

Psychohematology. Attempt to Summarise

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ABSTRACT

AIM: This article describes studies involving mental and personality disorders in patients with blood diseases - disorders typology, prevalence, risk factors for developing of mental disturbances and their treatment.

METHODS: The work is done on the basis of scientific literature search in various databases and analysis of the resulting material.

RESULTS: There was obtained information on the prevalence, typologies, risk factors and treatment of blood diseases in the available literature.

CONCLUSIONS: The presented data of literature suggests clinical heterogeneity and a wide range (from asthenic reactions to delirious states) of psychopathological disorders detected in blood diseases patients. The main risk factors are severe underlying disease, chemotherapy management (especially corticosteroids), elderly patients. In most cases of adjustment disorders there was observed a combination of several risk factors (both general and specific). In the context of the tolerability and safety of pharmacotherapy preference was given to atypical antipsychotics and new generations of antidepressants (SSRI, SNRI). It remains to study the mental disorders and personality disorders, which are formed in patients with specific malignant and nonmalignant (hemophilia, thrombocytopathy etc.) diseases and to develop differentiated approaches to pharmacotherapy and psychotherapy in such states.

Key words: Mental Disorders; Blood Disorders; Psychosis; Adjustment Disorders; Risk Factors; Treatment

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INTRODUCTION

Blood diseases (BD) are a heterogeneous group of malignant and non-malignant diseases in which mental disorders (MD) manifest on the average in a half of observations.

Comparable data of MD prevalence in BD patients (37,5-48%) presented in the works of J.Prieto *et al* (2002)^[1], D.Stark *et al*(2002)^[2], T.Sasaki *et al* (2000)^[3] and G.Lloyd *et al* (1984) conducted studies on samples of patients with different BD.

Thus, J.Prieto *et al* (2002)^[1] in a prospective study conducted from July 1994 to August 1997, observed 220 patients aged 16 to 65 years with various forms of leukemia, after bone marrow transplant (BMT). The authors evaluated the mental state of patients on admission and weekly during hospitalization until discharge or death. Prevalence of MD in the sample was 44.1%. Mood disorders are diagnosed in 14.1% cases, of which 12.3% - a major depressive episode, in 0.9% - dysthymic disorder, in 1.4% - induced corticosteroids mood disorder. Anxiety disorders were found in 8.2% of patients, including phobic disorder - at 1.8%, generalized anxiety disorder - at 1.8%, panic disorder - in 1.4 %, corticosteroid-induced anxiety disorder - at 4.0%.

The prevalence of adjustment disorder was 22.7%, including depressive reactions - 7.3%, anxiety - 6.8%, mixed (anxious-depressive) disorder - 8.6 % cases. Delirium was recorded in 7.3% patients. D.Stark *et al* (2002)^[2] in a study of 178 patients with non-Hodgkin's lymphoma, Hodgkin's disease, plasma cell hematological malignancies (also included patients with melanoma) revealed an anxiety disorder in 48% of cases. According to T.Sasaki *et al*(2000)^[4] and MD were diagnosed in 16 of 39 (41%) of patients suffering from leukemia. The study G.Lloyd *et al* (1984) 15 of 40 (37.5%)

patients with malignant lymphomas related to the most severe BD pole and had significant mental pathology^[5].

There are 2 studies which are somewhat different from the previous ones. Thus, T.Hosaka *et al* (1994) conducted a study in which the individual types of MD in 31 patients with BD were distinguished. Using in a more rigorous methodology (structured interview based on the criteria of DSM-IV) can be explained by the fact that diagnoses of acute leukemia (AL) were made at a much lower proportion (29%) patients in comparison with the data cited above^[6].

On the other hand, F.Hurtado *et al* (1993)^[7] identified mental disorders in 77% of cases as a result of a survey of a homogeneous group of 22 patients with leukemia. Although the authors do not offer their own explanation of such a high figure, more than 2 times superior to the values obtained in most other studies, we can assume that one of the reasons for this discrepancy is the impact factor of somatic condition, traditionally regarded as a significant predictor of higher frequency and severity mental disorders, comorbid somatic diseases.

The large epidemiological study of MD prevalence in the inpatient hematological clinic was conducted by D.Vybornykh (2014). The author investigated a number of epidemiological parameters of the patients: sociodemographic data, a prevalence of mental disorders in the studied patients, receiving psychotropic drugs in the past, compliance in relation to the treatment of BD and so on. It was found that the overall prevalence of mental disorders among the examined patients corresponds to 71.3 %. Among certain BD and psychopathological syndromes disclosed in the studied patients, adjustment disorders (54.7%), chronic sleep disorder (6.6 %) and somatogenic psychoses (3.3 %) dominated. It was established that a vast majority of patients adhere to regimen prescribed by physicians, seeking medical help in time, and only among persons with mental illness and severe personality disorders disclosed violations of the therapeutic cooperation, which in extreme cases can lead to delays in diagnosis and inappropriate treatment of the blood system diseases^[8].

Thus, despite the marked differences in the data, BD characterized by high comorbidity with MD, which confirms the relevance of their further study.

THE IMPACT OF MD ON THE COURSE OF THE BD

Information about the adverse effects of comorbid MD on the clinical outcome and quality of life of patients with BD are presented in table 1.

SOMATOGENIC PSYCHOSES

Typological differentiation of somatogenic psychoses, despite the undoubted scientific and practical relevance, remained insufficiently developed until recently. In most studies, the polymorphic manifestations of somatogenic psychoses were united in collective term "psychosis" or qualified in accordance with the ethiopathogenetic factors which play the role of master of classifiers.

The first of these areas are combined heterogeneous psychoses by their clinical manifestations - from abbreviated (subsyndromal) to clinically completed and protracted forms. When discussing the studied psychopathological disorders, some authors suggest that such abnormalities in BD limited by formation of the certain features of perception disorders (hypnagogic hallucinations) and affective disorders (perplexity and anxiety) on the background of asthenia^[9-11].

J.Haber (1952) describing somatogenic psychoses in polycythemia^[12] pointed out that the clinical picture is limited by psychopathological conditions of stupor, confusion and visual hallucinations. Other researchers identify more complex psychopathological disorders (mainly in the terminal period BD) - amentia, epileptiform exaltation, delirium, delusional disorders^[3,12,13,14].

