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Epigenetic characteristics of antidepressant drugs

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Епигенетични характеристики на антидепресантите

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РЕЗЮМЕ

Депресията е едно от най-значимите и инвалидизиращи психиатрични заболявания в световен мащаб и поради това е с важен обществен приоритет. Редица доказателства допускат ключова роля на епигенетичната регулация на мозъчните функции в етиологията на невропсихиатричните разстройства. Доказано е, че епигенетичните механизми като ДНК метилиране и модификации на хроматина се повлияват от действието на редица лекарства, включително и антидепресанти. Това насочва интересът на специалистите към изследване на епигенетични вариации, предизвикани от психотропни средства и към проучване на потенциала на епигенетичната терапия при лечението на психиатричните заболявания. Скорошни данни демонстрират действието на антидепресанти и ЕКТ като директни епигенетични модификатори. В настоящия обзор обстойно разглеждаме молекулярните механизми, участващи в епигенетичните промени, предизвикани от антидепресанти. В заключение посочваме, че обобщените данни и съвременното познание на изложените факти дават възможност за нови диагностични и терапевтични подходи в лечението на психиатричните разстройства.

ABSTRACT

Depression is one of the most prevalent and disabling psychiatric disorders worldwide and therefore an important public health priority. Mounting evidence suggests that epigenetic regulation of brain functions is important in the etiology of psychiatric disorders. Epigenetic mechanisms, such as DNA methylation and chromatin modifications, are influenced by many pharmaceutical compounds including antidepressants. It is therefore of interest to investigate how psychiatric drugs are of influence and what the potential epigenetic therapy for psychiatric disorders is. Recent findings suggest that different classes of antidepressants as well as ECT are direct epigenetic modifiers. In this review we have summarized the current data on the molecular mechanisms affected by antidepressants at the level of epigenetics. The recent advances in our understanding of this developing field show new diagnostic and therapeutic approaches for treatment of psychiatric disorders.

Introduction

Psychiatric disorders are characterized by behavioral abnormalities that often persist over a life time and are among the most debilitating of all medical illnesses. Although there are lots of drugs that are nowadays used to treat these disorders, still many patients have sub-optimal recovery and a significant number of individuals remain treatment resistant. Thanks to the advancement of genetic sciences and the development of new techniques in the last decade it has generally been assumed that psychiatric diseases are caused by combinations of genetic polymorphisms or mutations that interact with hazardous environmental factors. Mounting evidence suggests that epigenetic regulation of brain functions is important in the etiology of psychiatric disorders. The recent interest for the role of epigenetics in brain functions has led researchers to explore the possibility that drugs can modify epigenetic processes involved in psychiatric disorders.

Major depressive disorder (MDD) is a devastating neuropsychiatric disorder encompassing a wide range of cognitive and emotional dysfunctions and has a variety of socioeconomic consequences, including unemployment, reduced work performance and marital dysfunction. Moreover, the prevalence of depressive disorders is expected to continue its growth to become the second leading cause of disease burden by the year 2030 [20]. Despite extensive research efforts in past decades, the etiology of depression remains elusive, its diagnosis uncertain and the pharmacotherapy inefficient.

The antidepressants currently used, which target the monoaminergic pathways, require weeks to months of treatment and exhibit very poor or no response in nearly 50% of patients [17]. In addition, there is a marked inter-individual variability in the vulnerability to develop depression, as well as in response to antidepressant treatment. After a multitude of studies, it has become clear that depressive disorders and individual reaction to therapy are typical case of gene × environment interactions [18]. Stress, early-life experiences, abuse and parental violence, and pre-natal exposure to toxins are environmental factors that can influence the vulnerability to develop depression [28, 29]. To address the dynamic changes of depressive symptoms and their response to treatment, recent studies focus on epigenetic mechanisms.

The term "epigenetics" refers to all heritable changes in gene expression that are not coded in the DNA sequence itself, which only alter phenotype without changing genotype. There are three main categories of epigenetic modifications: DNA methylation, chromatin modifications, and non-coding RNA expression [12].

Well-known varieties of DNA methylation, which is accomplished by several types of DNA methyltransferase (DNMT) enzymes, include methylation of cytosine nucleotides that are followed by guanine or adenine, and hydroxymethylation that is a temporary product during the conversion of methylated cytosines to unmethylated cytosines. Unlike other tissues, hydroxymethylation is quite abundant in the human brain. While DNA methylation generally suppresses gene expression, hydroxymethylation can induce gene expression and appears to play a key role in functional plasticity of neuronal cells. Histone proteins posttranslational modifications (HPTMs) at their N-terminal tails include methylation, acetylation, phosphorylation, ubiquitination, sumoylation, etc. HPTMs may suppress or increase the expression of interconnected genes depending on the identity and location of those amino acids. Several types of enzymes such as histone acetylases, histone deacetylases (HDACs), histone methylases and demethylases are involved in histone modifications [25]. Experimental evidence has shown that the mammalian transcriptome includes a number of small noncoding RNAs (sncRNAs), such as short-interfering RNAs and microRNAs (miRNAs), which have been implicated in epigenetic silencing of specific genes [23]. There is incredible complexity in the regulation of the epigenome and evidence suggests that histone modifications and DNA methylation can also interact [11].

Effective antidepressant treatment may be associated with epigenetic changes in genes conferring risk for depression

It has been repeatedly suggested that effective treatment with antidepressants increases peripheral levels of brain derived neurotrofic factor (BDNF) [24] and that a nonincrease of BDNF plasma levels within the first week of treatment could predict treatment resistance with high sensitivity [33] BDNF is an important pro-survival factor for the developing and adult brain, through modulation of neuronal plasticity [26] and has been implicated in the etiology of depression. In line with the reduced serum BDNF levels observed in depressed individuals, a hypermethylation of the BDNF gene promoter in patients with depressive disorder has been reported. At first a post-mortem analysis of DNA methylation in the Wernicke's area of subjects who committed suicide revealed lower BDNF expression associated with increased DNA methylation of four CpG sites located at BDNF promoter 4 [14]. Furthermore, there were investigated the methylation levels of 13 CpG sites within the BDNF exon IV promoter in a sample of depressed patients treated with several antidepressants [32]. A lower methylation was observed in the final responders, without a significant interaction of gender or class of antidepressant. This was paralleled by a decrease of BDNF plasma levels during the first week of treatment.

Currently used antidepressants may display epigenetic effects

➢ Imipramine

Imipramine is a tricyclic antidepressant and inhibits the reuptake of serotonin and norepinephrine. Tsankova et al, 2006 investigated the effectiveness of imipramine on epigenetic regulation of the *Bdnf* gene in the hippocampi of mice [35]. Chronic social defeat led to repression of *Bdnf* and an increase in histone dimethylation of H3K27. Treatment with imipramine caused hyperacetylation of H3 at the *Bdnf* promoters, mediated by downregulation of *Hdac5*. Moreover, the efficacy of imipramine was blocked by overexpression of *Hdac5*, suggesting that downregulation of *Hdac5* is essential to the efficacy of imipramine. The authors commented that since histone H3 hypermethylation was not affected by imipramine, this remained a possible target for antidepressant therapy.

➢ Amitriptyline

Amitriptyline is a tricyclic antidepressant. In rat astrocytes, amitriptyline induced DNA hypomethylation without affecting histone acetylation. Moreover it reduced enzymatic activity of DNMT1without altering its protein levels [27]. The reduction was due to decrease in levels of histone methyltransferase G9a, known modulator of DNMT1. In vitro amitriptyline increased H3 acetylation by inhibiting HDAC activity [19].

