

Assessment of Heart Rate Variability in The Diagnosis of Addictive Disorders and / Refinement Stage of the disease Screening, Alcohol, Drug Addiction, heart Rate Variability, Regression Statistical Analysis (RSA), Withdrawal Syndrome



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Abstract

The present paper represents a comparative evaluation of screening approaches in the differentiation of states' abstinent - intoxication "in individuals at different stages of substance dependence with regard to the effects of depressive self-assessments. The analysis is the data of two our own observational studies, in which the first study covered the period from 2003 to 2008 and was conducted on 567 patients - non-medical opiate users. In the second group - 120 patients - with alcohol addiction. Assessment of mental status (Beck Scale), clinical and laboratory diagnosis, the study of heart rate variability (HRV) were conducted. The most significant in the screening assessment will be such manifestations of substance withdrawal syndrome scale - awareness of attraction to alcohol and other psychoactive substances (AOPS) dysphoria. When adding estimates of HRV in the regression equation of binary and the separation of the groups' sobriety - transition state "were important parameters such as the degree of activation of the sympathetic central nervous system (Amode%), RR interval mean value and the index of activity sympathetic adrenal system (SAT). It is noted that the considered approach allows to predict the dependence of AOPS on the basis of data obtained using pulsometrisheskogo interface, psychodiagnostics and clinical and laboratory data. This technique can be useful not only for studying the phenomenon of craving for "chemical" addiction, but also serve to assess the quality of treatment and rehabilitation in these patients.

Keywords: Screening; Alcohol; Drug addiction; Heart rate variability; Regression statistical analysis (RSA); Withdrawal syndrome

Introduction

What is wrong with the existing psychoactive substance screening methodology? This is the absence of the common point of view on it as long as there exists a loophole in the term "abuse" and the scholastic search for a diagnostic border between the state

of health and the disease caused by the psychoactive substances. For example, there is no single identification of the severity of violations, the consequences of virtually any type of psychoactive substances. At the same time, the proposed interpretations of the

term's "use" and "abuse" of psycho-active substances are blurred [1].

The use or ingestion of psychoactive substances is a factor that increases the risk of harmful or dangerous consequences, and "chemical" dependence is a behavioral pattern of compulsive search [2]. So, the clinical patterns of alcohol intake are not bidirectional (abuse and dependence) but are links of one chain in a general deterioration of the condition (NLAES; 1991, 1992). In our opinion, there can be only one interpretation: if psychoactive substances were taken in and how serious the "pharmacological" effects associated with this might be. After all, the main task is to completely eliminate the use of psychoactive substances, and not to manipulate the words: "less-more", "this is possible, but this is not". Otherwise it will be like this: "Well, the consequences are already irreversible, time for a priest."

When planning treatment of many mental disorders such as affective disorders, attention deficit disorder, personality problems, mental disorders of adolescence there comes a necessity to develop non-invasive sobriety control systems associated with the need to exclude possible psychoactive substances usage. It is necessary to take into account that the assessment continuum here can have a multi-polar character with such polar diagnostic points as "health" - "disease". It is possible to distinguish the following clinical conditions (diagnoses) of the considered continuum with a definite trajectory of development caused by the use of psychoactive substances: "withdrawal <risk behavior (experimentation) <abuse <early dependence <chronic dependence".

Existing Ways to Assess Attraction / Dependence on Psychoactive Substances

Comparison of the diagnostic effectiveness of verbal screening methods for the assessment of dependence on psychoactive substances

Addictive disorders are usually associated with the use of AOPS. Comparative analysis of approaches to determine the dependence shows inadequacy of reliable methods [3]. There is now a large number of verbal scales used to assess the "chemical" addiction, including the widely used systems like AUDIT with sensitivity (SE) 87%, specificity (SP) 88% [4-7], the questionnaire CAGE (SE 62%), questionnaires for emotional addiction [8]. Oriented individual nosological forms based on DSM-IV criteria addiction severity index (Addiction Severity Index - ASI) [9] and the European addiction severity index (EUROPASI), specific tests of SP = 85%, sensitivity SE = 80% [1,5,6]. Such tools as screening test of substance abuse (Drug Abuse Screening Test - DAST) [10,11], the profile of addiction Maudsley (Maudsley Addiction Profile - MAP) might also be mentioned [12]. Drug and Alcohol Problem Quick Screen testing the problem of drugs and alcohol usage should be included in this list as well. (Drug and Alcohol Problem Quick Screen - DAP) [13]. We should also mention the questionnaire for fine screening of substance abuse (Substance Abuse Subtle Screening Inventory - SASSI) [14], the index of