V.I.Maksimenco (1967) observed 2 cases of somatogenic psychoses in patients with Hodgkin's disease: fantastically illusory oneiric with anxiety and depression in the background of somatogenic asthenia and "hypoactive" delirium (asthenic disorders with phenomena of disorientation and hypnagogic hallucinations)^[16].

K.V.Mosketi and K.S.Ternovoy (1970) observed a development of hallucinatory-delusional syndrome in patients with polycythaemia vera^[17] and have suggested the connection of the psychopathological disorders with coagulologic ones associated with impaired brain tissue trophism observed in the presence of endarteritis. A focused study of mental pathology in BD presented in B.A.Tselibeev works, the results of which are summarized in the monograph "Psikhicheskie rasstrojstva pri somaticheskikh zabollevaniyakh" (Mental disorders in somatic diseases) (1972)^[18]. The author emphasizes that in the terminal period of acute leukemia the psychotic disorders preceded by severe asthenia, and often by apathetic depression, are quite common. At the same time delirious disorders dominate - from a reduced to a "hyperactive" delirium.

In a study dated by 1964 B.A.Tselibeev *et al* revealed the formation of consciousness obnubilation with delusions of self-blame and poisoning accompanied by severe fatigue and depressive state during the exacerbation of chronic myeloid leukemia (CML). The authors present 2 cases of somatogenic psychoses in patients

Table 1 MD influence on the course of BD in post-transplant period.

Autors	MD	Consequences
E.Colon <i>et al</i> (1991)	Depressive symptoms of various structures in post-transplant period	Increased mortality after BMT ($p=0,041$)
R.Gregurek <i>et al</i> (1996)	Anxiety before transplantation	Increased risk of BMT complications
J.Prieto <i>et al</i> (2002)	Anxiety / depressive adjustment disorder Delirium	Significant increase in the length of hospital stay
R.Illescas-Rico <i>et al</i> (2002)	Depression and/or anxiety in the pre-transplantation period	The deterioration of the clinical prognosis of transplantation
R.Akaho <i>et al</i> (2003)	Anxiety and depressive disorders in the post-transplant period	Lower survival rates in post-transplant period in men
K.Syrjala <i>et al</i> (2004)	Severe depression before HSCT	Slowing down of physical and mental recovery after transplantation
J.Prieto <i>et al</i> (2005)	Major depressive disorder	High 1- and 3-year mortality after HSCT
N.Grulke <i>et al</i> (2007)	Depression in the post-transplant period	Depression was not a strong correlation with after transplantation survival

MD: mental disorders; BD: blood diseases; HSCT: Hematopoietic stem cells transplantation; BMT: bone marrow transplantation.

with Hodgkin's disease (one patient revealed the delusional ideas of poisoning ended in terminally ill with amentia; the other - in periods of physical state deteriorating - had psychomotor agitation with fragmentary delusions, auditory and visual hallucinations). The authors noted schizophreniform psychosis manifestation with the development of perception deceptions (death threats neighbors "voice" inside the head) in 4 polycythaemia vera patients; reduction of psychotic symptoms was accompanied by the asthenia formation. In another case, the development of persecution and self-blame delusions and then Cotard syndrome preceded by debut with anxiety and fears. In the other 2 patients acute paranoid psychosis and organic dementia were revealed^[19].

Thus, psychoses in BD patients often occur in the form of delirium disorders, with incidence, according J.Prieto *et al* (2002) is equal to 7.3%^[1], but as consistent with the results of other studies^[12,19], this measure reaches 41-43%. It can be assumed that these differences are due to inequality of the BD severity in the studied samples.

In this context it is possible to consider the results obtained by other authors. Thus, J.Fann *et al* (2002) showed signs of delirious clouding of consciousness in more than half (54%) of patients who underwent BMT. The authors identify risk factors of delirium in before transplantation period: low cognitive functioning, a high level of urea nitrogen, alkaline phosphatase, and magnesium salts in blood, lack of physical activity. In addition, a development of severe delirium during BMT, according to the authors, contribute to high levels of blood creatinine, past total irradiation, an extremely high rate of alkaline phosphatase, female gender, older age, and an abuse of alcohol or narcotic drugs^[21]. High prevalence of psychoses, according to data cited in the article, can be explained by the prevalence of patients diagnosed with severe onco-hematological pathology (acute leukemia, lymphosarcoma), as well as a significant number of persons with drug / alcohol addiction and delirious disorders in the past history among them.

D.Ross and C.Alexander (2001), describing the delirious clouding of consciousness in cancer patients, focus on the fact that in the terminal stage of disease (including hematological diseases), the prevalence of delirium can reach 85%^[13]. The factors contributing to the development of delirium, identified by the authors were hypoxia, infection (e.g. banal urinary tract infection), fever, opioid or benzodiazepines withdrawal reaction. The study showed that delirium is reversible in approximately 50% of the terminal patients. The authors note, that factors associated with an increased risk of delirium in patients older than 80 years are follow: blurred vision, severe medical comorbidity, signs of dehydration, cognitive impairment, and somatogenic asthenia.

A number of studies contain anecdotal observations. So, S.Passik and M.Cooper (1999) describe a 59-year-old woman with acute myeloid leukemia (AML) and pain of unknown etiology who developed a delirium and increasing the dose of prochlorperazine complicated by extrapyramidal syndrome^[4].

B.Meyers and R. van Ojen (2004) identified hypoactive delirium against the background of somatogenic asthenia limited by disorientation in space and time and fragmentary "visions" in a 21 years old patient with B-cell lymphoma; this condition was cut short by stimulant methylphenidate^[22]. M.Chawla and J.Lindesay (1993) report a case of a 65-year-old woman with polycythaemia vera and delirium^[23].

P.Silberfarb and G.Bates (1983) describe five observations (patients of middle and old age with severe multiple myeloma requires the use of high doses of chemotherapy drugs, including corticosteroids)^[24]; 4 patients had delirious clouding of consciousness, and 1 - delirium

replaced by depression.

There exists some data about the probability of occurrence of delirium in MM and acute leukemia involving the hyperammonemic encephalopathy which is characteristic for this disease^[25-30].

In a systematic study of D. Vybornykh *et al* (2006) presented the somatogenic psychoses typology in patients with BD (118 cases). Three types of psychoses: (1) delirium [73 (61.9%) cases]; (2) endogenomorphic psychoses [38 (32.2%) cases] (hallucinatory-paranoid states [19 (50% of 38) cases], depressive - delusional states - 16 cases (42.1% of 38), oneiric states- [3 (7.9%) patients (38)]; (3) somatogenically provoked attacks of paroxysmal schizophrenia 7 cases (5.9%) were identified^[31].

