interaction of individual differences associated with differential response in pharmacotherapy trials. Understanding and harnessing such differences could pave the way toward pharmacogenetic treatments where specific serotonergic medications are given to individuals of the distinct neurobiological condition to which they will respond best. Although we hope for a laboratory measure that someday could test the serotonergic vulnerability factor, we suggest that age of onset appears to be the best and easiest prognostic indicator of serotonergic treatment response to date.

Acknowledgments

We are grateful to the National Institute on Alcohol Abuse and Alcoholism for its support of B. A. Johnson through Grant 7 R01 AA010522-12. We also thank Robert H. Cormier, Jr., BA, for his assistance with manuscript preparation.

REFERENCES

Achenbach TM, Edelbrock CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. Monogr Soc Res Child Dev 1981;46:1–82. [PubMed: 7242540]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. Revised 3rd ed.. Washington, DC: American Psychiatric Association; 1987.

Babor TF, Dolinsky ZS, Meyer RE, Hesselbrock M, Hofmann M, Tennen H. Types of alcoholics: concurrent and predictive validity of some common classification schemes. Br J Addict 1992a; 87:1415–1431. [PubMed: 1330126]

Babor TF, Hofmann M, DelBoca FK, Hesselbrock V, Meyer RE, Dolinsky ZS, Rounsaville B. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry 1992b;49:599–608. [PubMed: 1637250]

Bowman KM, Jellinek EM. Alcohol addiction and its treatment. Q J Stud Alcohol 1941:98–176.

Branchey L, Shaw S, Lieber CS. Ethanol impairs tryptophan transport into the brain and depresses serotonin. Life Sci 1981;29:2751–2755. [PubMed: 7329204]

Buss AH, Durkee A. An inventory for assessing different kinds of hostility. J Consult Psychol 1957;21:343–349. [PubMed: 13463189]

Buydens-Branchey L, Branchey MH, Noumair D, Lieber CS. Age of alcoholism onset. II. Relationship to susceptibility to serotonin precursor availability. Arch Gen Psychiatry 1989;46:231–236. [PubMed: 2919952]

Carpenter KM, Hasin DS. Reliability and discriminant validity of the Type I/II and Type A/B alcoholic subtype classifications in untreated problem drinkers: a test of the Apollonian–Dionysian hypothesis. Drug Alcohol Depend 2001;63:51–67. [PubMed: 11297831]

Chick J, Aschauer H, Hornik K. Investigators' Group. Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. Drug Alcohol Depend 2004;74:61–70. [PubMed: 15072808]

Cloninger CR. A systematic method for clinical description and classification of personality variants: a proposal. Arch Gen Psychiatry 1987a;44:573–588. [PubMed: 3579504]

Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 1987b;236:410–416. [PubMed: 2882604]

Dundon W, Lynch KG, Pettinati HM, Lipkin C. Treatment outcomes in type A and B alcohol dependence 6 months after serotonergic pharmacotherapy. Alcohol Clin Exp Res 2004;28:1065–1073. [PubMed: 15252293]

Fils-Aime ML, Eckardt MJ, George DT, Brown GL, Mefford I, Linnoila M. Early-onset alcoholics have lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. Arch Gen Psychiatry 1996;53:211–216. [PubMed: 8611057]

Fleiss, JL. Statistical Methods for Rates and Proportions. Vol. 2nd ed.. New York: John Wiley; 1981.

George DT, Rawlings R, Eckardt MJ, Phillips MJ, Shoaf SE, Linnoila M. Buspirone treatment of alcoholism: age of onset, and cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid concentrations, but not medication treatment, predict return to drinking. Alcohol Clin Exp Res 1999;23:272–278. [PubMed: 10069556]

Heinz A, Higley JD, Gorey JG, Saunders RC, Jones DW, Hommer D, Zajicek K, Suomi SJ, Lesch KP, Weinberger DR, Linnoila M. In vivo association between alcohol intoxication, aggression, and serotonin transporter availability in nonhuman primates. Am J Psychiatry 1998;155:1023–1028. [PubMed: 9699688]

Jellinek EM. Alcoholism, a genus and some of its species. Can Med Assoc J 1960;83:1341–1345. [PubMed: 13789799]

