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Genetic and psychosocial factors for benzodiazepine addiction. An analysis based on the results of the authors' own research conducted in a group of benzodiazepine addicted and non-addicted individuals*

Poszukiwanie genetycznego i psychospołecznego podłoża uzależnienia od benzodiazepin. Analiza w oparciu o wyniki pracy własnej

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Purpose: In spite of the fact that the addictive potential of benzodiazepine (BDZ) drugs has been known for a long time, benzodiazepine addiction remains a common problem for psychiatry to deal with. The etiology of benzodiazepine addiction is very complex. Among the risk factors, the course of the treatment, demographic status and psychological features of a patient seem to play an important role. The aim of this study was to investigate both psychological and genetic factors differentiating benzodiazepine addicts from non-addicted users.

Methods: We analysed a cohort of 120 individuals treated with benzodiazepines divided into two groups: benzodiazepine addicts and non-addicted benzodiazepine users (the control group). In both groups we measured genetic polymorphisms of GABA A2 and MAOA. In both groups some psychometric measurements were performed – we investigated the level of depression, anxiety as a state and as a trait, personality features and the dominant coping style using the Beck Depression Scale, Hamilton Anxiety Scale, Five-Factor Personality Inventory NEO-FFI and the Coping Inventory for Stressful Situations [4,10,17,36,41,44].

Results: There are some psychological and situational risk factors for benzodiazepine addiction such as high neuroticism, introversion and lack of the ability to release tension through interpersonal contacts, dominance of emotional coping style and high accumulation of critical life events during both childhood and adulthood. The genetic background still remains a field for further exploration.

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Conclusions: The genetic background for BDZ addiction remains a field for further exploration.

Key words: addiction • benzodiazepines • etiology • genetics

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Introduction

Dependence and addiction are terms describing the same phenomenon but have slightly different connotations. The term "dependence" carries a greater biological connotation while the term addictions relates more to the psychological compulsion. Being aware of the strong physiological aspect of benzodiazepine dependence, in our work we try to analyse benzodiazepine use disorder as a very complex and multifactorial phenomenon, so we decided to choose the term addiction as more fully describing the psychological complexity of the issue. Due to their sedative, tranquilising, myo-relaxant and anti-seizure effects, benzodiazepine drugs are widely applied in various branches of medicine. Since their introduction in the 1960s, the popularity of benzodiazepines grew to reach a peak in the 1970s when diazepam became the most frequently prescribed drug in the United States [6]. The awareness of the risk of addiction to benzodiazepines was growing simultaneously with their growing prevalence. Not only the possibility of addiction was indicated but also other negative consequences of long-term benzodiazepine treatment such as impairment of cognitive functions, falls (specially in elderly patients), car accidents and development of tolerance [27,37]. In consideration of the above, temporary guidelines recommend short-term use of benzodiazepines and only for strict indications. Investigators note the possibility of preventing addiction by applying benzodiazepines for a short term (2-4 weeks) [2,3]. In spite of this knowledge, benzodiazepine addiction still affects a large group of patients [6,25,45,46]. So far little is known about the etiology of benzodiazepine addiction because regardless of the duration of treatment, individual differences in susceptibility to it are observed in different patients. The common risk factors are: the course of treatment (duration, applied dosages, circumstances of the beginning of treatment), critical life events, the lack of adequate intervention, and abuse of alcohol and other psychoactive substances. Some investigators indicate additional risk factors such as female sex, elderly age and associated somatic dysfunctions [1,4]. Some recent reports suggested higher susceptibility to benzodiazepine addiction among adults below the age of 65 in comparison to those over 65 [16]. The most frequently mentioned psychological factors predisposing to benzodiazepine addiction are anxiety and depressive disorders, neuroticism, and personality disorders of the borderline, histrionic and antisocial types [13,14,40]. However, in clinical practice benzodiazepine addiction is observed in a large group of patients without personality disorders. Therefore the question remains about the more subtle personality traits predisposing to addiction.