➢ Fluoxetine

Fluoxetine is very common antidepressant from the group of selective serotonin reuptake inhibitors (SSRI). In the hippocampus, fluoxetine reversed decreased histone H3K9 trimethylation but not H3K4 trimethylation induced by chronic restraint stress [13]. Chronic fluoxetine treatment of healthy rats decreases acetylation of H3 in the caudate putamen, the frontal cortex and the dentate gyrus. In addition, fluoxetine reversed reduced H3 acetylation in the same way as histone deacetylases (HDAC) inhibitors, suggesting a similar mechanism of action [4]. Furthermore, expression of the methyl-binding proteins MeCP2 and MBD1 was increased, accompanied by increased Hdac2 expression, further inhibiting transcriptional activity in these brain regions [2].

➢ Citalopram

Lopez, 2013 investigated the impact of chronic treatment with citalopram on BDNF expression in patients with depression [16]. The team reported increased BDNF mRNA levels with a significant correlation between change in depres-

sion severity and change in BDNF expression in treatment responders. Also, histone H3 lysine 27 trimethylation (H3K27me3) levels (a marker for silencing genes) at BDNF exon IV promoter were decreased. BDNF expression and H3K27me3 levels were negatively correlated.

➢ **Escitalopram**

Chronic treatment with the SSRI escitalopram reversed depressive symptoms in patients who had a higher methylation status of the *SLC6A4*gene [6]. Additionally, it has been reported that escitalopram reduced the hypermethylation in P11 gene and levels of DNMT1 and DNMT3a mRNA in the prefrontal cortex in a genetic rodent model of depression [22]. The P11 gene has been linked to functional expression of 5-HT (1B) [31] and thus is associated with depressive symptoms.

➢ **MAO inhibitors**

Evidence shows that monoamine oxidase (MAO) inhibitors phenelzine and tranylcypramine both inhibit demethylation of histone H3K4, resulting in a global increase in H3K4 methylation by breaking down lysine-specific demethylase 1 (LSD1), a histone demethylase that is structurally similar to MAO A and B [5]. LSD1 specifically demethylates mono- and dimethylated H3K4 and H3K9, thus inhibiting transcription [1].

Other compounds interfering with epigenetic mechanisms as potential antidepressants

➢ **HDAC inhibitors**

A well-balanced regulation of HDACs and HATs is essential to gene transcription. Compounds that inhibit HDACs have been extensively studied in models of neurodegenerative disorders

- **Valproic acid (VPA)**

VPA is a short fatty-chain acid commonly used in the treatment of epilepsy and bipolar disorder. VPA is the most extensively investigated compound in psychiatric epigenetics and a potent HDAC inhibitor of class I and II. We have summarized the current knowledge of the epigenetic mechanisms of VPA in a separate review (see there).

- **Sodium butyrate**

Sodium butyrate (SB) is a short fatty-chain acid that displays selective inhibition of HDAC class I and II. Similar to VPA, SB upregulates *BDNF*and *GDNF* mRNA levels in astrocytes, with marked increases in *GDNF* promoter activity and promoter-associated histone H3 acetylation [37]. It has also been shown that SB affects histone methylation [10]. Other findings suggested therapeutic role of SB on depressive-like symptoms in animals. However, the results have been inconsistent. Despite increased histone H3 and H4 acetylation in the hippocampus and the frontal cortex following SB administration SB only improved depression-like behavior in three of seven of depression-like behavior [9].

- **Trichostatin A**

Trichostatin A (TSA), an antifungal antibiotic, was also discovered to possess HDAC-inhibiting properties. In the hippocampus TSA induced transcription of promoter exon 1 but not of exon 4 of the BDNF gene, associated with hyperacetylation at H3K9 and H3K14 and increased BDNF protein levels. At the same time an increase in HDAC mRNA and protein levels was also observed, suggesting a compensatory mechanism in response to HDAC inhibition [34]. In astrocytes TSA upregulates both *BDNF*and *GDNF* mRNA levels, with marked increases in *GDNF* promoter activity and promoter-associated histone H3 acetylation [37]. TSA also induced transcription of depression associated genes: the melatonin MT1 receptor gene in glioma cells [15] and the Glucocorticoid Receptor (GR) gene [36].

- **MS-275**

MS-275 is a benzamide-based HDAC inhibitor that selectively targets class I HDACs. In mouse models of depression, infusion of MS-275 into the nucleus accumbens delivered strong anti-

depressant-like effects [30]. The effects of MS-275 on gene expression were even compared with the effects of fluoxetine.

➢ **METHYLDONOR COMPONENTS**

It is known that compounds such as homocysteine (metabolized to S-adenosyl-methionine) and folic acid may impact DNA methylation levels. Furthermore, individuals with folate deficiency are more likely to develop depression and less likely to respond to antidepressant drugs [7]. Interestingly, treatment with folate has been shown to reduce depressive symptoms [3]. In fact, BDNF levels in the hippocampus were reduced in an animal model following homocysteine treatment [21]. In addition, a reduction of BDNF levels by homocysteine was prevented by treatment with folic acid which increases DNA methylation. Indeed, elevated homocysteine levels have been associated with major depression [8]. These data further support the fact that clinical response to antidepressant drugs, as well as risk for depression, are associated with dynamic changes in DNA methylation.

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Integral food-engine model for health promotion

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Интегрален хранително-двигателен модел за промоция на здравето

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РЕЗЮМЕ

Съвременният поглед върху новите политики в приетата от 57-та Световна здравна асамблея „Глобална стратегия за храненето, физическата активност и здравето" очертават и новите приоритети свързани със здравно-промотивни програми и модели за формиране на здравословен начин на живот. Целта която си поставихме е да се разработи интегрален хранително – двигателен модел за промоция на здравето. Неговата концептуална рамка очертава архитектурна структура вкючваща системни и целенасочени действия целящи укрепване на позитивното здраве и предотвратяване на негативното здраве.

Тази прицелна намеса в здравословната обществена политика се позиционира в пресечните полета на процеса на хранене и физическата активност. Това твърдение въз основа на аналитичния научен подход, се базира на солиден доказателствен материал.

В контекста на казаното, по определено внимание отделяме от една страна на храненето което заема основна позиция, детерминирана от многообразни научни изследвания, доказващи ролята и първостепенното му значение, като ключов елемент в промоция на здравето. Из-

ABSTRACT

The modern view on new policies adopted by the 57 th World Health Assembly "Global Strategy on Diet, Physical Activity and Health" outline new priorities related to health promotional programs and models for the formation of a healthy lifestyle. The goal that we set ourselves is to develop integrated food – motor model for health promotion. His conceptual framework outlines the architectural structure included with systematic and targeted actions aimed at strengthening positive health and prevention of adverse health.

This targeted intervention in healthy public policy position in the cross fields of process of eating and physical activity. This statement based on analytical scientific approach is based on solid evidence.

In light of the foregoing, in particular pay attention on the one hand feeding it occupies a major position determined by various scientific studies demonstrating the vital role and its importance as a key element in health promotion. It is known that when it is not consistent with the scientific requirements can trigger a multitude of disease states.

On the other hand physical activity is an important tool and a fundamental means of improving the physical and mental health, including major factor

вестно е, че когато то не е съобразено с научните изисквания може да придизвика множество болестни състояния.

