Influence of impulsiveness, suicidality, and serotonin genes on treatment outcomes in alcohol dependence – a preliminary report

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Summary

Aim: The aim of this study was to identify risk factors for relapse by investigating relationships among suicidality, impulsiveness, genetic markers of serotonin activity, and drinking outcomes in alcohol-dependent patients.

Subjects and methods: Ninety alcohol dependent patients were followed for 12 months after a baseline assessment was performed, which included an evaluation of suicidality and impulsiveness. DNA samples were collected to investigate polymorphisms of genes involved in synthesis and activity of the serotonin system. Genetic polymorphisms and baseline measures of suicidality and impulsiveness were analysed as predictors of relapse.

Results: Relapse rates were significantly higher among patients with a history of suicidal attempts recorded at the baseline assessment. Impulsiveness was not directly related to relapse. The genetic analysis showed that patients with the G/G genotype in the 5HTR1A gene polymorphism were more likely to relapse, whereas patients with the C/C genotype were more likely to abstain. Moreover, there was a strong trend for an association between the G/G genotype and a history of suicide attempts.

Conclusions: Preliminary analyses suggested that a history of suicidality predicted relapse in alcoholic patients while controlling for other variables. Polymorphisms of genes involved in serotonergic function also contributed to a higher risk of relapse in alcohol dependent patients. These preliminary analyses as well as other potential relationships between the variables of interest require continued investigation with a larger sample size.

alcoholism / relapse / suicide

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INTRODUCTION

Alcohol dependence is a chronic disease with persistent susceptibility to relapse. Most treated alcoholics, regardless of therapy applied, achieve only short-term periods of abstinence and then return to drinking. Research studies show that 35% of treated alcohol-dependent patients fail to maintain abstinence for even 2 weeks after the completed treatment program, and 58% relapse during the first 3 months [1]. Polich et al. [2] reported that over 80% of treated alcohol-depend-

ent subjects experienced serious drinking problems during the 4 years following completion of addiction treatment. In the MATCH study, only 35% of inpatients remained abstinent at 1-year follow-up [3].

Identifying predictors of relapse, a key feature of alcohol dependence, is essential for understanding the complex pathogenesis of the disease and improving treatment. A number of patient-related factors that increase risk for relapse have been identified, among them: severity of alcohol dependence [8] and co-morbid psychopathology [4], including affective [5] & anxiety [6] disorders and antisocial personality [7]. Moreover, pathophysiological factors, such as central dopamine hypofunction [9], enhanced high frequency beta EEG activity [10], sleep disorders [11], decreased plasma beta-endorphin levels [12] and changes in ERP indicating reduced frontal lobe activity [13] seem to play a role in increasing susceptibility to relapse. Suicidality and impulsiveness may also be considered as important risk factors of relapse [14, 15], however, relationships among them are not well investigated.

Most studies confirm close relationships between impulsiveness, suicide, and alcohol use disorders [15, 16]. In at least one study, lifetime risk of suicide was even higher in individuals with alcohol dependence than in those with mood disorders [17]. There is strong evidence to suggest that suicidality, impulsiveness, and depression share a common genetic basis and biological substrate of 5-HT dysfunction [18, 19, 20]. A direct relationship between serotonin activity and relapse in alcohol dependent patients has not been investigated yet.

AIM OF THE STUDY

The general objective of our research study was to analyse relationships among suicidality, impulsiveness, genetic markers of serotonin activity, and relapse in alcohol-dependent patients.

SUBJECTS AND METHODS

The study was performed on a group of 90 patients, both males and females, with the diagnosis of alcohol dependence according to DSM-IV criteria [21], treated in residential addiction treatment centers (58 patients) and outpatient facilities (38 patients) in Warsaw. All study subjects participated in the usual treatment program at each center. Patients with acute withdrawal symptoms and those with less than 25 points on the Mini Mental State Examination were excluded from the study cohort. Both the Bioethics Committee at the Medical University of Warsaw and the Medical Institutional Review Board at the University of Michigan approved the research protocol. The patients received detailed information about the aim and course of research study and signed the consent form.

The research study had a prospective design and included 3 visits for all patients completing the study. The baseline assessment took place within 2 weeks of beginning treatment. The next visits occurred after one month and subsequently at 6 and 12 months. The baseline assessment included collection of a blood sample and evaluation using a variety of psychometrically valid scales selected to measure potential predictors of outcome. The scales included an evaluation of severity of psychiatric symptoms (Brief Symptom Inventory [22], SF–36 questionnaire [23]), domains of personality (NEO-FFI [24]), social support (MOS Social Support Scale [25]), suicidality (Beck Suicidal Ideation Scale [24] and a structured questionnaire constructed for the purpose of this study), severity of depression and hopelessness (Beck Hopelessness Scale, Beck Depression Inventory [27, 28]) and impulsiveness (Barratt Impulsiveness Scale BIS–11 [29]). In addition to the BIS, which is a self–administered, subjective measure, impulsiveness was assessed by means of a "Stopping Task" procedure, delivered by a computerised program and considered to be an objective neurophysiologic measure of impulsiveness [30]. Demographic information, history of childhood abuse, and a history of suicide attempts were obtained with a structured questionnaire constructed for the purpose of this study. Patients also completed the Alcohol Timeline Follow-Back Interview in order to evaluate baseline drinking and treatment outcomes [31].