Johnson BA. Serotonergic agents and alcoholism treatment: rebirth of the subtype concept—an hypothesis. Alcohol Clin Exp Res 2000;24:1597–1601. [PubMed: 11045870]

Johnson BA. Role of the serotonergic system in the neurobiology of alcoholism: implications for treatment. CNS Drugs 2004;18:1105–1118. [PubMed: 15581381]

Johnson BA, Ait-Daoud N. Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Psychopharmacology 2000;149:327–344. [PubMed: 10867960]

Johnson BA, Ait-Daoud N, Prihoda TJ. Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: from hypotheses to preliminary clinical evidence. Alcohol Clin Exp Res 2000a;24:737–742. [PubMed: 10832917]

Johnson BA, Cloninger CR, Roache JD, Bordnick PS, Ruiz P. Age of onset as a discriminator between alcoholic subtypes in a treatment-seeking outpatient population. Am J Addict 2000b;9:17–27. [PubMed: 10914290]

Johnson BA, Javors MA, Roache JD, Seneviratne C, Bergeson SE, Ait-Daoud N, Dawes MA, Ma JZ. Can serotonin transporter genotype predict serotonergic function, chronicity, and severity of drinking? Prog Neuropsychopharmacol Biol Psychiatry 2008;32:209–216. [PubMed: 17950969]

Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Bordnick PS, Ait-Daoud N, Hensler J. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 2000c;284:963–971. [PubMed: 10944641]

Kampman KM, Pettinati HM, Lynch KG, Whittingham T, Macfadden W, Dackis C, Tirado C, Oslin DW, Sparkman T, O'Brien CP. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of Type A and Type B alcoholism. J Clin Psychopharmacol 2007;27:344–351. [PubMed: 17632217]

Kranzler HR, Del Boca F, Korner P, Brown J. Adverse effects limit the usefulness of fluvoxamine for the treatment of alcoholism. J Subst Abuse Treat 1993;10:283–287. [PubMed: 8315702]

Kranzler HR, Burleson JA, Brown J, Babor TF. Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. Alcohol Clin Exp Res 1996;20:1534–1541. [PubMed: 8986200]

Kranzler HR, Pierucci-Lagha A, Feinn R, Hernandez-Avila C. Effects of ondansetron in early- versus late-onset alcoholics: a prospective, open-label study. Alcohol Clin Exp Res 2003;27:1150–1155. [PubMed: 12878921]

Kranzler HR, Burleson JA, Korner P, Del Boca FK, Bohn MJ, Brown J, Liebowitz N. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 1995;152:391–397. [PubMed: 7864265]

LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: clinical evidence. Biol Psychiatry 1994;36:326–337. [PubMed: 7993959]

Linnoila, M. Handbook of Antisocial Behavior. New York: John Wiley & Sons; 1997.

Linnoila M, Virkkunen M. Biologic correlates of suicidal risk and aggressive behavioral traits. J Clin Psychopharmacol 1992;12:19S–20S. [PubMed: 1374432]

Linnoila, M.; Virkkunen, M. Psychopharmacology of depression. In: Montgomery, SA., editor. British Association for Psychopharmacology Monograph. Oxford, United Kingdom: Oxford University Press; 1994. p. 170-184.

Linnoila M, Virkkunen M, George T, Higley D. Impulse control disorders. Int Clin Psychopharmacol 1993;8:53–56. [PubMed: 7504705]

MacAndrew C. The differentiation of male alcoholic outpatients from non-alcoholic psychiatric outpatients by means of the MMPI. Q J Stud Alcohol 1965;26:238–246. [PubMed: 14320345]

Mark TL, Kranzler HR, Song X, Bransberger P, Poole VH, Crosse S. Physicians' opinions about medications to treat alcoholism. Addiction 2003;98:617–626. [PubMed: 12751979]

McBride WJ, Li TK. Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol 1998;12:339–369. [PubMed: 10348615]

McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients: The Addiction Severity Index. J Nerv Ment Dis 1980;168:26–33. [PubMed: 7351540]

McNair, DM.; Lorr, M.; Droppleman, LF. Manual of the Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service; 1971.