От друга страна физическата активност е важен инструмент и фундаментално средство за подобряване на физическото и психическото здраве на човека, в т.ч. основен фактор регулиращ енергийния баланс на организма и контрола върху телесната маса.

В заключение бихме желали да отбележим, е с помоща на междусекторния подход, изграждането на „ балансирано комбиниране“ от здравословно хранене и активна физическа активност се превръща в широко спектърно профилактично средство срещу редица хронични неинфекциозни заболявания. В този аспект реализирането на научно-обусновани и подкрепящи политики, програми и модели за промоция на здравето са предпоставка и гарант за увеличаване на здравния потенциал което ще осигури здравна закрила, здравна сигурност и социално благополучие фокусирани върху подобряване на популационния здравен статус.

Ключови думи: промоция на здравето, хранително-двигателен модел.

in regulating the energy balance of the body and control body weight.

In conclusion we would like to note with the help of a cross-sectoral approach, building „ balanced combination ‘’ of a healthy diet and active physical activity becomes a wide spectrum prophylactic against a number of chronic non-communicable diseases. In this aspect, the implementation of scientifically sound and supportive policies, programs and models for health promotion are a prerequisite and guarantee for increasing health potential which will provide health protection, health security and social welfare focused on improving population health status.

Keywords: health promotion, food-engine model

Health promotion is an integral part of the healthcare reform. The 57th World Health Assembly approved a “Global strategy on diet, physical activity & health”.

A close overview of the modern policies of this strategy will outline the new priorities related to health-promotion programs and models that help form a healthy lifestyle. One of the leading principles for the realization of this strategy relates to the need to make healthy choices easier. Bearing in mind that the strength of health promotion lies in its multidisciplinary character, we can define it as a new, comprehensive and scientific approach whose philosophy can be summed up as “health for the healthy”. This is a positive concept which incorporates activities that foster individual and social health and wellbeing alike.

This is an evolving concept that includes encouraging a lifestyle and other health-conductive social, ecological and personal factors, and a strategy that connects people with their environment and combines personal choice with public responsibility for health, the final goal being the establishment of a healthier future. Health promotion embraces both the impact of the individuals on certain health factors and the influence of the environment to enhance the factors and change those of them that prevent healthy lifestyle.

Nutritionists rightly point out the paramount importance of the “food model” of people for their health status.

Nutrition is one of the basic and vital processes and it is also an approach to health promotion that impacts on the physiological, mental and social status and development of the individual. So it can be viewed in biological, psycho-social and economic aspects. These aspects determine diet as a risk and preventive factor essential for human health.

Modern public health policies aim to provide the necessary healthy food for all population groups and approve balanced and adequate diets. Food programs and models themselves should be used for health promotion. On the local level, this can be introduced via schools, health and welfare services, especially for vulnerable groups, children, single-parent families, old people, etc. Therefore, a scientific nutritional approach to preventive healthcare would contribute for the reduction of death rate from coronary heart disease, brain stroke, stomach cancer, etc.

Physical activity is an important tool for the improvement of physical and mental health. Lack of physical activity is a risk factor of a great number of chronic non-infectious diseases of high social importance like coronary artery disease, brain stroke, hypertension, non-insulin dependent diabetes mellitus 2, osteoporosis, obesity etc.

A group of WHO experts provide data that the physical activity level of 2/3 of the population above 15 years of age is below the recommendations. Almost 5-10% of the mortality results from insufficient physical activity. At present 60% of the population of Europe have sedentary lifestyles.

A number of scientists confirmed and further developed the data about the preventive effect of optimum physical activity which improves the functioning of the human organism and enhances physical strength and mental stability.

All should start with better health awareness in the majority of the population and that will lead to a conscious personal choice and inner conviction in active physical regime as a major component of the healthy lifestyle. This preventive factor is broad, accessible and easy to perform.

Therefore, motivation of healthy diet and physical activity from early to old age are essential preconditions and a guarantee of improved quality of life.

On the basis of the situation analysis, the realities and the challenges related to health promotion and its great medical and social significance, **our objective** is to develop an integral food-engine model for health promotion. Its conceptual frame defines an architectural structure of systematic and targeted actions aiming to strengthen positive health and avoid negative health. This intervention in the public healthcare policy is positioned at the cross section of diet and physical activity.

In this relation, hereby we offer an integral food-engine model consisting of the following stages and phases:

STAGE 1

Risk management

Phases

1. Identification of risks to diet and physical activity.
2. Defining of the causality between the investigated risks and the social and health phenomena by a measurement of the basic level from the feasibility study of:
   - Educational diagnosis: it characterizes health awareness in the sphere of diet and physical activity.
   - Behavioral diagnosis: it characterizes factors related to dietary and physical habits.
   - Anthropologic diagnosis: it characterizes anthropometric indicators related to diet and physical activity.
   - Epidemiological diagnosis: characterizes the healthcare system status and tendencies.
3. Development of intervention programs in the following spheres of activity:
   - Health education – impact on knowledge, perceptions, values, attitudes and behavior related to health promotion.
   - Prevention of diseases related to diet and physical activity (a set of measures to limit the risk of diseases) on the primary level (avoidance of the disease) and on the secondary level (early diagnostics to stop the progress and reduce the duration of the disease and the risk of complications)
   - Health protection – establishment of a healthy social policy and control providing reliable protection of the population.
4. Monitoring of the interventions performed.
5. Assessment of the effect of elimination or reduction of the impact of investigated risks causing health damage by measuring the level of final studies and assessment of the following:
   - The process – change of diet-and-activity-related risks to behavior.
   - The impact – measurement of behavior.
   - The results – change of health status indicators.

Stage 2

Definition of priority ideas, objectives and tasks for the establishment of sustainable health behavior by skills of self-awareness, self-regulation and self-assessment related to healthy diet and adequate physical activity.

Stage 3

Formulation of a stable public healthcare policy which will make healthy choices of diets and physical activities, all readily available to all members of society.

Stage 4

Introduction of an integral health promotion program to increase the health activity and anti-risk behavior in relation to diet and physical activity, with the immediate objective of establishing a healthy lifestyle for the individuals, the social groups and society as a whole. That will contribute to the achievement of the ultimate goal of improving the health status of the population.

As a new philosophy of public healthcare, the idea of health promotion is "by adding health to life", i.e. by health improvement, "to add years to life", i.e. to increase longevity.

By all that was said above we tried to show that the realization in practice of the proposed integral food-engine model will make it possible to achieve the following lifestyle changes conductive to health:

- Knowledge and motivation of health-strengthening behavior
- Promotion of positive health behavior
- Limitation of behavior that is harmful to health

In **conclusion**, we would like to emphasize that with the help of the inter-sector approach, the "balanced combination" of healthy diet and physical activity becomes a broad-spectrum means of prevention of a number of chronic non-infectious diseases. In this aspect, the creation of scientific policies, programs and models of health promotion is a prerequisite and a guarantee of the improvement of health potential which will provide health protection, health safety and social wellbeing, all focused on the improvement of the population's health status.