DNA was isolated from blood samples using Gentra kits in the Laboratory of Psychopharmacology at the Medical University Warsaw Department of Psychiatry. DNA samples were then sent to and analyzed using Polymerase Chain Reac-

tion (PCR) methods in the Neurogenetic Laboratory at the University of Michigan in Ann Arbor. Genetic analyses included polymorphisms in genes involved in synthesis and activity of the 5-HT system: the tryptophan hydroxylase 2 gene (TPH2), the promoter region for the serotonin transporter gene (SLC6A4 – 5HTTLPR), and genes for serotonin receptor subtypes (5HTR1A [C1018G] and 5HTR2A [T102C]).

Relapse was defined as any drinking during the follow-up period after completing the treatment program. According to the data collected at the second and third follow-up visit, study subjects were divided into two groups: patients who relapsed and patients who remained abstinent. The groups were then compared using variables measured at the baseline assessment, especially genetic polymorphisms, impulsiveness and suicidality. The statistical analyses were performed using chi-square, Student t, and Mann-Whitney tests as well as a logistic regression analysis in order to determine the predictive value of analyzed variables. The SPSS statistical software was used.

RESULTS

Out of 90 patients who ultimately entered the study and filled out the baseline questionnaire, 59 subjects completed the study (3 visits), and of those, 29 patients relapsed and 30 remained abstinent. All 31 patients lost to follow-up were conventionally classified as having relapsed for the purpose of this analysis [32]. Information received later from collateral sources supported the probability of this hypothesis. Therefore, out of 90 patients included, 60 subjects were considered as relapsed (relapse rate 67%), and 30 as abstinent. The average period of observation (time from the baseline to the final follow-up visit) was 11.5 months.

Men comprised 73% of the study sample, and mean age was 42.5 ± 9.7 years, with a range from 20 to 64 years. At baseline, 37 subjects (41%) were unemployed, 35 (39%) were married, and 18 (20%) were divorced. The mean age at onset of alcohol problems was 22.4 ± 8.1 years, and mean duration of alcohol dependence of 21.0 ± 11.4 years. The patients reported an average daily alcohol consumption of 147.4g of pure etha-

nol (0–225g) for the 90 days prior to entering the treatment program. At the baseline assessment, 39 patients (43%) reported at least one suicide attempt in the past and 18 (20%) confirmed suicidal thoughts.

Patients who relapsed were significantly more likely to be younger, male, to have financial problems, and to experience physical abuse before 18 years of age. Patients who were abstinent during follow-up reported receiving more social support, had fewer financial problems, and scored significantly higher on the neuroticism domain in the NEO-FFI inventory. The BIS analysis revealed only a statistical trend for higher impulsiveness in relapsed patients (p = 0.059), whereas the objective measure (Stopping Task) did not show any meaningful differences. Patients reporting at least one suicide attempt in the past were significantly more likely to relapse than patients without history of suicidality (p = 0.008).

The logistic regression analysis showed that suicide attempts in the past reported at the baseline assessment were the strongest predictors of relapse compared to other variables, which were significant in univariate analyses (age, gender, financial problems, psychiatric severity, social support, daily amount of alcohol consumed, neuroticism score).

The polymorphism of the serotonin receptor gene 5HTR1A (C1018G) differentiated the two analyzed groups. Patients with the G/G genotype were more likely to relapse, whereas patients with the C/C genotype were more likely to abstain. Moreover, there was a strong trend for an association between the G/G genotype (associated with relapse) and a history of suicide attempts. Among patients with a history of suicide attempts reported at the baseline, 28% had the G/G genotype compared to 4% of patients without suicide attempts (chi^2 = 5.89; df = 2; p=0.052).

Polymorphism of 5HTR1A gene was not associated with the level of impulsiveness in alcohol-dependent patients. Polymorphisms of other genes included in analyses (TPH2, 5HTR2A, 5HTTLPR) did not differentiate the two groups. However, we found that the C/C genotype in polymorphism of the tryptophan hydroxylase 2 gene (TPH2) was associated with a high level of impulsiveness as measured by the Stopping Task test(p = 0.003).

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Table 1. Baseline characteristics of patients who relapsed and abstained.