Miller, WR.; Marlatt, GA. Manual for the Comprehensive Drinker Profile. Odessa, FL: Psychological Assessment Resources; 1984.

Miller WR, Del Boca FK. Measurement of drinking behavior using the Form 90 family of instruments. J Stud Alcohol Suppl 1994;12:112–118. [PubMed: 7722987]

Naranjo CA, Sellers EM, Kaplan HL, Hamilton C, Khouw V. Acute kinetic and dynamic interactions of zimelidine with ethanol. Clin Pharmacol Ther 1984;36:654–660. [PubMed: 6237836]

Naranjo CA, Kadlec KE, Sanhueza P, Woodley-Remus D, Sellers EM. Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther 1990;47:490–498. [PubMed: 2328557]

Naranjo CA, Sellers EM, Sullivan JT, Woodley DV, Kadlec K, Sykora K. The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther 1987;41:266–274. [PubMed: 3469057]

Naranjo CA, Sullivan JT, Kadlec KE, Woodley-Remus DV, Kennedy G, Sellers EM. Differential effects of viqualine on alcohol intake and other consummatory behaviors. Clin Pharmacol Ther 1989;46:301–309. [PubMed: 2673621]

Pettinati HM. The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. J Clin Psychiatry 2001;62:26–31. [PubMed: 11584872]

Pettinati HM, Volpicelli JR, Kranzler HR, Luck G, Rukstalis MR, Cnaan A. Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res 2000;24:1041–1049. [PubMed: 10924008]

Pettinati HM, Volpicelli JR, Luck G, Kranzler HR, Rukstalis MR, Cnaan A. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol 2001;21:143–153. [PubMed: 11270910]

Schuckit MA, Tipp JE, Smith TL, Shapiro E, Hesselbrock VM, Bucholz KK, Reich T, Nurnberger JI Jr. An evaluation of type A and B alcoholics. Addiction 1995;90:1189–1203. [PubMed: 7580817]

Selzer ML. The Michigan alcoholism screening test: the quest for a new diagnostic instrument. Am J Psychiatry 1971;127:1653–1658. [PubMed: 5565851]

Sobell, LC.; Sobell, MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten, RZ.; Allen, JP., editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Totowa, NJ: Humana Press Inc; 1992. p. 41-72.

Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49:624–629. [PubMed: 1637252]

Swann AC, Johnson BA, Cloninger CR, Chen YR. Relationships of plasma tryptophan availability to course of illness and clinical features of alcoholism: a preliminary study. Psychopharmacology 1999;143:380–384. [PubMed: 10367555]

Tyrer, P. Personality disorder and social functioning. In: Peck, DF.; Shapiro, CM., editors. Measuring Human Problems: A Practical Guide. Chichester, United Kingdom: John Wiley & Sons; 1990. p. 119-142.

Virkkunen M, Linnoila M. Serotonin in early onset, male alcoholics with violent behaviour. Ann Med 1990;22:327–331. [PubMed: 2291840]

Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, Howes MJ, Kane J, Pope HGJ, Rounsaville B, et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Arch Gen Psychiatry 1992;49:630–636. [PubMed: 1637253]