opioid dependence (Opiate Treatment Index - OTI) [15], as well as Russian assessments of the rehabilitation potential for drug dependence (Order of the Ministry of Health dated October 22, 2003 N 500), a test of changes in taste tests [16], tools for assessing the craving for psychoactive substances [17,18]. Nevertheless, the urgency of the problem necessitates the development of new approaches to the earliest diagnosis of craving and using of psychoactive substances [19].

Comparative evaluation of biological methods for diagnosing the states "withdrawal of psychoactive substances - intoxication"

Screening systems for working with biological material are immunochemical methods conducted with the use of strip strips (opiates, cannabinoids, etc.). Biochemical laboratory methods are well known for the detection of alcohol dependence in particular, which, according to S.H. Rikoon [9], have a sensitivity between 10% for carbohydrate-deficient transferrin (carbohydrate-deficient transferrin - CDT) [20] and 52% GGT (GammaGT) 56% in aspartate aminotransferase (AST). Thus, different functions are "superimposed" on these various tests: sorting patients in the prehospital environment (for example, the presence or absence of psychoactive substances intake), forecasting and stratification of patient groups (depending on the severity and form of addiction) and daily assessment of the severity of withdrawal and the effectiveness of therapy (with the assessment of the risk of manifestations of psychotic disorders - delirium). The process of assessing an individual for possible latent use of psychoactive substances can be divided into several stages according to their increasing complexity. One of these classifications involves three stages of examination:

- i. Simplified or screening
- ii. Integrated
- iii. Specialized or deep

Objective: A comparative assessment of screening approaches to the differentiation of the "state of withdrawal - intoxication" states in individuals at different stages of substance dependence and the effect of depressive self-assessments on the results of this diagnosis [19].

Factors affecting the quality of screening of psychoactive substances

It is necessary to take into account the influence on the results of screening and heterogeneity of the subjects - gender, age, duration and activity of taking in psychoactive substances, comorbidity. The examination is usually different from screening as it allows you to make a treatment plan, whereas screening only reveals the existence of a problem. Since the formation of dependence on various addictive drugs is based on general neurochemical changes in the activity of monoamine mediator systems, in our opinion, screening methods should first of all assess the degree of activation of the central mechanisms caused by "chemical"

positive reinforcement of sympathoadrenal regulation, i.e. containing catecholamines - dopamine, norepinephrine and the endogenous opiate system (vagoinsular effects). Pathobiological manifestations of such a response are fairly stable and last for some time, so differences in the assessment can be interpreted as a random measurement error. It can be assumed that the measurement of this phenomenon may be sufficiently reliable [21].

Materials and Experiments

The methodology of the study

The analysis is the data of two our own observational studies, in which the first study covered the period from 2003 to 2008 and was conducted on 567 patients at the age of $27,9 \pm 7,1$ years where there were 84% of men being non-medical opiate users. The average score of depressive symptoms according to the Beck Scale was $21,4 \pm 9,4$ points. Gender differences in self-assessments were not found ($P = 0,013$). In the second cohort there were 120 patients observed in the period from 2007 to 2009, 90% of them were men with alcohol addiction. The average age was $40,9 \pm 8,6$ years. Ratio on the Beck scale was $14,3 \pm 11,3$ scores ($P = 0,631$). Criteria: first consultation (D0) - prior to hospitalization, the scale of abstinence symptoms, where the suitability for Cronbach's alpha is 0.81, self-assessment Beck Depression Inventory test (0.74) with a mandatory questionnaire reflected in the total structure of consumption of surfactants. Their heart rate variability (HRV) on the bases of the statistical and spectral analysis with the usage of the pulse detector was examined. (Mark Borisovich Stark, Novosibirsk). General laboratory and biochemical examinations were conducted according to the existing treatment protocols (order of Ministry of Health of the Russian Federation of 28.04.1998, N 140). Our calculation and analysis of the results of research conducted with the help of licensed programs Excell and SPSS 22.0 and were based on logistic regression. In the differential diagnosis of intoxication / release under the influence of surfactants there was used statistical method for calculating. The area under the ROC curve (area under receiver operating characteristic curve - AUC), which is to test the zero degree of prediction was 0.5 and for cases with a maximum degree it was accounted as 1.