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RISK STRATIFICATION IN MULTIPLE MYELOMA

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СТРАТИФИКАЦИЯ НА РИСКА ПРИ МНОЖЕСТВЕН МИЕЛОМ

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РЕЗЮМЕ

Цел: Оценка на цитогенетичните прогностични фактори и стратификация на риска при новодиагностицирани пациенти с множествен миелом. **Материал и методи**: Оценени са общо 92 новодиагностицирани болни с множествен миелом, изследвани с FISH и/или конвенционален цитогенетичен анализ. Стратификация на риска е извършена при 87 (94.6%) от тях, като са използвани два различни прогностични модела – mSMART и IMWG. Статистическата обработка е извършена с програма SPSS v21, а оценката на преживяемостта – чрез метода на Kaplan-Maier и log-rank test. **Резултати:** В нашия анализ е ус-

ABSTRACT

Aim: Assessment of cytogenetic prognostic factors and risk stratification in newly-diagnosed patients with multiple myeloma. **Patients and methods:** We analyzed tha data of 92 newly-diagnosed patients with multiple myeloma with performed FISH and / or conventional cytogenetic analysis. Risk stratification was performed in 87 (94.6%) of them, using two different prognostic algorithms – mSMART and IMWG. The program SPSS v21 was used for statistical data processing, survival was assessed with the Kaplan-Maier method and a log-rank test. **Results:** We found the following incidence of abnormalities associated with adverse prognosis in multiple

тановена следната честота на хромозомните аберации, свързвани в различни проучвания с неблагоприятна прогноза при пациентите с ММ: 39 (42.4%) от 92 пациенти с монозомия/делеция на хромозома 13 (del13); 22/92 (23.9%) – с amp1q; 15/92 (16.3%) – с del1p; 15/92 (16.3%) – с del17p; 8/92 (8.7%) – с t(4;14) и 2/92 (2.2%) – с t(14;16). Стратификацията на риска, извършена въз основа на тези резултати, установява достоверно различна обща преживяемост между рисковите групи, независимо от използвания прогностичен модел (mSMART или IMWG). **Обсъждане:** Двата модела за стратификация на риска дават реална оценка на очакваната средна преживяемост в съответните прогностични групи и могат да служат като база за риск-адаптиран подход в лечението на пациентите с множествен миелом. **Заключение:** При множествения миелом **с**тратификацията на риска е важен етап в диагностичния процес, който помага за индивидуализиране на лечението и подобряване на преживяемостта.

Ключови думи: множествен миелом, стратификация на риска, риск-адаптиран подход.

myeloma: monosomy/deletion of chromosome 13 (del13) in 39 (42.4%) of 92 patients; amp1q – in 22/92 (23.9%); del1p – in 15/92 (16.3%); del17p – in 15/92 (16.3%); t(4;14) – in 8/92 (8.7%) and t(14;16) – in 2/92 (2.2%) patients.We performed risk stratification, based on these results, using the mSMART and IMWG models. Our data show significant differences in outcomes betwee nrisk groups, regardless of the prognostic model being used. **Discussion**: The two risk stratification models give a realistic assessment of the expected median overall survival according to the risk status and can serve as a basis for a risk-adapted approach in newly-diagnosed multiple myeloma patients. **Conclusion:**Risk stratification is an important milestone in multiple myeloma diagnostics, which can help individualize treatment and improve survival.

Key words: multiple myeloma, risk stratification, risk-adapted approach.

I. INTRODUCTION

Multiple myeloma (MM) accounts for 1% of all malignant diseases and 10-15% of hematologic neoplasms. It originates from bone-marrow plasma cells and its major clinical features are bone disease, renal impairment, hypercalciemia and anemia. Though still an incurable disease, in recent years major advantages were made in diagnostics and treatment of multiple myeloma. The establishment of stem cell transplantation as standard of care and the introduction of novel agents (proteasome inhibitors and immunomodulatory agents) lead to significant improvement of outcome.These changes resulted in the achievement of molecular remissions and prolonged disease-free survival, with a cure being possible in some of the patients. In other cases, however, the disease shows resistance to treatment and an aggressive course, irrespective of the therapeutic approach. In an attempt to explain this heterogeneity a number of prognostic factors were identified, which are related to tumor biology, including some cytogenetic markers.

Genomic characteristics of the malignant clone is an important aspect of multiple myeloma pathogenesis. It is well known that the disease is associated with certain cytogenetic abnormalities, some of which are associated with poor prognosis. The detection of these abnormalities with fluorescence in situ hybridization can identify a group of patients with high risk who should be treated differently compared to those with standard risk. None of the known prognostic factors alone can explain the heterogeneous course of the disease. That is why risk stratification models have been proposed, combining cytogenetic markers with patient-related factors, tumour burden factors, markers of

plasma cell proliferative rate and gene expression profiling. The goal of this prognostic stratification is applying a risk-adapted therapeutic approach, or individualized treatment according to genomic characteristics of disease. The published recommendations for risk-adapted therapy (mSMART) are not based on results of large randomized trials, that is why they are not widely accepted. In the International Myeloma Working Group (IMWG) Consensus on Risk Stratification in Multiple Myeloma, 2014 an attempt has been made to create an uniform algorithm for risk stratification. The experts point out that in myeloma so far there are a number of factors associated with prognosis but few predictive markers. While prognostic factors are widely used and have their role in risk stratification, predictive markers would help individualize treatment, which is a major goal of risk-adapted therapy.

The aim of this study is assessment of cytogenetic prognostic factors and risk stratification in newly-diagnosed patients with multiple myeloma, using two different prognostic models – mSMART and IMWG.

II. PATIENTS AND METHODS

1. Patients

We analyzed the data of 92 newly-diagnosed patients with multiple myeloma with performed FISH and/or conventional cytogenetic analysis. 64 of them were diagnosed and treated in the Department of hematology, MMA – Sofia and 28 were patients of other hematologic clinics in Sofia, Plovdiv and Pleven. Most of the cytogenetic analyses were performed in the Cytogenetic laboratory in MMA, Sofia. 14 patients were analysed in the university cytogenetic laboratories in Plovdiv (13 patients) and Pleven (1 patient). All the patients have signed informed consent for genomic studies.

The average age of the analysed patients was 63.6 (39-85) years. The other patient characteristics are presented on table 1.

Table1. Patient Characteristics

Characteristics		Number(n=92)	Percent(%)
1. Gender	Male	49	53.3%
	Female	43	46.7%
2. Myeloma type	IgG	57	62%
	IgA	17	18.5%
	Light chain	18	19.6%
3. ISS stage	I	12	13%
	II	27	29.3%
	III	53	57.6%

2. Methods

2.1. Diagnosis –2003 IMWG diagnostic criteria were used (4)– table 2.

Table2. Diagnostic Criteria for Monoclonal Gammopathies and Multiple Myeloma

MGUS	„Smoldering" myeloma	Symptomatic multiple myeloma
• M–proteinin serum < 30 g/L • Bone marrow clonal plasma cells< 10% • No related organ or tissue impairment (no end organ damage, including bone lesions)	• M – protein in serum ≥ 30 g/L and/or • Bone marrow clonal plasma cells ≥ 10% • No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms	• M-protein in serum and/or urine • Bone marrow (clonal) plasma cells or plasmacytoma • ≥ 1 CRAB* criteria

*C: Calcium zlevels increased(serum calcium >0.25 mmol/l abovethe upper limit of normal or > 2.75 mmol/l)

R: Renalinsufficiency (creatinine >173 mmol/l)

A: Anemia (Hb< 10 g/dLor 2 g/dLbelowthe lower limit of normal)

B: Bone lesions (≥ 1 lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)

Adapted from: IMWG. Br J Haematol.2003; 121:749–757.