So far the focus of most research has been on the genetic background of alcohol addiction. As regards benzodiazepine addiction parallel risk factors are an open field for investigations. In the present study we assumed the occurrence of particular genetic predispositions to benzodiazepine addiction. To isolate the candidate genes which might be involved in predispositions to benzodiazepine addiction, we focused our analysis on the mechanism of benzodiazepine effects and on similar studies on alcohol addiction. Two polymorphisms were chosen: GABA A subunit alpha 2 and the gene metabolising catecholamine MAO A, 30 bp in the promoter region. The reason for choosing GABA A and MAO A polymorphisms for the present analysis was their potential association with addiction and anxiety.

GABA A receptors are the benzodiazepine binding sites. Gamma-aminobutyric acid (GABA) plays an important role in the central nervous system as the main inhibitory neurotransmitter in the brain and the spinal cord. GABA A as the inhibitory system is the target of benzodiazepine activity. GABA(A) receptors occur in the whole brain, mostly in the basal ganglia, cerebellum, spinal cord and limbic system. They consist of α1-6, β1-3, γ1-3, δ, ε, θ, π, ρ1-3 subunits and have a CL ion channel [30,32]. Activation of the chloral channel by gamma-aminobutyric acid leads to an influx of CL ions and as a result the hyper-polarisation of postsynaptic cell membranes

and increased activation threshold for incentive neurotransmitters in the CNS. The result is inhibited excitability of cell membranes. The interaction between benzodiazepine drugs and the GABA receptor is based on the following mechanism. The receptor has binding sites for GABA as well as some sites where GABA is mediated, including a binding site for benzodiazepines (between subunits α and γ of the receptor complex). Benzodiazepines indirectly influence the CL channel of the GABA (A) receptor by intensifying the response to gamma-aminobutyric acid. The activation of the neurotransmitter leads to the inhibition of excessive arousal characteristic for anxiety states or insomnia. So far, an association between different subunits of the GABA(A) gene polymorphism and particular disorders such as alcoholism, schizophrenia, anxiety or affective disorders has been proved [21]. Research conducted on mice led to the conclusion that GABAA 2 receptors, widely spread in the limbic system, mediate the anxiolytic action of benzodiazepines [26]. It has been ascertained that the alpha-2 variant of the gamma-aminobutyric acid receptor subunit type A (GABAA 2) is associated with the risk of alcohol addiction and so is subunit β1 of the GABA (A) receptor [18,23,30]. Polymorphism of the gene encoding the subunit α2 receptor has been associated with both alcohol addiction and polytoxicomania [11]. Some reports suggest that GABA2 not only influences the potential for addiction by increasing the sensitivity to alcohol effects but also plays a significant role in increasing susceptibility to other substance addictions [24]. It has also been discovered that subunit α2 of the GABA(A) receptor is a target for benzodiazepine action. Laboratory tests on mice showed that mice with a punctual mutation in GABA2 became non-sensitive to the anxiolytic effect of diazepam by desensitising subunit α2 to the drug, but it remained sensitive to diazepam's sedative action. The introduction of a similar mutation in the GABA 3 gene did not modulate the anxiolytic action of diazepam. The study showed that subunit α2 of the GABA (A) receptor is fundamental for the anxiolytic action [18]. The GABAA 2 rs 279826 polymorphism was frequently mentioned among other polymorphisms associated with conditioning of the susceptibility to alcohol addiction due to sensitisation to alcohol effects during initial ingestion [9,22]. Consequently, this particular polymorphism became the focus of the present investigation.

