1-ère Année. Juin 1919. No. 1.

Bulletins et Mémoires de la Société
DE
Neurologie, Psychiatrie et Psychologie
DE
JASSY

SOMMAIRE:

Jassy.—Imprimerie «Progresul» A. Grünberg rue Stefan cel Mare 4.

Bulletin of Integrative Psychiatry

New series of "Bulletinset Mémoires de la Société de Neurologie, Psychiatrie et Psychologie de Iassy", edited by "Socola" Hospital of Psychiatry Iaşi from 1919 to 1946

Editorial Board: "Socola" Institute of Psychiatry Iaşi
Address: Şoseaua Bucium nr. 36, cod poştal 700282, Iaşi, România

Images on the first page represent: Inaugural board of "Socola" Hospital of Psychiatry Iaşi
The cover of the first number of "Bulletins et Mémoires de la Société de Neurologie, Psychiatrie et Psychologie de Iassy"
The image on the first cover represents the main building of "Socola" Institute of Psychiatry Iaşi

Free images from: httpsfreephotos.onlineitemfree-high-res-geometric-polygon-background & Designed by rawpixel.com / Freepik

ISSN: 1453-7257

Published by "Socola" Institute of Psychiatry Iaşi, Romania

Editura „Gr. T. Popa" Iasi
University of Medicine and Pharmacy *„Grigore T. Popa",* Iaşi
16th Universităţii Str.

Typeset by Tipografia Universităţii de Medicină şi Farmacie
"Grigore T. Popa" Iaşi, str. Universităţii nr. 16, cod. 700115, Tel. 0232 301678

Seria Nouă | New Series
An XXVIII nr. 2 (93) | Year XXVIII No. 2 (93)
Iunie 2022 | June 2022
Frecvența: Trimestrială | Frequency: Quarterly

BPI

Bulletin of Integrative Psychiatry

Buletin de Psihiatrie Integrativă

Official Publication of
"SOCOLA" INSTITUTE OF PSYCHIATRY
Iași, Romania

PUBLISHER: "SOCOLA" INSTITUTE OF PSYCHIATRY IAȘI

PUBLISHER: "SOCOLA" INSTITUTE OF PSYCHIATRY IAȘI

The Bulletin of Integrative Psychiatry tries to continue the tradition initiated at "Socola" Hospital in 1919, when a group of intellectuals, medical doctors and personalities from other professions founded the Society of Neurology, Psychiatry and Psychology in Iași. Even from its beginnings, the Society edited a journal entitled "Bulletins et Mémoires de la Société de Neurologie, Psychiatrie et Psychologie de Iassy", the first publication of the kind in Romania, which was unique also by its vision and opening towards biology, psychology, sociology and philosophy and by its prestigious board of editors: C. I. Parhon, Gh. Preda, Constantin Fedeleș, Arnold Stocker, P. Andrei, Corneliu Popa-Radu, I. A. Scriban, well known personalities, some of them being physicians of great culture and scientific qualification.

Starting from 1920, the Association and its Bulletin, born and edited at "Socola", due to their remarkable scientific activity have contributed to the organization of 18 congresses, which are mentioned in the description of "Socola" Hospital activities.

In 1947, the last number of "The Bulletin of the Society", edited in French, was banned as a result of the interdictions imposed by extremist tendencies. From its first number in 1919 and until 1947, "The Bulletin of the Society" published 2,412 articles.

The journal or "The Bulletin of the Society" has appeared under several titles: "Bulletin et Mémoires de la Société de Neurologie, Psychiatrie et Psychologie de Iassy" (between 1919 and 1922), then "Bulletin de l'Association des Psychiatres Roumains" and from 1923 it has changed its title several times.

After the year 1947, all publications at "Socola" Hospital were included in the "Medico-Surgical Journal of the Society of Physicians and Naturalists in Iași", another prestigious scientific journal which has been published without interruption since 1886.

Starting from 1994, Professor Dr. Tadeusz Pirozynski, Professor dr. Petru Boișteanu, Professor dr. Vasile Chiriță, Conf. dr. Radu Andrei and Dr. M. E. Berlescu have revived the tradition of publications at "Socola" Hospital, editing the new "Bulletin of Integrative Psychiatry".

At the end of 2014, "Socola" Hospital became the "Socola" Institute of Psychiatry, which has increased its responsibilities regarding medical assistance, scientific research, didactic activity, professional training and also the development of editorial activity.

Journal B+ CNCS and Indexed IDB by Index Copernicus, DOAJ, Erih Plus, Gale Cengage, CEEOL, Crossref

Editorialcontact:contact@buletindepsihiatrie.ro

Publishercontact:

Editura „Gr. T. Popa" Iaşi
University of Medicine and Pharmacy Iaşi
16th Universităţii Str.
Tel. 0232 301678
www.umfiasi.ro

Summary

BPI Bulletin of Integrative Psychiatry
Buletin de Psihiatrie Integrativă

Editorial

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Ukraine war – a national trauma

Ana Caterina Cristofor, Vasile Chiriţă

Ana Caterina Cristofor – M.D., PhD., Lecturer, Senior Psychiatrist, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
Vasile Chiriță - M.D., Ph.D, Professor of Psychiatry, Senior Psychiatrist, Academy of Medical Sciences of Romania

More than three months have passed since the Russian invasion of Ukraine began. On the early morning of the 24th of February 2022 Ukrainians woke up into a nightmare, a remarkable outburst of the south region conflicts which were tormenting the nation since 2014. Trauma is described as the emotional reaction to an extensive distressing event such as war. National trauma as a concept was postulated in 1992 and applies to the members of an extensive group, such as a nation or other well-defined group of people. It is certain that this war is a national trauma for Ukrainians, while to some extent, one should argue that it crosses national boundaries and affects us all.

An emerging economy and former soviet republic in eastern Europe, Ukraine's population as it was recovering from the strains caused by the Covid-19 pandemic was under siege and people had to abandon their households in search of shelter. In early 2020, before the pandemic, the World Health Organization designated Ukraine's population for being at a high risk for mental health issues as they already carry a high prevalence for depression compared to similarly developed countries in the region (1).

In times of war physical integrity is periled due to causes like: absence of immediate access to medical service, improper management of previous chronic conditions, lack of medication, delay of nonurgent interventions and, ultimately direct injuries. Concerning the out of sight injuries, the psychological effects, as numerous studies show, chronic warfare, as a lived experience, creates significant social and psychological distress and increases the risk for psychiatric conditions such as post-traumatic stress disorder (PTSD), anxiety, and depression, suicidal thoughts and alcohol abuse.

Complex PTSD, a separate condition according to ICD-11, involves the core symptoms as PTSD along with: emotional dysregulation, negative self-view and difficulties to maintain relationships. Commonly, people with complex PTSD experienced prolonged trauma or passed

through repetitive traumatic events. Looking back to the long-term period of armed conflicts in the Donbas region, would be expected that certain individuals who already faced trauma are at risk to develop complex PTSD if triggered by re-experiencing terrifying situations. Compared with PTSD, complex PTSD is more severe and long-lasting and can assimilate the enduring personality change after catastrophic experience diagnosis.

It is estimated that since February 24th, 6.8 million Ukrainians fled to neighboring countries, most of them to Poland and other western countries, while Romania offers refuge to almost 100.000. It is also estimated that another 8 million people have been displaced within Ukraine (2).

Approximately 2 million refugees are children and according to UNICEF another 2.5 million children have been displaced within Ukraine (3). This sums up to 60% of minors across Ukraine facing constrained relocation and accommodation by reasons of safety. Ukraine has one of the lowest natality rates in Europe and latest estimates also report that more than 200000 children have been deported to Russia.

Hence, many Ukrainian children face family separation, lack of access to education, uncertain access to food and shelter, improper accommodation in the forms of refugee camps. Experiencing life threatening events in childhood and adolescence or severe psychological trauma such as the loss of one parent poses serious threats to their mental health. For example, studies among children affected by the Israeli-Palestinian conflict report post-traumatic stress disorder prevalence ranging from 18% to 68.9% (4). In one study among children exposed to the ongoing Syrian Civil War, 60.5% meet the criteria for at least one psychological disorder (5).

Besides PTSD and depression, other reported disorders include acute stress reactions, attention deficit hyperactivity disorder, panic disorder, anxiety disorders specific to childhood and sleep disorders. In later childhood, children exposed to conflict-related trauma are predisposed to externalizing symptoms, including behavioral problems and oppositional/defiant disorders.

Civil communities across Europe came forth for Ukrainians and organizations and NGO's offer accommodation, guidance for health evaluation and instruments to assess mental health issues such as depression, anxiety, trauma exposure, post-traumatic stress disorder, both for adults and children. In Romania, Ukrainian citizens get health insurance based on OUG nr.15/27.02.2022. Despite governmental and civil efforts to tent to the needs of refugees, it is hard to accurately predict the extent of their needs in terms of mental health access and without even considering the language barriers. In just 3 months, refugees from Ukraine outnumbered ones from Syria, a conflict 11 years in the making. Children's needs for mental health evaluation and assistance are especially at risk in Romania as our health system lacks pediatric psychiatrists. Considering that Romania shelters close to 100.000 Ukrainian refugees, and around 30% of them are children, of which up to 60% may develop a psychiatric disorder, our medical system needs to be prepared to provide medical care to approximately 18,000 new pediatric psychiatric patients.

Since the beginning of the invasion 7 Ukrainians presented at the on-call room in the Socola Institute of Psychiatry. Out of

them 4 were admitted into the hospital and 3 were redirected towards other medical services. These numbers are insignificant compared to the estimated number of cases that might require mental health assistance. Given this discrepancy, one must consider whether the services we are providing are known to the refugees. The Emergency Act issued by the Romanian Government states that Ukrainian refugees and any other people coming from the war afflicted areas of Ukraine are given access not only to emergency medical care but also special medical assistance and treatment in outpatient facilities without the need to provide a physician's referral and without having to solicit official asylum status. To our best knowledge there isn't any publicly available official statistics regarding refugees' addressability to outpatient facilities. Within the first days of the conflict both the government and the civil community responded promptly, kindly and efficiently to the needs of our neighbors. As time goes on and we begin to see that the conflict is not soon to die off we have to think forward and address the issues that, as we know from previous experiences, are coming.

REFERENCES

1. WHO, Ukraine WHO Special Initiative for Mental Health Situational Assessment, 2020. Available at: https://www.who.int/docs/default-source/mental-health/special-initiative/who-special-initiative-country-report--ukraine--2020.pdf?sfvrsn=ad137e9_4
2. UNHCR, Ukraine refugee situation. Available at: https://data.unhcr.org/en/situations/ukraine.
3. UNICEF, Two million refugee children flee war in Ukraine in search of safety across borders. Available at: https://www.unicef.org/press-releases/two-million-refugee-children-flee-war-ukraine-search-safety-across-borders.
4. Thabet AM, Thabet SS, Vostanis P, The Relationship between War Trauma, PTSD, Depression, and Anxiety among Palestinian Children in the Gaza Strip, Health Science Journal, 2010, 10 5:1.
5. Perkins JD, Ajeeb M, Fadel L, Saleh G. Mental health in Syrian children with a focus on post-traumatic stress: a cross-sectional study from Syrian schools. Soc Psychiatry Psychiatr Epidemiol, 2018; 53(11).

BPI Bulletin of Integrative Psychiatry
Buletin de Psihiatrie Integrativă

Articles

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Mini-review on some neuropsychiatric perspectives of modern neuromarketing studies

Cristina Martiniuc, Ioannis Mavroudis, Alin Ciobîcă, Florn Alexandru Lucai

Cristina Martiniuc - Department of Biology, Faculty of Biology, Alexandru Ioan Cuza University, Iasi, Romania
Ioannis Mavroudis - Laboratory of Neuropathology, Electron Microscopy First Department of Neurology, Aristotle University, Thessaloniki, Greece, Leeds Teaching Hospitals, UK
Alin Ciobica – PhD, researcher, Academy of Romanian Scientists, Bucuresti, Center of Biomedical Research, Romanian Academy, Iasi
Florn Alexandru Lucai - "Gheorghe Asachi" Technical University of Iasi

ABSTRACT

The term neuromarketing has been the subject of much scientific debate over the past 20 years. Large companies immediately recognized the value of neurological research applied to consumer behavior and invested millions in in-depth studies that explained the underlying purchasing decisions.

Neuromarketing or scientifically known as consumer neuroscience is a new field that integrates sciences such as neurology, psychology and marketing. Still, there are a lot of controversies in this area of research. Some say it is the best tool for research that can accurately reflect consumers' preferences and choices, while others argue that neuromarketing is becoming a tool for manipulation. When the brain becomes an open book for the advertising industry, a big question of ethics arises. Another problem that may be of interest for the study of consumer neurology is what happens to vulnerable people who are struggling with addiction problems or psychiatric illnesses. In this context, this paper aims to analyze several studies on the fundamental concepts of neuromarketing, as well as its implications from an ethical point of view. In this article we will explore the possible repercussions of consumer neuroscience from the psychiatric perspective of addictions.

KEYWORDS:

Consumer neuroscience, neuromarketing, consumer behaviour, neuroimaging tools; neuroscience ethics, addictions, clinical disorders.

INTRODUCTION

The ability to read customer thoughts has become the main goal for all marketers. The marketing industry today aims to find out exactly what is happening in the minds of consumers in order to predict the complex and ever-changing behaviors of customers. If until a few years ago companies considered that a consumer buys a product only for its utility, now research suggests that all impulses to buy are made on an emotional basis. (1)

Marketing researchers quickly realized that there is no single discipline that can answer all the questions related to the purchase decision, so they approached the subject from a multidisciplinary point of view in order to understand consumer behavior (2). This new born discipline is coined as "neuromarketing." Is a term that is used in describing the field of study known as "the application of neuroscientific methods in analyzing and understanding how humans behave in reference markets and the marketing exchanges" (3).

Neuro-marketing is an interdisciplinary science that applies practices and techniques from neuroscience, psychology and marketing and measures consumer awareness and emotional responses to various marketing stimuli (4).

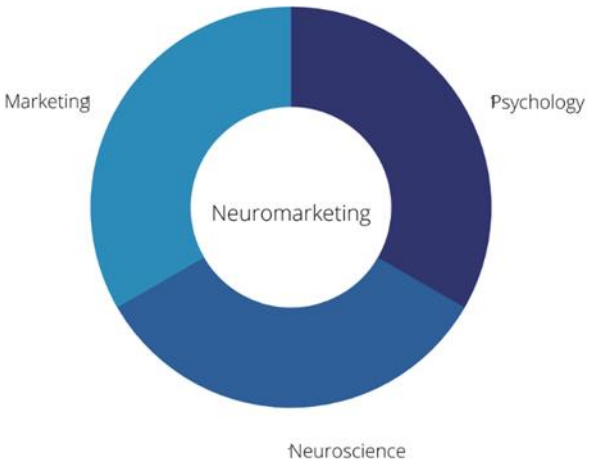

Figure 1: Basic fields in neuromarketing

In the last 30 years, research in neuroscience has made remarkable progress and research institutions have focused more on neuro-genetic research, banking brain and neurological studies (5). Published research in the field of consumer neuroscience has addressed academic topics such as the nature of brain activity that is influenced by consumer behavior and the accuracy of decision prediction, and neuromarketing has become now an effective tool for improving marketing campaigns (6).

The term neuromarketing was first used in 2002 by Professor Ale Smidts, from Erasmus University in Rotterdam, and is described as the science that studies the brain and how activities are processed in the context of consumer behavior (buying behavior - how and why people buy) (7). In the following years there has been a considerable increase in the application of neuroscience (and its neuroscientific methods) to analyze and understand human behavior in different contexts. Tallis & Taylor (8) even used the term “Neuromania” to refer to the multiple fields of study that use neuroimaging to explain the forms of human behavior regarding brain activities.