2.2. Staging according to the International Staging System (ISS)(3) – table 3.

Table 3. International Staging System for Multiple Myeloma*

Stage	Criteria
I	Serum β2-microglobulin< 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Not stage I or III
III	Serum β2-microglobulin ≥ 5.5 mg/L

*Adapted from: Greipp PR,et al.J Clin Oncol. 2005; 23: 3412–3420.

2.3. Cytogenetic studies

2.3.1. Conventional cytogenetic analysis

The following cytogenetic techniques were used: modification of the direct bone-marrow method of Tjo & Whang; 24 hcultivation of unstimulated bone marrow; chromosome preparations using Rothfel & Siminovitch technique and trypsin-Giemsa staining with modification (Whang & Fedoroff). In each case at least 11 metaphases were analysed and if a clonal abnormality was suspected – between 25 and 50 metaphases (6).

1.1.2. Fluorescent in situ hybridization (FISH)

The method is used to directly demonstrate DNA sequences on metaphase chromosomes or interphase nuclei, allowing the localization of a specific fluorescent-labeled DNA sequence. The following locus – specific and fusion-gene probes were used: 1p36/1q21; 13q14/13qter; 14q32 (BA); 17p13/SE17; FGFR3/IGH for t(4;14); MYEOV/IGH for t(11;14) and MAF/IGH for t(14;16) (6).

2.4. Risk stratification

Risk stratification was performed using 2 different prognostic models – mSMART (Mayo Stratification of Myeloma and Risk-Adapted Therapy), 2013 (5) and IMWG Consensus on Risk Stratification of Multiple Myeloma, 2014 (1) – table 4 and table5.

Table 4. mSMART Risk Stratification of Active Multiple Myeloma*

High risk	Intermediate risk	Standard risk
FISH del 17p t(14;16) t(14;20) GEP –high risk signature	FISH t(4;14) Cytogenetic del 13 Hypodiploidy PCLI ≥ 3%	All others including: FISH t(11;14) t(6;14)

GEP – gene expression profiling; PCLI – plasma cell labeling index

*Adapted from: Mikhael, J.R. et al. Mayo Clin Proc. 2013; 88: 360–376

Table 5. IMWG Risk Stratification in Multiple Myeloma*

	High risk	Standard risk	Low risk
Parameters	ISS II/III and del17p or t(4;14)	Others	ISS I/II and absence of del17p, t(4;14) and amp1q and age< 55 years
Median OS	2 years	7 years	>10 years
% Patients	20%	60%	20%

*Adapted from: Chng, W.J.et al. Leukemia. 2014 Feb;28(2):269-77.

2.3. Statistics

The program SPSS v21 was used for statistical data processing, survival was assessed with the Kaplan-Maier method (7). Kaplan-Meier curves for progression-free survival (PFS, defined by the time between diagnosis and occurrence of progression, relapse, or death) and overall survival (OS) were plotted and compared using the log-rank test.

III. RESULTS

Conventional cytogenetic analysis was performed in 49 (53.2%) patients. In 37(75.5%) of them clonal abnormalities were found, while the remaining 12 (25.5%) patients were with normal caryotype. The FISH method was performed on fixed interphase nuclei of bone-marrow aspirate. It was used in 76 patients and in 69 (90.8%) of them pathologic changes were found. In 7 (9.2%) patients the percent of pathologic findings was below the cutoff of 5%. Using these 2 cytogenetic methods the incidence of abnormalities associated with adverse prog-

nosis in multiple myeloma was as follows: monosomy/deletion of chromosome 13 (del13) in 39 (42.4%) of 92 patients; amp1q – in 22/92 (23.9%); del1p – in 15/92 (16.3%); del17p – in 15/92 (16.3%); t(4;14) – in 8/92 (8.7%) and t(14;16) – in 2/92 (2.2%) patients.

Risk stratification according to mSMART

Risk stratification was performed in 87 patients (94.6%), the remaining 5 (5.4%) patients could not be placed into a particular risk group because of insufficient information.We used most of the recommended cytogenetic prognostic factors: del17p, t(14;16), t(4;14), Cdel13, hypodiploidy and t(11;14). The other 4 tests: FISH for t(14;20) and t(6;14), PCLI and GEP are not routinely performed in our center. The distribution and survival of patients in each risk group can be seen on table 6.

Most of the patients were placed into the standard risk group –54% of the cases. Almost equal number of patients fell into the intermediate- and high-risk groups – about 20%. Median survival was significantly different between the three groups (p<0,001): 62 months in the standard-risk group, 41 months in the intermediate-risk group and 21 months in the high- risk group. 3-year OS was respectively 65%, 57% and 21% – fig. 1.

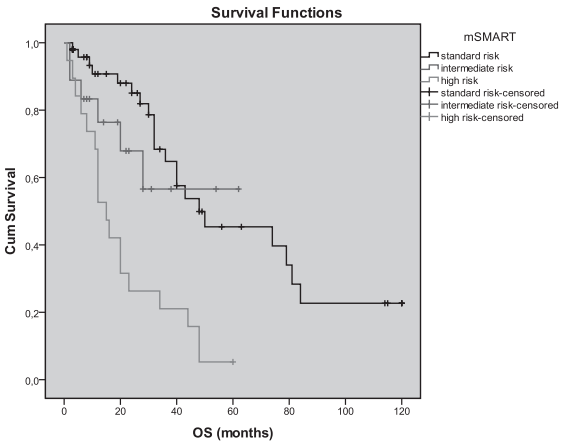

Fig.1. Median OS in mSMART risk groups

Median PFS was similar in the standard- and intermediate-risk groups (27.3 months and 25 months respectively), but significantly lower in the high-risk group (11.9 months), p=0.002) – fig.2.

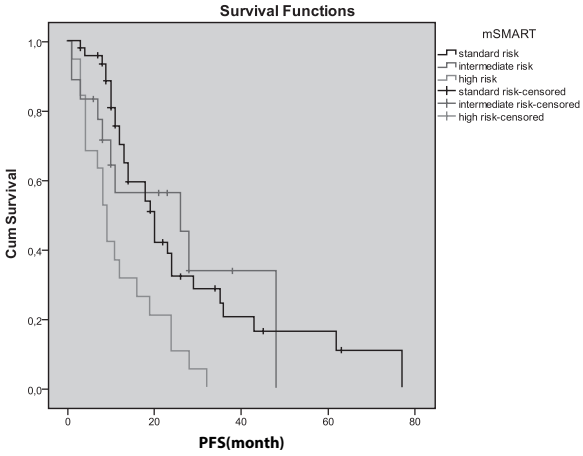

Fig.2.Median PFS in mSMART risk groups

Table 6. mSMART Risk Stratification–Patient Distribution and Survival

Risk groups	Number (%) ofpatients	Median OS (months)	3-yearOS %	95% CI		Median PFS(months)	95% CI	
				Lower Bound	Upper Bound		Lower Bound	Upper Bound
Standard risk	50 (54,3%)	62,2	64,8%	48,043	76,317	27,363	19,660	35,066
Intermediate risk	18 (19,6%)	41,3	56,6%	28,329	54,346	25,044	14,793	35,295
High risk	19 (20,7%)	20,9	21,1%	13,249	28,541	11,895	7,709	16,081
No stratification	5 (5,4%)	16,7	–	–	–	–	–	–
All	92 (100%)	49,3		38,817	59,708	22,968	17,800	28,137
P – Log Rank (Mantel-Cox)	<0,001					0,002		

RISK STRATIFICATION ACCORDING TO IMWG

We performed risk stratification in 87 (94.6%) patients, the remaining 5 (5.4%) patients could not be placed into a particular risk group because of insufficient information. The distribution and survival of patient according to their IMWG risk status can be seen on table 7.