Assessment of vegetative tone

The calculation of the Kerdo index, or vegetative index (VI), was carried out according to the formula $VI = (1 - DBP / pulse) \times 100$, here DBP - diastolic blood pressure. With complete autonomic equilibrium (normotonia) in the cardiovascular system, the SI is 0. If the coefficient is positive, then sympathetic influences prevail, if negative, then parasympathetic tone prevails [22].

The following Groups were distinguished:

- i. The first (normotonic) group was with a simultaneous increased tone of both departments (sympathetic and parasympathetic) of the nervous autonomic system (17

patients, 3.9%); in this case, it is impossible to identify the predominance of the tone of one of the sections of the autonomic nervous system, their tone is balanced.

- ii. The second (sympathotonic) consisted of patients with hypertonicity of the sympathetic department (336 patients, 75.8%) with a decrease in the tone of the parasympathetic department of the autonomic nervous system.
- iii. The third (91 patients, 20.2% - vagotonic) - with a predominance of parasympathetic influences, with a decrease in sympathetic.

Study of pathopsychological changes

Based on an assessment of depressive reactions the questionnaire includes 20 test scales which, after quantitative processing, show the level of depression and related conditions [23]. The following scales were analyzed: mood; pessimism, a sense of failure, dissatisfaction, a sense of guilt, a sense of punishment, self-loathing, self-incrimination ideas, suicidal thoughts, tearfulness, irritability, impaired social connections, indecision, body image, loss of working capacity, sleep disturbance, fatigue, loss of appetite, weight loss, preoccupation with bodily sensations, loss of libido. Although the test on depressive self-esteem is well known to doctors, we nevertheless initially made a statistical assessment of the questions, clarifying how much they could fit the scope of the study. The analysis of the suitability of the stepped and dichotomous scales (yes / no answers) of the Beck questionnaire using the Cronbach alpha method did not reveal differences in the information content of the answers, where the significance level of all scales of the questionnaire was almost equally high and amounted to 0.84 - step and 0.86 points in the case of application of dichotomous assessments.

Study of the clinical manifestations of withdrawal status

We list the symptoms included in the opiate withdrawal assessment scale: yawning, lacrimation, photophobia, sweating, sneezing, runny nose, chills, allergic manifestations, muscle discomfort, mydriasis, awareness of attraction to surfactants, dysphoria, low mood, anxiety, weakness, sleep disturbances, dyspepsia, changes in blood pressure (systolic blood pressure > 120 mm Hg), tachycardia (heart rate > 92 beats per minute). The basis is not a stepwise, but a dichotomous scale, i.e. the presence or absence of a symptom was recorded. The analysis of the suitability of the scales (dichotomous) of the clinical manifestations of cancellation states by the Cronbach alpha method showed their acceptable reliability and amounted to $\alpha = 0.74$.

Periodization of time intervals in achieving a sober state.

The following division into temporary stages of achieving remission was used in the work:

- i. State of withdrawal 0-6 days (detoxification proper),

- ii. Cancellation status 7-10 days (transitional state),
- iii. Withdrawal period 11-30 days; remission 31-180 days,
- iv. Remission of 6-12 months.

Study of the structure of consumption of psychoactive substances

The questionnaire included interval scales for consumption intensity over the last month: alcohol, anasha, hallucinogens, heroin, cocaine, artisanal opiates, tram, psychostimulants, sleeping pills, barbiturates, sedatives, nasvay and other substances (entered in a separate line). The tolerance differential (DfT) to alcohol and other psychoactive substances (AOPS) was calculated. DfT = the sum of AOPS consumption activity points / the amount of AOPS consumed, where the suitability of this scale is quite acceptable and amounted to $\alpha = 0.63$.

