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A BRIEF SCREENING CHART FOR DISTINGUISHING UNIPOLAR FROM BIPOLAR DEPRESSION DURING FIRST DEPRESSIVE EPISODE

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Abstract

The study focused on the search for differences between depression within bipolar disorder (BD) and unipolar depression (UPD), based on the cited findings in the scientific literature and the results from the studied clinical samples. The ultimate goal of the study was to develop a screening chart for bipolar depression (BPD) during first depressive episode.

One hundred and forty consecutively hospitalized patients, 23 men and 37 women with UPD and 23 men and 57 women with BPD diagnosed with M.I.N.I. PWC 5.0.0 Bulgarian Version (DSM–IV) and Hamilton Depression Rating Scale (HDRS-17) were examined with a specially designed screening chart for bipolar depression (SCBPD). The chart encompasses 69 parameters covering demographic data, somatic and psychiatric comorbidities, personal development, onset, course, clinical markers, cognitive deficits, and disease outcome all aimed at detecting differences between UPD and BPD.

Fifteen significant parameters such as clinical symptoms, comorbidities (alcohol abuse), behavioural and temperamental characteristics were isolated on the basis of the applied screening chart. These grouped factors were called an abbreviated screening chart for bipolar depression (ASCBPD). The receiver-operating characteristic (ROC) curve showed that ASCBPD correctly classified 76 of 80 cases (95.00%) as BPD (sensitivity) and correctly classified 58 out of 60 cases (96.67%) as UPD (specificity). The ASCBPD has shown high reliability, validity, and accuracy in discriminating BPD from UPD during index depressive episode.

Clinical symptoms such as mood reactivity and mood swings, impulsivity, irritability, affective alternation, increased motor drive and logorrhoea along

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with comorbidity such as alcohol abuse, behavioural and temperamental traits can serve reliably for differentiating BPD from UPD.

Key words: bipolar disorder, bipolar depression, unipolar depression, screening chart

Introduction. The distinction between unipolar and bipolar depression is important, as it has significant implications for treatment and prognosis. Individuals with bipolar depression may require different pharmacological and psychotherapeutic interventions compared to those with UPD, and the long-term course of the illness may also differ. BD is a chronic disease with a progressive course comprising of manic, hypomanic, mixed, and depressive episodes, and significant subsyndromal symptoms that are often present. This symptomatic variety leads to a reduced quality of life, functional, and cognitive impairment, and ultimately to a premature death [1,2]. The complexity of BD is complicated by the presence of medical (e.g., hypertension, diabetes, obesity) and psychiatric comorbidities such as anxiety and personality disorders, attention-deficit/hyperactivity disorder, and alcohol and illicit substances abuse [3]. The 2013 Global Burden of Disease Study indicated that 48.8 million people worldwide suffered from BD, with the disease being more prevalent in women and patients aged 25–29 years [4].

In addition, among mental disorders, BD ranks fifth in terms of years of healthy life lost [5]. Patients with BD have up to 20–30 times greater suicide rate compared to that of general population [6, 7] making it one of the most lethal psychiatric diseases.

The delay in correct diagnosis of BD is stretching up to 10 years, and has been a challenge for psychiatrists having had great implications for treatment and long-term prognosis, especially given the fact that nearly 40% of patients with initial depression switch to mania/hypomania during 3 to 13-year follow-up [3,8–10]. Basically, the accurate diagnosis of BPD is complicated by three factors [11]: (a) significant overlap in symptomatology between unipolar and bipolar depression; (b) failure of therapists to recognize previous hypomanic symptoms, and (c) failure of patients to report them. On the one hand, prescribing antidepressant as monotherapy for BPD increases the risk of switching into opposite affective pole and leads to mixed states or initiates rapid cycles. It can also induce poor or partial response to the treatment and builds up a resistance to antidepressants [1,12]. On the other hand, UPD patients unnecessarily exposed to mood stabilizers would worsen their depressive state [12]. It is a well-known fact that at least 50% of later diagnosed bipolar patients begin with a depressive episode [13] and because of that they are diagnosed as having UPD. Due to that misdiagnosis only 20% of BD patients receive the correct diagnosis within the first year of treatment [14].

The aim of the present study is to collect data and to develop a set of predictive criteria for the diagnosis of BD during index depressive phase, long before the manifestation of first manic/hypomanic episode has occurred. In order to achieve

this task, the author compares and evaluates a set of demographic data, as well as some family diseases, ontogenetic factors relevant to the studied samples. The clinical symptomatology in both groups were systematically explored and scrutinised with the idea of developing a screening chart that could serve to distinguish BPD from UPD during index depressive episode.