Standard-risk group was again the biggest one – 63% of the patients. The proportion of high-risk patients was about 23% and of those with low risk – nearly 9%. Median survival was significantly different between the three groups (p=0,016): 79 months in the low-risk group, 53 months in the standard-risk group and 25 months in the high-risk group. 3-year OS was 100%, 54% and 29% respectively – fig. 3. Median PFS did not show significant difference between risk groups (p>0,05). These data should be interpreted with caution because the number of cases in some of the groups was too small.

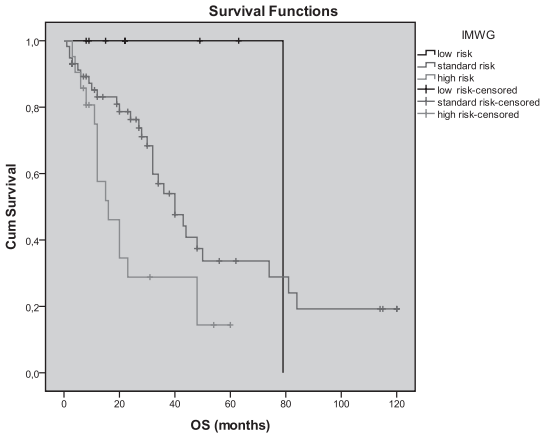

Fig.3.Median OS in IMWG risk groups

IV. DISCUSSION

By virtue of their experience along with published results Mayo Clinic experts have combined prognostic cytogenetic factors into a risk-adapted approach to patients with myeloma – mSMART (Mayo Stratification of Myeloma and Risk-Adapted Therapy). A group of high-risk patients has been identified who need a different (more aggressive and continuous) treatment strategy than those with standard risk. This approach is not intended to replace existing prognostic systems and not all tests are required (but rather preferred) for any given patient. At a minimum, metaphase cytogenetics or FISH studies should be performed. The purpose of this consensus is to offer a simplified,evidence-based algorithm of treatment decision making for patients with newly diagnosed myeloma (2).

The updated mSMART guidelines from 2013 include 3 risk categories. The intermediate-risk patients (about 20%) carry the t(4;14) abnormality (associated with fibroblast growth factor receptor 3 expression) or cytogenetic del13 and tend to be more responsive to therapy with the proteasome inhibitor bortezomib. The largest proportion of myeloma patients fall into the standard risk group (about 60%) and high-risk patients are about 20% (5).

The incidence by risk group in our study is very similar to Mayo Clinic data. In our cohort the median OS was significantly different between risk groups and the results are consistent with Mayo Clinic data (5). The reported by

Table 7. IMWG Risk Stratification – Patient Distribution and Survival

Risk groups	Number (%) of patients	Median OS (months)	3-year OS %	95% CI		Median PFS (months)	95% CI	
				Lower Bound	Upper Bound		Lower Bound	Upper Bound
Low risk	8 (8.7%)	79.0	100%	79.000	79.000	35.944	14.941	56.948
Standard risk	58 (63.0%)	53.0	54.0%	40.087	65.996	23.817	17.464	30.171
High risk	21 (22.8%)	24.7	28.8%	15.652	33.759	16.437	9.924	22.950
No stratification	5 (5.4%)	16.7	–	–	–	–	–	–
All	92 (100%)	49.3		38.817	59.708	22.968	17.800	28.137
P – Log Rank (Mantel-Cox)	0.016					0.122		

them median OS for high-risk patients is 3 years, while intermediate- and standard-risk patients have OS of 4 to 5 years and 8 to 10 years, respectively. The lower median OS in our analysis can be explained with the shorter follow-up time of the patients and the fact that it is still not reached in almost half of them (48.9%). In our series the median PFS was very similar in standard- and intermediate-risk groups, but significantly lower in the high-risk group.

The IMWG combined genetics-ISS model (1) also divides newly-diagnosed MM patients into 3 risk groups by using serum albumin and β2-microglibuline (for ISS staging) and FISH for only three markers: (4;14), del17p13 and amp1q21. This algorithm can be applied to more than 90% of all myeloma patients. High-risk patients (about 20% of all MM patients) are either ISS II or III with the presence of either t(4;14) and/or 17p13 deletion detected by FISH have a median survival of about 2 years whereas low-risk patients with ISS I or II and absence of these high-risk genetics have 5- and 10-year overall survival rates of 70 and 51%, respectively. The rest of the patients (about 60%) fall into the standard risk group. At the present time, although we have the markers to stratify patients into different risk groups, IMWG does not recommend different treatment strategies for patients in the different risk groups. The only exception is the recommendation of bortezomib-based treatment for induction and maintenance for patients with t(4;14) as results from different trials have consistently showed that bortezomib-based treatment improved outcome of these patients.

Comparing the distribution and survival of our patients according to their IMWG risk status we can say that our results are consistent with the above stated data with the exception that the low-risk group in our analysis is very small (less than 9% of the cases). Median OS was significantly different in each group, but there was no statistical difference in median PFS.

The two risk stratification approaches give a realistic assessment of the expected median overall survival according to the risk status and can serve as a basis for individualized treatment of newly-diagnosed multiple myeloma patients. The proposed by IMWG algorithm is more accessible for use in daily clinical practice, since it requires only ISS staging and FISH testing for three cytogenetic markers: t(4;14), del17p13 and amp1q21. The disadvantage of this model according to us is the fact that patients with t (4;14) and del17p are placed in the same risk category, given the available scientific information for the different outcome of these groups of patients after treatment with proteasome inhibitors. The mSMART approach, on the other hand , takes into account this difference, but it requires access to a larger number of tests and is not applicable in all centers.

V. CONCLUSION

Risk stratification is an important milestone in the diagnostic and therapeutic process in patients with MM. Early identification of risk groups helps individualize treatment and improve survival. Multiple myeloma is a heterogeneous disease and the uniform approach to patients is not justified. Nowadays with the availability of many new treatment options the challenge to the clinician is even greater. By using a risk-stratified approach the most efficient and less toxic therapeutic combination can be found for each patient with this yet incurable disease.

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BOUNDARY BETWEEN THE FORENSIC PSYCHIATRY EXPERT/ PERSON EXAMINED RELATIONSHIP AND THE PSYCHIATRIST/ PATIENT RELATIONSHIP

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ABSTRACT

The imperious necessity of transposing the determinism of biopsychological and medical phenomena into the social and juridical perspective represents one of the desiderata of forensic expertise, because the mental patient represents a relevant example of particular physician/patient relationship, where forensic aspects are essential. This paper proposes a synthesis of the literature review in order to highlight the nature of forensic psychiatrists. We have focused on outlining the ethical norms that such psychiatrists must observe in order to prevent any prejudice to the expert endeavour and on underscoring the boundaries between the forensic psychiatry expert/patient relationship and the psychiatrist/patient relationship.

Keywords: psychiatrist, expert in forensic psychiatry, "do no harm" principle, proper judgment

INTRODUCTION

Psychiatry, more than any other medical discipline, is involved in the judiciary system due to the relationship between the medical condition and aggressive, disorderly, vandal behaviour, etc, to the ethical and legal issues raised by mentally ill defendants, to execution and self-representation, to social norms that forbid the prosecution of people with mental illnesses or disabilities caused by psycho-cognitive development retardation. In Romania, forensic psychiatry is not acknowledged as independent specialty: psychiatrists' areas of expertise include both clinical and general psychiatric services and expert activities within the legal field. Therefore, the duty of psychiatrists includes treating psychiatric patients with or without a criminal record, including patients within the corrections system (1, 2).