Meanwhile, technological advances in the field of neuroimaging have come up with new innovative solutions that have favored the development of this discipline, by adding portable, non-invasive technologies (7, 9). These advances have led to the increasing use of neuroscientific techniques to investigate the functionality of the brain and the unconscious reactions of humans in their daily activities. Today, we have the opportunity to investigate how central stimuli are perceived, processed, evaluated, and used by humans to make decisions in their daily interactions and activities (10).

The concern of marketers today is to find out the answer to the question that underlies consumer choices when it comes to one brand or another. Therefore, there will always be a concern about the factors that contribute to consumers' purchasing decisions. (7). The human brain is a black box (11) for scientists trying to find answers about what motivates people and what are the stimuli that cause them to act in a certain way. Considering the above, this mini-review aims to provide an overview of methods, and findings of consumer neuroscience and its implications for consumer research. In addition, we integrate aspects of consumer neuro-ethics and the how neuromarketing can influence people suffering from addictions and clinical disorders.

METHODOLOGY

Studies were searched in the main scientific databases (e.g. Pubmed, Sciencedirect, Scopus, Google Scholar), until 25 April 2022, by using the following keywords "neuromarketing", "neuroscience tools", "ethics in neuromarketing", "consumer neuroscience" and "addictions and consumer decision", “consumer neuroscience technics”. Cross-references for these key words were also counted in.

CONCEPT OF NEUROMARKETING

Studies in neuromarketing have a highly interdisciplinary character. Marketing management science is correlated with psychological knowledge and different medical fields (neurology, psychiatry and radiology) (12). It is important to distinguish the two concepts of this field: the first one is academic and it is referred as ‘‘consumer neuroscience’’ as suggested by Hubert and Kenning; the second one is the direct application of the neuroimaging techniques for the aims of marketing research industry, and we know it by term “neuromarketing” (13). In the last decades the number of publications about neuromarketing has increased from 10 (2000) to 250 (2010), and it was estimated that there were more than 300 companies specialized in this field in 2012 (2).

Neuromarketing studies showed how different areas of the brain work when consumers are exposed to market stimuli, giving researchers the opportunity to observe and analyze the correlation between consumer behavior and their neurophysiological systems. Given the knowledge we now have about the anatomy of the human brain, and taking into account the physiological features of each area of the brain, it is now possible for neuromarketing to model neural activities that identify the specific behavior of the human brain. By applying techniques in neuroimaging, researchers are able to track the activation of various areas of the brain when a reaction to a particular stimulus occurs, to differentiate specific tasks and create a pattern that can be used to describe the dynamics of human decisions. Also, they can pinpoint the normal mismatches that consumers experience in their actions and thoughts (7, 14).

All the research that has been done over the years on human behavior concluded that most mental processes that people experience take place at the subconscious level. These subconscious processes help us to better understand human nature and to accept that sometimes it is impossible to predict exactly what choices people will make in the future (15). Moreover, studies show that frequently what people think they want does not correspond with the decisions they make (16). This is one of the main reasons why marketers cannot rely solely on standard market research techniques that involve conscious responses (interviews, questionnaires, focus groups, etc.). (17).

NEUROSCIENCE TOOLS FOR CONSUMER RESEARCH

The marketing research methods used today are based on the ability and willingness of individuals to accurately report their attitudes and behaviors (18), often leaving room for mistakes, underreporting, or bias. Moreover, when it comes to factors that may affect real assessments, such as emotional or automatic reactions, individuals may not be able to express how they really feel about a situation or a product (19). Thus, there is a need to measure more objectively the direct and implicit processes in the human subconscious when it comes to choices and decisions in various contexts of consumption. (20).

The main instruments used in neuromarketing can be divided into three categories; tools that record the metabolic activity of the brain, tools that record the electric activity of the brain, and tools without recording brain activity (21, 22).

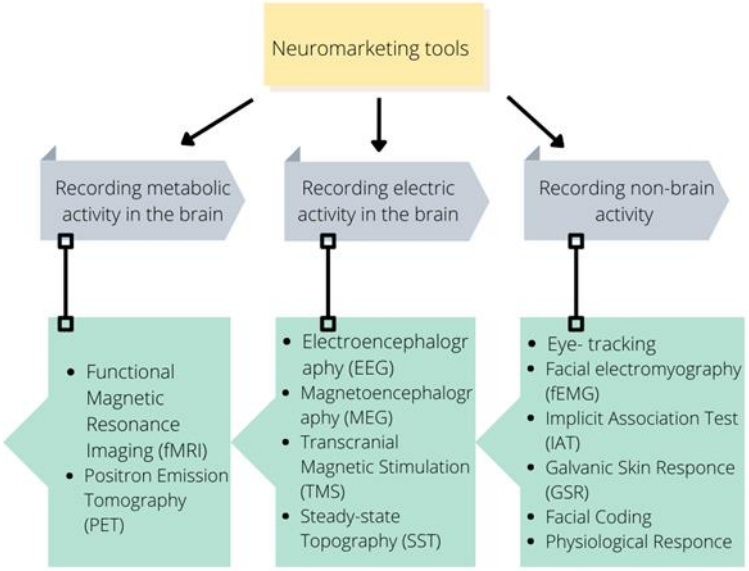

Figure 2: Classification of neuromarketing tools

Many consider fMRI the best technological innovation ever developed to conduct clinical and experimental research on the brain. This instrument is able to identify very precisely increased activity in a certain brain area while a stimulus is being presented. FMRI studies the blood flow in the vessel to measure the subject's brain (23). Most academicians and scientist consider fMRI the most powerful technique today because it has excellent spatial accuracy (24), that allows to record consumer's brain activity within its deep structures.

Positron emission tomography (PET) is also a tool that is used to measure metabolic activity in the consumer's brain, but is not so commonly used in marketing research because it uses the isotopes of the radioactive chemical material injects into the individual's blood vessel (25).

However, these tools are immense and require very large places; thereby, it is impossible to use them in normal circumstances, and last but not least, very costly. (26).

With the emergence of the digital era, the electroencephalography (EEG) was among first instruments which allowed the

researchers to explore the functioning of the brain (1). However, Baars, Franklin and Ramsoy (27) believe that electroencephalography provides little information about areas below the cortex, so this tool provides only partial answers for marketers. Electroencephalography is a non-invasive instrument that uses sensors capable of capturing electrical signals produced by brainwaves' activity and easily record data provided by surface neurons. Electroencephalography sensors are able to record very low frequency signals of brain activity and the more sensors there are, the better the brain is monitored.

Transcranial Magnetic Stimulation (TMS) is used to study the stimulation in a specific brain region by low and high frequencies on the participant's scalp (28). With this tool, a certain cortical area can be stimulated or inhibited. This type of instrument may be uncomfortable and sometimes improper to the neuromarketing specific research (29). Steady-State Topography (SST), records and measures electrical signals at the scalp in order to build a second-by-second picture of activity in the brain. The technology was first developed by Professor Richard Silberstein and his co-workers, at the Swinburne University of Technology, in the nineties.

One of the goals of neuromarketing research is to study consumer emotions. For the analysis of emotions, researchers frequently use instruments such as Electrocardiogram, to measure heart rate, and Galvanic Skin Response (emotions through perspiration). By both this, researchers can monitor autonomic activity and assess the individual's internal emotional state. The GSR is known to be a good technique to measure the emotional arousal dimensions, sweat glands, and changes in skin conductance.

Eye Tracking is a modern neurophysiological tool that have been use for studies in marketing, behavioral psychology, and cognitive psychology field. (30). Today ET is used to record eye movements, fixation, and pupil dilation. This instrument allows the measurement of different processes in the brain when the individual is exposed to different stimuli. Therefore, it provides to marketers a wealth of information about the consumer's perception of a particular brand or advertisement. (31).

Reaction time can be measured by the IAT technique. This technology has been shown to be very useful for neuromarketing studies on cognitive psychology and consumer behavior (1). By means of this instrument, it can be measured brand awareness (e.g., recall and recognition of a brand), brand perception, emotional valence (e.g., positivity or negativity), and measure the reaction time of the participants toward stimuli.

ETHICS

With the growing interest in consumer neuroscience research, there have been criticisms of the ethics of this new field. Some critics believe that once the processes of the human subconscious are revealed, companies will use this sensitive information to their advantage. The effects that new technologies have on the lives of individuals must be analyzed both in terms of the benefits and the risks involved. Therefore, the use of neuroimaging tools in the study of consumer behavior should be questioned primarily in the light of human principles that it may violate. Confidentiality, dignity, integrity, autonomy, are bioethical principles and intrinsic human values that cannot be overlooked. (32).

Protecting vulnerable groups is essential in setting the boundaries of researches, especially unprotected groups such as

children, people with psychiatric disorders or prisoners (33). Using these technologies on vulnerable people can lead to negative influences or even deception (34). Over the years, researchers have noticed an alarming increase in consumerism among children that has a negative impact on their physical and mental health. Exploiting emotions to influence buying behavior has led to increased consumption among both adults and minors. Large companies often use psychological findings on the basic needs of children and the relationship between child and parent to sell their products more efficiently. In the last 10 years there has been an alarming increase in childhood obesity, drug and alcohol use, but also a deterioration in mental and emotional health among youths. (32).

However, from a scientific point of view, neuromarketing is far from being able to allow the researcher to design a marketing action so captivating as to affect the free will of the consumer, although claims of this kind have been made, founded and unfounded (35). Often the lack of information about neuromarketing techniques leads to confusion and misinterpretation. Inadequate public information about consumer neuroscience leads to the mislabeling of this science as unethical or even abusive, threatening the privacy and autonomy of the individual.

In this regard, many researchers point to some ethical issues that should be considered when using neuromarketing techniques. Murphy, Illes, and Reiner (36) mention that there are two major ethical issues that need to be take into consideration in neuromarketing research. One, is to protect vulnerable parties from harm, and second, is to protect consumer autonomy if neuromarketing reaches critical effectiveness. Murphy et al. (36) also consider that there is an urge for a ‘code of ethics’ to be adopted by the neuromarketing industry. They recommend that all neuromarketing researches should protect subjects from coercion, fully disclose ethical principles used in the study, and accurate represent the scientific methods to businesses and other interested party.

ADDICTIONS AND NEUROMARKETING PRACTICES

Addiction research has brought to light a number of important issues that need to be considered in understanding consumer behavior. The first aspect is that error is a fundamental component of the reward and reinforcement system because it makes the difference between success and failure. But this system is being modified in the brain of the chronic drug user. This also leads to a modification of how pleasure forecast mechanisms translate sensory information and previous experiences (37). For example, tobacco addiction, caused by nicotine use, generates neuroadaptations in main systems which represent the core of reward, reinforcement and hedonic forecast (38). Also functionally, these brain areas are related to emotional systems and anxiety (39), indicating that analysis on addiction provides important information about how consumers respond to products and services, while experiencing different emotions and affective states.

It has been argued that once the "buy button" is identified, it is only a matter of time before large corporations use this information to influence consumer behavior or to cause addiction to their products. Those who share this view are of the opinion that the psychological techniques already used in marketing campaigns bear part of the blame for the massive increase in medical problems such as obesity, diabetes, alcoholism, lung cancer, etc. Advertising does not coerce the

individual, but tries to change behavior at a subliminal level. The brain's ability to associate emotions with situations or stimuli provides an effective means for marketers to associate a product with a desire.

Decision making for brand preference, brand choice and loyalty, involve conscious and non-conscious information processing. For examples, some studies have demonstrated that compulsive buyers are more vulnerable to shopping triggers due to increased sensitivity to any stimulus that offers emotionally-charged rewards (40). For this reason, it is considered that they would be more easily affected by environmental triggers, such as media effects or brand recognition. (41, 42). For individuals with BSD, "retail therapy" is the primary way of coping with stress, discomfort, and negative feelings. The same goes for tobacco addicts. The intensification of anxiety caused by withdrawal will increase the tendency to consume nicotine (43), as consumption will help reduce uncertainty and increase reward at the same time. Thus, we can see that addiction alters the same systems that are also used in decision-making and product selection. According to Volkow, Baler and Goldstein (44) addiction Addictions disrupt brain circuits involved in cognitive control, reward, and behavior. These systems are also responsible for motivation, memory and emotion and their alteration leads to changes in cognitive control through the continued desire to use drugs (45).

Although the information presented so far supports the view that addictions are a sensitive topic when discussing neuromarketing practices, some researches suggest that studying consumer neuroscience may even be beneficial in reducing some of the problems raised by Commercial Alert. For example, if we look at the differences between brain activity of people with buying-shopping disorder and people without, we may find the answer to the impulse to spend more than they need.

CONCLUSIONS

Neuroscience research has provided empirical evidence about many assumptions that previously were unclear regarding the decision-making process. Although the frontal cortex was until recently considered to play a major role in decision making, we now know that emotions, memory, and reward contribute in weighting decisions (46, 47). Marketers have only recently realized that they need to study and understand how the human brain works in order to predict consumer behaviour. There are thousands and thousands of chemical, social and sensory stimuli that are processed by our nervous system and that can improve or diminish the consumer experience. Therefore, decision making is a complex process that involves brain structures responsible for memory, attention, emotion, reward, motivation and more. Another aspect that stands out in most of the research is that advertising is directed at a general audience without considering how it may affect vulnerable people or people with addiction problems. Addiction research offers new insights into the neural processes involved in consumption habits, which makes necessary the inclusion of factors such as anxiety, pleasure and uncertainty for a more accurate study.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES