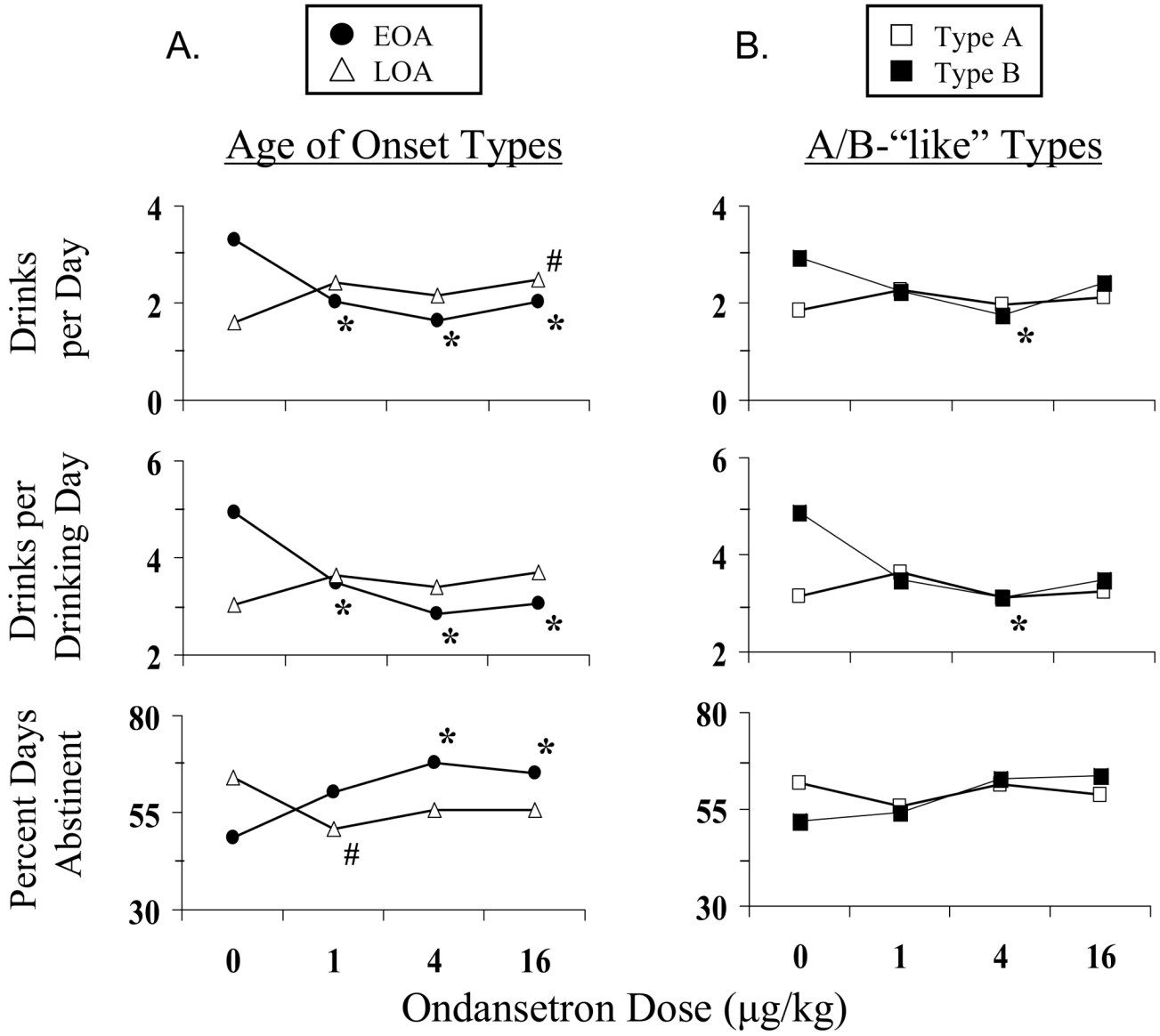

Figure 1.

Endpoint mean outcome drinking measures (drinks per day, drinks per drinking day, and percent days abstinent) observed for different ondansetron doses (A) when subjects were classified by age of onset [early-onset alcoholism (EOA) vs. late-onset alcoholism (LOA)] and (B) when subjects were clustered by Type A vs. Type B. Sample sizes for the 0-, 1-, 4-, and 16-µg/kg doses of ondansetron were 34, 35, 38, and 32, respectively, among the LOA subjects; 22, 32, 39, and 39, respectively, among the EOA subjects; 36, 37, 47, and 39, respectively, among the Type A subjects, and 20, 30, 30, and 32, respectively, among the Type B subjects. *Significantly less drinking than placebo ($p < 0.05$, Dunnett's *t*-test). #Significantly more drinking than placebo ($p < 0.05$, Dunnett's *t*-test).