	Relapse n=60	Abstinence n=30	p
Age (years)	40.4 ± 10.2	45.7 ± 7.9	0.041
Women, n (%)	12 (20.0)	12 (40.0)	0.034
Education (years)	13.6 ± 3.8	12.2 ± 2.7	0.285
Employed, n (%)	20 (33.3)	16 (53.3)	0.065
Not enough money for needs, n (%)	43 (73.3)	15 (50.0)	0.037
Married, n (%)	17 (28.3)	17 (56.7)	0.193
Living alone, n (%)	12 (20.0)	2 (6.6)	0.159
Suicide attempts in the past, n (%)	32 (53.3)	7 (23.3)	0.008
Physical abuse before 18 years of age, n (%)	27 (45.0)	7 (23.3)	0.033
Baseline Psychiatric Severity (BSI)	69.7 ± 44.3	51.6 ± 34.3	0.051
Barratt Impulsiveness Scale	73.5 ± 10.6	69.0 ± 10.0	0.059
Social Support (MOSSSS)	60.2 ± 17.5	69.0 ± 17.5	0.046
NEO-FFI, Neuroticism subscale	66.9 ± 12.4	60.4 ± 8.2	0.028
Mean daily alcohol consumption (g)	181.3 ± 18.5	96.8 ± 9.0	0.053
Stopping task – stop reaction time (msec)	225.6 ± 69.2	193.0 ± 89.6	0.166

Chi-square, t-Student, and Mann-Whitney tests were used.

Statistical significance: $p < 0.05$

Table 2. Logistic regression analysis for predictors of relapse

	Odds Ratio	(95% C.I.)
Suicide attempts*	6.85	(1.62–28.98)
Physical abuse before the age of 18	3.06	(0.71–13.28)
Gender	2.88	(0.71–11.65)
Not enough money for needs	1.94	(0.45–8.42)
Daily alcohol consumption	1.06	(0.99–1.13)
Baseline psychiatric severity	1.01	(0.99–1.03)
Age	0,96	(0,89–1,04)

*$p < 0.01$

95% C.I. – 95% Confidence Interval

Table 3. Polymorphism C1018G of 5HTR1A (rs6295) in relation to relapse rate in alcohol-dependent patients

	Genotype			Allele	
	CC	CG	GG	C	G
Patients relapsed (n=60)	5 (8%)	38 (64%)	17 (28%)	24 (0.40)	36 (0.60)
Patients abstained (n=30)	16 (53%)	12 (40%)	2 (7%)	22 (0.733)	8 (0.267)

Chi-square test: $p = 0.041$; $p = 0.0029$

DISCUSSION

Our research study showed that relapse is a frequent problem in the course of alcohol dependence. During one-year follow-up, only 1/3rd of patients remained abstinent, whereas 2/3rds relapsed despite involvement in an active alcohol abuse treatment program. Our findings are consistent with results in many previous studies [4, 5, 7, 8, 32, 33]. Similar to other research, this study showed that low social support, severity of psychopathology, and high level of neuroticism may be related to relapse. Data from this study also suggest that relapse should be considered as a complex phenomenon with both biological and psychosocial risk factors.

There were two novel findings, not previously reported in the literature. First, in our study sample, a past history of suicide attempts significantly predicted relapse. Patients who at the baseline assessment reported suicidal attempts in the past were more likely to relapse during follow-up. This relationship may possibly be explained by an association of suicidality with both depression and high level of impulsiveness.

A second new finding was the relationship among 5HTR1A polymorphism, suicidality and relapse rates in alcohol dependent patients. Patients with the G/G genotypes may be considered to have worse prognosis in the treatment for alcohol dependence. The results of other research studies suggest that this genotype may also be linked to poor outcomes in the treatment of depression (higher severity of symptoms and worse response to SSRIs; M. Burmeister unpublished results).

The G/G genotype in C1018G 5HTR1A polymorphism seems to influence the activity of the serotonin receptor, resulting in an increase of risk for relapse, suicidal behaviour or depression. This particular data is consistent with the other findings of this research study which suggests that suicidality is a strong risk factor for relapse. The specific genotype (G/G) of the serotonin receptor 5-HT1A gene may be hypothetically responsible for coexisting suicidal tendencies and relapse susceptibility.

C and G alleles analysed in this study influence activity of the 5HT1A receptor (by affecting transcription factors NUDR/DEAF–1), which is a presynaptic autoreceptor that decreases the activity of the serotonin system. Allele G is responsible for high activity of the receptor and allele C for low activity [34]. This may mean that patients with G/G genotype will have decreased activity of 5-HT system, because the specific ligand of the autoreceptor, serotonin, is bound more easily and strongly. Thus, people with C/C genotypes will be characterised by high serotonin activity, and those with G/C genotype by intermediate activity.

The results of our study demonstrate that decreased serotonergic function may contribute to the higher risk of relapse in alcohol-dependent patients. The activity of the 5-HT1A receptor may be the clue to understanding the pathophysiological mechanism of coexisting depression and relapse.

It must be emphasized that this is only a preliminary report. This research study is continuing with a larger sample size and a longer follow-up period. This may allow for better verification of described relationships and further investigation of relapse in alcohol dependent patients.

CONCLUSIONS

1. A history of suicide attempts reported at the beginning of the addiction treatment program predicted relapse in alcohol dependent patients.
2. Lower serotonergic function may contribute to a higher risk of relapse and suicide in alcohol dependent patients.
3. Impulsiveness had no significant impact on the risk of relapse in alcohol dependence.

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