1. Vlasceanu Sebastian. (2014). Neuromarketing and evaluation of cognitive and emotional responses of consumers to marketing stimuli, 127, 753–757.
2. Hilke Plassmann, Carolyn Yoon, Fred M. Feinberg, Baba Shiv (2010). Consumer Neuroscience. In Wiley International Encyclopedia of Marketing. Methodological approaches in neuroscience, Part 3. Consumer Behavior, 1-8.
3. Nick Lee, Amanda J Broderick, Laura Chamberlain. (2007). What is "neuromarketing"? A discussion and agenda for future research, 63(2):199-204.
4. Aida Azlina Mansor, Salmi Mohd Isa. (2020). Fundamentals of neuromarketing: What is it all about?, 1-7.
5. Eric Racine, Judy Illes. (2007). Emerging ethical challenges in advanced neuroimaging research: Review, recommendation and research agenda. Journal of Empirical Research on Human Research Ethics: An International Journal 2 (2):1–10.
6. Mehri Shahriari, Davood Feiz, Azim Zarei, Ehsan Kashi. (2019). The Meta-Analysis of Neuro-Marketing Studies: Past, Present and Future, 1-13.
7. Chiemelie Benneth Iloka, Kenechi John Onyeke. (2020). Neuromarketing: a historical review, 1-9.
8. Raymond Tallis , Matthew Taylor (2011). Neuromania? RSA Journal, 157(5547), 48.
9. Gianluca Borghini, Pietro Aricò, Ilenia Graziani, Serenella Salinari, Yu Sun, Fumihiko Taya, Anastatios Bezerianos, Nitish V. Thakor, Fabio Babiloni (2016). Quantitative Assessment of the Training Improvement in a Motor-Cognitive Task by Using EEG, ECG and EOG Signals. Brain Topography, 29(1), 149–161.
10. Sebastian Gluth, Jörg Rieskamp, Christian Büchel. (2012). Deciding When to Decide: Time-Variant Sequential Sampling Models Explain the Emergence of Value-Based Decisions in the Human Brain, 32 (31), 1-13.
11. Nannan Cao. (2016). Research on Theory Sources of Art Consumer Behavior Model, 1-4.
12. Andrija Javor, Monika Koller, Nick Lee, Laura Chamberlain, Gerhard Ransmayr. (2013). Neuromarketing and consumer neuroscience: contributions to neurology, 13:13, 1-12.
13. Mirja Hubert, Peter Kenningy. (2008) A current overview of consumer neuroscience, Journal of Consumer Behaviour. 7: 272–292.
14. Icaro Luiz Dos Santos Jordão, Marina Teixeira De Souza, Jorge Henrique Caldeira De Oliveira, Janaina De Moura Engracia Giraldi. (2017). Neuromarketing applied to consumer behaviour: an integrative literature review between 2010 and 2015. International Journal of Business Forecasting and Marketing Intelligence, 3(3), 270.
15. Giovanni Vecchiato, Patrizia Cherubino, Arianna Trettel, Fabio Babiloni. (2013). Neuroelectrical Brain Imaging Tools for the Study of the Efficacy of TV Advertising Stimuli and their Application to Neuromarketing, p 1-9.
16. Maarten A.S. Boksem, Ale Smidts. (2015). Brain Responses to Movie Trailers Predict Individual Preferences for Movies and Their Population-Wide Commercial Success, 52(4), 482-492.
17. Gemma A. Calver, Michael J. Brammer. (2012). Predicting Consumer Behavior: Using Novel Mind-Reading Approaches, 3(3), 38-41.
18. Richard E Petty, David W. Schumann. (1983). Central and Peripheral Routes to Advertising Effectiveness: The Moderating Role of Involvement, 10(2):135-146.
19. Norbert Schwarz, Gerald L. Clore. (2003). Mood as Information: 20 Years Later, Psychological Inquiry. An International Journal for the Advancement of Psychological Theory, 14(3), 296-303.
20. Dan Ariely, Gregory S. Berns. (2010). Neuromarketing: the hope and hype of neuroimaging in business, 11(4): 284–292.
21. Leon Zurawicki. (2010). Neuromarketing: Exploring the Brain of the Consumer. Pp.43-50.
22. Hilke Plassmann, Tim Ambler, Sven Braeutigam, Peter Kenning. (2007). What can advertisers learn from neuroscience? International Journal of Advertising. The Review of Marketing Communications, 151-175.
23. Christophe Morin. (2011). Neuromarketing: The New Science of Consumer Behavior, 48, 131–135.
24. Hilke Plassmann, Vinod Venkatraman, Scott Huettel, Carolyn Yoon. (2015). Consumer Neuroscience: Applications, Challenges, and Possible Solutions, 52(4), 427-435.
25. Ahmed H. Alsharif, Nor Zafir Md. Salleh, Rohaizat Baharun, Mohd Yusoff. (2021). Consumer Behaviour Through Neuromarketing Approach, 344-354.
26. Cherubino Patrizia, Martinez-Levy Ana C, Caratù Myriam, Cartocci Giulia, Di Flumeri Gianluca, Modica Enrica, Rossi Dario, Mancini Marco, Trettel Arianna. (2019). Consumer behaviour through the eyes of neurophysiological measures: State-of-the-art and future trends, 1-41.
27. Bernard J. Baars, Stan Franklin, Thomas Zoega Ramsoy. (2013). Global workspace dynamics: cortical “binding and propagation” enables conscious contents, 1-22.
28. Nick Lee, Leif Brandes, Laura Chamberlain, Carl Senior. (2017). This is your brain on neuromarketing: reflections on a decade of research, 878-892.
29. David J.F.du Plessis, NicoNouwen, Arnold J.M.Driessen. (2011). The Sec translocase, Biochimica et Biophysica Acta (BBA) – Biomembranes, 851-865.
30. Seong Wook Chae, Kun Chang Lee. (2013). Exploring the effect of the human brand on consumers' decision quality in online shopping: An eye-tracking approach, 37 (1), 83-100.
31. Vitor Costa Rozan Fortunato, Janaina de Moura Engracia Giraldi, Jorge Henrique Caldeira de Oliveira. (2014). A Review of Studies on Neuromarketing: Practical Results, Techniques, Contributions and Limitations, 6 (2), 1-20.

32. Yesim Isil Ulman, Tuna Cakar, Gokcen Yildiz. (2014). Ethical Issues in Neuromarketing: ‘‘I Consume, Therefore I am!’’. 1-14.
33. Luna Florencia, Macklin Ruth. (2012). Research involving human beings, vulnerability and exploitation. In H. Kuhse & P. Singer (Eds.), A companion to bioethics (pp. 459–468).
34. Martha J.Farah (2005). Neuroethics: The practical and the philosophical. Trends in Cognitive Sciences, 9(1), 34–40.
35. Christopher R Madan. (2010). Neuromarketing: the next step in market research? 1(1), 1-9.
36. Emily R. Murphy,Judy Illes,Peter B. Reiner. (2008). Neuroethics of neuromarketing, 7: 293–302.
37. Morten L. Kringelbach. (2005). The human orbitofrontal cortex: linking reward to hedonic experience, 6, 691–702.
38. Suzanne N Haber, Brian Knutson. (2010). The Reward Circuit: Linking Primate Anatomy and Human Imaging, 35, 4–26.
39. J.K.Abramsa, P.L.Johnsona, A.Hay-Schmidt, J.D.Mikkelsenb, A.Shekhard, C.A.Lowry. (2005). Serotonergic systems associated with arousal and vigilance behaviors following administration of anxiogenic drugs, 133(4), 983-997.
40. Monika Kukar-Kinney, Nancy M.Ridgway, Kent B.Monroe. (2009). The Relationship Between Consumers’ Tendencies to Buy Compulsively and Their Motivations to Shop and Buy on the Internet, 85(3), 298-307.
41. Wayne S. DeSarbo, Elizabeth A. Edwards. (1996). Typologies of Compulsive Buying Behavior: A Constrained Clusterwise Regression Approach, 5(3), 231-262.
42. Stephen Kellett, Jessica V. Bolton. (2009). Compulsive buying: A cognitive–behavioural model, 16(2), 83-99.
43. George F.Koob. (2009). Neurobiological substrates for the dark side of compulsivity in addiction, 56(1), 18-31.
44. Nora D.Volkow, Ruben D.Baler, Rita Z.Goldstein. (2011). Addiction: Pulling at the Neural Threads of Social Behaviors, 69(4), 599-602.
45. Alejandro Salgado-Montejo, Carlos Velasco, Cristina Blanco, Enrique Guarin. (2011). What can tobacco Addiction teach us about consumer decision making? Consumer behavior, hedonic forecast and reward, 1-11.
46. Antoine Bechara, Hanna Damasio, Antonio R. Damasio. (2000). Emotion, Decision Making and the Orbitofrontal Cortex, 10(3), 295–307.
47. Matthias Brand, Katharina Heinze, Kirsten Labudda, Hans J. Markowitsch. (2008). The role of strategies in deciding advantageously in ambiguous and risky situations 9, 159–173.

Correspondence

Cristina Martiniuc,
Department of Biology, Faculty of Biology, Alexandru Ioan Cuza University, B dul Carol I, no 11, Iasi, Romania cmartiniuc@gmail.com

Submission: 02 mar 2022
Acceptance: 10 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Biology versus culture in assuming the ”right” body

Nicoleta Ciobanu-Hașovschi, Vasile Chiriță, Cristinel Ștefănescu

Nicoleta Ciobanu-Hașovschi - M.D., ”Socola” Institute of Psychiatry, Romania
Vasile Chiriță - MD, PhD, Professor, Honorary Member of the Academy of Medical Sciences, Romania
Cristinel Ștefănescu - M.D., PhD, Professor of Psychiatry “Grigore T. Popa“ University of Medicine and Pharmacy, Iași, Romania, senior psychiatrist ”Socola” Institute of Psychiatry, Iași Romania

ABSTRACT

The issue of sex, gender and their relationship with the human body, a complex aspect of human health, has caused, throughout history, controversies and debates, with far-reaching consequences for the life of both the individual and society as a whole. The most well-known theories about this interdisciplinary subject have been: the patriarchal theory, the feminist one, the poststructuralist, and the postmodern ones. From considering them as fixed, immutable features, to a clear biological/social distinction, the debates regarding the cultural or strictly biological determinism of sex and gender develop by including gender identity in this debate, which influences the role of gender, a historical conditioning element of family, social, cultural and political life of the individual. Whether belonging to psychiatry or just culture, the topics in discussion and the specifics of the people involved have undergone changes over time, with very concrete consequences on their personal lives. The present paper brings some observations on this subject, up to the present moment, when the changes taking place are trying to avoid the stigmatization and marginalization of people with non-traditional gender identities. In conclusion, the “sex/gender/identity/gender roles” spectrum is in a continuous interdisciplinary analysis and undergoes adaptations that reflect the individual and social evolution. It remains for the future to reveal the sustainability and adequacy in time of the current concepts and to what extent they improve the individual`s quality of life and protect the social balance.

KEYWORDS:
Sex, gender, gender identity, theories, gender dysphoria.

INTRODUCTION

As a complex aspect of human health, issues related to sex, gender and the relationship with the human body have throughout history provoked serious debates and consequences on multiple levels of individual and social life. The existence of full concordance between the above categories has been considered an implicit feature of human beings perceived as "normal", "healthy". So, living in accordance with biological sex is usually taken for granted. However, in modern society, the phenomenon of explicitly feeling a mismatch between biological sex, gender and gender identity is increasingly common; although, as a rule, from a socio-cultural point of view, since ancient times the categories of female/male have had clear connotations, with individuals assuming specific roles in terms of identity, social, professional matters etc., modern society has seen a reconsideration of these notions, with the consequence of a fundamental re-evaluation of standards. Conceptual changes have shifted from the psychiatric field to new variants of identity normality.

Significant changes began to take place as early as the 18th century, with an emphasis towards the 20th century. Initially based on the aim of emancipating women in society by gaining civil rights (to education, inheritance, voting, etc.), the theme was taken over from the field of sociology by Western academic feminist movements (1).

Subsequently, in the 1980s, the first women's studies appeared and the first feminist studies saw the light of print in the 1990s. The literature shows that gender studies, which also emerged in this context, promoted the concept that gender was more a relationship between women and men, an institutional power structure, than an individual characteristic. Sexuality was understood as a fundamental dimension of patriarchal control of bodies.

In Romania and other Eastern European countries, gender studies emerged after the 1990s (in the form of gender modules at faculties in traditional university centers, and since 1998, a Master's degree in Gender Studies has been established at the National School of Political and Administrative Studies in Bucharest).

The representative concepts identified by accessing the literature are the following:

THE PATRIARCHAL THEORY (corresponding to a so-called cultural-material order dominated by men, as a group), states that sex and gender are the same thing, being: natural, immutable, fixed, biologically determined and have specific assigned roles (of wife/mother, husband/father). They also have specific attributes and qualities. So, consequently, sex equals gender, equals body. Traditionally, in many cultures, "feminine" attributes and qualities would be: the person born female becomes: feminine, heterosexual, marries a man, has children, takes care of the family, lives more at home, etc.

Culturally enshrined 'masculine' attributes and qualities would be: the individual is born male and becomes: masculine, heterosexual, marries a woman, has children, maintains family, is sometimes aggressive, combative, socially and politically active, etc.

THE FEMINIST THEORY in the 1960s and 1970s considered sex to be biological and gender to be a social construct. The consequence is that relations between women and men, as well as gender roles, are the result of education and socialisation considered patriarchal. Patriarchal culture and education teach women and men to behave in a certain, specific way, which is detrimental to women. However, the revolutionary consequence becomes that, according to the social concept of gender, it is possible to unlearn what we have been taught.

The positive effect of the debates, studies and interdisciplinary research in this field has been the gaining of fundamental rights for women which were non-existent before: political, economic, professional rights, rights over one's own body, sexuality, condemning and combating violence against women, etc.

Gender, also analysed from the perspective of the concept of power, from the 1980s onwards, has become complex, intersectional and interlinked with axes of discrimination such as race, age, ethnicity, class and sexuality, thus concluding that there are not only differentiations and hierarchies between men and women, but also between women (black women versus white women, women from different countries, which has subsequently been confirmed for men).

THE POST-STRUCTURALIST PHILOSOPHICAL THEORY OF LANGUAGE, considered by the authors to be the second phase of feminist theorising, postulates the idea that sex, gender and sexuality are conceptualised in relation to 'the prevailing culture' (Judith Butler) (2). This creates a 'normal' of personal and group expectations regarding the characteristics of a person according to their sex. Even when the child's sex ('boy' or 'girl') is verbally established at birth, the linguistic 'sexualization' of the body takes place, with the imposed result of the male-female dichotomy corresponding to the 'normal expectations'.

POSTMODERN AND POSTSTRUCTURALIST FEMINIST THEORIES consider the biological and the social (sex and gender) to be constructs imposed by a violent cultural system through which bodies are controlled and manipulated, with different effects on access to benefits. It is also considered that patriarchal logic is built on dualistic mechanisms, e.g. mind-body or male-female. Thus, men are rational and women are emotional, etc. These stereotypes are dichotomous and antagonistic and affect not only the individual but the whole system whereby men have a monopoly on resources to the detriment of women.

THE THEORY OF GENDER EQUALITY is currently being applied at the European level, with significant cultural, social and political implications. For conservative societies, such as Romanian society, the developments we are referring to require time to adapt, as the level of education in this area is relatively low, traditionalist, and the collective consciousness is reluctant to adopt new models.

The European Union's gender equality discourse promotes the meaning of the sex-gender distinction and corresponds to the conception of the second wave of the feminist movement: sex is biological and gender is a variable historical construct, therefore subject to change at any time, and there is no causal relationship between the two.

More recently, the concept of gender has begun to encompass men, going beyond women's issues. Critics of this model argue that it is only aimed at equalising and quantifying indicators in European programs, such as the number of women in management structures, the pay gap, the number of women benefiting from various European programs, etc. It is clear that the gender concept is now increasingly being used as a political tool at a global level.

Worldwide, however, a 'masculinist' culture is still considered to prevail, with the aim of biological survival dependent on women. While 'naturalness and normality' are nowadays increasingly seen as cultural constructs with ever-changing content, masculinist cultural precepts use arguments such as the loss of traditional moral values. This actually masks the fear of losing the privileges that come from being the representative of the 'norm' and 'normal' 'decreed' by men in a particular social organisation.

In conclusion, we can say that the field of sex and gender is still highly controversial and interdisciplinary. The respective terms have had varying meanings over time. As an additional element of confusion, in Romanian, the term "sex" refers both to being male or female and to sexuality. In the medical sense, the terms 'sex' and 'sexual' refer to innate biological characteristics, specifically male or female, understood in the context of reproductive capacity: sex chromosomes, gonads, sex hormones, the clearly defined internal and external genitalia (3). Variants of

genetic and non-genetic sex are specified in the literature. The biological specialisation of the human organism into male/female has as its biological end sex reproduction. Genetic sex is determined by chromosomal configuration. As is known, statistically, in humans and other mammals, males have the XY chromosomal configuration and females: XX, but in nature, there are other systems for determining genetic sex, such as: in birds - the ZW system: ZZ - male / ZW - female (4), in insects - X0 system: males have one sex chromosome - X0 / females have 2, XX (5), in fungi more complex allelic mating systems are identified, so the sexes are not accurately described as male, female or hermaphrodite (6). Sexually, the following variants are found in nature: female, male, hermaphrodite, intersex, undefined (allelic). But for some species of the animal kingdom, sex is determined by environmental factors acting during their development, or later in life. For example, in some reptiles, sex determination during the embryonic phase is temperature-dependent (7). In some turtles, males differentiate at lower incubation temperatures than females. Clownfish are initially male and then the largest fish in a group becomes female.

In the psychiatric field, the term gender, used to designate the role played in society, usually legally recognised, as boy or girl, male or female, needs to be corrected in view of the fact that, in the modern understanding, biological factors are seen as factors contributing to the development of gender, in interaction with social and psychological factors (and not as determining factors) (8), thus avoiding gender segregation.
The literature defines "assigned gender" as the initial designation as male/female (9), "atypical gender", in which somatic characteristics are not statistically typical of individuals of the same assigned gender within a society and historical period, "gender nonconforming" in which behavioural characteristics are statistically non-typical (3), "reassigned gender", which refers to the official and usually legal change of gender and often involves a series of medical procedures (9).