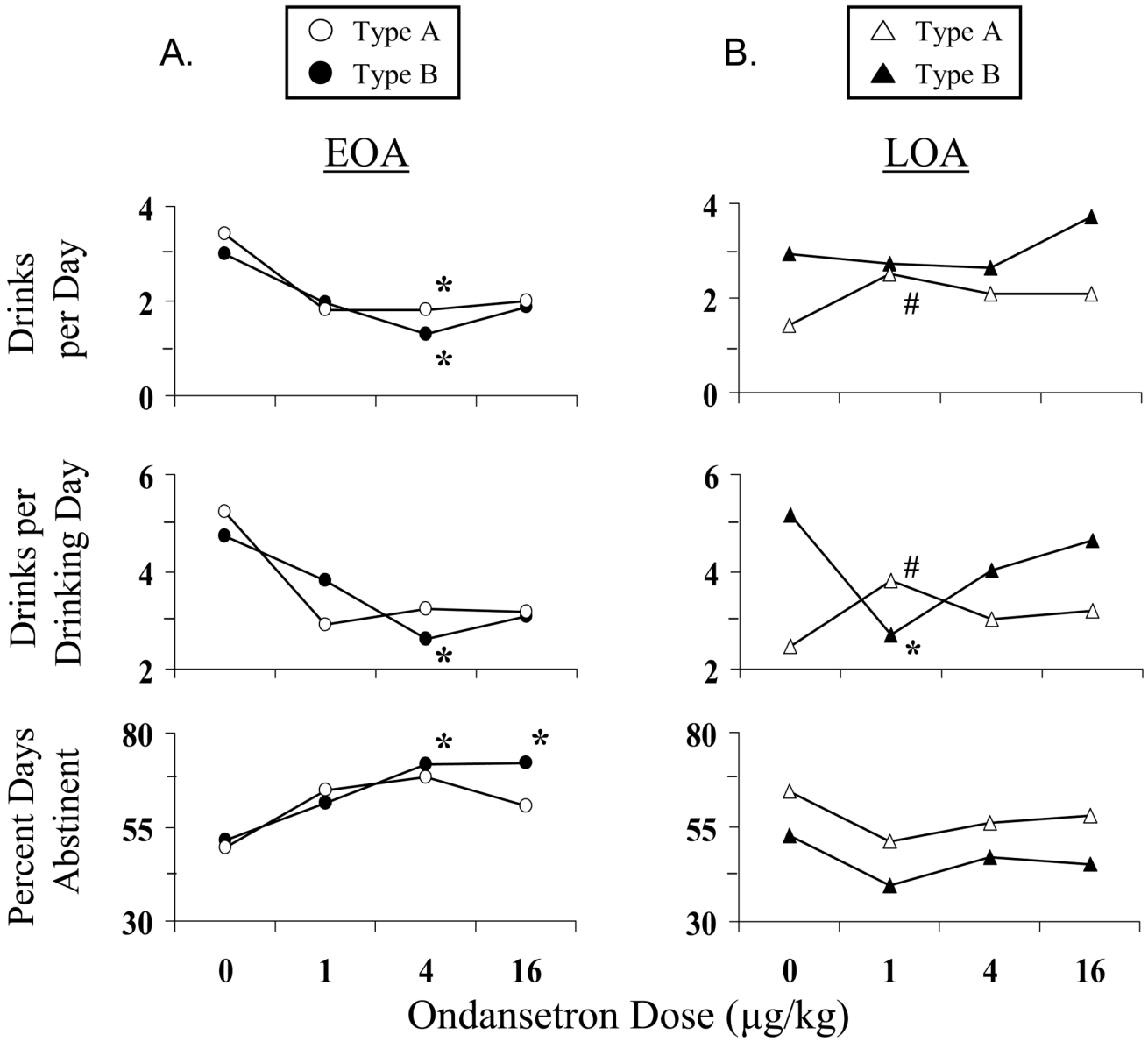

Figure 2.

Endpoint mean outcome drinking measures (drinks per day, drinks per drinking day, and percent days abstinent) observed for different ondansetron doses (A) when early-onset alcoholism (EOA) subjects were subdivided into Type A vs. Type B clusters and (B) when late-onset alcoholism (LOA) subjects were subdivided into Type A vs. Type B clusters. Sample sizes for the 0-, 1-, 4-, and 16-µg/kg doses of ondansetron were EOA-Type A = 10, 9, 18, and 16, respectively; EOA-Type B = 12, 23, 21, and 23, respectively; LOA-Type A = 26, 28, 29, and 23, respectively, and LOA-Type B = 8, 7, 9, and 9, respectively. *Significantly less drinking than placebo ($p < 0.05$, Dunnett's *t*-test). Significantly more drinking than placebo ($p < 0.05$, Dunnett's *t*-test).