As another risk factor for somatogenic psychoses in malignant BD the organic lesion of CNS with metastasis in the brain or spinal cord (neuroleukemia) is considerable. Emergence of psychoses is preferable for acute leukemia, occurring with hyperleucocytosis (white blood cell count in the peripheral blood more than $30 \times 10^9/L$), although they are observed infrequently in neuroleukemia^[32].

At the same time neuroleukemia, regarded as a significant factor in the development of psychosis, may promote a development of dementia^[33]. Involvement of the CNS in lesion by leukemic cells is a well-recognized complication of acute lymphoblastic leukemia (ALL) in children, but with the improvement of the results of systemic therapy and long-term survival the prevalence of this complication increases in adults. Among psychopathological disorders, associated with neuroleukemia, the authors mention psycho-organic syndromes.

Among CNS lesions that may cause MD in patients with BD, refers to "Ophelia Syndrome" - paraneoplastic limbic encephalitis described in patients with Hodgkin's disease^[34], on which background likely development of memory loss and delirium^[35].

At the end of the delirium in patients with BD, many authors observed encephalopathy with cognitive disabilities. Thus, J. Fann *et al* (2007) note that in patients who had delirium during myeloablative hematopoietic stem cell transplantation (CCTS), within 80 days after suffering a psychosis preserved cognitive impairment^[20].

Among other disorders reported about the development of paranoid psychosis in ALL patient, where after the antipsychotic treatment step, which led to pernicious narcolepsy, it was chosen the electroconvulsive therapy (ECT) as a therapeutic method^[11].

M.Jablonski *et al* (2002) describe the manifestation of somatogenically provoked depressive-paranoid psychosis in patients with acute leukemia that developed during chemotherapy and BMT and require hospitalization in a psychiatric hospital^[36].

Psychotic depression in polycythaemia vera (one observation of each) was found by D.Murray and R.Hodgson (1991)^[37], M.Mazzoli and F.Benazzi (1992)^[38], as well as C.Fones and W.Tsoi (1995)^[39].

Two observations, regarded by the authors of the publications to psychogenic psychoses, allow (taking into account the characteristics of the debut and disease pattern) to doubt such qualifications and assume a somatogenic nature of conditions mentioned above.

D.Moss (1980) describes a case of paranoid disorders in men suffering from CML (without manifest psychoses in history)^[40]. At the final stage of the course chemotherapy (after 2 weeks from the date of persisting) decreased mood occurred in a patient, he refused examinations and treatment, stating that doctors are trying to kill him in the last 2 days. Later the idea of ability to independently control the symptoms of the disease such as body temperature and the number of leukocytes in the blood joined. There was convinced that focusing on these parameters may prevent any deterioration.

This state lasted less than a week and docked independently after completion of chemotherapy. The author treats the described symptoms like delusional in psychodynamic terms. From our point of view, based on the detection the relationship of delusional disorders with hypothymic signs in patient, and spontaneous relief of them in the end of somatogenic factor (chemotherapy) impact, a condition, seen in patients, can be considered as a transient somatogenic psychosis with depressive-delusional content.

M. Irwin (1984) describes an acute psychotic episode in a 13-year-old boy suffering from ALL. Against the background of chemotherapy and massive antibiotic therapy the boy expressed anxiety and insomnia for 2 days. He claimed that his brain was "switched", became a Rubik's Cube puzzle provides answers to questions about his life and death. It seemed that the cube allowed him to read the thoughts of others, and they in turn read the information from his brain. Periodically he became extremely agitated, shouting that flows through his brain and mucus clogs it. Regimen was supplemented with antipsychotics (quetiapine 400 mg / day) and rational psychotherapy. About a week later his condition improved, and after 2 months of antipsychotics were cancelled. At follow-up examination (one year) the patient remains in remission without MD. The author argues that in this case the onset of psychosis has contributed not a toxic effect of cytotoxic drugs (for which there is considerable evidence in the literature), and psychotic - "emotional reaction" to the BD^[41]. Nevertheless, on this basis the total can be regarded as part of this observation somatogenically provoked (lymphoblastic leukemia, effects of cytotoxic drugs and radiation) episode of schizophrenia with elements of the Clerambault syndrome.

Pointing to the possibility of somatogenic psychoses development during treatment with chemotherapy drugs, the majority of authors point out that most often the corticosteroid hormones acted as a precipitating agent. In a series of clinical manifestations of somatogenic psychoses being connected with the side effects of corticosteroids, addressed a wide range of psychopathological disorders (anxiety, depression, hypomania, auditory and visual hallucinations, delusional disorders, memory disorders, disorders of the body schema, insomnia and even catatonia)^[41,42,43].

F. Stiefel *et al* (1989)^[45] indicate that, despite the undoubted positive effect associated with the introduction of corticosteroid hormones in cancer, their use may be associated with the formation of psychopathological disorders (iatrogenic / pharmacogenic effects). Severe affective disorder as a result of the use of corticosteroids is now reported less frequently, but there are mild mood changes (from the euphoria in the early treatment of depressive disorders to the resumption of symptoms of the underlying disease).

The authors emphasize that corticosteroids should be performed with a psychiatric history, physical status, cancer localization process of treatment, the presence of pain, complications - especially on the part of the central nervous system. Information about the observations, which revealed psychotic conditions associated with corticosteroids is presented in Table 2.

Descriptions of pharmacogenic psychoses manifestation of which is connected with the noncorticosteroid cytotoxic drugs are contained in Table 3.

Interferon-alfa (IFN-alfa), immunomodulatory cytokine is used to treat certain diseases, including chronic hepatitis, melanoma and CML. During IFN-alfa therapy may arise severe MD, including depression with suicidal thoughts and paranoid psychoses^[46]. The psychotic conditions with mood disorders like depression^[47-49] and mania^[50] and bipolar disorder^[51] when using IFN-alfa are

described.

A. van Gool *et al* (2003) note that IFN-alfa is able to induce depressive symptoms, but the likelihood of receiving other MD is not so obvious. An acceptable pathophysiological theory of cytokine-induced MD does not exist, but this relationship is empirically confirmed by some researchers^[52] (Table 4).