The Results of the Study

The most important in assessing the screening of alcohol consumption in individuals with drug addiction will be such scale

substance withdrawal syndrome as realization of addiction to psychoactive substances - 9,1 points (P = 0,002) and dysphoria 2,8 points (P = 0,094). Summary statistics for the fifteen questions will be 25.8 points (P= 0,105). The percentage of correct predictions is 65.3%. It turned out that it is possible to screen in order to determine the structure of desire for AOPS. So, on the scale of abstinence symptoms we can definitely speak about the impact on the subsequent condition of the patient in achieving sobriety, smoking marijuana. They were visible manifestations: algic 4,27 (P = 0,039), dysphoria 3,52 points (P = 0,061), a sense of physical weakness 2,79 (P = 0,095). The generalized statistics was 22,8 points. When adding HRV values to a binary regression equation and separating into the groups "sobriety - transition state " such parameters as the degree of activation of the sympathetic part of the central nervous system (Amode%) 2,23 points (P = 0,135), the mean value of RR interval and index sympathoadrenal activity (SAT) 1,7 points (P = 0,194) meant a lot. Hematocrit index of 3.5 points (P = 0,061), and also hemoglobin index of 1.8 points (P = 0,185) were important at general blood tests to assess "abstinent - nonabstinent" parameters (Table 1).

Table 1: Evaluation of diagnostic capabilities of different tests to detect alcohol-mediated addictive behavior (N = 567).

Valuation Scale and Other Biomarkers	Type of Psychoactive Substances, which was Discontinued due to Opioid Dependence	Operational Characteristics of Diagnostic Procedures (%)				
		PPV	NPV	SE	SP	P
Scale of withdrawal symptoms (SWS) in opioid dependence	Alcohol	89	45	79	72	74
	Marijuana	88	47	74	74	72
	Hypnotics	19	1	80	80	5
SWS + assessment Beck scale [23]	Alcohol	94	9	95	88	64
	Marijuana	89	29	82	82	65
	Hypnotics	71	4	83	92	20
Heart rate variability, spectral analysis	Alcohol	90	71	73	57	84
	Marijuana	79	60	61	62	70
	Hypnotics	58	9	70	85	23
Heart rate variability, integrated indicators	Opioid intoxication - remission	79	7	81	92	28
Identifying states "intoxication - abstinent" in alcohol dependence						
Urinalysis		96	75	82	67	92
Complete blood count		96	73	86	60	92
Heart rate variability, integrated indicators		100	56	94	100	96

Key: SWS - Scale of withdrawal symptoms. PPV (positive predictive value) - the probability of having the disease with a positive (abnormal) test result. NPV (negative predictive value) - the probability of the disease in the absence of a negative (normal) test result. SE - sensitivity (sensitivity). SP - cpetsifichnost (specificity). P - prevalens (prevalence).

In general, the scale of abstinence symptoms with an average of 77% Se and Sp 75%, when added to the analysis of the Beck depression scale testing diagnostic value increased by 9 ÷ 12% (see tab. N 1). The highest possible in the assessment of intoxication - in remission for consumers AOPS was comprehensive assessment

of HRV (Se 81%, Sp 92%). In the steady state the main aim of such tests is to justify the need for a treatment plan, which helps to develop follow-up strategy of anticraving therapy aimed at specific "chemical" triggers the craving for AOPS. For example, the existing latent alcoholism while taking "heavy" drugs becomes dominant

vicarious discharge, laying the foundation for the subsequent drug relapse. In alcohol addicted patients, the combination of opiates and alcohol usage and the intensity of alcohol usage will have the Mode (Mo) index of the heart rate (AUC = 1,0; P = 0,001). It was significantly correlated with a coefficient of variation of heart rate CV ($r = -0,15$; P = 0,01) and the index of VLF (Very Low Frequency) ($r=0,22$; P=0,01). These are a sensitive indicator of effective central control metabolic processes (neuroendocrine level), and they allow us to predict the formation of energy-deficient states. Perhaps, these mathematical characteristics of heart rate will help us to determine not only the level of emotional stress, but also to identify patients at risk of compulsive behavior and drug relapse. When referring to the instrumental data obtained using the pulse detector, the prediction accuracy increases by 2,4 times. Indicators of remission were based on the analysis of parameters of heart rate variability. In the initial intervals of remission there may be some activity of cortico-limbic system approaches the state of the autonomic balance and further restoration of an independent contour autonomic self-regulation. With the abolition of the states (0 - 10 days), effect on remission will have options such as the dynamics of reduction of depressive self (AUC = 0,768; CI 0,657 ÷ 0,878; P = 0,0001), to reduce the intensity and somatic vegetative pathopsychological disorders (AUC = 0,723 , CI 0,599 ÷ 0,848; P = 0,0001).