The specificity of forensic psychiatry is to determine the causes of an offence starting from the effects. Underlying ontological, motivational, cultural, anthropological, psychological and psychiatric motivations become fascicules from which the univocal character of a truth derive, mostly concerning a diagnosis, deduced by relating to the notions of normalcy and mental

health. Legal bodies may require from an expert only opinions pertaining to his/area of expertise and strict specialty (2, 4).

Generalities on the notions of capacity and proper judgment

The presence or absence of proper judgment concerning a human action correlates logical criteria regarding the assessment of the consequences and psychological criteria that include cognition, affect and volition related to the previous life experience, through the capacity to anticipate (using representations) potential consequences, as well as proper judgment criteria for the affective integration of its consequences, the moral norms, the right projection of reality and the capacity to make the difference between good and evil, legal and illegal. Forensic methodology has proven the need to use the concept of mental capacity as representing all mental life synthesis functions and all personality traits. This actually represents a complex aptitude, more far-reaching, more integrating and closer to the concept of responsibility that it attempts to define, mostly because it can also be related to the great categories of mental conditions and to the intensity of their disorders (2, 3, 4).

As a notion specific to forensic psychiatry theory and practice, mental capacity represents the possibility or faculty of elementary and synthesising mental functions of acting correctly and properly in relation to the objects, phenomena and categories of the environment, for a flexible and harmonious adjustment of the individual to the environment. Mental capacity is an abstract notion, just like responsibility, designating a feature of human psyche and characterizing the subject from the perspective of his/her cognitive, affective-volitional, anticipative-acting, axiological and ethical-moral integrity and unity. It is not a function of the psyche in the psychological meaning of the term, but it expresses the functionality of psyche as a whole and in its complex relationships with the environment. Thus, mental capacity is the implicit adaptive potentiality of normal, typically developed psyche, and it represents the mandatory premise of responsibility and the general framework of proper judgment (1, 3, 5).

Nature of expert's activity in forensic psychiatry

Forensic psychiatric examination has the role of providing to the legal system certain elements meant to determine the liability of a person involved in the commission of a crime punishable by law or to attest mental health in cases with civil implications (the capacity to test, to draft a purchase and sale agreement, a document of donation, etc) (1, 6). Forensic psychiatric expertise is an interdisciplinary activity whose purpose is to detect psychopathological conditions and their influence upon the individual's capacity of appraising the contents and consequences of his/her acts, as well the individual's possibility of expressing freely the volitional character of an act committed. The fundamental task of forensic psychiatric expertise is to assess the proper judgment of a person, by focusing on the mental status when he/she committed the act (2, 4). Hence, a forensic psychiatry expert is bound to know the background of elementary notions on crime, guilt, responsibility/responsibilities, mental capacity, proper judgment, specific competence, motivation, motive, mobile, consent and confidentiality. Confidentiality raises particular issues in forensic psychiatry, mostly when it concerns obtaining the consent of both the offender and the victim: the expert must be persuaded that they are both aware of the way the information will be used. In certain situation, an expert may have to explain the purpose of the examination and that the outcomes will be made known only to those entitled to it; hence, the victim chooses whether to accept or decline the examination altogether (5, 6).

Considering the complexity of the issue of proper judgment and of its psychosocial determinism, it is necessary to individualize its appraisal, but without limiting it by predeter-

mined patterns that establish correlations between the type of illness and proper judgment. The ethical principles characterizing the responsibility of the forensic expert are similar to those guiding the responsibility of medical profession in general; however, it must be stated that forensic psychiatry also has ethical implications upon the individual, the society and the legal field, to which it is closely connected. In this context, current ethics guidelines suggest that psychiatric therapists should avoid acting as expert witnesses for their patients. Some opinions even complain of a genuine misrepresentation of justice or even of a disrespect of the profession per se if a psychiatrist testifies for his/her patients in court. This causes the ambiguity of ethical and intellectual boundaries of forensic psychiatry (6, 7, 15).

Good practice ethics guidelines in the field of forensic psychiatry posit objectivity and neutrality as sine qua non values. At the same time, it is fundamental to preserve the autonomy and relative anonymity of the examiner (of the forensic psychiatrist). Consecutively, it is mandatory to protect the confidentiality of forensic evaluation. The time and length of forensic psychiatric evaluation must be established from the beginning and observed as rigorously as possible; the fee for the evaluation must be symbolical and well established. The forensic psychiatrist is bound to avoid all personal relationships with the person examined both in the present and in the future, after proving the absence of such relationships in the past. It is also fundamental to obtain the informed consent of the examined patient in order to conduct the evaluation, except for cases where the expertise is required by the law (11, 15).

"Do no harm" vs. "do good"

In the context of mental health from a forensic perspective, psychiatrists operate outside standard medical setting, considering that the underlying ethical principles of their professional conduct do not overlap the aspect of the classic physician/patient relationship. The patient's benefit is counterbalanced by the benefit of the society, which determines several ethical dilemmas. They derive precisely from the conflict between the good of the patient and the public good, the latter meaning public safety in this case (11).

Do no harm is the fundamental, Hippocratic oath of the medical profession. *Do no harm* in medical practice does not mean not harming the patient intentionally, because it is implicit that no physician has any interest of doing such thing. Hence, a physician may do harm by making sudden, abrupt reveals that lack compassion or empathy, or by lying, by providing partial information or by avoiding the truth. A harmless conduct in the field on mental health with forensic impact implies making sure that the actions required from an expert really promote justice. *Doing good* (the principle of benefit) entails – besides respecting autonomy and limiting harm – an active contribution to the individual's wellbeing. *Do good* is an ethical norm viewed from a philosophical perspective as a moral obligation but also a merit, an act of charity, reason for which a person may not be labelled immoral just because of failing to produce a benefit through his/her actions. These controversies must be clarified by providing examples of beneficial actions while mentioning the limits of experts' obligations, as well as the level from which the provision of a benefit is more of an option that of an obligation. Ultimately, doing good includes protecting the rights of others, preventing harm or removing the conditions for potential unfortunate events, helping disabled persons or saving persons in imminent danger (11, 13, 15).

In the context of forensic psychiatry, specialists (psychiatrists) activate outside their usual medical setting. In this situation, the underlying ethical principles of professional conduct do not overlap those imposed by the classic physician/patient relationship. In a legal context, the principle of benefit and no harm is considered secondary to the principle of truth.

The patient's benefit is frequently counterbalanced by the benefit for society; ethical dilemmas derive precisely from the conflict between the patient's good and the public good and safety. The need to protect public good/safety is often the fundamental justification for non-voluntary treatment. If a psychiatrist considers that a patient is a potential threat to public safety, then he/she may assume that the duty toward society prevails over the duty toward the patient's wellbeing. This is a crucial difference from the traditional ethics specific to the therapist/patient relationship, outside any forensic implication (8, 13, 14).

Therefore, forensic psychiatry is not primarily guided by the benefit of the individual, but by the benefit of society, in the spirit of justice. Most of the times, the assessment of the person who committed a certain offence brings no benefit to the person; on the contrary, under certain circumstances, such assessment endangers the financial and legal interests of the person in question. For instance, in some cases, the conclusions of the expertise may contradict the statements of the defendant. Hence, forensic psychiatrists usually guide themselves by the moral principles of society. When they serve the interests of justice, they must adhere to the general moral rule of telling the truth (1, 8, 12).