A development of MD in connection with the use of other drugs is also considered. In particular, is cited the case of "secondary anxiety" in the appointment of antiemetic drug ondansetron (Zofran), the patient, received allogeneic BMT for CML (Ph-positive)^[53]. On the 2nd day of Zofran admission, the patient developed (based on clinical description) an episode of acute generalized anxiety. Such condition was stopped by the appointment of lorazepam 1 mg / day. Neurological disorders have been identified. Ondansetron was temporarily cancelled, but when it was resumed taking the drug again anxiety developed again: the patient complained that "she is not herself" – can not think clearly because of her absent-mindedness. The state was cut short by using lorazepam in the same dose. J. Caplan (2006)^[54] gave observation, in which a patient after 4 hours of 1-fold dosing ATRA, used for the treatment of acute promyelocytic leukemia, began to complain of severe anxiety, followed by delirium, which was cut short in 48 hours by intravenous infusion of haloperidol.

Anecdotal reports, which describe somatogenic psychoses in BD, complicated by encephalitis (herpes infection) are shown in some studies (Table 5), which does not make a definitive judgment about the peculiarities of psychopathological manifestations of such disorders.

D. Vybornykh *et al* (2008) studied the risk factors for somatogenic psychoses in patients with BD^[32]. It was found that in all cases of studied somatogenic psychoses they are formed on the background of severe BD, accompanied by the development of multiple organ pathology (acute renal, hepatic, cardiovascular failure), massive intoxication, severe electrolyte disturbances (hypercalcemia, hyponatremia or hypernatremia), myelosuppression (agranulocytosis, thrombocytopenia, anemia). Somatogenic psychoses formed with effects of exogenous factors are these: cytotoxic drugs - 103 observations (87.2%) (of which 68 (57.6%) - in combination with glucocorticoid therapy), once in 2 patients (1.7%) (in patients with aplastic anemia) were used glucocorticoid drugs without cytotoxic drugs; administration of interferon-alfa - 5 observation (4.2%), viral encephalitis - 5 observation (4.2%) (in 3 cases - herpetic, 2 - caused by Epstein-Bar) neuroleukemia - 3 cases (2.5 %). Somatogenic psychoses associated with a course of chemotherapy, which included a combination of cytostatics with glucocorticoid therapy (68 patients, 57.6%), presented the entire spectrum of psychotic conditions observed in patients studied sample: delirium reduced - 31 observation of 68 (45.6%), delirium deployed - 16 (23.5%); endomorphic psychoses - hallucinatory-paranoid - 7 (10.3%), depressive-delusional - 6 (8.8%); oneiric - 3 (4.4%), somatogenically provoked attacks of schizophrenia - 5 (7.4%).

ADJUSTMENT DISORDERS

According to different authors, adjustment disorders are psychogenic disorders associated with physical illness situation and are among the most frequent forms of MD in inpatients and outpatients^[55]. The highest prevalence of adjustment disorders have been reported in patients with severe, life-threatening medical illness, which include cancer.

Prevalence of adjustment disorders in patients with malignant

tumors varies quite widely - from 20 to 100%, depending on the methodological and diagnostic approaches used by different researchers^[56-62].

Analysis of works devoted to adjustment disorders in patients with BD is complicated by the fact that some of them have been performed on small samples and even individual casuistic observations, and some of them were based solely on psychometric techniques. According to different authors^[1,61,64], the prevalence of adjustment disorders in this group of patients varies about 22,6-53,3%.

According to J.Prieto *et al* (2002)^[1], adjustment disorders in patients with BD were detected in 22.7% of patients. T.Sasaki *et al*(2000)^[3] among the 39 examined patients with BD in 9 (23%) identified adjustment disorder. Comparable calculations leads T.Hosaka *et al* (1994)^[61]: 7 out of 31 (22.6%) patients - with adjustment disorder. F.Hurtado *et al* (1993)^[7] during the examination of 22 patients with acute leukemia in 17 (77%) identified MD, among which the most frequent were adjustment disorder (82%) and psychosomatic disorders (59%).

It is emphasized that anxiety disorders, post-traumatic stress

disorder (PTSD) and depressive disorders are mainly among adjustment disorders. Thus, J.Devlen *et al* (1987)^[64] evaluated 90 patients at a mean of 32 months after diagnosis of Hodgkin's disease or non-Hodgkin's lymphomas. As a result of the psychiatric examination in 48 (53.3%) patients were found to have anxiety, depression or a combination of anxiety-depressive disorder adaptation, of whom 21 (23.3%) patients - syndromic completed, in 27 (30%) - subsyndromal (borderline) level.

M. dos Santos *et al* (1991) summarized the data obtained in the course of the year in the hematology ward. During a 6-month period, the authors examined a group of hospitalized patients with leukemia, Hodgkin's disease and non-Hodgkin lymphomas, using semi-structured interviews. Adjustment disorders prevalence (depression and / or anxiety) were assessed (using the diagnostic criteria for DSM-II-IR) in the range of 20-40%^[62].

The prevalence of adjustment disorders, occurring with predominance of anxiety, according to different authors, is 6,5-33%. Thus, D.Stark *et al* (2002)^[2] during a survey of 178 patients found 18% of patients who met the criteria of ICD-10 for anxiety adjustment disorders. The latter, according to a survey of literature,

Table 2 Iatrogenic (pharmacogenic) psychoses induced by corticosteroids / chemotherapy including steroid hormones.

Autors	Number of cases	BD	Medication	MD	Reversal
J.Ducore <i>et al</i> (1983)	2	ALL	Prednisone	Delirium	Reducing the dose of steroids and chlorpromazine administration
J.Grigg (1989)	1	MM	Prednisone, melphalan, cymedine	Catatonnia	NA
W.Friedenberg <i>et al</i> (1991)	1	MM	Dexametazone	Delirium	NA
B.Sutor <i>et al</i> (1996)	1	ALL	Prednisone	Depression	Electric convulsive therapy
S.Venkataramam <i>et al</i> (1988)	1	ALL	Prednisone	Mania	Discontinuation of prednisone
D.Morris <i>et al</i> (2005)	1	ALL	Dexametazone	Anxiety-phobic disorder with panic attacks	Risperidone
G.Gomez <i>et al</i> (1984)	1	Non-Hodgkin's lymphoma	Vincristine, bleomycin, prednisone	Delirium	chlorpromazine

NA: not available; BD: blood disease; MM: multiple myeloma; ALL: acute lymphocytic leukemia.

Table 3 Iatrogenic (pharmacogenic) psychoses induced by cytostatics.