Material and methods. ***Participants and recruitment.*** The study consists of two phases of 140 consecutively hospitalized patients treated at Sofia Mental Health Centre "Prof. N. Shipkovenski": 01.2007–06.2008 (first phase) and 10.2016–07.2018 (second phase). In total 23 men and 37 women with UPD were included ($n = 60$) with mean age 45.4 (± 11.3) and, respectively, 23 men and 57 women ($n = 80$) with BPD with mean age 42.9 (± 10.8).

Inclusion criteria: men and women 18–65 years old diagnosed either with major depressive disorder or recurrent depressive disorder, or BD I, BD II, and cyclothymic disorder presenting a current depressive episode.

Exclusion criteria: the study did not include patients with comorbid medical illnesses or other psychiatric disorders; addiction to psychoactive substances and alcohol; mental retardation IQ < 70; epilepsy or permanent neurological deficits; cognitive impairment and borderline personality disorder. Diagnostically doubtful cases, as well as those with BD III (medication-induced hypomania resulting from administration of antidepressants) were also excluded.

The study was conducted in accordance with the Declaration of Helsinki and the rules of Good Clinical Practice (ICH-GCP). All subjects provided written informed consent after a complete description of the study procedures and participated without receiving any form of payment.

Clinical assessment. A structured clinical interview M.I.N.I. PWC 5.0.0 Bulgarian Version (DSM – IV/TR) was used for the diagnoses. The Hamilton Depression Rating Scale (HDRS 17) was applied to verify the diagnoses. An investigator-designed screening chart for bipolar depression (SCBPD) was administered to each patient. Both samples were tested with the Mood Disorders Questionnaire (MDQ) [14] and the Bipolar Disorder Rating Scale (BDRS) [15].

Design and procedures. *First stage:* after having been diagnosed by the authors with M.I.N.I. and Hamilton Depression Rating Scale (HDRS 17) with a total score of ≥ 17, patients were retested with the same clinical tools by another experienced clinician. All patients in the sample were interviewed in a structured manner in order to complete the SCBPD. *Second stage:* Mood Disorders Questionnaire (MDQ) is a short and easy-to-use self-report scale to screen for BD. Patients complete the self-administered questionnaire translated into Bulgarian. *Third stage:* the researchers filled in Bipolar Disorder Rating Scale (BDRS) for each patient within a clinical interview procedure. *Fourth stage:* a statistical analysis was carried out to obtained data from the three previous phases. *Fifth stage:* based on the outcome of the obtained results, a shortened version of SCBPD entitled abbreviated SCBPD or ASCBPD has been developed.

Statistical assessment. The data were processed with the program for statistical analysis – the IBM SPSS Statistics software 20.0. p-value ($p < 0.05$) was chosen as a level of significance (α) at which the null hypothesis was rejected. The following methods were applied: one-sample Kolmogorov-Smirnov's test; Chi square (χ^2) test and Fisher's exact test; Student's t-test for distribution; Mann–Whitney's U test; item analysis for the internal consistency of the scale; correlation analysis for reliability; Pearson's coefficient for validity of ASCBPD; Hosmer and Lemeshow's test for a logistic model; stepwise logistic regression; receiver operating characteristic cure (ROC) to determine the sensitivity and specificity of ASCBPD and the area under the curve (AUC) was assessed by different ranges of cut-off points to determine the ASCBPD's bipolar diagnosis cut-off.

Results. The SCBPD consists of more than 69 indicators comprising a constellation of demographic characteristics parameters, somatic and psychiatric comorbidities, individual psychosocial development, onset, course, clinical symptoms, aspects of cognitive impairment, and disease remissions all aimed at picking up the specific profile of BPD. By means of a descriptive and item analysis, fifteen factors with a statistical significance related to the diagnosis of BPD were established (Table 1).