Closely related to the categories analysed is the concept of gender identity, which is of great importance to the development of the individual concerned, as it is a category of social identity which refers to the individual's self-identification as male, female or sometimes as something other than male or female. While The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-4) classified "Gender Identity Disorder" as a psychiatric disorder (10), this is no longer found in the current classification. The conceptual changes are justified by the stated intention to avoid stigmatizing people with such characteristics.

Thus, "Gender Identity Disorder" has been replaced in DSM-5 by "Gender Dysphoria", where the focus is on dysphoria as a clinical problem and not on identity per se. Characteristics would be: profound mismatch between a person's biological sex and the gender they experience and express in society, marked discomfort, desire to belong to the gender they identify with, specific behaviours such as: wearing clothing belonging to the desired gender, characteristic behaviours, duration of manifestation longer than 6 months.

The World Health Organisation's International Classification of Diseases and Related Health Problems, 11th Edition (ICD-11), classifies gender incongruence as HA60 and childhood gender incongruence as HA61 (11).

Gender incongruence is defined by a marked and persistent incongruence between an individual's experienced gender and assigned sex. Gender-specific behaviour and preference per se are not a basis for diagnostic assignment.

Childhood gender incongruence is characterized by a marked incongruence between experienced/expressed gender and assigned sex in prepubertal children. It includes a strong desire to be of a gender other than the assigned one; a strong dislike of one's own sexual anatomy or anticipated secondary sexual characters and/or a strong

desire to have the primary and/or anticipated secondary sexual characters corresponding to the experienced gender. Duration must be greater than 2 years. Corresponding synonyms are Childhood gender dysphoria, Childhood psychosexual identity disorder, and Childhood gender identity or role dysphoria.

Adolescent or adult gender incongruence is characterized by marked and persistent incongruence between experienced and assigned gender, often leading to a desire to transition, to be accepted and live as a person of the agreed gender, through hormonal treatment, surgery or other health services to alter the body as much as possible to the agreed gender (11).

In conclusion, it follows that in ICD-10, the chapter "Gender identity disorders" has been included in the category "mental disorders" (12). Throughout the 20th century, both the ICD and the DSM have analysed the transgender phenomenon from psychopathological positions, as it refers to the discrepancy between biological sex and gender identity, which can cause "mental distress". Thus, the phenomenon has been considered a mental disorder (13).

After the year 2000, conceptions changed, in view of the social stigma associated with any mental disorder. It was considered that the distress and dysfunctions created were more likely to be the result of social rejection, discrimination and sexual violence towards individuals with other gender variants and behaviour (14).

Studies have confirmed, however, that transgender people are at increased risk of developing mental disorders, but that, in general, there are insufficient health services for transgender people (15). Therefore, in order to facilitate access to therapy and reimbursement for health services, an ICD code is needed, and the WHO has recommended that transgenderism be maintained in the ICD-11.

CONCLUSIONS

In conclusion, the spectrum of concepts 'sex/gender/gender identity/gender role' is undergoing continuous interdisciplinary analysis and adaptations reflecting individual and societal developments, which are also reflected in health policies globally (15), although there are particularities and differences, sometimes significant, from one country to another. It remains for the future to reveal the sustainability and appropriateness over time of current concepts and the extent to which they can lead to improving the quality of life of the individual and protecting the social balance.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors declare that they have no potential conflicts of interest to disclose.

REFERENCES

1. Stoller RJ. Sex and gender: On the development of masculinity and femininity. New York City Science House, First Edition. New York. 1968
2. Smith – Laing T. Judith Butler`s Gender trouble. Macat International Limited. The Macat Library. 2017
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th Edition. Washington DC. 2013
4. Stevens L. Sex chromosomes and sex determining mechanisms in birds. Sci Prog. 1997;80 (Pt 3):197-216.
5. Hake L, O'Connor C. Genetic mechanisms of sex determination. Nature Education. 2008; 1(1):25
6. Watkinson SC, Boddy L; Money N. The Fungi. Academic Press. London. 2015
7. Janzen FJ, Phillips PC. Exploring the evolution of environmental sex determination, especially in reptiles. Journal of Evolutionary Biology, 19: 1775-1784. 2006
8. Rathus SA, Nevid JS, Fichner – Rathus L. Human sexuality in a world of diversity. 9th Edition. Pearson. London. 2013
9. Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. Nat Rev Urol. 2011;8(5):274-282.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th Edition. Washington, DC. 1994

11. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 11th Edition. Geneva. 2019
12. World Health Organization. The ICD-10 classification of mental and behavioural disorders. Geneva. 1993
13. Drescher J, Cohen-Kettenis P, Winter S. Minding the body: situating gender identity diagnoses in the ICD-11. International Review of Psychiatry 24(6):568-77. 2012
14. Robles R, Fresán A, Vega-Ramírez H, et al. Removing transgender identity from the classification of mental disorders: a Mexican field study for ICD-11. Lancet Psychiatry. 2016;3(9):850-859.
15. Cantemir A, Cantemir I, Costache A, Dobrin I et al. Medical and social assistance for the transgender community: difficulties and particularities in psychiatric and psychotherapeutic assistances. Revista de cercetare și intervenție socială, 2021.74:149-163.

Correspondence:

Vasile Chiriță,
MD, PhD, Professor, Honorary Member of the Academy of Medical Sciences, Romania,
d.stigma@gmail.com

Submission: 30 mar 2022
Acceptance: 05 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Describing some metabolic manifestations in zebrafish models and their possible neuropsychiatric relevance

Iuliana Luca, Alexandrina Curpan, Dobre Cristina Elena, Alin Ciobîcă

Iuliana Luca - Department of Biology, Faculty of Biology, "Alexandru Ioan Cuza" University of Iasi
Alexandrina Curpan - Department of Biology, Faculty of Biology, "Alexandru Ioan Cuza" University of Iasi
Dobre Cristina Elena - MD, PhD, Socola Institute of Psychiatry Iasi
Alin Ciobîcă - PhD, researcher, Department of Research, Faculty of Biology, "Alexandru Ioan Cuza" University of Iasi, Center of Biomedical Research, Romanian Academy, Iasi, Romania

ABSTRACT

Diabetes is one of the pressing matters of today modern society due to its difficulty in diagnosis as it can progress fast and become evident or progress slow and go undetected for years, and also its manifestations can differ from individual to individual. The alarming rate of increase of diabetic individuals is worrisome as it is influenced by a plethora of environmental factors, from poor alimentation influenced by political, social-economical and geographical factors to the genetic predisposition of developing it through a parents-to-off-springs mechanism. Throughout history, scientific community has moved from one animal model to another in an attempt to find the perfect candidate to replicate pathologies whereas keeping their suffering in the lows. Over the past few decades, zebrafish has become a well established alternative for pathologies modelling due to its advantages such as low cost, easy maintenance and manipulation, external fecundation, complex behavior and similarity to the human body. In this article, we have presented the current methods of inducing different type of diabetes using zebrafish animal model. Depending on the need and purpose of the research, diabetes can be induced through chemical methods by administrating substances such as glucose and streptozotocin, through diet by means of high caloric intake and through genetic manipulation. All of these methods allow for a better understanding of the pathology and offers the ground for finding more and better therapeutic options.

KEYWORDS:
Zebrafish, diabetes, glucose, Alzheimer, high-caloric diet

INTRODUCTION

Diabetes is a condition that affects the population in an alarming way and can cause damage even if kept under pharmaceutical control; this is due to the metabolic memory or inheritance effect (1). The phenomenon was discovered around the 1990s, and since then it has been necessary to experiment with animal models illustrating the symptoms of diabetes and metabolic memory (2–4). The first diabetic model was a canine one, studying diabet-related retinopathy. Following this research, other types of animal models have started to emerge (5–8) to several different species of animals, including zebrafish, which is becoming increasingly popular(9). The methods used for experimental induction of diabetes range from viral, hormonal, chemical, surgical, genetic, immunological (antibodies) to even a combination of some.

At the heart of metabolic memory are epigenetic processes that allow organisms to adapt to external stimuli, and at the same time give the cell the ability to retain these adaptations even after the external stimulus has been removed (10). Epigenomics consists of biochemical changes in DNA and histone proteins in an organism that can be passed on to offspring through genetic inheritance(11). Therefore, the environmental conditions affect the epigenome, and the modified genetic expression profiles resulting from the epigenetic processes can be transmitted by cell division, as a result these changes have come to the attention of researchers as molecular mechanisms underlying human pathologies (12–14).

At first the zebrafish was used in studies for the development of vertebrates, but later it was used for the study of various human pathologies (15). Among the advantages of using this model are: low acquisition and maintenance costs, transparency of embryos, high multiplication rate, short generation time, the possibility of using a variety of tools in the manipulation of genes (16), the ability to induce similar diabetic complications with humans, diabetic retinopathy, diabetic nephropathy and the possibility of the fish to regenerate its affected caudal fins, the affected pancreas, as well as the possibility of restoring the state of euglycemic condition, a condition that is desired to reach patients who had undergone a transplant(17). Also, the possibility of beta cell regeneration leads to the elimination of the hyperglycemic state, the body returning to the euglycemic state from a physiological point of view, but with continuous impairment of the regeneration capacity of the limbs, characteristic of the acute diabetic state (17).

Zebrafish has been mentioned as a laboratory animal by Streisinger et al, (1981)(16). Along with the above-mentioned characteristics of zebrafish, it should be noted that its small size gives the possibility of transcriptomic and proteomic analysis (18), as well as the similarity of genes in 70% with humans, glucose regulation, similar to that of mammals, make it a suitable model for the study of diabetes and metabolic memory (19).

Although still most of the papers are still preferring rodents to study diabetes, some have used zebrafish as an animal model. Inducing diabetes, of any kind, can lead to neurodegeneration over time through the use of several methods (20). Among the methods used are genetic methods, which are more accurate, and non-genetic methods, which are less expensive and faster to induce. A scoring system was used to determine which model was best suited and the best method of inducing hyperglycemia. In awarding the score, the emphasis was on the time of induction of hyperglycemia, the shorter the

score, the higher the score, and the longer it lasts (21).

METHODS/PATTERNS FOR INDUCING HYPERGLYCAEMIA IN ZEBRA FISH

1. GLYCOSE - BASED METHODS FOR INDUCING HYPERGLYCAEMIA

These methods are cheap and easy to induce. The protocols took into account the time of induction of the hyperglycemic state, the glucose concentration and the life stage of the fish, larval or adult.

1.1 Hyperglycaemia model by alternative immersion in 2% and 0% glucose solution

By this method, the alternative exposure of zebrafish to a 2% and 0% glucose solution for 30 days, was manifested by retinopathy and increased blood glucose levels (22).

1.2 Model of hyperglycemia by immersion in glucose solution with gradual increase of its concentration

Starting from the model proposed by Gleason et al, (2007)(22) and Connoughton et al, (2016) (23) observed that Gleason's method depends on age, because following the same protocol he observed that older fish developed a hyperglycemic state for 2 months, and the younger group of fish developed a hyperglycemic state for a month, returning to a euglycemic state after returning to a new habitat. Thus, Connaughton et al., (2016) (23) applied another method based on increasing the glucose concentration during the induction of the hyperglycemic state. It started with a concentration of 1% for 2 weeks, 2% in the next 2 weeks, then using a concentration of 3% for young adults for the next month, so the younger group of fish had a stable state of hyperglycemia during the 2 months of induction.

1.3 Hyperglycemia model based on chronic immersion of zebrafish in 110 mM glucose solution

Another method of inducing hyperglycemia was proposed by Capiotti et al, (2014)(24), who chose the 110 mM glucose solution for 14 days. During which time ractopamine was evaluated as an indicator of non-enzymatic blood glucose in protein ions in the eyes of zebrafish. Then antidiabetic drugs such as glimpyride and metformin were administered. The advantages of this method are the short induction time and the stable hyperglycemic state.

1.4 Model of hyperglycemia by chronic immersion in 4% glucose solution

This model was proposed by Carnovali et al, (2016)(25), immersion of zebrafish in 4% glucose solution for 28 days with the desired effects: insulin resistance and retinal vasculopathy.

1.5 Model of hyperglycemia by alternating immersion in 4%, 5% glucose solution

Singh et al., (2019)(26) adopted a method that mimics the condition of the fetus in mothers with pre-existing and gestational diabetes, namely the alternation of glucose with a concentration of 4% and 5% on individuals from 3-5 hours post-fertilization with retinopathic effects in adulthood.

1.6 Model of hyperglycemia by immersion in 130 mM glucose solution

According to this method initiated by Jung et al., (2016)(27), fish from 3-6 days postfertilization were immersed in 130 mM solution and retinopathic disorders, vascular membrane thickening and increased vascular permeability were obtained.

2. DIET-BASED METHODS

Obesity, processed food and in large quantities promote diabetes (28). Zebrafish with kidneys, pancreas, adipose tissue and skeletal muscle can be used successfully to create a hyperglycemic pattern. These models are based on a rodent study (29).

2.1 Model of hyperglycemia based on obesity

Knowing that obese people can develop diabetes, the fish were fed 8 times a day for 8 weeks, noting that even a month after stopping treatment, the blood sugar level remains high and antidiabetic drugs can be tested, glucose and deep RNA sequencing to verify this pattern (30).

2.2 Hyperglycemia model based on a high fat diet (HFD) containing 1% egg yolk

The principle behind diabetes induction is also obesity, as mentioned earlier. The diet used is based on shrimp, brine and 1% egg yolk for 10 weeks. This method induced insulin resistance by decreasing the insulin receptor substrate 2 (IRS2) and glucose transporter 2 in the liver, thereby increasing the amount of insulin in the muscles and liver tissues (31).

3. CHEMICAL MODELS FOR INDUCING HYPERGLYCEMIA

3.1 Bisphenol F-induced hyperglycemia model

Bisphenol F causes endocrine and physiological disorders, liver toxicity, in vitro studies demonstrating its cytotoxic effects, cell dysfunction, DNA damage and chromosomal aberrations. Zhao et al., (2018)(32), following a study of the influence of bisphenol F in maintaining glucose homeostasis in zebrafish larvae, observed that zebrafish had elevated insulin levels, significantly lower levels of gene transcripts encoding insulin receptor substrate, all of these aspects demonstrating insulin resistance and this model would be a suitable approach in this regard.

3.2 Bisphenol S-induced hyperglycemia model

Among the cardiac, obesity, metabolic effects of bisphenol are the neurobehavioral and diabetic effects (33). Another study showed that bisphenol S causes diabetes. Insulin levels have been reduced but gluconeogenesis and glycogenolysis in the liver have been intensified, arguing that BPS is a diabetic agent in zebrafish.

4. HYBRID METHODS FOR INDUCING HYPERGLYCEMIA

These methods are based on studies of rodents that can be applied to zebrafish. Among these combined methods, the combined diet with high cholesterol and high glucose creates a pattern of hyperglycemia for larval zebrafish. This study was also based on the study by Wang et al, (2013)(34), which used this hybrid method (COL 10%) and an exposure of zebrafish to a high-concentration glucose solution (2% glucose) with effects such as vascular disorders, one of the specific manifestations of diabetes, along with increased insulin, glucagon, glucose, triglycerides and cholesterol (34). This diet was also applied to adult zebrafish for 19 days inducing hyperglycemia and in which other parameters were followed to understand the inflammation and apoptosis related to the induced glycemic state. Although the amount of glucose and glucagon increased we cannot say the same about the expression of mRNA, insulin and insulin receptors whose increase was not significant, in fact emphasizing the previous study, namely that this approach would be more appropriate in the stages of zebrafish larvae (35).