Autors	Number of cases	BD	Medication	MD	Reversal
H.Braun, W.Eicke, (1955)	1	Hodgkin's disease	Mustin	Delirium	NA
J.Holland <i>et al</i> (1974)	1	ALL	L- asparaginase	Delirium	discontinuation of the drug
J.Slaughter <i>et al</i> (2000)	1	ALL	Cytarabine, daunorubicin	Transient schizophreniform psychosis (panic attack with mentism)	Clonazepame
H.Nakamae <i>et al</i> (2002)	1	CML	Busulfan, cyclophosphamide	Hallucinatory-paranoid psychosis	Clonazepame, haloperidol

NA: not available; BD: blood disease; ALL: acute lymphocytic leukemia; CML: chronic myelogenous leukemia.

Table 4 Iatrogenic (pharmacogenic) psychoses induced by IFN-α.

Autors	Number of cases	BD	Medication	MD	Reversal
D.Strite <i>et al</i> (1997)	2	CML	IFN-α	Bipolar disorder, manic episode	Lithium, valproic acid, haloperidol, clonazepam
J.Thome, U.Knopf (2003)	1	CML	PegIntron	Acute manic psychosis	NA
S.Besisik <i>et al</i> (2003)	1	CML	IFN-α	Major depressive disorder	Alprazolam
U.Wandl <i>et al</i> (1992)	1	CML	IFN-α	Depressive-paranoid psychosis	NA
S.Sacchi <i>et al</i> (1999)	2	CML	IFN-α	paranoid psychoses	NA
N.Kayser <i>et al</i> (2001)	1	CML	IFN-α	delirium	discontinuation of the drug

NA: not available; BD: blood diseases; MD: mental disorders; CML: chronic myelogenous leukemia; IFN-α: interferon-alfa.

Table 5 Somatogenic psychoses in the blood diseases, complicated by viral encephalitis (herpes infection).

Autors	Numbers of cases	BD	MD	Reversal
P.Sirota <i>et al</i> (1988)	1	CLL	Depressive-delusional psychosis	Haloperidol, maprotiline
A.Bosi <i>et al</i> (1990)	1	CML after BMT	Visual hallucinations	Ganciclovir
M.Iscar <i>et al</i> (1997)	1	AML	Delirium	Ganciclovir
Y.Kawano <i>et al</i> (2000)	1	Aplastic anemia, after BMT	Delirium	Ganciclovir
Y.Kim <i>et al</i> (2002)	1	AML after BMT	Delirium	Ganciclovir
M.Schmidt-Hieber, <i>et al</i> (2011)	1	AML	Delirium	Ganciclovir
Bhanushali MJ, <i>et al</i> (2013)	1	AML	Delirium	Ganciclovir

MD: mental disorders; BD: blood diseases; BMT: bone marrow transplantation; CML: chronic myelogenous leukemia; AML: acute myelocytic leukemia; CLL: chronic lymphocytic leukemia.

was performed by T.Sasaki *et al* (2000), some authors estimated the prevalence of adjustment disorders in about 20-33%^[65-67]. T.Hosaka *et al* (1994) of 31 patients with BD showed 2 (6.5%) patients with anxiety adjustment disorders^[6].

Some authors distinguish among anxiety disorders in patients with BD conditions are regarded by them as PTSD. Thus, the study of E.Black and C.White (2005)^[68] in which included 36 patients (questionnaires were used: PTSD Checklist Civilian Version (PCL-C), the Impact of Events Scale-Revised (IES-R) and 2 questionnaire of fear of recurrence). In 17% of the patients signs of PTSD were revealed, and between fear of recurrence and PTSD statistically significant correlations were found.

The study of S.Smith (2008)^[69] in 7.9% of patients with non-Hodgkin's lymphomas showed full compliance with the criteria for PTSD, and a further 9.1% - partially. Risk factors independently associated with PTSD, were lack of social support, negative evaluation of prospects in life and intensive care, and positive - employment and availability of insurance. In addition, some demographic characteristics (belonging to the Negroid race, low levels of education and young age) and clinical factors (disease activity, newly diagnosed and high comorbidity) were independently associated with PTSD.

When BD revealed depression, including depressive adjustment disorders. A.Frances and M.Popkin (1988)^[70] described a case, in which depression was formed 6 months after the diagnosis of acute lymphoblastic leukemia and a course of chemotherapy. In the structure of depressive symptom hypochondriacal disorder occupies a prominent position. The authors diagnosed organic depressive syndrome, but we consider this condition as depressive adjustment disorder, as it evolves traumatic events (BD) besides the immediate impact of somatogenic factors.

C.Fones and W.Tsoi (1995)^[39] described a patient with polycythaemia vera, in which the disease is manifested by simultaneous depression, having the features of adjustment and organic disorders.

P.Davidson (1964)^[71] described a case, showing a development of conversion disorders (stuttering) within hystero-depressive adjustment disorder in a Hodgkin's disease patient.

T.Sasaki *et al* (2000)^[3] gave their own data on the frequency of depressive adjustment disorders in 39 (8%) of patients with leukemia, and point out that, according to different authors, the prevalence of these disorders is between 20 and 40%^[66-69]. Unfortunately, the authors do not discuss the differences in the values of indicators found in the cited study and other authors (8% vs. 20-40%).

T.Hosaka *et al* (1994)^[6] revealed depressive adjustment disorders in 5 of 31 (16.1%) patients with BD.

K.Malyszczak *et al* (2005) found that the depressive adjustment disorders occur in 29% of BD (compared with 11% in patients with other somatic diseases)^[72].

M.Mohammadi *et al* (2014) revealed on the background of depressive adjustment disorders 146 suicide attempts and 63 completed suicides in the Swedish population of 46 309 patients with hematologic malignancies studied from 1992 to 2009. The authors note that suicide attempts are more frequent in patients with a history of mental illness and in immigrants^[73].

The literature provides evidence of development of not only anxiety and depression.

H.Onishi *et al* (2004)^[74] described a conversion disorder with hysterical convulsions until the "hysterical arc" in a 21-year-old female patient with AML. A traumatic situation related to BMT, was

aggravated by the fact that her relapse coincided with the death of her close friend, suffered from leukemia too.

Some authors suggest a possibility of a manifestation of somatoform disorders in patients with Hodgkin's disease. W.Weddington (1982) and D.Cella *et al* (1986) note that there are often arise a psychogenic nausea and sometimes vomiting in patients with this disease receiving chemotherapy^[75,76].