Another imperious moral principle is the respect for the person, which implies that the forensic expert must inform the defendant that there will be no physician/patient relationship and no therapeutic relationship. At the same time, the forensic expert must provide information on the limits of confidentiality, which are specific to forensic evaluations. It is important to highlight that the introduction of medical ethical principles in the theory of forensic expertise practice is a dangerous endeavour (2, 4, 12).

On a general note, eleven main rules related to forensic psychiatry practice were determined: to ensure the expert's objectivity and neutrality, to respect the autonomy of the person examined, to protect the confidentiality of forensic expertise, to obtain the informed consent of the person to be examined (when expertise is not required by a court of law), to interact verbally with the person examined, to avoid any type of relationship (past, present or future) with the patient, to forbid any kind of sexual relationship with the person examined, to maintain a certain degree of anonymity of the expert, to utter clearly the fee for the examination, to ensure a proper setting for the examination and to determine an estimate duration of the evaluation (3, 4, 6).

One of the most common ethical dilemmas in the practice of forensic psychiatry concerns the confusion between the role of psychiatric physician and the role of legal expert. This leads to the principle that the psychiatric physician of a defendant should avoid any involvement in forensic endeavours concerning his/her patient. The main argument in the sense is represented precisely by the contradictions that emerge in the context of public good prevailing over individual good, which endangers the therapeutic relationship. The attempt of accomplishing both functions implies the danger of failing to accomplish any of them properly, because specific psychiatric therapy may be prejudiced by forensic endeavour, while forensic endeavour may be endangered by the therapeutic element of the relationship between the expert and the person examined, which is the physician/patient relationship (6, 7, 13).

Forensic activity requires the informed consent of the patient and mostly avoiding victimization or labelling derived from diagnostic errors or from ambivalent expert conclusions. It must not be forgotten that psychiatric labelling ensues stigma from the community and a behavioural adjustment of the patient to his/her new status. Expert labelling may be the consequence of including the illness within a rigid classification system, of solving certain social problems using subjective psychiatric criteria (thus abusive or circumstantial diagnoses). Even under such circumstances, a physician should still be considered a representative

of justice; hence, his/her conclusions pertain to justice (6, 15). This implies the need to replace excessive paternalism in expertise with the avoidance of any suspicions of abuse from the part of medical authorities. In expert matters, the consent of the patient – if the patient is fully aware – must be clear. Under these circumstances, respect for the human being – and for the autonomy of the person, implicitly – and the physician's independence become the basic principles of any expert's responsibility. One may definitely include forensic psychiatry among high-risk specialties, which concern the scientific quality of the acts and the prophylaxis of potential abuses. In a legislative context, it is important to know that forensic psychiatric expertise explains, but does not exonerate; that it sometimes reaches conclusions that can be argued, while other times it reveals scientific truths to be proven by investigations. Acts must be correlated with the multiple technical and behavioural qualities required from an expert, which concern neutrality and objectivity, as well as character qualities, related to the full awareness of one's own limits. Only by observing the aforementioned aspects can expert decisions be ethical and only seldom cautious or equiprobable, to avoid being risky. At the same time, an expert must determine the prophylaxis of primary, secondary and tertiary abuses. A great risk that any expert should be aware of is to avoid any psychiatric victimisation (thus not providing the patient with a refuge in his/her illness), any victimisation caused by diagnostic errors or by ambivalent expert conclusions (5, 13, 14).

In the infinite sphere of deviant behaviours, an expert is called to bring psycho-medical scientific arguments, which provide to justice a dynamic interpretation of a complex causal process and which determine a link through cause reconstruction methods, starting from analyzing the effect. This entails the imperious necessity of transposing the determinism of biopsychological and medical phenomena into the social and juridical perspective as one of the desiderata of forensic expertise. The mental patient represents a relevant example of particular physician/patient relationship, where forensic aspects are essential (8, 14).

The mental patient is not only ill; he/she also presents a certain degree of social danger, which sometimes entails a particular behaviour of the society toward him/her: involuntary admission. The admission and treatment consent suffers several fluctuations determined by the evolution of the illness: there are moments when the patient is mentally present, thus able to consent to admission and treatment. Lack of treatment or other factors may determine a worsening of the patient's state, which leads to the decrease or disappearance of full mental faculties and of proper judgment, with serious personal and social consequences, which entail a degradation of the general state, an interruption of treatment, etc – hence the emergence of a downward spiral. The mental patient benefits from special medical and legal measures known as forensic safety measures. They protect the patient from the consequences of his/her acts and the society from traumas generated by a person partially or totally lacking proper judgment (9, 12, 14).

The physician/ mental patient relationship is analyzed by studying various internal law sources on mental patients, by presenting forensic psychiatric expertise and by analyzing the safety measures required by the examination of a mental patient. The International Code of Medical Ethics states that a physician must act only in the patient's interest when he/she performs a medical act with a potential harmful effect upon the patient's mental or somatic condition. On the other hand, Ethical guidelines of forensic psychiatry practice ask forensic psychiatrists to elaborate their clinical evaluation and to apply the data obtained through legal criteria in the spirit of honesty, thus of the effort to obtain objectivity. Therefore, they state once again the difference between the traditional ethics applicable to the physician/patient relationship in the absence of any forensic involve-

ment and the ethics of a forensic psychiatrist acting as an expert in forensic psychiatric practice (7, 9, 11).

International guidelines for forensic expertise determined three main obligations of the forensic psychiatrist: providing an objective evaluation, maintaining confidentiality within the limits imposed by legal demands and revealing any existing or potential conflict of interests that may irreversibly endanger the quality of forensic expertise. Forensic psychiatry must be governed by the same moral rules and principles as general medicine, but there are certain particularities addressed strictly to forensic psychiatrists. Therefore, they do not act mainly in the patient's interest and for his/her benefit during their evaluations as part of civil or criminal procedures. These evaluations do not always serve the medical interest of a patient; in many cases, their outcomes may prejudice the non-medical interests of a patient (3, 10).

General psychiatry provides physicians who work in forensic psychiatry. These are psychiatrists who act as expert witnesses in court, who perform forensic evaluations, who work in general psychiatric hospitals or in security or maximum security hospitals. Considering this context, this is a question of weighing up the possibility of providing an impartial and neutral opinion on a patient from the forensic expert and the possibility of being honest, correct and good with a patient from the psychiatrist. Here is where we must set the boundary between the role of clinician and the role of expert (3, 9, 10).

Conclusions

In the forensic context, the relationship between a psychiatrist and the individual examined is characterized by the interference of a third party, represented by justice; psychiatrists must fulfil their duties primarily toward justice. Forensic psychiatry established as secondary the duty toward the person examined. Hence, in the judiciary and legal world, the "do no harm" and "do good" principles lose their primacy to the principle of truth. The mission of the forensic psychiatrist is complex and extremely demanding, because it involves observing strict moral rules that are fundamentally different from those guiding the traditional physician/patient relationship.

Forensic psychiatric expertise is a niche practice that must meet rigorous ethical standards. This involves paying more attention to the nature of confidentiality and to the clear determination of roles. Hence, in this area of activity, it is recommendable to assume non-confidentiality and to inform the person examined of it beforehand.

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ПРИМЕРИ:

Статия от списание:

1. McLachlan, S., M. F.Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Глава (раздел) от книга:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

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