T a b l e 1. Fifteen factors significantly associated with a diagnosis of BPD

Parameter		Diagnosis		Total	X^2	df	p
		UPD ($N = 60$)	BPD ($N = 80$)	($N = 140$)			
Bipolar spectrum family loading	No	55 (91.7%)	61 (76.3%)	116 (82.9%)	5.74	1	0.0166‡
	Yes	5 (8.3%)	19 (23.8%)	24 (17.1%)			
Hypersensitivity (*highly sensitive person*)	No	40 (66.7%)	19 (23.8%)	59 (42.1%)	25.90	1	0.0000‡
	Yes	20 (33.3%)	61 (76.3%)	81 (57.9%)			
Truancy/absence from work	No	60 (100%)	67 (83.8%)	127 (90.7%)		1	0.0006†
	Yes	0 (0%)	13 (16.3%)	13 (9.3%)			
Physical aggression and violence	No	60 (100%)	74 (92.5%)	134 (95.7%)		1	0.0374†
	Yes	0 (0%)	6 (7.5%)	6 (4.3%)			
Alcohol abuse	No	60 (100%)	65 (81.3%)	125 (89.3%)		1	0.0001†
	Yes	0 (0%)	15 (18.8%)	15 (10.7%)			
Evening brightening and activity invigoration	No	53 (88.3%)	8 (10%)	61 (43.6%)	85.57	1	0.0000‡
	Yes	7 (11.7%)	72 (90%)	79 (56.4%)			
Frequent job changes	No	59 (98.3%)	58 (72.5%)	117 (83.6%)	16.67	1	0.0000‡
	Yes	1 (1.7%)	22 (27.5%)	23 (16.4%)			
Mood alternation (*switching to the opposite mood pole*)	No	60 (100%)	57 (71.3%)	117 (83.6%)		1	0.0000†
	Yes	0 (0%)	23 (28.8%)	23 (16.4%)			
Mood fluctuations	No	55 (91.7%)	4 (5%)	59 (42.1%)	105.62	1	0.0000‡
	Yes	5 (8.3%)	76 (95%)	81 (57.9%)			

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Table 1 – *Continued from previous page*

Parameter		Diagnosis		Total	X^2	df	p
		UPD ($N = 60$)	BPD ($N = 80$)	($N = 140$)			
Impulsiveness	No	60 (100%)	55 (68.8%)	115 (82.1%)	22.83	1	$0.0000^{\ddagger}$
	Yes	0 (0%)	25 (31.3%)	25 (17.9%)			
Staying up late	No	53 (88.3%)	17 (21.3%)	70 (50%)	61.72	1	$0.0000^{\ddagger}$
	Yes	7 (11.7%)	63 (78.8%)	70 (50%)			
Irritability	No	44 (73.3%)	13 (16.3%)	57 (40.7%)	46.28	1	$0.0000^{\ddagger}$
	Yes	16 (26.7%)	67 (83.8%)	83 (59.3%)			
Mood reactivity	No	48 (80%)	24 (30%)	72 (51.4%)	34.31	1	$0.0000^{\ddagger}$
	Yes	12 (20%)	56 (70%)	68 (48.6%)			
Increased verbal output (*talkativeness*)	No	58 (96.7%)	34 (42.5%)	92 (65.7%)	44.65	1	$0.0000^{\ddagger}$
	Yes	2 (3.3%)	46 (57.5%)	48 (34.3%)			
Increased motor drive (*restlessness*)	No	49 (81.7%)	40 (50%)	89 (63.6%)	14.85	1	$0.0001^{\ddagger}$
	Yes	11 (18.3%)	40 (50%)	51 (36.4%)			

‡ Pearson Chi-Square
† Fisher's Exact Test

The results obtained from BPD group (see Table 1) showed a positive familial burden for bipolar disorders (23.8%; $p = 0.0166^{\ddagger}$) and hypersensitivity (76.3%; $p = 0.0000^{\ddagger}$). Significant differences were reported between the unipolar and bipolar groups regarding physical aggression and violence ($p = 0.0374^{\dagger}$) and alcohol abuse ($p = 0.0001^{\dagger}$).

Truancy/absence from work (16.3%; $p = 0.0006^{\dagger}$) and frequent job changes (27.5%; $p = 0.0000^{\ddagger}$), were more common in the BPD group and testify for significant social dysfunctions. Clinical symptoms such as mood swings, staying up late, evening chronotype (evening brightening and energy invigoration), affective fluctuations, mood reactivity, irritability, psychomotor restlessness, anhedonia, increased verbal output have shown significant differences between the studied groups and clearly underline the specific profile of BPD (Table 1). From now on, the selected indicators will be called the abbreviated screening chart for bipolar depression – ASCBPD.