MODEL VERIFICATION METHODS

Among the main indicators of the existence of type 2 diabetes are first and foremost fasting and postprandial glycemia (22, 23, 36), followed by the insulin resistance test, the glucose tolerance test, glycosylated hemoglobin and last but not least the response tests to antidiabetic drugs. In zebrafish larvae, harvesting is more difficult because the amount of blood is low, as a result the larvae will be homogenized and colorimetric tests will be used. In the case of adult fish, the harvesting methods vary from harvesting from the dorsal aorta, by cardiac puncture, tail ablation and up to decapitation (37). Zang, (2013) tries to discover a repetitive, non-lethal and ethical method in performing these tests (38).

In order to test the insulin resistance of zebrafish, methods are used that start with direct measurement of insulin (31), insulin receptors (39), methylglyoxal (40), related mediators (41) and even insulin injection. The glucose tolerance test confirms type 2 diabetes in zebrafish and can be performed intraperitoneally and orally in adult fish and in larvae by gene expression tests (42).

HbA1C is also a marker of glycemic control in patients with diabetes. In zebrafish, fructose is extracted from the eyes of the zebrafish or n-hydroxynonenal and methylglyoxal are used as indicators of diabetes (43). Antidiabetic response tests use metformin, tolbutamide, pioglitazone as antidiabetic drugs. These can affect glucose metabolism (24, 44, 45).

Zebrafish has come to the attention of researchers due to its metabolic and diabetic characteristics, due to its real resemblance to humans, due to the possibility of inducing the diabetic condition by chemical, genetic, diet, and even hybrid methods. And, although genetic models appear to be among the first in the ranking, those based on non-genetic means, even if they require a longer period of time, are less expensive and do not focus on the researcher's experience to induce it (46).

The methods chosen must take into account what type of diabetes is to be induced, whether or not it is a genetically induced model, the purpose of the study, the facilities available to the researcher and his professional experience. Future prospects for inducing this syndrome in zebrafish will include new technologies that will facilitate the approach of new therapeutic methods in inducing diabetes.

All these aspects could also have an increased relevance considering that Alzheimer's disease could be considered type 3 diabetes.

The literature confirms that TD2M causes the brain to become resistant to insulin, induces oxidative stress and hence certain cognitive disorders (47). Molecular, biochemical, and histopathological lesions found in Alzheimer's disease are also associated with disorders in the signaling pathway of insulin in the brain as well as with insulin-like growth factor (IGF) disorders (48). This aspect is also supported by experiments based on streptozotocin as a method of inducing experimental diabetes, which affects acetylcholine homeostasis, and can cause cognitive impairment (49) and treatments used to treat experimental diabetes in animal models used (50).

From all these mentioned characteristics we can speculate that Alzheimer's disease can be considered a type 3 diabetes mellitus.

Moreover, as we previously described, all these neuropsychiatric manifestations can also be studied in zebrafish since there are

essential similarities with those of humans in terms of brain structure (9), e.g. they have a lateral pallium that plays the role of the hippocampus in the human brain (51), as well as neurotransmitters such as acetylcholine, glutamate, dopamine, serotonine or GABA (52). Also our group previously described complex zebrafish models of Parksinon's disease (53) and autism (54).

CONCLUSIONS

As the world is facing a continuously growing percentage of diabetic individuals, especially in children and teenagers due to poor food choices which are often influenced by external factors (socio-economical, political, geographic), the need for reliable animal models and non-invasive efficient treatment options is of utmost importance as current diabetes treatment options are often not a „glove-fits-all" type of approach.

Over the past several years, the scientific community has shifted towards the use of zebrafish for pathological modelling due to the advantages they present over their predecessors such as the low-cost, easy maintenance and manipulation, the high genes homology to human, complex behavior, and external fecundation which allows embryo and larval visualization from an early stage. As we have presented in this review, zebrafish is an outstanding candidate for replication human pathologies, from metabolic symptoms and syndromes to neurological as well as possible correlations between them.

Depending on the type of diabetes that needs to be induced and the environmental factor that needs to be studies, zebrafish offers it all. Either if its by chemical induction through substances such as glucose or streptozotocin, diet-based through high-caloric intake and induction of obesity or even genetic, zebrafish is a perfect candidate for studying the progression of diabetes from an early developmental stage to the adult life as well as different therapeutic approaches.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES

1. Ihnat MA, Thorpe JE, Kamat CD, Szabó C, Green DE, Warnke LA, et al. Reactive oxygen species mediate a cellular "memory" of high glucose stress signalling. Diabetologia. 2007;50(7):1523–31.
2. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281(21):2005–12.
4. Diabetes Control and Complications Trial, Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000;342(6):381–9.
5. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes. 1987;36(7):808–12.
6. Hammes HP, Klinzing I, Wiegand S, Bretzel RG, Cohen AM, Federlin K. Islet transplantation inhibits diabetic retinopathy in the sucrose-fed diabetic Cohen rat. Horm Metab Res. 1993;34(6):2092–6.
7. Kowluru RA. Effect of reinstitution of good glycemic control on retinal oxidative stress and nitrative stress in diabetic rats. Diabetes. 2003;52(3):818–23.
8. Roy S, Sala R, Cagliero E, Lorenzi M. Overexpression of fibronectin induced by diabetes or high glucose: phenomenon with a memory. Proc Natl Acad Sci U S A. 1990;87(1):404.
9. Lieschke GJ, Currie PD. Animal models of human disease: zebrafish swim into view. Nat Rev Genet. 2007;8(5):353–67.
10. Bjornsson HT, Daniele Fallin M, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. Trends Genet. 2004;20(8):350–8.

11. Mosammaparast N, Shi Y. Reversal of histone methylation: biochemical and molecular mechanisms of histone demethylases. Annu Rev Biochem. 2010;79:155–79.
12. Cooper ME, El-Osta A. Epigenetics: mechanisms and implications for diabetic complications. Circ Res. 2010;107(12):1403–13.
13. Pirola L, Balcerczyk A, Okabe J, El-Osta A. Epigenetic phenomena linked to diabetic complications. Nat Rev Endocrinol. 2010;6(12):665–75.
14. Villeneuve LM, Reddy MA, Natarajan R. Epigenetics: deciphering its role in diabetes and its chronic complications. Clin Exp Pharmacol Physiol. 2011;38(7):451–9.
15. Goldsmith JR, Jobin C. Think small: zebrafish as a model system of human pathology. J Biomed Biotechnol.2012.
16. Streisinger G, Walker C, Dower N, Knauber D, Singer F. Production of clones of homozygous diploid zebra fish (Brachydanio rerio). Nature. 1981;291(5813):293–6.
17. Intine R V., Olsen AS, Sarras MP. A Zebrafish Model of Diabetes Mellitus and Metabolic Memory. J Vis Exp. 2013;(72):50232.
18. Nolte H, Hölper S, Housley MP, Islam S, Piller T, Konzer A, et al. Dynamics of zebrafish fin regeneration using a pulsed SILAC approach. Proteomics. 2015;15(4):739–51.
19. Jurczyk A, Roy N, Bajwa R, Gut P, Lipson K, Yang C, et al. Dynamic glucoregulation and mammalian-like responses to metabolic and developmental disruption in zebrafish. Gen Comp Endocrinol. 2011;170(2):334–45.
20. Zang L, Maddison LA, Chen W. Zebrafish as a model for obesity and diabetes. Front Cell Dev Biol. 2018;6:91.
21. Tamadon A, Hu W, Cui P, Ma T, Tong X, Zhang F, et al. How to choose the suitable animal model of polycystic ovary syndrome?. 2018;01(02):95–113.
22. Gleeson M, Connaughton V, Arneson LS. Induction of hyperglycaemia in zebrafish (Danio rerio) leads to morphological changes in the retina. Acta Diabetol. 2007;44(3):157–63.
23. Connaughton VP, Baker C, Fonde L, Gerardi E, Slack C. Alternate Immersion in an External Glucose Solution Differentially Affects Blood Sugar Values in Older Versus Younger Zebrafish Adults. Zebrafish. 2016;13(2):87–94.
24. Capiotti KM, Antonioli R, Kist LW, Bogo MR, Bonan CD, Da Silva RS. Persistent impaired glucose metabolism in a zebrafish hyperglycemia model. Comp Biochem Physiol B Biochem Mol Biol. 2014;171(1):58–65.
25. Carnovali M, Luzi L, Banfi G, Mariotti M. Chronic hyperglycemia affects bone metabolism in adult zebrafish scale model. Endocrine. 2016;54(3):808–17.
26. Singh A, Castillo HA, Brown J, Kaslin J, Dwyer KM, Gibert Y. High glucose levels affect retinal patterning during zebrafish embryogenesis. Sci Reports. 2019;9(1):1–13.
27. Jung SH, Kim YS, Lee YR, Kim JS. High glucose-induced changes in hyaloid-retinal vessels during early ocular development of zebrafish: a short-term animal model of diabetic retinopathy. Br J Pharmacol. 2016;173(1):15–26.
28. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790–7.
29. Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose-fed rats. Metabolism. 1982;31(6):608–12.
30. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes. 2006;55(6):1537–45.
31. Meng XH, Chen B, Zhang JP. Intracellular insulin and impaired autophagy in a zebrafish model and a cell model of type 2 diabetes. Int J Biol Sci. 2017;13(8):985–95.
32. Zhao F, Wang H, Wei P, Jiang G, Wang W, Zhang X, et al. Impairment of bisphenol F on the glucose metabolism of zebrafish larvae. Ecotoxicol Environ Saf. 2018;165:386–92.
33. Zhao F, Jiang G, Wei P, Wang H, Ru S. Bisphenol S exposure impairs glucose homeostasis in male zebrafish (Danio rerio). Ecotoxicol Environ Saf. 2018;147:794–802.
34. Wang Z, Mao Y, Cui T, Tang D, Wang XL. Impact of a Combined High Cholesterol Diet and High Glucose Environment on Vasculature. PLoS One. 2013;8(12):e81485.
35. Wang JJ, Li YJ, Lai K, Zhong QM, Demin KA, Kalueff A V., et al. High-glucose/high-cholesterol diet in zebrafish evokes diabetic and affective pathogenesis: The role of peripheral and central inflammation, microglia and apoptosis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;96.
36. Yang BY, Zhai G, Gong YL, Su JZ, Peng XY, Shang GH, et al. Different physiological roles of insulin receptors in mediating nutrient metabolism in zebrafish. Am J Physiol - Endocrinol Metab. 2018;315(1):E38–51.
37. Jagadeeswaran P, Sheehan JP, Craig FE, Troyer D. Identification and characterization of zebrafish thrombocytes. Br J Haematol. 1999;107(4):731–8.
38. Zang L, Shimada Y, Nishimura Y, Tanaka T, Nishimura N. A Novel, Reliable Method for Repeated Blood Collection from Aquarium Fish. https://home.liebertpub.com/zeb. 2013;10(3):425–32.
39. Houbrechts AM, Beckers A, Vancamp P, Sergeys J, Gysemans C, Mathieu C, et al. Age-Dependent Changes in Glucose Homeostasis in Male Deiodinase Type 2 Knockout Zebrafish. Endocrinology. 2019;160(11):2759–72.
40. Moraru A, Wiederstein J, Pfaff D, Fleming T, Miller AK, Nawroth P, et al. Elevated Levels of the Reactive Metabolite Methylglyoxal Recapitulate Progression of Type 2 Diabetes. Cell Metab. 2018 Apr 3;27(4):926-934.e8.
41. Nath AK, Ma J, Chen ZZ, Li Z, Vitery M del C, Kelley ML, et al. Genetic deletion of gpr27 alters acylcarnitine metabolism, insulin sensitivity, and glucose homeostasis in zebrafish. FASEB J. 2020;34(1):1546–57.
42. Jiménez-Amilburu V, Jong-Raadsen S, Bakkers J, Spaink HP, Marín-Juez R. GLUT12 deficiency during early development results in heart failure and a diabetic phenotype in zebrafish. J Endocrinol. 2015;224(1):1–15.

43. Armbruster DA. Fructosamine: structure, analysis, and clinical usefulness. Clin Chem. 1987;33(12):2153–63.
44. Matthews B. A zebrafish model system for drug screening in diabetes.Dissertation. 2019.
45. Wang H, Long Q, Marty SD, Sassa S, Shuo L. A zebrafish model for hepatoerythropoietic porphyria. Nat Genet 1998;20(3):239–43.
46. Zang L, Shimada Y, Nishimura N. Development of a Novel Zebrafish Model for Type 2 Diabetes Mellitus. Sci Reports. 2017;7(1):1–11.
47. Jalbert JJ, Daiello LA, Lapane KL. Dementia of the Alzheimer Type. Epidemiol Rev. 2008;30(1):15–34.
48. Jellinger KA. Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. Neurodegener Dis. 2008;5(3–4):118–21.
49. Wang XP, Ding HL. Alzheimer's disease: epidemiology, genetics, and beyond. Neurosci Bull. 2008;24(2):105–9.
50. De La Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis. 2005 ;7(1):45–61.
51. Kalueff A V., Echevarria DJ, Stewart AM. Gaining translational momentum: more zebrafish models for neuroscience research. Prog Neuropsychopharmacol Biol Psychiatry. 2014;55:1–6.
52. Panula P, Sallinen V, Sundvik M, Kolehmainen J, Torkko V, Tiittula A, et al. Modulatory neurotransmitter systems and behavior: towards zebrafish models of neurodegenerative diseases. Zebrafish. 2006;3(2):235–238.
53. Robea MA, Balmus IM, Ciobica A, Strungaru S, Plavan G, Gorgan LD, et al. Parkinson's Disease-Induced Zebrafish Models: Focussing on Oxidative Stress Implications and Sleep Processes. Oxid Med Cell Longev. 2020;2020.
54. Robea MA, Ciobica A, Curpan AS, Plavan G, Strungaru S, Lefter R, et al. Preliminary Results Regarding Sleep in a Zebrafish Model of Autism Spectrum Disorder. Brain Sci. 2021;11(5):556.

Correspondence:

Alexandrina Curpan,
Department of Biology, Faculty of Biology, "Alexandru Ioan Cuza" University of Iasi,
andracurpan@yahoo.com

Submission: 04 apr 2022
Acceptance: 30 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

The inclusion of people with disabilities reflected in the online press

Maria Alexandrescu. Mihaela Grasu

Maria Alexandrescu - Ph.D., associate lecturer, ”Dumitru Stăniloae” Faculty of Orthodox Theology, ”Alexandru Ioan Cuza” University Iași
Mihaela Grasu – Ph.D., associate lecturer, Psychology and Education Sciences Faculty, ”Alexandru Ioan Cuza” University Iași

ABSTRACT
The article begins with the presentation of the semantic field of definitions, as they appear in the current or specialized language in dictionaries or legislation, then continues with a brief description of the main significant moments of disability in Romania, especially the introduction of the term social inclusion in our social policies. At the same time, the main models of approaching disability are presented: the medical one considers that biological or psychological problems create difficulties for these people, the social model emphasizes the environment not adapted to their needs, while the model based on fundamental human rights promotes respect for dignity.

The second part of the article includes the quantitative and qualitative analysis of a sample of articles from the online written press (*Ziarul de Iaşi*) from 01.01.2020 to 31.01.2022.

The purpose of our research is to conduct an analysis of press articles to describe, on the one hand, how the image of people with disabilities is reflected in the local press, and, on the other hand, to highlight the role that the media plays in the social inclusion of people with disabilities.

KEYWORDS:
Disability, handicap, social exclusion, social inclusion, media.