Monoamine oxidase A (MAO A) – an enzyme metabolising monoamines such as dopamine, norepinephrine and serotonin – plays an important role in the central nervous system, modulating temperament, anxiety and depression levels. It was found that a low level of MAOA in the prefrontal cortex was associated with heightened aggression, fear conditioning and diminution of social end exploratory behaviour. MAOA gene polymorphisms located in chromosome X were associated with impulsive and aggressive behaviour, antisocial personality disorder, attention deficits, anxiety disorders and addictions [19]. Results obtained from healthy volunteers were used to identify the relation between personality traits and MAOA as a kind of continuum. Whereas, at one extreme of the continuum such traits as consideration/insight are to be found, aggression/impulsiveness are placed at the other. Likewise, the association between high levels of MAOA and better adaptive abilities was indicated in healthy individuals [39]. There are some reports on the associations between adverse life events and the genotype, suggesting the influence of MAOA not only on the temporary regulation of emotions but also on the process of transforming emotional experience [28]. It has been proved that the interaction between the experience of maltreatment in childhood and the variant of the MAOA gene is a predicator of antisocial behaviour and alcoholism. Similarly, the mutual interaction between early childhood stress and the variant of the serotonin transporter gene is a predicator of alcohol abuse in monkeys and depression in humans [12]. Taking into consideration the above reports, we selected the MAOA polymorphism as a candidate gene potentially associated with susceptibility to benzodiazepine addiction.

Material and methods

The study was conducted at the Department and Clinic of Psychiatry, Pomeranian Medical University in 2008–2011 on a cohort of 120 individuals treated with benzodiazepines. The participants were divided into two groups: the investigated group of benzodiazepine addicted patients and the control group including persons who were treated with benzodiazepines in the past but did not reveal any symptoms of addiction to them. The diagnosis or exclusion of benzodiazepine addiction was made by qualified psychiatrists using a structured interview. The diagnosis was established according to the ICD-10 classification diagnostic criteria for dependence syndrome:

- a strong desire or sense of compulsion to take benzodiazepines;
- difficulties in controlling benzodiazepine-taking behaviour in terms of its onset, termination, or levels of use;
- a physiological withdrawal state when benzodiazepine use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
- evidence of tolerance, such that increased doses of benzodiazepines

are required in order to achieve effects originally produced by lower doses;

- progressive neglect of alternative pleasures or interests because of benzodiazepine use, increased amount of time necessary to obtain or take the substance or to recover from its effects;

- persisting with benzodiazepine use despite clear evidence of overtly harmful consequences, such as harm

to the liver through excessive drinking, depressive mood states after periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm [29].

The presence or the absence of dependence and addiction to benzodiazepines was the basic difference between the two groups. The groups were matched for demographic parameters: each one contained 40 women and 20 men; the average age was 53.27 in the investigated group and 54.12 in the control group. The participants were of Polish nationality, Caucasian race, over the age of 18.

The essential difficulty during the recruitment to the investigated group was the criterion of sex, as among patients with diagnosed benzodiazepine addiction women were distinctly more numerous. This phenomenon was concordant with other clinical observations and data confirming that while the population of alcohol addicts was dominated by men the diagnosis of BDZ addiction is much more frequent among women. Some investigators notice the domination of women in elderly patients using benzodiazepines in difficult life situations [5]. Different sources report that benzodiazepine addiction is observed in women more often than in men in the proportion of 2:1 [34]. There were no statistically significant differences between the investigated groups with regard to the level of education, occupational activity, family situation or the way of living (alone vs. with a family). Diagnoses in the investigated group, apart from benzodiazepine dependence, were: anxiety disorders, mixed anxiety-depressive disorder (n=28) and adaptive disorders (n-18), panic disorder (n=11), somatisation disorder (n=3), and in the addicted group 3 participants were diagnosed with personality disorder (1 – histrionic personality disorder, 1 – emotionally unstable personality disorder, 1 – paranoid personality disorder). The exclusion criteria were: addiction to substances other than benzodiazepines, alcohol or nicotine, presence of withdrawal symptoms, schizophrenic psychosis, severe anxiety or depressive symptoms and cognitive disorders in dementia.