When assessing the balance of the autonomic nervous system, the restoration of the physiological limits of the heart rate is important (AUC = 0.839; CI 0.743 ÷ 0.935; P = 0.0001), i.e. decreased sympathetic tone. Of the wave spectral characteristics of the important directions of changes HF (High Frequency) is attributed to the self-regulation of respiratory (AUC = 0,786; CI 0,678 ÷ 0,893; P = 0,0001) and is characterized by the ability to adapt to even minor physical activities related to self-service. In the withdrawal period of 11 - 30 days of abstinence important in predicting the stability of remission will be those of the wave spectral characteristics of HRV reflects the ratio of the level of the central and autonomic regulation loop, the coefficient vagosympathetic balance (LF / HF), where it is associated with increasing activity of the sympathetic nervous system and is an unfavorable prognostic factor (AUC = 0,969; CI 0,908 ÷ 1,02; P = 0,0001). Possible cause might be continuing high levels of emotional stress. This confirms the high diagnostic value of VLF index which reflects the degree of influence of the central ergotropic (AUC = 0,813; CI 0,677 ÷ 0,948; P = 0,0001). During the formation and consolidation of remission (30 - 180 days), an indicator of success of rehabilitation measures are such HRV which primarily involve assessments of the level of regulation of vasomotor sympathetic ANS (autonomic nervous system) as normalized index bass nLF%, and the index of centralization (index of centralization - IC) (AUC = 0,960; CI 0,883 ÷ 1,103; P = 0,0001), there is a favorable prognosis when they decline. The growth of these indices can be associated with the preservation of a high level of psycho-emotional stress and the risk of drug

breakdown. An increase in mean arterial pressure is associated with a risk of addictive behavior (AUC = 1.0; P = 0.0001).

Discussion

The need to develop non-invasive control systems for abstinence from alcohol and other psychoactive substances is relevant when planning the treatment of many mental disorders - affective disorders, attention deficit disorder, personality problems, mental disorders of various age periods. It should be taken into account that the assessment continuum can be of a bipolar nature with diagnostic points remote from each other, such as "health" - "disease". The following clinical conditions (diagnoses) of the continuum under consideration can be distinguished with a certain development trajectory caused by the use of psychoactive substances: "abstinence <risky behavior (experimentation) <abuse <early dependence <chronic dependence". It is necessary to take into account the effect on the results of screening and heterogeneity of the subjects - gender, age, duration and activity of alcohol and other psychoactive substances, comorbidity. Examination usually differs from screening in that it allows you to draw up a treatment plan, while screening - to identify only the presence of a problem. Since the formation of dependence on various addictive drugs is based on general neurochemical changes in the activity of monoamine mediator systems, screening methods, in our opinion, should primarily assess the degree of activation of the central mechanisms caused by "chemical" positive reinforcement of sympathetic adrenal regulation, i.e. containing catecholamines - dopamine, norepinephrine and the endogenous opiate system (vagoinsular effects). The pathobiological manifestations of such a response are quite stable and hold for a certain time, therefore, differences in the assessment can be interpreted as a random measurement error. It can be assumed that the measurement of this phenomenon may have sufficient reliability.

In conclusion, it must be emphasized that in stationary conditions, the main task of express screening tests is the need to justify a treatment plan. This helps to develop a subsequent strategy for conducting anti-cracking therapy aimed at specific "chemical" triggers of attraction to alcohol and other psychoactive substances. For example, existing latent AOPS intake while taking "hard" drugs becomes the dominant vicarious attraction after discharge, laying the foundation for a subsequent drug breakdown. When accessing instrumental data obtained using a pulse detector, the accuracy of the prediction increases by 2.4 times. The approach outlined by us makes it possible to predict the structure of AOPS consumption based on data obtained using the heart rate interface. Despite some conventions of such an interpretation, this technique may be useful not only for studying the phenomenon of pathological attraction in AOPS addiction. It allows for "hidden" screening to identify drug risk groups not only among adults, industrial workers, but also schoolchildren, students, and also in various social groups.

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