INTRODUCTION

People with disabilities are one of the social categories with a high risk of social exclusion. They are considered the largest minority in the world because, according to estimates, between 15.6% and 19.4% of the population live with a disability (1). According to these data, in Romania, the number of people with disabilities is underreported, as in the official statistics of the National Authority for People with Disabilities only 3.86% of the country's population is certified as having a disability (2). One of the reasons is that people with mild disabilities are not sufficiently motivated to take the necessary steps to obtain the certificate, because the incentives they receive are insignificant. Another reason is that people active in the labor market, who lose

part or all of their ability to work, obtain invalidity pensions and only a part of these people are registered in the database of the National Authority for Persons with Disabilities (3).

In general, the terms handicap and disability are defined in relation to normality and refer to a state of helplessness, which limits a person on the move or in activity. To these notions, the sociologist Goffman (4) associated the meaning of stigma, an attribute by which the person ends up being discredited. For example, in Romanian, the notion of "handicap" has become almost synonymous with the notions of "invalidity, incapacity, deficiency". In this regard, several researchers have looked for definitions of people with disabilities that cover the problem area and no longer label them.

Out of a desire to provide a standardized and unified language for practitioners and researchers, in 1980, the World Health Organization (5) adopted the following concepts:
- impairment, meaning any abnormality of body structure or impairment of the function of an organ or system;
- disability, which refers to the consequences of a deficiency on the individual, understood in terms of functional performance or activity;
- handicap, defined as any disadvantage suffered by a particular person as a result of a deficiency or disability, which prevents him or her from carrying out all or part of the tasks considered normal for him or her (in relation to age, sex and. different social and cultural factors).

The approach to disability can be done from the perspective of several theoretical models. According to the medical model, disability is considered a problem of the person, being caused by illness or deficiency. In order to be able to adapt to the environment, the person needs medical interventions and recovery. Treating the problem of people with disabilities according to this model generates dependence and passivity, inducing them a low self-esteem.

The social model, adopted in the early 1970s, considers that the source of the problems is the inability of society to adapt to the needs of people with disabilities. This creates barriers that limit their full participation in community life.

In addition to the mentioned models, Manea (6) also presents the bio-psycho-social model according to which disability arises from the interaction of health conditions with environmental and personal factors. Thus, disability is manifested either by difficulties in some functions or structures of the body, or by performing certain activities ("activity limitations") or by restrictions on participation in involvement in certain areas of life.

From a religious perspective, the theologian Chirilă (7) identifies several types of addiction / disability: 1) *positive dependence*, respectively the dependence of creation on the Creator; 2) the second type includes a series of terms taken from the Holy Scriptures, which are included in the register of *physical disability*, such as: "meth" (8: Lev. 24: 19-20), "deformed" (8: Lev. 22:25), "weak, suffering, incurably ill" (8: Jer. 10: 9), "blind, weak" (8: Zah 11:17), but also of the *spiritual disability*, which refers to those people who are indifferent to the words or the Law of God (8: Isa. 43: 8), "The blind guides who snatch the mosquito and swallow the camel! The blind Pharisee!" (8: Matt.23, 24-28).

Therefore, we note that there are similarities in the approach to disability. Both perspectives urge us to respect our neighbor, with or without disabilities. If in the terrestrial world we receive sanctions for violating the rights of persons (with or without disabilities), all the more so our entry into the Kingdom of God is conditioned by the love of our fellow man, becoming one of the fundamental conditions of subjective salvation for any person, that is, communion man with God. The Savior exhorts us, "Bear one another's burdens, and so fulfill the law of Christ" (8: Gal. 6: 2). God the Father Himself, out of love for the world, sent His Only Begotten Son, in order to reconcile man with

God, that is, to raise and heal those with various infirmities (8: Matt. 11: 3-5; Mark 22-25).

In Romania, prior to World War II, the key words for people with disabilities were related to illness and infirmity. At first, the Church supported them, and then the state intervened more and more.

The communist regime promoted the care of people with disabilities in institutions, which were organized according to age, type or degree of disability. People with mild or moderate disabilities were educated in special schools, qualified and employed according to their ability to work. People with severe disabilities remained invisible in institutions so as not to "spoil" the image of a prosperous society. For this reason in 1989, in Romania, we find only two organizations of people with disabilities: the National Association of the Deaf and the Association of the Blind.

One of the first measures taken immediately after the Revolution was the establishment of the State Secretariat for Persons with Disabilities (9). In 1992, the first laws on social protection (10) and employment (11) appeared.

In 2002, the Romanian Government developed the first National Strategy on Special Protection and Social Integration of Persons with Disabilities, in accordance with international regulations (12). The aim of this strategy was to achieve a holistic vision of the special protection system for people with disabilities. In 2006, Law 448 on the Protection and Promotion of the Rights of Persons with Disabilities was adopted, which emphasizes the integration of people with disabilities into the labor market, the education system and the creation of care and recovery services in local communities (13).
In the period 2019-2021, the National Authority for the Rights of Persons with Disabilities, Children and Adoptions carried out a project in order to strengthen the mechanism for coordinating the implementation of the EU Convention on the Rights of Persons with Disabilities. The results of this project were the basis for the elaboration of a new National Strategy on the Rights of Persons with Disabilities for the period 2021-2027 (14).

METHODOLOGY

The research was carried out in the media field, represented by the online written press, an important source of information for the general public. We aimed to identify the factors that contribute to the social integration of people with disabilities that are covered by the print media. To achieve this goal, we opted for quantitative and qualitative analysis of a sample of articles from the online print media. We selected the local daily newspaper with a great impact on the public, *Ziarul de Iași* (15), which we monitored for a period of two years, from 01.01.2020 to 31.01.2022. The quantitative analysis aimed at quantifying the number of press materials, frequency by year and by topic, while the content analysis covered the main topics of the articles.

We used the following keywords: handicap, impairment, disability, special needs, autism, Down syndrome, and we identified a number of 84 articles. The articles included in the corpus were identified and extracted from the archives of *Ziarul de Iași* and arrange according to the order of publication. The articles were read in order to identify the main themes and sub-themes.

RESULTS

The quantitative analysis of the collected data shows that *Ziarul de Iași's* interest in the issue of disability is growing. Thus, for the year 2020, a number of 27 articles were identified, while for the year 2021 their number almost doubled, reaching 46 articles, and in 2022 we identified a number of 11 articles only in January.

Following the content analysis of the articles, we identified the following topics:
- social involvement through awareness campaigns, charities, donations, volunteering (29 articles);
- projects carried out in favor of people with disabilities (18 articles);
- information on legal rights, statistical data,

the latest scientific findings, the health status of people with disabilities in conditions related to COVID (18 articles);
- violations of the rights of persons with disabilities (17 articles);
- presentation of successful cases, in order to destigmatize people with disabilities (two articles).

SOCIAL INVOLVEMENT THROUGH AWARENESS CAMPAIGNS

Most articles focus on social involvement to raise awareness of the issues of people with disabilities. For example, the Star of Hope Foundation in Iași organized a series of campaigns, such as the *Gala of Good Deeds* or the *Most Beautiful Gift*, in order to raise funds for recovery therapies for children with disabilities. There are also annual events to mark International Day of Persons with Disabilities (December 3) or Autism Recognition Day (April 2), on which various activities have been held with the support of the entire community. In addition, it is worth mentioning the involvement of some state institutions in this type of action, for example, the Iași County School Inspectorate held a series of events related to the International Day of Persons with Disabilities, but also organizes its own event in June, Special and Specially Integrated Education Days, event marked by a series of conferences, debates, artistic moments, etc.

PROJECTS FOR PEOPLE WITH DISABILITIES

A number of 18 articles deal with ongoing projects for people with disabilities. Most of the projects targeted children with special needs and teachers who were able to benefit from training or exchange of experience in other countries. Also, 5 articles were intended to present the projects of the *Alături de voi* Association on the social economy, as a solution to increase the employment of people belonging to vulnerable groups, a category that includes people with disabilities. In general, most of the projects presented are based on European funding, however we mention that the Iasi County Council also funded the project *Active Social Inclusion for Children with Disabilities*, initiated by the *Star of Hope Romania* Foundation.

LEGISLATIVE AND STATISTICAL INFORMATION, SCIENTIFIC NEWS

Another category of articles are those that inform the public about the legal rights of people with disabilities, explaining in a meaningful way all the transport facilities or the procedure for enrolling in vocational education for students with disability. Also in this category, we included the presentation of statistical data from the reports prepared by the authorities (16), information on COVID infection of people with disabilities in residential centers, and articles that describe a specific category of disability or present the latest scientific findings.

VIOLATION OF THE RIGHTS OF PERSONS WITH DISABILITIES

In another category of articles, journalists draw attention to the violation of the rights of people with disabilities, presenting various situations: either the authorities do not honor their commitments in favor of this category and discriminate against it, or serious abuse or neglect occurs within the family. At the same time, there are cases of people who are falsely included in a category of disability and who have unduly benefited from a series of rights (17).

SUCCESS STORIES

Two articles refer to success stories and have the role of destigmatization by bringing positive connotations on this social category. For example, an article shows a child with autism playing the trumpet (18).

DISCUSSIONS

The perspective from which the phenomenon of disability is interpreted is reflected in the way society intervenes in their social integration. People with disabilities were initially considered to be dependent on others because they could not take care of themselves, then they were labeled as inferior and subject to recovery and rehabilitation to reach normalcy. Over time, society has begun to become inclusive, in the sense that it promotes responsibility, takes into account diversity and respects the fundamental rights

of all people. The term social inclusion has its origins in the institutional environment, being defined as the policy of response to situations of social exclusion (19).

The media responds to the need of non-governmental organizations to make known their initiatives (charity campaigns) in order to mobilize the public for such activities. Thus, a study conducted in 2016 (20) investigates the philanthropic behavior of Romanians. The results show that 63% of the adult population made at least one cash donation to an non-governmental, a school or a church.

Our research shows that the media present cases of violations of the rights of people with disabilities, as confirmed by another study, which showed that there is an increasingly critical discourse in the media about the abuse of and violation of the rights of persons in the psychiatric system of the Republic of Moldova (21).

A recent paper (14) shows that in mainstream schools the number of teachers trained to work with children with disabilities and / or special educational needs is extremely low, 68 % of secondary schools in the country do not even have a teacher trained in the field of inclusive education. The initial training of teachers in mainstream schools superficially covers the topic of special psycho-pedagogy, and, at a practical level, teachers who teach children with disabilities face difficulties. In this regard, teacher training projects in the special educational needs presented in the media are welcome.

The education system that is not very inclusive as inappropriate and inaccessible jobs are the main barriers in the absence of people with disabilities in the labor market. Statistics show that 51% of people with some limitations and only 12% of people with severe limitations have a job, while 74% of people aged 20-64, without limitations, are employed (14). In order to increase the employment rate of people with disabilities, a series of favorable legislative and fiscal measures have been adopted, including the creation of social enterprises (22, 23). Defined by the Social Economy Law (24), social enterprises allocate at least 90% of the profit to achieve social objectives, in the general interest of a community. For example, social enterprises, by making the work environment more accessible and adaptable to the needs of people with disabilities, have the capacity to capitalize on their special abilities, thus restoring their financial independence.

More and more non-governmental organizations are developing economic activities to obtain sources of funding for social projects. If in 1989 in Romania, there were only two organizations of people with disabilities: the National Association of the Deaf and the Association of the Blind, in the first three years after the Revolution their number reached 150, and most were based on external funding. In 1998, these resources decreased drastically, which led to a reduction in services, a decrease in the number of members, the migration of highly qualified staff to other sectors (25). In 2008, the social economy represented a financing solution used by 2353 non-governmental organizations from Romania that carried out economic activity, and in 2015 their number increased to 5302 (26). Our research showed that *Ziarul de Iași* also dedicated a number of articles to projects on the development of social enterprises.

CONCLUSIONS

Following this research, we notice that the local press is involved in the social inclusion of people with disabilities in the following ways:

- firstly, through its articles on awareness-raising and public awareness campaigns, presenting disability as a community-wide issue.
- makes available to the general public legislative information, statistical data, scientific news, which, on the one hand, helps people with disabilities and their families to know their rights and

access them, and, on the other hand, presents situations of non-compliance of the rights of persons with disabilities, which violates the principle of equal opportunities.
- presents European projects, which benefit people with disabilities, bringing to the public's attention the success stories of people in this category, thus changing the image of them.

EU funding has also encouraged the association of three main community actors, legal authority, business and civil society. Among the social actors, who fight for the cause of people with disabilities presented in the press, we note, first of all, associations, as forms of organization of civil society, built around the concept of collective interest and involvement of citizens. In addition, there is an increasingly active role of state institutions, such as the School Inspectorate, with the network of mainstream or special schools, and the County Council.

Finally, the results of our research show that the local press, through the articles it promotes, contributes to the formation of public opinion, in the sense that this category of people can integrate socially through the support and involvement of the community. The media, through the quality and accuracy of the information provided, is an essential component in monitoring the rights of people with disabilities. It promotes projects implemented for the benefit of people with disabilities, disseminates and raises awareness of the rights of the public. Therefore, the message sent by the press, regarding people with disabilities, contributes, to a large extent, to the change of the collective mentality.

ACKNOWLEDGEMENTS AND DISCLOSURES
The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES
1. World Health Organization, The World Bank. World Raport on Disability. 2011
2. Ministry of Labor and Social Protection, National Authority for the Rights of Persons with Disabilities, Children and Adopts. Statistic Data. 30 september 2020.
3. Societatea Academică din România. Diagnostic: Exclus de pe piața muncii. Piedici în ocuparea persoanelor cu dizabilități din România. (Diagnosis: Excluded from the Labor Market. Obstacles in the Employment of People with Disabilities in Romania). 2009.
4. Goffman, E. Stigma. Notes on the Management of Spoiled Identity. New York. Penguin Books 1990.
5. World Health Organization. International Classification of Impairements, Disabilities and Handicaps. A Manual of Classification relating of the Consequences of Disease. Geneva 1980.
6. Manea, L. Significances of Disability in the Romanian Social Protection System. In Zamfir, E., Stănescu, S. M., Arpinte, D. (coord.). Social Assistance in Romania after 25 Years: Answer to the Problems of Transition - selected text. Cluj-Napoca. Editura Şcoala ardeleană Eikon 2015; 437-466.
7. Chirilă, I. Despre dizabilitate. (About Disability). Studia Universitatis Babeş-Bolyai Bioethica 2010; 1;11-28.
8. Biblia sau Sfânta Scriptură, cu aprobarea Sfântului Sinod. (The Bible or Holy Scripture, with the approval of the Holy Synod). Bucureşti. Editura Institutul Biblic şi de Misiune al Bisericii Ortodoxe Române 1995.
9. Decision no. 1100/1990 regarding the establishment of the State Secretariat for the Disabled. Official Monitor of Romania no. 295 of 21.11.1992.
10. Law no. 53/1992 on the social protection of disabled people. Official Monitor of Romania no. 119 of 04.06.1992.
11. Law no. 57/1992 on the employment of disabled persons. Official Monitor of Romania no. 131 of 12.06.1992.
12. Decision no. 1215/2002 for the approval of the National Strategy on the special protection and social integration of persons with disabilities in Romania. Official Monitor of Romania no. 853 of 26.11.2002.
13. Law no. 448/2006 ("republished") on the protection and promotion of the rights of persons with disabilities. Official Monitor of Romania no. 1 of 03.01.2008.
14. Ministry of Labor and Social Protection, National Authority for the Rights of Persons with Disabilities, Children and Adopts, The World Bank. Diagnoza persoanelor cu dizabilități în România (Diagnosis of people with disability in Romania). 2020.
15. www.ziaruldeiasi.ro.
16. Iekel, P. Bilanțul activității Biroului Teritorial Iași al Instituției Avocatul Poporului. (The activity report of the Iași Territorial Office of the People's Advocate Institution). Ziarul de Iași 25.01.2022.
17. Manoliu, N. Ieșeancă condamnată pentru "aranjarea" de certificate false de handicap, pentru pensie. (Woman from Iași convicted for "arranging" false disability certificates for pension). Ziarul de Iași 27.09.2021.
18. Craus, S. Proiect lansat de Fundația Star of Hope pentru 20 de copii cu dizabilități. (Project launched by the Star of

Hope Foundation for 20 children with disabilities). Ziarul de Iași 01.09.2021.
19. Stănescu, I. Incluziunea socială la nivelul Uniunii Europene. (Social Inclusion at the Level of the European Union). In Zamfir, C., Stănescu, S., Briciu C. (coord.). Politici de incluziune socială în perioada de criză economică. (Policies for Social Inclusion in Times of Economic Crisis). Bucureşti. Editura Expert 2010.
20. Asociația pentru Relații Comunitare. Tendințe ale comportamentului filantropic în România. Donatori individuali. Sectorul de afaceri. Organizații neguvernamentale. (Trends in Philanthropic Behavior in Romania. Individual Donors. Business Sector. Non-governmental Organizations). 2016.
21. Borzin, A. Perceptions regarding Persons with a Psychiatric Diagnosis. BPI 2019;1; 81-85.
22. Oreianu, I. A., Rebeleanu, A. Aspecte privind integrarea socio-profesională a persoanelor cu dizabilități, din perspectiva economiei sociale. (Aspects regarding the Socio-professional Integration of People with Disabilities, from the Perspective of the Social Economy). Journal of Social Economy 2016; 6; 2; 31- 47.
23. Lambru, M., Petrescu C. Exploring the Role of Social Enterprises within the Romanian Welfare System. Calitatea vieţii 2020; 1; 24–45.
24. Law no. 219/2015 on the social economy. Official Monitor of Romania no. 561 of 28.07.2015.
25. Vasilescu D. Oameni asemenea. Persoanele cu handicap din România. Grupul de Studiu al Problematicii Handicapului. (People like that. People with Disabilities in Romania. Disability Study Group) Bucureşti. Editura Compania 2001
26. Barna, C. Activitatea economică a organizațiilor neguvernamentale. (Economic Activity of Non-governmental Organizations). Fundația pentru Dezvoltarea Societății Civile. România 2017. Sectorul neguvernamental – Profil, tendințe, provocări. (Romania 2017. Non-governmental Sector - Profile, Trends, Challenges). București 2017.