The laboratory material was taken from all participants after receiving from them written informed consent, followed by psychometric tests. The study protocol was accepted by the Bioethical Commission of the Pomeranian Medical University. The recruitment took place at general psychiatric wards, daily wards and the outpatient clinic of the Clinic of Psychiatry and also at the general medical care units in Szczecin. The DNA used for analysis was isolated from blood or saliva samples taken in both groups. The analysed polymorphisms were typed using the polymerase chain reaction in real time (real-time PCR). For each investigated polymorphism the Hardy-Weinberg equilibrium test has been provided (http:\\linkage.rockefeller.edu/soft). The financial support for the research was provided by the scientific grant MNiSW no. N N 402466640.

The aim of the psychometric investigation was to establish the level of depressiveness and impulsiveness, and to identify the dominating coping style and the presence of critical life events prior to benzodiazepine addiction. The data about the first benzodiazepine treatment (circumstances, initial dosages, duration) were collected in a structured interview. The authors created a structured questionnaire containing 57 questions (close ended and open ended – descriptive questions) relating to the demographic data, life experience, traumatic events, the circumstances of benzodiazepine treatment and the participant's attitude to benzodiazepines. The circumstances of the initiation of benzodiazepine treatment and the average benzodiazepine dosages applied during the first treatment are shown in Table 1 and Table 2.

Table 1. Mann-Whitney U test for the benzodiazepine dosage applied during first treatment. Results for $p < 0.05$

	Rank sum Investigated group	Rank sum Control group	Z	P	N Investigated group	N Control group
Dosage	3001.500	1654.500	2.497413	0.012511	55	41

Table 2. Circumstances of the first benzodiazepine treatment in the group of benzodiazepine addicts and in the control group

Circumstances of the first benzodiazepine treatment	BDZ addicts	Control group	BDZ addicts	Control group	p
	Number of individuals		%		
Bereavement reaction	4	6	6.67	10.00	0.2553
Domestic violence	12	3	20.00	5.00	0.0072
General family troubles	8	16	13.33	26.67	0.0351
Problems at work	9	3	15.00	5.00	0.0352
Alcohol abstinence syndrome	6	1	10.00	1.67	0.0270

To assess the psychological features of participants, psychometric methods were used such as the Hamilton Anxiety Rating Scale [18], State–Trait Anxiety Inventory [36,41], Beck Depression Inventory [4], Five-Factor Personality Inventory [44], and Coping Inventory for Stressful Situations [10]. The results of psychometric investigations indicated some differences between groups of addicted and non-addicted participants in their personality predispositions, coping styles, life events and also in the course of benzodiazepine treatment:

- First, it was proved that factors associated with the course of treatment such as high dosages, long duration, specific circumstances leading to the need of use and also using benzodiazepines without medical consultation are important risk factors for addiction.
- The personality factors predisposing to addiction included high neuroticism, introversion and lack of the ability to release tension through interpersonal contacts, a dominating emotional coping style and rarely using the coping style based on task solution.
- High accumulation of critical life events during both childhood and adulthood might also predispose to addiction.

The above conclusions were already comprehensively laid out in the article "Psychosocial characteristics of benzodiazepine addicts compared to not addicted benzodiazepine users" in Progress in Neuro-Psychopharmacology & Biological Psychiatry [20].

Daily dosage of benzodiazepines applied during the first treatment

For statistical analysis benzodiazepine dosages were recounted according to the conversion unit 10 mg of diazepam (see: http://hyperreal.info/node/3210#ixzz1kNJPEdDM).

Results

Gamma-aminobutyric acid polymorphism (GABA-A)

With regard to GABA polymorphism there were no differences between the addicted and control groups. For patients in both groups the genotype A/G was more and the genotype G/G was the less frequent one (Table 3). The contribution of particular genotypes of the GABA gene in both groups was similar, regardless of the level of anxiety measured by the Hamilton Scale. The type of GABA(A) did not affect either the dosage of medication in the first treatment or the number of drug sources during further treatment. An association was observed between the genotype and the level of neuroticism, which was usually higher in persons with A/A and lower in persons with A/G genotype variants (Table 4). With regard to coping style, individuals with the genotype A/G more frequently applied the task oriented coping style in comparison to those with genotype A/A or G/G (Table 5). Such associations of the GABA(A) gene and the coping style, however, did not differentiate the group of benzodiazepine addicts in any way.