Table 1

Items Used in the Development of Type A/B Clusters

Item	Current Study Assessment Used	Original Measure of Babor et al. (1992a,b)	Alcohol-Related Behavior Dimension
1	Total weighted MAST score	Total weighted MAST score	Lifetime severity
2	Years of heavy drinking	Years of heavy drinking	Years of heavy drinking
3	Child Behavior Checklist	Childhood Behavior Checklist	Childhood disorder
4	MacAndrew Alcoholism Scale	MacAndrew Alcoholism Scale	"Bipolar character" dimension
5	Age of onset of problem drinking (question B28 of the Comprehensive Drinker Profile)	Age at onset of: first regular drinking, getting drunk regularly, heaviest drinking, and diagnosis of alcoholism	Age of onset of problem drinking
6	Percentage with alcoholic first-degree relatives by family history (DSM-III-R)	Percentage who have first-degree relatives with a "serious alcohol problem" by family history	Familial alcoholism
7	Average standard drinks per day (Form 90 interview, 90-day TLFB method)	Average daily alcohol consumption in 6 months before treatment	Ounces of alcohol consumed per day
8	POMS-depression score	Number of depressive symptoms from the DIS	Depressive symptoms
9	POMS-tension-anxiety score	Total score on the Taylor Manifest Anxiety Scale from the Minnesota Multiphasic Personality Inventory	Anxiety severity
10	Percentage with DSM-III-R diagnosis of antisocial personality disorder	Number of antisocial personality disorder symptoms from the DIS	Antisocial personality disorder symptoms
11	ASI-medical	84-item index of alcohol-related conditions from Cornell Medical Index and "other sources"	Medical conditions
12	ASI-treatment	Symptoms of dependence experienced in last 6 months	Dependence syndrome
13 14	ASI-family/social Social Functioning Questionnaire	5-item scale of frequency of alcohol-related social problems during last 6 months	Social consequences
15 16	ASI-employment ASI-legal	5-item scale of frequency of alcohol-related physical consequences during last 6 months	Physical consequences
		5-point Likert scale of frequency of benzodiazepine use in last 6 months	Benzodiazepine use
		6-item scale to rate salience of "relief drinking"	Relief drinking
17 18 19	Buss-Durkee Inventory-assault Buss-Durkee Inventory-indirect hostility Buss-Durkee Inventory-verbal hostility		

MAST, Michigan Alcoholism Screening Test; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, Revised Third Edition (American Psychiatric Association, 1987); TLFB, timeline follow-back; POMS, Profile of Mood States; DIS, Diagnostic Interview Schedule; ASI, Addiction Severity Index.