Correspondence:

Mihaela Grasu,
Ph.D., associate lecturer, Psychology and Education Sciences Faculty, ”Alexandru Ioan Cuza” University Iași, grasumihaela73@gmail.com

Submission: 04 mar 2022
Acceptance: 12 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Ginko biloba leaves extract for the treatment of anxiety, stress, and depression

Maryam Rahmannia, Mohammad Javad Ghapanchian, Somayeh Bagheri – kelayeh, Soheil Baymani Nejad, Aida Etedali, Sorour Rajabalipour, Hossein Pourmontaseri, Shirin Orandi, Alireza Hashemi Shiri, Niloofar Deravi

Maryam Rahmannia- Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Mohammad Javad Ghapanchian - Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Somayeh Bagheri – kelayeh - Tehran University of Medical Sciences, Tehran, Iran
Soheil Baymani Nejad - Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Aida Etedali - Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Sorour Rajabalipour - Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Hossein Pourmontaseri - Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran
Shirin Orandi - Department of Clinical Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Alireza Hashemi Shiri - Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran
Niloofar Deravi - Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Anxiety, stress and depression are exceedingly comorbid psychological illnesses that the predominance will expand to the second most important risk of morbidity and sociodemographic burden. Due to several side-effects of chemical drugs, numerous specialists and patients prefer complementary herbal therapies like *ginkgo biloba* extracts (GBE) to medicate the illnesses. In this review, we summarized the antidepressant, anxiolytic and

antistress properties of GBE. We perceived that GBE could be beneficial for treatment of these disorders. Although experience of repeated studies on models and humans have proved reliability of antidepressant properties of GBE, further clinical trials are still required to validate the anti-stress and anti-anxiety effects of GBE on humans.

KEYWORDS
Ginko biloba, antidepressant, Anxiolytic, Antistress, Herbal medicine.

INTRODUCTION

Anxiety and depression are universal brain disorders (approximately 7.3% and 7% prevalence). These disorders are characterized by stress-linked mood problems and may cause early death (1, 2). Surprisingly, the prevalence of depression is 3 times higher in young people and women are 1.5 to 2 times more susceptible to anxiety and depression (3, 4). Sleep disorder, weight loss or gain, retardation, fatigue, concentration and decision-making challenges, and even tenderness of suicide are the most reported depression symptoms (5). Furthermore, these complications caused a significant number of years of life lost to disability in multiple countries (6). Therefore, controlling mental health challenges became an important aim for many researchers (7).

Scientists have long been aware of the close relationship between anxiety and depression (8); Moreover, notable comorbidities of these patients cause several difficulties in treatment. (9,10). Despite the proper efficiency of these treatments, all these therapies have considerable adverse effects as well (11).

Herbal therapies have been used for a long time to treat depression. For many years, scientists carried out many trials to target monoamine transmission systems of the brain, such as norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (12). 20(S)-protopanaxadiol, extracted from *ginseng*, developing NE and 5-HT in the mice brain and decrease depression pathogenesis (13). Moreover, *Paeonia lactiflora* Pall is another traditional Chinese treatment that restricts depression symptoms. The root extract of this blessed species diminishes monoamine oxidase activity and (14). *Albizia julibrissin*, *Perilla frutescens* and several components of *Rhodiola rosea* are the other ancient candidates for depression treatment (12). To date, the herbal treatments for anxiety have been emphasized on repairing dysregulated brain mechanisms, such as noradrenergic, glutamatergic, and serotonergic pathways (15). For example, *Bacopa monnieri* restricts anxiety by enhancing 5-HT2C receptors (16). Studies on other species, like *Valeriana officinalis*, *Centalla asiatica*, *Humulus lupulus*, and *Matricaria recutita* showed detectable anti-anxiety properties, based on inhibiting glutamate receptors (17).

Ginkgo biloba extract (GBE) is another promising herbal treatment for several mental disorders such as dementia and anxiety (18). Besides, GBE downregulates 5-HT, dopamine, and NE uptake, through an unclear mechanism (19). Herein, we review the different aspects of GBE effects on depression, anxiety, and stress.(fig 1)

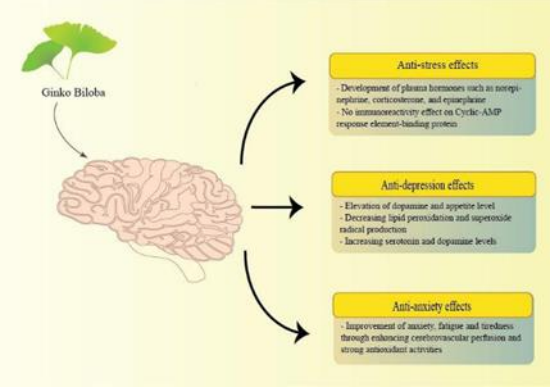

Fig 1. Possible regulatory effects of GB in treatment of brain disorders. GB

METHODS

This study reviews the data about Ginko biloba leaves extract for the treatment of anxiety, stress, and depression. English articles were searched up to December 2020 through various databases including ISI Web of Science, SID, Google Scholar, PubMed, Scopus, and Science Direct. The searched keywords included Ginko biloba, Antidepressant, Anxiolytic, and Antistress. The references of the relevant studies were also searched manually.

Anti- stress effects of GBE

In 1994, *Rapin et al.* aimed to evaluate the anti-stress properties of *Ginkgo biloba* (*G. biloba*) leaves among young and old rodent models. The extract of these leaves showed a detectable development of plasma hormones such as norepinephrine, corticosterone, and epinephrine; moreover, despite noxious environmental influences, GBE ameliorates cognitive impairment, especially in old rats (20). Although the next study on *Ginkgo* showed relatively encouraging treatments for memory and aging-related cognitive disorders but started a new quarrel about anti-stress uses of GBE (21). Further, *Rai et al.* carried out another experimental trial on herbal treatments against chronic stress (CS) and acute stress (AS) to measure anti-stress effects of GBE and *Panax ginseng*. This study demonstrated that GBE has better success in treating acute stress and Panax ginseng for the latter (22). In the following, scientists tried lipophilic extracts of Ginkgo leaves (LEG). This study introduced intact carboxylic acid, one of the LEG bioactive components, as a promising anti-depressant and anti-stress agent (23). Supporting previous results, another trial on mice treated with GBE showed significant anti-stress effects; furthermore, analyzing cortex and hippocampus samples demonstrated no detectable immunoreactivity effect on Cyclic-AMP response element-binding protein (24). Recently, *Yuan et al.* introduced GBE as a protecting treatment. GBE successfully preserved rodent models against chronic unpredictable mild stress (25). Therefore, future trials on humans are required to prove the clinical function of this blessed species in controlling stress. Table 1 summarizes the data of the studies on the anti-stress effects of GBE.

Table 1. Studies addressing the anti-stress properties of Ginko biloba.

Author/ year	**In-vivo studies**	**Outcomes**
Rapin et al./ 1994	In first stage, Mice were allowed to adapt environment for 15 days. Models were divided to different groups based on age (4 months and 20 months) and administration (placebo, 50 or 100mg/kg GBE). Daily inoculation occurred half an hour before exams (continued for 3 weeks).	GBE repaired stress symptoms in both ages. These results proved *G. biloba* leaves as a promising therapy for stress.

Jezova et al./ 2002	The study was designed as a double blind, randomized, parallel, placebo-controlled trial among 70 participants. A single p.o dose of 120 mg of *G. biloba*, 40 mg/ml GBE or placebo were administered.	GBE decreases blood pressure that may influence effect of stress stimuli on cortisol release.
Rai D et al./ 2003	Daily 100 mg/kg *P. ginseng* and 30 mg/kg GBE inoculated to male rats.	*G. biloba* is more efficient in acute stress, while *P. ginseng* is proper for chronic stress
Kalkunte et al./ 2007	Rodent models (Charles Foster rats) were adapted to the environment a week before the exams. Rats were divided into various groups based on inoculation (1. 50 mg/kg Ginkocer and GBE, 2. 50 or 100 mg/kg LEG). Oral administration was done 1 hour before tests.	LEG successfully restricted stress and significantly improved behavioral status.
Ward et al./ 2002	6 male mice got 100 mg/kg/day GBE for 20 month and were examined by the Morris water maze and elevated plus-maze. At last, tissue samples from hippocampus and cortex were analyzed.	Notable difference (F= 4.98 in Morris water maze and no significant result in elevated plus-maze) proved anti-stress effects of GBE. This product had no significant involvement in immunoreactivity to CREB.
Yuan-Qing et al./ 2017	Study evaluated the function of GBE in rats with unpredictable chronic mild stress.	Marked difference between GBE treatment and Saline treatment. Oral administration of GBE prevents CUMS(chronic unpredictable mild stress).

Anti-depressant effects of GBE

Many articles have proved that GBE has significant effects on mental disorders (26). The first study on a chronic depression cases, treated with an unstable regimen of bupropion plus Ginkgo, showed promising results. The mental situation of patients continued to become better even while using GBE without bupropion (27). Moreover, successful experience of administrating GBE to treat unipolar depression, introduced this product as a reliable therapy (28).

Experimental studies on the anti-depressant effects of GBE developed notable results. For the first experimental attempts, this agent improved the immobility time of rats in the forced swimming test and tail suspension test (29). Additionally, Inoculating GBE to male rodent models, treated with lipopolysaccharide, showed a significant elevation of dopamine and appetite level (30). On the other hand, further studies suggested that decreasing lipid peroxidation and superoxide radical production may be responsible for the anti-depressant activities of GBE (31). At last, current studies showed that water-soluble polysaccharides of GBE ameliorate anxiety symptoms, in addition to depression, through increasing serotonin and dopamine levels (32). Therefore, based on several experimental trials, BGE demonstrated promising effects on depression among rodent models.

Studies on GBE anti-depressant effects faced several contrasts. *Hemmeter* et al. designed an innovative open non-randomized trial to

evaluate the anti-depressant effect of *Ginkgo*. Results of this trial showed that GBE improves depression and increases non-rapid eye movement stages among participants (33). In contrast, previous randomized attempts found no reliable GBE effects on winter depression symptoms (34). On the other hand, combining venlafaxine with GBE showed valuable results in treating depression symptoms (35). Moreover, while adding GBE, we can decrease venlafaxine in the treatment regimen to achieve the same efficacy with lower adverse effects (36). Debates between scientists continued until 2017. To put an endpoint to these controversies, *Nikfarjam et al.* carried out a trial to appraise the effects of *G. biloba* tablets on major depression and cognitive cases, previously received electroconvulsive therapy. This study suggests that GBEs, such as flavonoids, can significantly restrict cognitive and depression problems (37). Recent study on combination of GBE with citalopram develops depression symptoms through regulating inflammatory glial-derived proteins (38) (Tab 2).

Table 2. Studies addressing the anti-depressant properties of Ginko biloba.

Author/ year	**In-vivo studies/ clinical trials**	**Outcomes**
R. Sealey et al./ 1996	A young patient with unipolar depression received five or six doses of GBE (about 135 mg/day)	GBE activated NMDA-type glutamate receptor and diminished neurotransmitter uptake, such as norepinephrine, serotonin, acetylcholine and dopamine.
sakakibara et al./ 2006	1) FST(forced swimming test): 35 rats were divided into 5 groups and orally treated with: 15 mg/kg imipramine (1 group), 5, 10, and 50 mg/kg (3 groups), DW(deionized water) (1 group). 2) TST: 50 rats were divided into 5 groups and orally treated with: 30 mg/kg imipramine (1 group), 10, 50 and 100, mg/kg (3 groups), DW (1 group).	GBE improved both FST and TST(tail suppression test) in experimental models. This result showed that GBE has reliable anti-depressant effect on mice.
Yeh et al./ 2015	8-week-old Male Wistar rats were divided into 2 groups (1. 50 mg/kg GBE, 2. DW). The treatment continued for 1 week. After inoculation Escherichia coli LPS (100 μg/kw), further tests performed: food consumption, sucrose preference test, and dopamine level.	GBE restricted depressive-like disorders through increasing appetite (consumption of food and sucrose) and elevating dopamine level.
Rojas et al./ 2011	The study contains 2 control groups (1. Saline without FST / 2. Saline with FST) and 2 intervention groups (A. 15 mg/kg imipramine with FST and B. 40, 20, 10 or 5 mg/kg GBE with FST). After 17 days of implementing FST following injection,	GBE resulted in 39% decrease in immobility of models in FST.

	analysis of brain tissue and hormone levels performed.	
Chen et al./ 2019	The experimental models divided into 2 groups: 1) 300 mg/kg GPS 2) 30 mg/kg paroxetine Treatment continued for 4 weeks and 3-days experimentation, in the following.	Both GPS and paroxetine showed equal antidepressant properties and diminished immobility time in all tests.
Hemmeter U et al/ 2001	16 patients participated in an open non-randomized study to investigate effects of GBE on sleep situation and cognitive performance. The first group received 200mg/d trimipramine-monotherapy for 6 weeks and the latter group got 240mg/d GBE therapy for 4 weeks.	In this study GBE ameliorated sleep regulation and increased non-REM sleep through diminishing tonic CRH-activity.
Lingaerde O et al./ 1999	27 SAD(seasonal affective disorders) cases, suffering from WD(winter depression), participated in this study to investigate anti-depression effects of tablets, containing GBE (for 10 weeks).	The result showed no significant difference between groups and resulted in an unsuccessful administration of GBE.
Qin XS et al./ 2005	Depression rats, treated with combination of venlafaxine and GBE. Detection of BDNF and measuring behavioral changes performed to investigate anti-depressant effects of this regimen.	Adding GBE to venlafaxine showed promising results in treating depression models.
Liang Z-H et al./ 2019	Scientists inoculated GBE for 80 PSD(post stroke depression) patients to evaluate whether they can decrease venlafaxine doses in PSD treatment.	While adding GBE, the researchers successfully decreased venlafaxine and achieved the same efficacy with lower adverse effects.
Nikfarjam et al. / 2012	81 patients were divided into 2 group: 1) 3 times ECT in a week with a placebo. 2) 3 times ECT in a week with a capsule containing GBE. After intervention, Hamilton questionnaire and MMSE was taken.	Both exams showed that GBE provides significant development in depression and cognitive disorders. Therefore, GBE would be a good adjuvant treatment alongside ECT.
Dai et al./ 2018	136 patients suffering from depression were divided into 2 groups: 1) GBE + Cit 2) Cit	GBE significantly controlled depressive symptoms through decreasing S100B and had synergistic effects in combination with Cit.

