

## ORIGINAL ARTICLE

# Serbian and Austrian Alcohol-Dependent Patients: A Comparison of Two Samples Regarding Therapeutically Relevant Clinical Features

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(Received 2 December 2012; first review notified 2 January 2013; in revised form 18 January 2013; accepted 31 January 2013)

**Abstract** — **Aims:** To support the Serbian Expert Board in setting up reimbursement for modern pharmacotherapeutic support, we compared a Serbian sample of alcohol-dependent patients with an Austrian sample, in order to detect differences that might inhibit the introduction of anti-craving medications in Serbia. **Methods:** One hundred and twenty-seven (116 males) alcohol-dependent patients in Serbia and 136 in Austria (78 males) were enrolled consecutively from January 2011 to March 2012 and were assessed using the Lesch alcoholism typology instrument (LAT). **Results:** Age of onset was slightly higher in the Austrian sample (28.5 vs 30.0;  $P=0.10$ ). The Serbian sample showed a higher rate of anxiety disorders than the Austrian sample (89.8 vs 26.5%,  $P\leq 0.0001$ ). Suicidal tendencies, independent of alcohol intake or withdrawal syndrome, were higher in the Austrian sample (1.6 vs 13.2%  $P\leq 0.0001$ ). There was no difference between the two samples in Lesch-Type IV (26 vs 28); there was a slight excess in the Serbian sample of Type I (15 vs 10). In Austria, significantly more Type II patients (32 vs 52) had been included, while the Serbian sample comprised significantly more Type III patients. **Conclusions:** Austrian and Serbian patients are quite similar, without any showing any factor that would detract from the potential value of modern anti-craving medications in Serbia. The differences in anxiety disorders might be due to the 1990s war and should be investigated further.

## INTRODUCTION

Past decades have advanced the recognition and treatment of alcohol dependence (Johnson, 2010; Lesch *et al.*, 2011). Keeping in mind the diversity of clinical manifestations of the disease, the issue of reliable and distinctive subtypes responsive to different pharmaceutical treatments has been discussed over the last 100 years. Maisel *et al.* (2012) reviewed the studies of acamprosate and naltrexone in relation to patient subgroups, and outcome definitions. Age of onset of the problematic drinking, family history of alcohol dependence and typology (Cloninger *et al.*, 1981; Lesch, 1991; Babor *et al.*, 1992) have been found to be relevant in prescribing pharmaceutical treatment with anti-craving medication (e.g. acamprosate appears to be more effective in Lesch-Type 1 and 2, and naltrexone in Lesch-Type 3 and 4; Kiefer, 2005; Leggio *et al.*, 2009).

Perhaps due to culturally based differences in drinking habits, as well as diversity of approaches in Southern European countries, differences can be seen between Northern and Southern European treatment approaches. In Austria, a central European high-income country, specific inpatient and outpatient treatment programs according to subgroups of alcohol dependence have emerged. Serbia, a South-Eastern European post-socialist upper-middle-income country that experienced severe burdens in recent decades, is developing treatment approaches to meeting the heterogeneity of patients and improve outcomes.

Since 1956, alcohol dependence has been recognized as a psychiatric disease, and indeed many conceive of it as a chronic brain disease with a relapsing course. The diagnostic definitions in ICD-10 and DSM-IV are fairly consistent with each other, but neither gives a lead to help treatment

decisions. For treatment, we have to take into account that the patients come from different backgrounds, with different precipitants and different social problems that led to their excessive drinking and, sometimes, to dependence. To address these problems of heterogeneity, the Lesch alcoholism typology (LAT) was introduced in 1991. This instrument assesses items of major importance for the course and treatment of alcohol dependence, including age of onset, family history, co-morbidity, alcohol-related disabilities and the Lesch typology itself (in 11 questions to be filled in). In brief, Lesch defines four types. Type I ('allergy model') are mainly physiologically dependent patients drinking to treat withdrawal symptoms. Type II ('anxiety or conflict model') use alcohol to treat anxiety symptoms. In Type III ('depression model') patients enhance mood and treat depression with alcohol. In Type IV ('adaptation model') patients show pre-morbid cerebral defects that make it difficult to resist social drinking pressure. The LAT has been validated in various countries, especially for pharmacological treatment of withdrawal and relapse prevention (Lesch and Walter, 1996; Bleich *et al.*, 2004; Kiefer, 2005; Leggio *et al.*, 2009; Lesch *et al.*, 2011).

## TREATMENT APPROACHES IN SERBIA

According to World Health Statistics (World Health Organization, 2011a,b), the drinking pattern in Serbia has been scored 3 on a scale of 1–5, where 5 represents the most risky drinking pattern. Among Serbian adolescents, 97.4% consumed alcohol beverages, with 34.9% having the first experience with alcohol at age 14 or earlier (Djordjevic *et al.*, 2011).

Due to wide social tolerance toward alcohol abuse and dependence in the Balkans, alcohol dependence is not yet popularly recognized as a medical condition requiring treatment. It may take years before patients are motivated to seek treatment. Also, Serbian national spending on basic and clinical research and reimbursement of drugs in this field is very modest compared with the EU average (Jovanovic and Jakovljevic, 2011).