Table 3. GABRA genotypes in the group of benzodiazepine addicts (BDZ) and in the control group

Group	n	Genotypes			p
		A/A n (%)	A/G n (%)	G/G n (%)	
BDZ addicts	56	18 (32)	27 (48)	11 (20)	p=0.806
Control group	58	19 (33)	25 (43)	14 (24)	

Table 4. Neuroticism level and GABRA genotype

Scores	A/G	A/A	G/G	Total
Low	18	7	6	31
%	34.62%	18.92%		
Average	5	4	3	12
%	9.62%	10.81%		
High	29	26	16	71
%	55.77%	70.27%		
Total	52	37	25	114

Table 5. Results in task oriented coping style and GABRA genotype

Scores	A/G	A/A	G/G	Total
Low	20	24	16	60
%	38.46%	64.86%		
Average	23	9	5	37
%	44.23%	24.32%		
High	9	4	4	17
%	17.31%	10.81%		
Total	52	37	25	114

Monoamine oxidase (MAO-A) polymorphism

No connection was found between the MAO-A genotype and the occurrence of benzodiazepine addiction. Both, in the group of addicted probands and in the control group the prevailing genotype was 4/4 of the MAO-A gene. Admittedly, the heterozygote 3/4 MAO-A was more frequent in the addicted group than in the control group, but this difference was not statistically significant (Table 6).

Table 6. MAO A genotypes in the group of benzodiazepine addicts (BDZ) and in the control group

Group	n	Genotypes			p
		4/4 n (%)	3/4 n (%)	3/3 n (%)	
BDZ addicts	59	27 (46)	12 (20)	20 (34)	p=0.281
Control group	60	36 (60)	8 (13)	16 (27)	

The occurrence of particular genotypes of the MAO-A gene was analysed in relation to selected features and psychosocial phenomena such as anxiety level, tendency to obtain medications from many sources, tendency to use high dosages and the experience of maltreatment in childhood.

In both groups among participants with a high level of anxiety measured with the Hamilton Anxiety Scale the prevailing genotype was 4/4 MAO-A, while the genotype 3/3 MAO-A was more frequent among persons without any anxiety symptoms (Table 7).

Table 7. Results in Hamilton Anxiety Scale and MAO A gene

MAO A	No anxiety	Mild anxiety	Moderate anxiety	N
3/3	14 (21%)	5 (12%)	1	20
3/4	17 (25%)	15 (35%)	4	36
4/4	37 (54%)	23 (53%)	3	63
Total	68	43	8	119

Table 8. Number of sources to obtain benzodiazepine drugs in treatment continuation and the MAO A genotype

Number of sources	3/3	3/4	4/4	Total
0	0	1 (3%)	3 (5%)	4
1	16	26 (72%)	50 (79%)	92
2	2	7 (19%)	6 (10%)	15
3	2	2 (6%)	4 (6%)	8
Total	20	36	63	119

The analysis of the tendency to obtain medications from different sources showed that in both groups individuals with the genotype 3/4 MAO-A obtained benzodiazepine drugs from two sources almost twice as frequently as the individuals with the genotype 4/3 (Table 8).

Some associations were discovered between the genotype and analysed personality traits measured with the NEO-FFI questionnaire. It was observed that individuals with the genotype 3/3 more often had high scores in the neuroticism scale than individuals with the genotype 4/4 who were usually characterised by average scores in that scale (Table 9).