Reliability and validity of ASCBPD. In order to determine the reliability (internal consistency) of the ASCBPD, correlation analysis was applied. The results have shown a high Cronbach's alpha coefficient (0.87) and relatively low inter-item correlation (0.30) which indicate a good internal consistency of the ASCBPD. The difficulty [Mean (difficulty)] of the individual items is within the limits ($0.1 \div 0.9$). The discrimination coefficients [Corrected Item-Total Correlation (discrimination)] are relatively high around 0.4 and above this value. All this confirms the good reliability of the studied discrimination chart. To estab-

lish validity of ASCBPD, a correlation was sought between ASCBPD and MDQ, and ASCBPD and BDRS, respectively. A strong linear correlation was found ($r = 0.87$, $p = 0.000$) with the MDQ scale and no linear correlation ($r = 0.01$, $p = 0.862$) with the BDRS. However, by analysing all items of BDRS 13 factors has shown a significant difference ($p = 0.0103$ t-test) between the groups of UPD and BPD. A weak, but significant linear correlation was reported when ASCBPD was compared with BDRS (13 items) [($r = 0.21$, $r = 0.011$)].

Logistic regression model and accuracy. ASCBPD items were incorporated as predictors in a stepwise logistic regression with diagnosis bipolar vs. unipolar depression. As a result of stepwise logistic regression, only those of them with significant regression coefficients ($p < 0.05$) remained in the model. The Hosmer–Lemeshow's test used to assess the goodness of fit and calibrate the logistic regression models reported a good fit of the applied logistic model ($\chi^2 = 2.56$; $p = 0.6347$). The obtained results from the logistic regression were subjected to a receiver operating characteristic (ROC) curve analysis. ROC curve permits to define the accuracy (sensitivity and 1-specificity) of ASCBPD (Table 2).

T a b l e 2

Specificity and sensitivity of the ASCBPD

ROC analysis	Working diagnosis	Expected diagnosis		% Correct
		UPD	BPD	
Specificity	UPD	58	2	96.67
Sensitivity	BPD	4	76	95
Total %				95.71

Sensitivity shows that the model correctly classifies 76 out of 80 cases (95%) as bipolar depression. Specificity shows that 58 out of 60 cases (96.67%) were correctly classified as unipolar depression. The overall percentage of correctly predicted cases by the model was 95.71. ROC curve was built based on the applied logistic model. The total area under the curve is 0.985 (Fig. 1).

After the accuracy of ASCBPD was determined, the area under the ROC curve (AUC) was assessed by different range of cut-off points to determine the bipolar diagnosis. Figure 2 represents the ROC curve and AUC at different ranges of cut-off points.

The ROC analysis concluded that at cut-off 4 the AUC was the largest. This allows us to predict the following cut-offs for ASCBPD serving as diagnostic criteria: the cut-off between $0 \div 4$ points stands for UPD diagnosis and that of more than 4 points – for BPD diagnosis.

Discussion. The factors having association with the diagnosis of BPD such as family genetic loading with bipolar spectrum, alcohol abuse [10, 13, 16], and

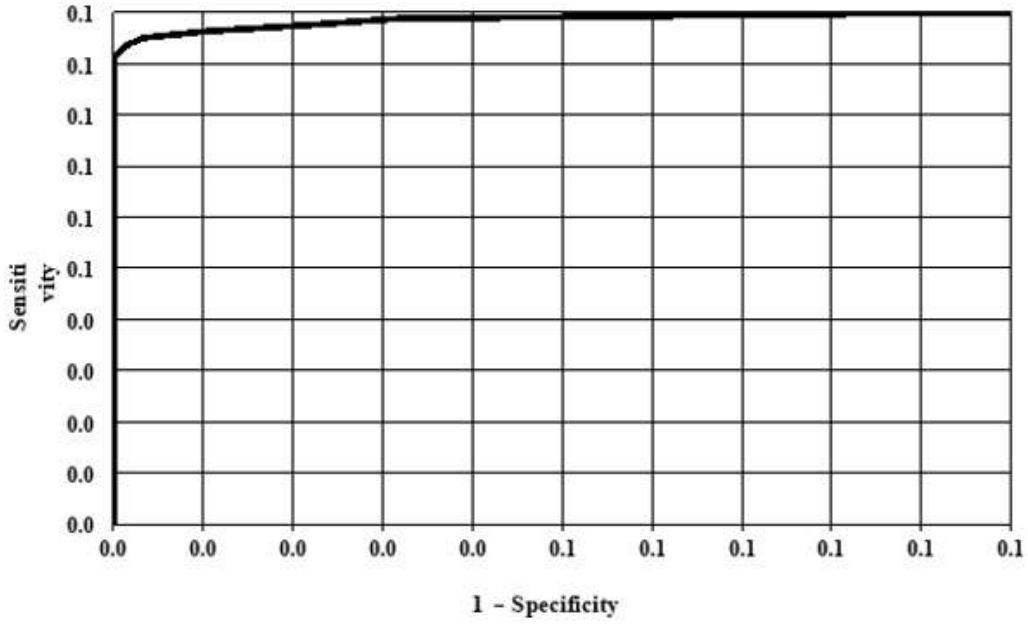

Fig. 1. Sensitivity and specificity of ASCBPD assessed by a receiver operating characteristics (ROC) curve