Treatment approaches for diagnosed alcohol addiction in Serbia is multidimensional with an array of health care professionals of different backgrounds. After diagnostic exploration, psychotherapeutic techniques are applied: individual and group therapy, community-based sociotherapy, which includes family therapy and self-help groups.

Drugs marketed for the treatment of alcohol dependence in Serbia are disulfiram, naltrexone and acamprosate. Choice of medication depends on physical co-morbidities, mainly liver function, temperament, typology and patients' motivation (Spanagel and Kiefer, 2008; Vyssoki *et al.*, 2010).

Naltrexone and acamprosate are not reimbursed, which limits their use. Alcoholism impacts on overall family gross income and its relationship to poverty in developing societies is well documented (Cerde *et al.*, 2010). In particular, in Western Balkans non-EU economies, although salaries are middle-range, there is high unemployment. Thus, motivated patients may be unable to purchase medicines they would need.

District Courts may mandate treatment for some legally prosecuted addicts (Jakovljević *et al.*, 2011). Many alcohol-dependent patients enter the treatment system at an advanced stage of the disease.

## BACKGROUND TO THIS STUDY

The Expert Board on Alcohol and Drug Addiction of the Serbian Ministry of Health hopes to persuade policy makers to reconsider the reimbursement of naltrexone and acamprosate. To support the Board, we investigated a Serbian sample of alcohol-dependent patients to see whether specific treatment subgroups could be defined. In Austria, subgrouping according to LAT is commonly used to individualize anti-craving medication. However, Serbia and Austria exhibit substantial differences not only in health care access and equity (OECD, 2010), but also in religious heritage, urbanization and attitudes to alcoholism (Jakovljević *et al.*, 2011). WHO gives 11.09 ml ethanol per adult per year for Serbia (recorded plus estimated unrecorded) for the year 2005 (Austria: 13.24 ml) [http://www.who.int/substance\\_abuse/publications/global\\_alcohol\\_report/msbgsruprofiles.pdf](http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf).

## PATIENTS AND METHODS

Between January 2011 and March 2012, we investigated consecutively admitted ICD-10 diagnosed alcohol-dependent patients (including some attending for post-admission follow-up) (according to ICD 10) in a psychiatric hospital in Vienna specialized to treat alcohol dependence and in a psychiatry clinic associated with the University Hospital, Kragujevac, Serbia. The main cause of hospitalization in all centers was alcohol dependence. Exclusion criteria were other substance abuse disorders (excluding nicotine dependence); history of other psychiatric disorder; any medical condition that is a

contraindication for the use of acamprosate, naltrexone or disulfiram and severe disorder of liver or kidney, tuberculosis or pneumonia. One hundred and twenty-seven (116 males) patients in Serbia and 136 in Austria (78 males) were enrolled. Of those, 73 (57.5%) Serbs and 37 (27.2%) Austrians were currently hospitalized, which represented repeated admission for 46 (36.2%) Serbs (up to 15 hospitalizations per patient) and 29 (21.3%) Austrians (up to 20 hospitalizations per patient). Alcohol tolerance was observed in 83 (65.4%) and 64 (47.1%) patients from Serbia and Austria, respectively, while 120 Serbs (94.5%) and 76 Austrians (55.9%) had experienced the alcohol withdrawal syndrome. The drinking pattern ranged from constant (76 (59.8%) of Serbs and 50 (36.8%) Austrians) to irregular (21 (16.5%) Serbs and 44 (32.4%) Austrians). At enrollment, only 58 (45.7%) Serbian and 47 (34.6%) Austrian patients had a partner, others being single, divorced or widowed. Information on patients' education level or employment was not recorded. Patients were assessed in Austria with the German version of the LAT and in Serbia the Serbian version of LAT ([www.lat-online.at](http://www.lat-online.at)). All the investigators were trained in the assessment procedure of the LAT. Using this instrument, we concentrated on items important for the treatment with anti-craving substances, such as gender, age of onset, suicidal tendencies, depression, anxiety and Lesch typology.

## Statistics

For normally distributed continuous variables (according to the Kolmogorov–Smirnov test), parametric methods were used (independent samples *t*-test) to calculate the significance of differences.  $\chi^2$ -test was used to calculate the significance of the difference between categorical variables, corrected for  $2 \times 2$  tables by continuity correction. The relationship between Lesch's typology and continuous variables was tested using the Pearson correlation test, and for the relationship between Lesch's typology and categorical variables we used the Spearman correlation test. All the statistical tests were two-sided, and *P*-value < 0.05 was considered significant.

## RESULTS

Table 1 shows what we regarded as the most important variables for anti-craving treatment.

No difference was found between the two samples regarding age. In Austria, significantly more females (7.9 vs 30.1%) had been included. Age of onset of the disease was slightly higher in Austria. The burden of a positive family history of alcohol dependence was high (~50%), but there was no difference between Serbia and Austria.