Table 9. Neuroticism level and the MAO A genotype

Scores	3/3	3/4	4/4	Total
Low	5	10 (28%)	16 (25%)	31
Average	1	7 (19%)	5 (8%)	13
High	14	19 (53%)	42 (67%)	75
Total	20	36	63	119

Table 10. Extraversion level and the MAO A genotype

Scores	3/3	3/4	4/4	Total
Low	6	16 (44%)	38 (60%)	60
Average	6	14 (39%)	12 (19%)	32
High	8	6 (17%)	13 (21%)	27
Total	20	36	63	119

Due to a large number of 3/3 homozygotes the above observations must be treated with caution. There was a significant association between the MAO-A genotype and the level of extraversion. Individuals with the genotype 3/3 were characterised by high extraversion. The 4/4 genotype was more often associated with high introversion than in other genotype groups (Table 10).

With regard to the coping style, persons with 3/3 and 4/4 MAO-A genotypes less often applied the task oriented coping style, using a more emotional coping style more frequently, whereas persons with the 3/4 genotype more often used the task oriented coping style and less frequently the emotion oriented coping style. Statistical analysis, however, did not confirm a significant correlation between the MAO-A genotype and the scores in the Emotion Oriented Coping Style scale (Tables 11 and 12).

Table 11. Results in Task Oriented Coping Style and MAO A genotype

Scores	3/3	3/4	4/4	Total
Low	12	14 (39%)	37 (59%)	63
Average	5	17 (47%)	17 (27%)	39
High	3	5 (14%)	9 (14%)	17
Total	20	36	63	119

Table 12. Results in Emotional Coping Style and MAO A genotype

Scores	3/3	3/4	4/4	Total
Low	4	14 (39%)	18 (29%)	36
Average	9	6 (17%)	19 (30%)	34
High	7	16 (44%)	26 (41%)	49
Total	20	36	63	119

The analysis did not confirm any correlation between the MAO-A gene polymorphism and the experience of physical or psychological violence in childhood. No significant difference was found between the genotype groups of MAO-A with regard to dosages during the first benzodiazepine treatment.

Discussion

None of the investigated genes determined the occurrence or lack of addiction. In both investigated groups some genetic influence was identified as responsible for the occurrence of a particular constellation of personality traits and the functioning style, but it did not differentiate the investigated groups.

The 4/4 MAO-A genotype both in addicted and non-addicted individuals was associated with a higher level of anxiety and introversion and at the same time with a smaller number of sources of obtaining benzodiazepine drugs. The individuals with 3/3 MAO-A genotype more often showed a lack of anxiety symptoms and were characterised by higher extraversion. No differences were found between the MAO-A genotype groups in the daily dosage of benzodiazepines applied during the first treatment. Both, in the group of addicted individuals and in the control group the prevailing genotype of the MAO-A gene was 4/4. Earlier reports confirmed that this genotype occurs more often in individuals with higher susceptibility to anxiety disorders (panic disorders and generalised anxiety disorders) [33]. Deckert et al. [8] described the associations between panic attacks and the MAO-A polymorphism with longer alleles (3a, 4 and 5) more active than allele 3. In the present investigation, the 3/3 MAO-A genotype occurred more often in individuals who did not show any anxiety symptoms. Those results are consistent with previous reports where the 3/3/genotype was associated with milder expression of the MAO-A gene, which led to slower metabolism of catecholamine (Sabol and Hamer, 1998). Other reports suggest that the lower activity of the MAOA allele 3 determines higher susceptibility to antisocial behaviour due to a lack of fear [32].

In both groups the associations between the MAO-A gene polymorphism and the experience of violence in childhood were investigated. Some investigators turn their attention to the interaction between maltreatment in childhood and the variant MAO-A gene as the predictor of later antisocial behaviour [7,12]. The results of Caspie's research demonstrated that the modulatory factor for the effects of maltreatment is the functional polymorphism of the mono-oxidase encoding gene. Children with the genotype producing high expression of MAO-A, who were the victims of maltreatment, do not often show antisocial personality traits in later adult life [38]. The analysis proved that the genotype might modify the sensitivity of a child to aggressive actions of his social environment. In the present investigation we tried to find out if the modulatory influence of MAO-A on the effects of maltreatment might be relevant also to the benzodiazepine abuse and addiction in adult life. Although, the analysis did not show such associations, we must take into consideration the factors associated with the gender. In Caspie's research the investigated group was male, while in the present research the majority of participants were female. Nor did our sample include individuals with strong antisocial personality features. It is possible that similar analysis conducted on a larger sample or on a more diverse population could produce different data.