Table 2

Baseline Characteristics of Type A/B and Age-of-Onset Groups

	Type B (n = 141)		Type A (n = 180)	
Variables	**EOA (n = 102)**	**LOA (n = 39)**	**EOA (n = 59)**	**LOA (n = 121)**
Gender, number (%)			[a]	
Male	77 (75.5)	26 (66.7)	47 (79.7)	76 (62.8)
Female	25 (24.5)	13 (33.3)	12 (20.3)	45 (37.2)
Current age (yr)	36.7 [a]	44.6	38.0 [a]	43.8
Ethnicity, number (%)				
White	70 (68.6)	29 (74.4)	39 (66.1)	90 (74.4)
Black	17 (16.7)	7 (18.0)	13 (22.0)	20 (16.5)
Hispanic	15 (14.7)	3 (7.7)	7 (11.9)	11 (9.1)
Social class, number (%)	[b]			
1–3	30 (29.4)	18 (46.2)	31 (52.5)	71 (58.7)
4–6	60 (58.8)	16 (41.0)	22 (32.8)	42 (34.7)
7–9	11 (10.8)	5 (12.8)	6 (10.2)	8 (6.6)
None	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drinking measures				
Form-90 drinks/day	9.0	10.0 [b]	7.6	6.8
Week-1 drinks/day	5.0	7.0 [b]	4.4	3.8
Week-1 drinks/drinking day	6.4	8.1 [b]	5.8	4.7
Week-1 percent days abstinent	45.9 [a]	23.7	35.2	32.1
Age of onset (yr)	19.6 [a,b]	32.2 [b]	20.8 [a]	35.0
Years of heavy drinking (yr)	17.1 [a]	12.5 [b]	17.2 [a]	8.9
Family history				
Percentage with alcoholic father	44.9	38.5	42.9	38.5
Percentage with alcoholic parents	51.5	46.2	47.4	46.2
Percentage with antisocial personality disorder diagnosis	24.51	10.3	5.1 [b]	8.3
ASI scores				
Medical	0.2 [b]	0.2	0.0 [a]	0.1
Employment	0.4 [b]	0.4 [b]	0.3	0.2
Legal	0.1 [b]	0.1	0.0	0.0

	Type B (n = 141)		Type A (n = 180)	
Variables	**EOA (n = 102)**	**LOA (n = 39)**	**EOA (n = 59)**	**LOA (n = 121)**
Family/social	0.4 [a,b]	0.3	0.3	0.3
Treatment	3.8 [b]	3.6	3.0 [a]	3.7
Psychiatric status	0.3 [a,b]	0.2	0.1	0.2
Weighted Michigan Alcoholism Screening Test score	36.0 [b]	36.0 [b]	22.0	20.6
MacAndrew Alcoholism Scale	26.7 [b]	27.2 [b]	20.9	22.3
Social Functioning Questionnaire	0.6 [b]	0.9 [b]	3.2	2.6
Child Behavior Checklist	13.1 [b]	13.0 [b]	8.7	7.5
Buss-Durkee Inventory subscales				
Assault	4.2 [b]	4.7 [b]	3.0	2.9
Indirect hostility	5.0 [b]	5.3 [b]	3.8	4.1
Irritability	5.9 [b]	6.2 [b]	3.6	4.1
Negativism	2.2	2.5 [b]	1.9	1.8
Resentment	3.9 [b]	3.5 [b]	2.0	2.2
Suspicion	3.9 [b]	3.4 [b]	2.5	2.6
Verbal hostility	7.3 [b]	7.3 [b]	5.6	6.0
Buss-Durkee Inventory-total	32.4 [b]	32.8 [b]	22.4	23.8
Profile of Mood States subscales				
Depression	25.6 [b]	26.7 [b]	7.1	8.8
Tension-anxiety	15.0 [b]	14.4 [b]	7.3	8.3
Confusion-bewilderment	11.6 [b]	11.3 [b]	5.3	5.5
Fatigue	11.9 [b]	10.4 [b]	5.0	5.2
Vigor	11.9 [b]	11.7 [b]	16.1	16.1
Friendliness	14.0 [b]	13.6 [b]	16.7	16.2
Anger-hostility	14.5 [b]	12.9 [b]	5.0	6.0
Profile of Mood States-total	116.0 [b]	115.5 [b]	57.1	64.9
Temperament and Character Inventory subscales				
Novelty seeking	22.1	22.8 [b]	20.8	20.6
Harm avoidance	17.6 [b]	17.9 [b]	12.8	12.8
Reward dependence	14.7	15.1	15.5	15.2
Persistence	4.8	4.6	5.3	4.8

Variables	Type B (n = 141)		Type A (n = 180)	
	EOA (n = 102)	LOA (n = 39)	EOA (n = 59)	LOA (n = 121)
Self-directedness	24.8 [b]	22.7 [b]	32.6	30.5
Cooperativeness	31.5 [b]	33.6	35.3	33.8
Self-transcendence	15.1	14.8	14.7	14.1

EOA, early-onset alcoholism; LOA, late-onset alcoholism.

[a] EOA is different from LOA ($p < 0.05$) within Type A or B cluster.

[b] Type B is different from Type A ($p < 0.05$) within EOA or LOA classification.