Affective disorders appear in both samples (15.0 vs 13.2%), but no significant difference was found. However, these data (~14%) suggest that co-morbidity should be further investigated. The Serbian sample showed a very high rate of anxiety disorders, significantly higher than in the Austrian sample (89.8 vs 26.5%). Suicidal tendencies, independent of alcohol intake or withdrawal syndrome, are significantly higher in the Austrian sample (1.6 vs 13.2%). There was no difference in suicidal tendencies under the influence of alcohol or the influence of withdrawal (14.2 vs

Table 1. Alcohol dependence, inter-country comparison of key clinical determinants

Clinical determinants	Serbia (n = 127)	Austria (n = 136)	P
Age (mean ± SD)	47.1 ± 10.39	46.7 ± 11.32	0.79
Gender (male/female)	116/10	78/41	≤0.0001*
Age of onset of alcohol dependence (mean ± SD)	28.48 ± 7.67	29.98 ± 13.44	0.10
Family positive history of alcohol dependence among first-order relatives	62	57	0.59
Co-morbidity of affective disorders (mood disorder/none/reactive depression/missing)	19/36/69/3	18/48/61/9	0.18
Co-morbidity of anxiety disorder (yes/no)	114/13	36/100	≤0.0001*
Suicidal tendencies without alcohol or withdrawal influence (independent of alcohol/alcohol related/none/missing)	2/18/105/2	18/17/91/10	≤0.0001*
Typology according to Lesch (Type I/II/III/IV)	15/32/54/26	10/52/46/28	0.10

\*Statistically significant.

12.5%). There was no difference between the two samples in Lesch-Type IV (20.5 vs 20.6%). There was a slightly higher rate in the Serbian sample of Type I (11.8 vs 7.4%). In Austria, significantly more Type II patients (25.2 vs 38.2%) had been included, while the Serbian sample comprised significantly more Type III patients (42.5 vs 33.8%). We also found differences in other items of the LAT (e.g. parents' attitudes, loss of control, age of tolerance and age of appearance of first withdrawal), but with respect to the use of medication in relapse prevention (acamprosate and naltrexone), these items are not important and therefore not shown.

## DISCUSSION

The reimbursement of drugs for medical treatment of alcohol dependence and relapse prevention is modest in Serbia compared with the EU average (Jakovljevic *et al.*, 2011). This study has helped to show that the types of alcohol problems for which anti-craving medicines are prescribed in Austria are found also in Serbia.

Meta-analyses (e.g. Maisel *et al.*, 2012) of the studies of acamprosate and naltrexone over the past 20 years reveal an overall positive conclusion, but clearly a number of studies failed to show beneficial effects. These findings can be partly explained by the likelihood that only certain subgroups of alcohol-dependent patients respond (e.g.: for the Lesch Typology, see Lesch and Walter 1996; Leggio *et al.*, 2009).

Our study showed that typology assessment can comfortably be used in a Serbian psychiatric department. The proportion of Type IV patients is similar to that found in other countries where the Lesch Typology has been used (Hillemacher and Bleich, 2008; Pombo and Lesch, 2009; Nakamura-Palacios *et al.*, 2011). For Lesch-Type I or II, in the Serbian sample 37% were so diagnosed. According to the results of other studies, these patients should benefit from a treatment with acamprosate. On the other hand, 63% of patients in Serbia were Type III or IV. These patients

would probably benefit from naltrexone (Lesch and Walter, 1996; Kiefer, 2005). However, while Austrian patients included in the study were treated according to the recommendations for the type they have been assigned to, <5% of Serbian patients for whom acamprosate or naltrexone was indicated received those drugs, probably due to high prices and lack of reimbursement.

The large difference in rates of anxiety disorders that were found may be partially explained by the traumatizing recent history of Serbia (French *et al.*, 2013). Unexpectedly, suicidal tendency unrelated to alcohol consumption observed in Austrian sample was higher than in Serbs, and this observation clearly needs additional investigation. In addition, underrepresentation of female patients within the Serbian sample could be explained by the cultural difference. As previously shown by Jakovljevic *et al.*, (2004), heavy alcohol consumers in Serbia are predominantly men, and in our study, only heavy drinkers were included.

## Limitations of the study

This was a cross-sectional study. The numbers in the four subtypes are often small. Interactions between anxiety disorders and suicidal tendencies, with and without alcohol dependence, might be fruitful in this traumatized population. In addition, the study lacks outcome data on differences in maintaining abstinence from alcohol or in reducing the number of heavy drinking days among the actual patients sampled in relation to different pharmacological approaches. This warrants future investigations.

*Funding* — The Ministry of Education, Science and Technological Development of the Republic of Serbia funded the collection of the Serbian data through approved Grant OI 175014. The publication of the study results was not contingent on the Serbian Ministry's approval.

*Conflict of interest statement.* M.J. has received a modest travel bursary for ESBRA 2011 congress attendance by Merck Serono. Other authors have no conflict of interest to declare.

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