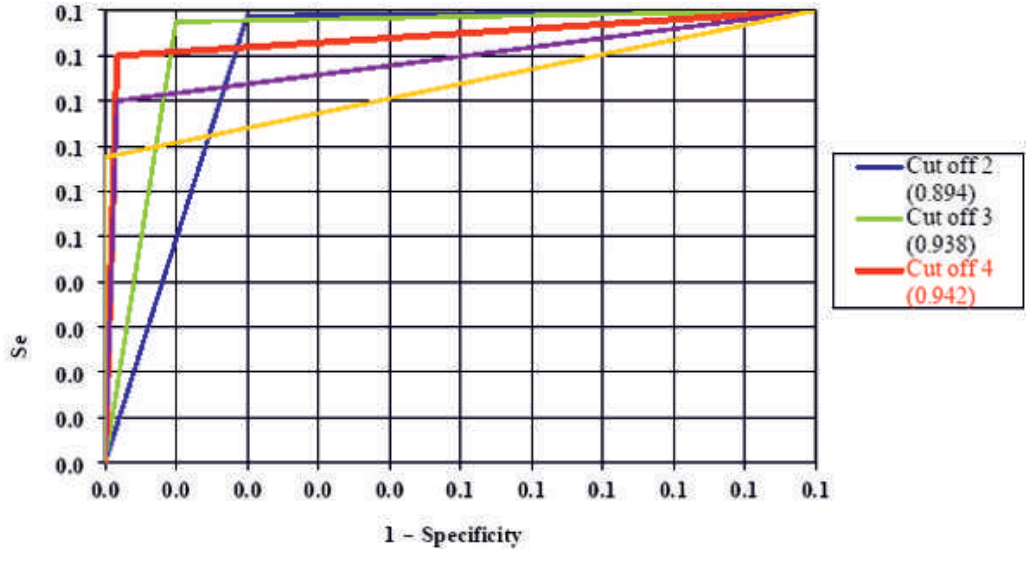

Fig. 2. ROC curve and area under the curve (AUC) at different ranges of cut-off points

aggressiveness are all in line with the obtained results from the studies in the field. Frequent job changes and sense of subjective professional failure, individual's hypersensitivity to external stimulation and interpersonal relationships, truancy, were found to be significant characteristics associated with bipolarity [10].

The most important part of the studied factors are clinical symptoms. These include evening chronotype (evening invigoration and surge of energy), mood alternation, mood swings, impulsivity, staying up late, irritability, mood reactivity, increased verbal output (logorrhoea), increased motor drive, impulsivity, and anhedonia. On the whole, these symptoms can be attributed to a mixed depression and can be conceptualised as a symptomatic continuum between unipolar depression and mania, with variable expressions of bipolarity representing different dimensions of underlying pathophysiological mechanisms [17, 18] and genetic vulnerability expressed by the endophenotypes. The endophenotypes refer to traits present in unaffected individuals that can be interpreted as a marker of disease predisposition, i.e. a genetic substrate potentially linked to the illness. All these clinical characteristics derived from the study (essentially cross-sectional parameters) have been confirmed in the great majority of other studies [8, 19, 20].

ASCBPD as a screening tool. The ROC curve is drawn up based on the used logistic model. The sensitivity of ASCBPD has shown that the model correctly classified 76 of 80 cases (95.00%) as BPD and specificity correctly classified 58 of 60 cases (96.67%) as UPD. The overall percentage of correctly predicted cases by the model was 95.71. The high sensitivity of the test is associated with a low rate of false negatives, i.e. of affected people misidentified as healthy. AUC is of 0.985. The performed simulations with variable cut-offs have found that at cut-off 4 the AUC was the largest 0.942. This allows us to define the following diagnostic cut-offs based on the score of the ASCBPD: for diagnosis of UPD $0 \div 4$ points and for that of BPD > 4 points.

Limitations. (1) The study did not distinguish between BD subtypes I and II. (2) The duration of depressive episodes was not reported. (3) The main limitation is sample size, which reduces the strength of our findings.

Most importantly for all clinicians is to be cautious of labelling and misdiagnosing, so it is advisable to use the screening scale as a supplementary tool.

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