R.Nesse *et al* (1983) described 6 cases, in which a development of unusual and persistent taste and olfactory sensations, repeating the taste and smell of previously administered chemotherapy in patients with Hodgkin's and histiocytic lymphoma were presented. Such people feel while performing activities associated in patients with a visit to the clinic and the situation of drug administration (going out of the car, which came to the clinic, thinking about spent a few months of treatment). The described feelings the authors regard as pseudohallucinations in nonpsychotic patients in a state of clear consciousness and interpret this phenomenon as part of the stress response or traumatic neurosis^[77]. We consider such states as a part of PTSD.

Given the reports (3 of them are described by us in the "Somatogenic psychoses") about the possibility of psychogenic psychoses manifestation in BD patients. B.Wanck (1982)^[78] presented an observation, in which a 59-year-old woman, who had never referred to a psychiatrist, was suspected on BD (erythroleukemia). In further examination she revealed leukemia. When learning of her illness, the patient underwent a brief delusional disorder with unsystematic ideas of persecution (delirium of misrepresentative disease). The patient showed anxiety, argued that doctors hide from her the diagnosis of a terminal illness, and thus want to kill her.

Within 3 days of haloperidol (10 mg / day) in combination with psychotherapy the state was cut shorted. The patient stated that it was relieved after the establishment of an accurate diagnosis. A discussion of the observation carried out from a psychological position: the authors argue that the situation of duality (in this case - uncertainty of the diagnosis) generates an anxiety, which can be reduced by introducing certainty in reporting information to the patient.

D.Vyborykh *et al* (2011) described adjustment disorders in patients with BD. Adjustment disorders in the sample represented a relatively wide range of psychopathological conditions. Among them are marked neurotic (anxiety-dissociative, anxiety-phobic), affective (anxiety-depressive, hypomanic) and schizophrenic (ie, occurring in patients with schizophrenia - dissociative and anxiety-coenesthopathic)^[79].

Risk factors for manifestation of adjustment disorders in patients with BD form which is common for all somatic disorders, as well as specific for this type of pathology. Among the first - the objective intensity of the disease symptoms (severity), especially its treatment and outcome. So, adjustment disorders often formed in acute and severe illnesses, adversely affecting the quality of life (decreased performance, a high probability of disability). These factors also belong to the constitutional (personality disorders), social (education level, material security, etc.), psychological, associated with a disease (semantics diagnosis, specialized hospitals, etc.)^[80].

To group 2 risk factors (specific to BD) researchers attribute the degree of anemia and peculiarities of a particular BD. Thus, F.Hurtado *et al* (1993)^[7] emphasizes that the degree of anemia correlates with the frequency formation of depressive and primarily asthenic-depressive states. In its turn, a rapidly progressive course of BD with the development of severe relapses and defeat of many groups

of lymph nodes also contributes to a manifestation of anxiety and depressive disorders and a need to find a specialized hospital.

Opinions about the participation of gender in adjustment disorders formation in BD are ambiguous and even contradictory. While some authors^[2,3,81,82] refer to the risk factors of a development of adjustment disorders the female sex, the others give opposite results. Thus, the study of B.Kawiecka-Dziembowska *et al* (2005)^[83] showed that more severe depression is more often detected in men. These differences may be related to heterogeneity of BD included in the study sample. The fact that the distribution by sex varies depending on the particular form of BD (from 1.3: 1 to 4: 1)^[84-86].

Separately allocated specific therapy side effects (formation of agranulocytosis, accompanied by fungal infection of the mucous oropharyngeal ulcers; thrombocytopenia with hemorrhages; related infectious diseases - pneumonia, etc.). So, according to J.Devlen *et al* (1987), the affective disorders are positively correlated with similar effects of treatment^[87]. In most cases, as indicated not only by the authors of the cited work, but other researchers^[1,7,66,87], a development of adjustment disorders is a combination of several risk factors (both general and specific).

BMT / HSCT

One of the situations in which adjustment disorders occur most frequently (50%) is BMT (leading treatment for malignant diseases^[88]) or HSCT^[89,90]. Successful transplantation requires an isolation of patients within a few weeks in order to avoid infection, as well as strict adherence to medical recommendations, since it is assumed the possibility of deterioration of the medical state of the patients during the actual intervention and medication.

BMT situation at all stages is associated with a high risk of formation of psychopathological disorders. Therefore F.Hoodin *et al* (2013) suggest a psychological screening of outpatients in pre- and post-transplant periods. Their findings suggest that a brief self-report psychological screen can be easily integrated into routine care of transplantation survivors, stimulate a discussion of psychological symptoms, and improves provider satisfaction with psychological symptom management^[91].

Thus, T.Sasaki *et al* (2000) revealed 16 patients with MD (12 - adjustment disorder anxiety and / or depressive content 2 - depersonalization disorders and brief psychotic disorder and delirium – one of each) among the transplanted 39 patients with various forms of leukemia. The authors did not observe differences in the characteristics of the manifestation MD depending on the type of BMT^[3].

M.Andrykowski (1994)^[92] pointed out to the most important factors of traumatic situation: an isolation in a sterile box, rapid and unpredictable change of the physical condition, frequent invasive medical procedures, treatment side effects, depending on the medical staff, repeated infections, "graft-versus-host" reaction in the review of psychiatric and psychosocial aspects of BMT. Urge intervention is associated with the identification of anxiety and depressive reactions of anger and hostility, "survivor guilt", insomnia, anorexia, delusional formations and "acting out" as one of the most common psychological defenses; often there is a violation of the therapeutic cooperation (noncompliance). Concerning the psychiatric aspects of selected problems, M.Andrykowski noted an importance of timely (before transplantation) to identify MD, which can affect the course of further intervention. In these states the author includes depressive disorder and personality disorders which can be associated with long-term survival following transplantation. The importance of

recognizing MD throughout the transplantation, the author explains that the last inhibit the interaction with the staff, conducting transplantation; limit the rational decision-making about the cost and benefits of the transplantation; reduce the absorption of information obtained in the course of therapy. Among these disorders is depression, that reaches the level of a major depressive episode as in step "preparatory" BMT phase^[93], and in combination with comorbid anxiety on a stage before entering the hospital^[94]. Among the symptoms that accompany the early post-transplant period, isolated symptoms of anxiety and depression (mild to moderate)^[95], and in the distant post-transplant period - the symptoms of depression and PTSD. As a predictor of risk avoidant coping authors identify the lack of social support^[96].