The GABRA genotypes did not differentiate the investigated groups. Both in the group of addicts and in the control group the individuals with the A/A genotype were characterised by higher neuroticism and the prevailing emotional coping style. Those observations are consistent with previous conclusions and literature data suggesting that neurotic persons did not often apply the coping mechanism based on a task and female patients with depression cope with stress mostly using emotional strategies [38,40].

The present data let us speculate that the individuals with the genotype A/G of the GABRA gene are more often characterised by higher flexibility in coping mechanisms while the presence of the A/A genotype is often associated with the rigid use of an emotional coping style.

Later investigations on the role of particular GABAA receptors suggested a significant role of the α1 subunit in the physical dependence on benzodiazepines [15].

Conclusions

Whereas the results of psychometric investigation presented more in depth elsewhere [20] gave some information about the psychosocial risk factors of benzodiazepine addiction, our genetic tests did not confirm any association between the investigated polymorphisms and BDZ addiction. None of the investigated genes was shown as the one determining the addiction. Some data suggested genetic predispositions to some constellations of personality features and functioning. The predispositions, however, did not differentiate the investigated groups. Some associations of the analysed polymorphisms with particular personality traits, such as extraversion, anxiety level and dominating coping style,

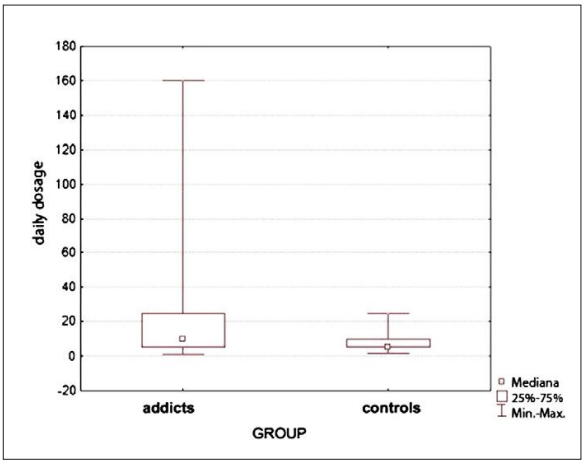

Fig. 1. Daily dosage of BDZ converted to 10 mg of diazepam in initial treatment (1-160 mg of diazepam). Source: http://hyperreal.info/node/3210#ixzz1kNJPEdDM

were found in both investigated groups. The genotype 4/4 MAO A in addicted persons as well as in controls was associated with a higher level of anxiety and introversion and with a smaller number of drug sources. Individuals with the genotype 3/3 MAO A more often revealed a lack of anxiety symptoms and high introversion. No association was found between the MAOA gene polymorphism and the impulsivity level. The results revealed no differences in the daily dosage of benzodiazepine drugs applied in the first treatment. The GABAA genotypes did not differentiated within the investigated groups. Both the group of addicted subjects and non-addicted individuals with the A/A genotype were characterised by higher neuroticism and the dominating emotional style of coping.

In clinical practice, doctors prescribing benzodiazepines might minimize the risk of addiction by following the recommendations of safe dosages and duration of treatment as well as by identifying any individual features or situational factors, which are recognised as risk factors. In the process of assessing personality features in a patient, the cooperation with psychologists might be valuable. A search for the genetic background of benzodiazepine addiction is still a growing field of scientific investigation. Considering the results of the present research, we expect that the genetic background for benzodiazepine addiction might be based on different mechanisms than that in alcohol addiction.

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