In the previously mentioned study J.Prieto *et al* (2002), whose goal was to assess a prevalence of MD during hospitalization in connection with HSCT and its effect on length of hospital stay^[1], it was showed that after correction of risk factors, determinate by hospitalization and staying in a hospital, mood disorders, anxiety or adjustment disorders ($p = 0.022$), CML ($p = 0.003$) and a higher toxicity associated with treatment ($p < 0.001$), with a high degree of statistical significance associated with a longer duration of hospitalization (median this figure amounted to affective, anxiety and adjustment disorders 22, 24 and 23 days, respectively, and the median for delirium - 33 days). At the same time, this measure was 20 days in the absence of MD. Hence the obvious conclusion about the need for early detection and treatment of psychopathological disorders suggests.

The high prevalence of MD in patients with BMT noted in other reports^[97,98]. In a multicenter study of 215 hospitalized and ambulatory patients, survivors of the HSCT and receiving active treatment, 47% patients identified mental disorders: adjustment disorder (32%), affective (6%) and anxiety (2%) disorders^[97].

J.Lavoie *et al* (2005)^[99] found in 7 (13.2%) cases of the 53 survivors after autologous HSCT for primary resistance or relapse of Hodgkin's disease anxiety or depressive adjustment disorders. Among the 39 patients who underwent allogeneic or autologous BMT, the authors identified nine (23.1%) cases in which before transplantation stage the adjustment disorder with anxiety and / or depression. Among other MD, identified in the pre- and posttransplant stages was registered affective (3 cases; 7.7%), depersonalization (2 cases; 5.1%), and brief psychotic disorder (1 case, 2.6%) and delirium (1 case, 2.6%). Furthermore, S.Sarkar *et al* (2014) note that often a situation of transplantation associated with fear of cancer recurrence (FCR) of BD, while being married ($b = 2.76$, $P = 0.026$), female gender ($b = 4.45$, $P < 0.001$) and depression ($b = 4.44$, $P < 0.001$) were significantly associated with FCR at baseline^[100]. At the same time J.Hefner *et al* (2014) demonstrate the high prevalence of distress in patients who have undergone allogeneic HSCT and associate fear of progression with a younger age^[101].

C.Meyers *et al* (1994)^[65] studied psychogenic disorders in BMT in a situation of isolation. Prior to transplantation, 40% of patients were detected anxiety disorder, and a severity of anxiety is significantly reduced during a hospitalization and remained low for the entire follow-up period, and a level of depression, on the contrary, is increased during hospitalization, but is decreased in the follow-up period.

Comparable data on the relationship of anxiety and depression, depending on the stage of transplantation presented by M.Hjermstad *et al* (1999, 2004)^[67,102] in a prospective study (the main sample - 131 patients with BD, who are appointed on the high-dose

chemotherapy and allogeneic or autologous transplantation; control - 123 lymphoma patients treated with standard chemotherapy). The authors noted that after allogeneic HSCT anxiety levels after one year was higher than in the other 2 groups (autoBMT, chemotherapy), although data were not statistically significant.

S.Lee *et al* (2005)^[103] studied 80 patients with psychiatric diagnoses or taking psychotropic drugs undergoing HSCT. Of these, 38 patients were examined using a battery of psychometric tests in the pre-transplantation period; 55 patients examined after transplantation. The excess of the average of standard indicators on the scales was found in 55% of patients in the pre-transplant period and 44% after transplantation.

It should be noted that the discussion of a problem of depression in BMT in the literature since the 70s of the XX century has a special attention^[104,105]. A.Molassiotis and P.Morris (1997)^[106] noted a high probability of severe manifestations of depression in BMT and presented 2 observations in which depression accompanied by suicidal attempts after transplantation, and 1 case - with suicidal thoughts during the period of isolation. The authors identify suicide risk factors: use of high doses of steroids, metabolism disorders, asthenia, weak family / social support, poor prognosis of a disease, side effects of drugs affecting the central nervous system, impaired body image (especially in adolescents or young adults), insomnia, chronic physical disease, organic CNS undiagnosed mental illness (comorbid depression), alcohol / drugs abuse, MD in a history.

A study of F.Baker *et al* (1997)^[107] conducted using a questionnaire of Center for Epidemiological Studies Depression - Center for Epidemiologic Studies Depression Scale (studied 437 patients with various hematologic malignancies undergoing bone marrow transplantation: autologous - 60.6% and allogeneic - 35.4%), depression (without specifying syndrome characteristics) were found in 1/3 (31%) patients.

Some sources give evidence on a relationship of personality disorders with BD. Thus, J.Matias *et al* (1995)^[108] studied 59 women (MMPI questionnaire and measurement scale aggression Ledesma): 35 diagnosed with breast cancer (group 1) and 24 - BD (group 2), and found significant differences in personality features in two groups. In the 1st group of patients showed a significant increase in performance on social introversion MMPI subscale and in terms of self-aggression, while in group 2 reported an increase on the scale of hypochondria, depression, paranoia, and allo-aggression.

Furthermore, A.Schumacher *et al* (2014) note that resilience (the relative resistance to stress) should be considered as a protective psychosocial factor for patients after BMT. A high degree of resilience can help patients to adapt to their situation and to resume their everyday life^[109].

The problem of MD in patients undergoing bone marrow transplantation, and is closely related to the issue of compliance^[63,110-113]. Improving the perception of pain and other subjective unbearable sensations that occur when performing such manipulations in patients (and especially in the context of comorbid depression^[113]) may violate compliance, which could result in rejection of invasive but necessary diagnostic and therapeutic procedures. Of special importance is the problem of compliance in the case of patients with schizophrenia, because in these conditions, along with interventions for diseases of the blood must have an adequate psychopharmacotherapy^[111,112].

THERAPY FOR BD PATIENTS WITH MD

The literature provides several reports of successful treatment of

psychotic disorders, comorbid with BD. In casuistic descriptions of I.Michopoulos *et al* (2010)^[114] and P.Sirota *et al* (1988)^[115], it is consider the cases of efficacy and safety of quetiapine in patients with bipolar depression, underwent BMT in AML and reduction of delusional depression (arosed after intravenous acyclovir) in combination therapy with haloperidol and maprotiline in patients with chronic lymphoid leukemia (CLL). According to the observations of D.Dixon and J.Craven (1993)^[116], in delirious disorders in patients with BD it is effectively prolonged intravenous administration of haloperidol.

S.Passik and M.Cooper (1999)^[4] gave recommendations for treatment of delirium disorders in patients with BD: treatment of the underlying disease with the abolition of drugs, unnecessary at this stage of therapy and could aggravate the disturbances of consciousness, the appointment of antipsychotic drugs to treat an agitation and productive psychopathological disorders. It is preferable to the use of atypical antipsychotics, less likely to cause extrapyramidal side effects.

Data about treatment of adjustment disorders in patients with BD are limited by description of 2 casuistic cases: panic attacks relief in patients with acute leukemia by clonazepam 2 mg / day^[117] and claustrophobia (CML patients who underwent HSCT) by the appointment of lorazepam 2 mg / day^[118].

D.Vybornykh (2007, 2014) developed therapeutic approaches to treatment of studied MD. Therapy of somatogenic psychoses in the studied patients had stepped nature. The aim of the first phase was psychosis reduction, the second - to support treatment to prevent relapse of psychotic disorders. A preference was given to intravenous administration of psychotropic drugs (in most cases - through the venous catheter). A bulk of therapeutic intervention focused on the first stage. The treatment have a short duration and include the use of antipsychotic of butyrophenone series (haloperidol 15 mg / day used usually in the intensive care unit) under delirious disorders. If necessary of the rapid relief of anxiety / sleep disorders the therapeutic scheme is supplemented by diazepam (20 mg / day).

The therapy of endogenomorphic psychoses demanded more intense effects (daily doses of antipsychotics were increased haloperidol up to 20-30 mg) and longer duration (up to 2 weeks). Under moderate and poorly expressed psychomotor agitation in some patients was used trifluoperazine (up to 10 mg / day). In the second stage of endogenomorphic psychoses treatment dosage of psychotropic drugs was decreased (haloperidol 5 mg / day, trifluoperazine to 5 mg / day). The longest (1.5-2 months) treatment with the maximum dose of drugs (20-40 mg / day) required somatogenically provoked attacks of schizophrenia. In this purpose adjusted in accordance with the dynamics of somatic pathology (dose decreased with physical state worsening). Clinically significant side effects during the psychotropic drugs or adverse interactions with somatotropic drugs (including corticosteroids - prednisolone, dexamethasone and cytostatics - cytarabine, rubomycin, vincristine, cyclophosphamide) wasn't noted^[119,120].

The treatment of patients with BD, which revealed adjustment disorders, led to the relief of the reactive states in 81.3% of patients. There was a two-stage therapeutic tactics in relieving of anxiety and dissociative disorders. In the first phase the dissociative disorders were treated. This, along with pharmacotherapy, dominated by preparations class of atypical antipsychotics, especially in cases where the patient refuses medical treatment because they do not see the need, apply psychotherapeutic effects (rational and behavioral therapy, the study of the social situation of the patient in order to eliminate secondary benefits from the disease), aimed at arresting

of the dissociative disorders^[121]. In this case, in recognition of his disease patients anxiety level rises. In the second stage provided relief of anxiety disorders appointment of tranquilizers. The most comprehensive therapeutic effect was registered in patients with anxiety and phobic adjustment disorders. Especially significant reduction of psychopathological disorders observed in patients with a predominance of the anxiety somatisation in the structure of the reaction (in the foreground of various pathological bodily sensations - massive vegetative disorders, pains, conversions, while the content of anxiety is usually confined thanatophobia and panic attacks are rare and rudimentary). In the treatment of such conditions adjustment disorders improvement under the influence of tranquilizers occurred as early as 3-5 day of admission. Patients reported a reduction of phobias, anxiety fears, as well as the severity and duration of somatization symptoms. Identify and improve general well-being, which the patient connects with both somatic and with psychotropic therapy. Patients are more likely involved in the discussion of the problems associated with the necessity of their own participation in the treatment of physical illness. Almost equally significant therapeutic effect was registered in patients with anxiety and depressive reactions. In particular, patients with depressive adjustment disorders are shown to reduce the severity of depression. Patients report improved mood while reducing a drowse, depression, notes an increase in physical capacity, a burst of energy. The severity of hypochondriac phobia reduces as well. Noting the restoration of the former composure, patients reported a decrease in anxiety concerns about the state of his health, stress that before too pessimistic about the situation, dramatized the prognosis of the disease and its social consequences. The most resistant to therapy were schizophrenic adjustment disorders. Such adjustment disorders were jugulated to varying degrees in 65.5%. In observations with dissociative schizophrenic reactions the latests were sufficiently resistant to the therapy. Only about 2/3 of the observations were able to achieve a therapeutic effect as an increase of compliance of patients. Clinical efficacy of past generations neuroleptics (quetiapine, sulpiride, etc.) is most pronounced in regard to essential cenestopathies in patients with anxiety-coenaethopathic adjustment disorders. The lowest efficacy was observed in patients with fantastic cenestopathies. An intermediate position on the response to therapy occupied elementary and painful cenestopathies. The drugs used in pharmacotherapeutic schema in cases of adjustment disorders in the studied patients had good tolerability and safety. There were no clinically significant interactions between drugs used to treat the underlying disease (cytostatics, antibiotics) and psychotropic drugs, which is largely due to a presence of different metabolic pathways of these drugs. However, in rare cases, side effects of psychotropic drugs observed, described in patients not suffering from BD. In particular, in 3 cases, while taking the antidepressant sertraline, dyspepsia was observed (bloating, nausea, diarrhea), did not require discontinuation of the drug, but only a temporary reduction of dosage. In one case (in elderly patient with concomitant somatic and hematologic pathology) with risperidone the first signs of extrapyramidal disorders brought to light (coarse tremor of fingers), which forced us to cancel the drug^[122].

The presented data of literature suggests clinical heterogeneity and a wide range (from asthenic reactions to delirious states) psychopathological disorders detected in BD patients. The main risk factors are the severe underlying disease, chemotherapy management (especially corticosteroids), elderly patients. In most cases of adjustment disorders observed a combination of several risk factors (both general and specific). In the context of a tolerability and safety

of pharmacotherapy the preference given to atypical antipsychotics and new generations of antidepressants (SSRI, SNRI).

It remains to study the mental disorders and personality disorders, which are formed in patients with specific malignant and nonmalignant (hemophilia, thrombocytopathy etc.) diseases and to develop the differentiated approaches to pharmacotherapy and psychotherapy of such conditions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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