Hence, we require to design novel extended trials among human subjects to light more aspects of GBE and its combinations with other therapies in controlling depression.

Anxiolytic effects of GBE

From the first studies, GBE showed unique anti-anxiety effects. In an experimental trial, flumazenil significantly neutralized traditional therapies (diazepam) but showed no

obstruction on GBE activities (39). Surprisingly, low and high doses of GBE showed reliable efficiency and safety in controlling anxiety (40). Furthermore, combining GBE regimen with traditional therapies improved anxiety, fatigue and tiredness through enhancing cerebrovascular perfusion and strong antioxidant activities (41) (tab 3). Despite GBE provides reliable treatments with and without other drugs for anxiety, further studies are still required to discover all aspects of this merciful herbal treatment (42).

Table 3. Studies addressing anxiolytics properties of Ginko biloba.

Author/ year	**In-vivo studies/ clinical trials**	**Outcomes**
Kuribara et al./ 2003	Oral 0.5 or 1 g/kg, p.o. of GBE were administered in male mice and 1 day after injection, the plus-maze test was taken.	Unlike ginkgolide-B and ginkgolide-C, ginkgolide-A has a significant effect on anxiety. Therefore, GBE would be a promising anti-anxiety treatment.
Woelk et al./ 2007	107 participants with adjustment or generalized anxiety disorder with anxious mood were divided into 3 groups: 1) Placebo 2) high dose GBE (480 mg) 3) low dose GBE (240 mg) After 4 weeks, several analyses include HAMA was performed.	The high dose GBE decreased the HAMA score more than the low dose (-14.3 vs. -12.1). These results introduce GBE as a safe anti-anxiety agent.
Alsmadi et al./ 2018	99 participants were treated with GBE and psychoeducation sittings to compare the anti-anxiety activity of GBE with psycho-education sittings.	The results of the anti-anxiety analysis were in favor of GBE. This product reduces physical tiredness and promotes activity scores.

CONCLUSIONS

Extract of *G. biloba* leaves showed promising efficiency and safety in several studies. The different components of *G. biloba* control mental disorders through regulating neurobiological mechanisms such as dopamine, serotonin, inflammatory glial-derived proteins. Despite the long history of repeated studies on rats and humans, that proved GBE as a reliable anti-depressant treatment, we require further clinical trials to evaluate the anxiolytic and anti-stress effects of GBE on humans.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES

1. Yeh KY, Shou SS, Lin YX, Chen CC, Chiang CY, Yeh CY. Effect of Ginkgo biloba extract on lipopolysaccharide-induced anhedonic depressive-like behavior in male rats. Phytother Res. 2015;29(2):260-6.
2. Stein DJ, Scott KM, de Jonge P, Kessler RC. Epidemiology of anxiety disorders: from surveys to nosology and back. Dialogues Clin Neurosci. 2017;19(2):127-36.
3. Bandelow B, Baldwin D, Abelli M, Bolea-Alamanac B, Bourin M, Chamberlain SR, et al. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. The World Journal of Biological Psychiatry. 2017;18(3):162-214.
4. Chand SP, Arif H. Depression. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2021, StatPearls Publishing LLC.; 2021.
5. Treating depression and anxiety in primary care. Prim Care Companion J Clin Psychiatry. 2008;10(2):145-52.

6. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743-800.
7. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol. 2014;43(2):476-93.
8. Gorman JM. Comorbid depression and anxiety spectrum disorders. Depress Anxiety. 1996;4(4):160-8.
9. Thibaut F. Anxiety disorders: a review of current literature. Dialogues Clin Neurosci. 2017;19(2):87-8.
10. Ballenger JC. Anxiety and Depression: Optimizing Treatments. Prim Care Companion J Clin Psychiatry. 2000;2(3):71-9.
11. Seldenrijk A, Vis R, Henstra M, Ho Pian K, van Grootheest D, Salomons T, et al. [Systematic review of the side effects of benzodiazepines]. Ned Tijdschr Geneeskd. 2017;161:D1052.
12. Liu L, Liu C, Wang Y, Wang P, Li Y, Li B. Herbal Medicine for Anxiety, Depression and Insomnia. Current neuropharmacology. 2015;13(4):481-93.
13. Xu C, Teng J, Chen W, Ge Q, Yang Z, Yu C, et al. 20(S)-protopanaxadiol, an active ginseng metabolite, exhibits strong antidepressant-like effects in animal tests. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(8):1402-11.
14. Mao QQ, Ip SP, Ko KM, Tsai SH, Xian YF, Che CT. Effects of peony glycosides on mice exposed to chronic unpredictable stress: further evidence for antidepressant-like activity. J Ethnopharmacol. 2009;124(2):316-20.
15. Nutt DJ, Ballenger JC, Sheehan D, Wittchen HU. Generalized anxiety disorder: comorbidity, comparative biology and treatment. Int J Neuropsychopharmacol. 2002;5(4):315-25.
16. Toriizuka K, Kamiki H, Ohmura NY, Fujii M, Hori Y, Fukumura M, et al. Anxiolytic effect of Gardeniae Fructus-extract containing active ingredient from Kamishoyosan (KSS), a Japanese traditional Kampo medicine. Life sciences. 2005;77(24):3010-20.
17. Awad R, Levac D, Cybulska P, Merali Z, Trudeau V, Arnason J. Effects of traditionally used anxiolytic botanicals on enzymes of the γ-aminobutyric acid (GABA) system. Canadian journal of physiology and pharmacology. 2007;85(9):933-42.
18. Van Gaalen MM, Stenzel-Poore MP, Holsboer F, Steckler T. Effects of transgenic overproduction of CRH on anxiety-like behaviour. European Journal of Neuroscience. 2002;15(12):2007-15.
19. Di Renzo G. Ginkgo biloba and the central nervous system. Fitoterapia. 2000;71:S43-S7.
20. Rapin JR, Lamproglou I, Drieu K, Defeudis FV. Demonstration of the "anti-stress" activity of an extract of Ginkgo biloba (EGb 761) using a discrimination learning task. General Pharmacology: The Vascular System. 1994;25(5):1009-16.
21. Jezova D, Duncko R, Lassanova M, Kriska M, Moncek F. , Reduction of rise in blood pressure and cortisol release during stress by Ginko biloba extract (EGb 761) in healthy volunteers. Journal of Physiology and Pharmacology. 2002;53(3):337-48.
22. Rai D, Bhatia G, Sen T, Palit G. Anti-stress effects of Ginkgo biloba and Panax ginseng: a comparative study. Journal of pharmacological sciences. 2003;93(4):458-64.
23. Kalkunte SS, Singh AP, Chaves FC, Gianfagna TJ, Pundir VS, Jaiswal AK, et al. Antidepressant and antistress activity of GC-MS characterized lipophilic extracts of Ginkgo biloba leaves. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2007;21(11):1061-5.
24. Ward CP, Redd K, Williams BM, Caler JR, Luo Y, McCoy JG. Ginkgo biloba extract: cognitive enhancer or antistress buffer. Pharmacology Biochemistry and Behavior. 2002;72(4):913-22.
25. Yuan-Qing H, Chao-Yue M, Ye P, Jie Z, Li-Jing Y, Xiao-Chun L, et al. Ginko biloba extract (GBE) could prevent chronic unpredictable mild stress induced behavioralalterations in rats by food method. International Journal of Food and Nutritional Sciences. 2017;6(1):43.
26. Ströhle A, Holsboer F. Stress responsive neurohormones in depression and anxiety. Pharmacopsychiatry. 2003;36(S 3):207-14.
27. Vadnal R. Inositol and Ginkgo biloba as Adjuncts in Chronic Depression: Case Report. Nutritional neuroscience. 1998;1(4):315-7.
28. Sealey R. Surviving Unipolar Depression-The Effectiveness of Ginkgo Biloba. J Orthomolec Med. 1996;11:168-72.
29. Sakakibara H, Ishida K, Grundmann O, Nakajima J, Seo S, Butterweck V, et al. Antidepressant effect of extracts from Ginkgo biloba leaves in behavioral models. Biol Pharm Bull. 2006;29(8):1767-70.
30. Yeh KY, Shou SS, Lin YX, Chen CC, Chiang CY, Yeh CY. Effect of Ginkgo biloba extract on lipopolysaccharide-induced anhedonic depressive-like behavior in male rats. Phytotherapy research. 2015;29(2):260-6.
31. Rojas P, Serrano-García N, Medina-Campos ON, Pedraza-Chaverri J, Ögren SO, Rojas C. Antidepressant-like effect of a Ginkgo biloba extract (EGb761) in the mouse forced swimming test: role of oxidative stress. Neurochemistry international. 2011;59(5):628-36.
32. Chen P, Hei M, Kong L, Liu Y, Yang Y, Mu H, et al. One water-soluble polysaccharide from Ginkgo biloba leaves with antidepressant activities via modulation of the gut microbiome. Food & function. 2019;10(12):8161-71.
33. Hemmeter U, Annen B, Bischof R, Brüderlin U, Hatzinger M, Rose U, et al. Polysomnographic effects of adjuvant ginkgo biloba therapy in patients with major depression medicated with trimipramine. Pharmacopsychiatry. 2001;34(02):50-9.

34. Lingaerde O, Fφreland A, Magnusson A. Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial. Acta Psychiatrica Scandinavica. 1999;100(1):62-6.
35. Qin XS, Jin KH, Ding BK, Xie SF, Ma H. Effects of extract of Ginkgo biloba with venlafaxine on brain injury in a rat model of depression. Chin Med J (Engl). 2005;118(5):391-7.
36. Liang Z-H, Jia Y-B, Wang M-L, Li Z-R, Li M, Yun Y-L, et al. Efficacy of ginkgo biloba extract as augmentation of venlafaxine in treating post-stroke depression. Neuropsychiatric disease and treatment. 2019;15:2551.
37. Nikfarjam M, Goudarzi I, Heidari S, Parvin N. Effect of Ginkgo Biloba Tablets on Patients with Major Depression Treated with Electroconvulsive Therapy. Journal of Mazandaran university of medical Sciences. 2012;22(88):62-9.
38. Dai C-X, Hu C-C, Shang Y-S, Xie J. Role of Ginkgo biloba extract as an adjunctive treatment of elderly patients with depression and on the expression of serum S100B. Medicine. 2018;97(39).
39. Kuribara H, Weintraub ST, Yoshihama T, Maruyama Y. An anxiolytic-like effect of Ginkgo biloba extract and its constituent, ginkgolide-A, in mice. Journal of natural products. 2003;66(10):1333-7.
40. Woelk H, Arnoldt K, Kieser M, Hoerr R. Ginkgo biloba special extract EGb 761® in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial. Journal of psychiatric research. 2007;41(6):472-80.
41. Alsmadi AM, Tawalbeh LI, Gammoh OS, Shawagfeh MQ, Zalloum W, Ashour A, et al. The effect of Ginkgo biloba and psycho-education on stress, anxiety and fatigue among refugees. Proceedings of Singapore Healthcare. 2018;27(1):26-32.
42. Kumar Singh S, E Barreto G, Aliev G, Echeverria V. Ginkgo biloba as an alternative medicine in the treatment of anxiety in dementia and other psychiatric disorders. Current drug metabolism. 2017;18(2):112-9.

Correspondence:

Hossein Pourmontaseri,
Student Research Committee, Fasa University of Medical Sciences, Avicenna Sq, Fasa, Fars, Iran,
hossein.prm2000@gmail.com

Submission: 15 apr 2022
Acceptance: 02 jun 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Quality of life predictors in patients with Alzheimer's disease dementia

Laura C. Doliș, Mihnea C. Manea, Maria G. Puiu, Adela M. Ciobanu, Roxana Chiriță, Mirela Manea

Laura Cristina Doliș - MD, PhD student, Doctoral School 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest, Romania; Psychiatrist Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry, Bucharest, Romania;
Mihnea Costin Manea - MD, PhD, Associate professor, Department of Psychiatry and Psychology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania, Senior psychiatrist Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry
Maria Gabriela Puiu - MD, PhD, Lecturer, Department of Psychiatry and Psychology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; Senior psychiatrist Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry, Bucharest, Romania
Adela Magdalena Ciobanu - Professor of Psychiatry, Neuroscience Department, Discipline of Psychiatry, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; Senior psychiatrist, Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry
Roxana Chiriță - M.D., PhD, Professor of Psychiatry Grigore T Popa University of Medicine and Pharmacy, Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași
Mirela Manea - MD, PhD, Professor of Psychiatry - Department of Psychiatry and Psychology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania; Senior psychiatrist Department of Psychiatry, 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry

ABSTRACT

Objectives: In this study, we set three significant objectives: the first examines possible differences in personal and environmental factors that influence the quality of life experienced by patients with Alzheimer's disease dementia; the second examines differences in quality of life from the patient's and their relatives' perspectives. The third goal is to determine whether personal and socio-demographic characteristics have an impact on the quality of life experienced by Alzheimer's disease dementia patients.

Materials and methods: Between March 2018 and April 2019, data were taken from the caregivers of 145 beneficiaries institutionalized in centers for the elderly in Arad County. Assessment tools such as MMSE, Reisberg, Cornell, GAFS, and QOL-AD scales were used.

IBM SPSS Statistics Version 22 software (IBM Corp for Windows, Armonk, NY), JASP, and JAMOVI software were used to analyze statistical data.

Results: Exact Fisher test results revealed statistical significance for: level of functionality, level of depression, number of interactions, visits, type of institutionalization and fee (F level of functionality = 10,280, F depression in dementia = 18,804, F visits = 16,858, F type institutionalization = 14,496, F tax = 11,136, F interactions = 19,768, p <0.05). The verification of statistically significant differences in the quality of life according to the perspective of the patient and his relatives revealed that this hypothesis is supported by statistical data (U = 5622, p <0.0001).

Alzheimer's patients' perceived quality of life is influenced by personal and socio-demographic characteristics. We employed the ordinal form of the research variables for this, and the regression model we developed turned out to be statistically significant (R2 = 0.65, p 0.001).

Conclusions: The level of functionality, type of institutionalization, fee, and interactions influence the quality of life.

KEY WORDS:
Alzheimer's, dementia, quality of life, personal and socio-demographic factor.

INTRODUCTION

According to available data, the number of individuals living with dementia globally is currently estimated to be around 35 million, and this number is likely to double by 2030 and triple by 2050(1). Dementia is recognized as a condition with significant economic consequences, with an estimated yearly cost of around $ 800 billion. As a result, dementia is regarded as one of the most severe health issues we face today (2).

Dementia is a progressive disease, and while some people can keep their independence for a long time, others will require more progressive assistance in their everyday tasks, especially as the disease progresses. In many nations, family members are seen as the primary source of this form of care. For example, in the United Kingdom, people with dementia and their relatives now bear two-thirds of all dementia care expenditures, costing the UK economy billions of pounds each year (3).

There are less health resources and dementia care services in Latin American countries (for example, Brazil), strengthening the assumption that people with dementia should be cared for by their relatives. In Asian countries like China, the lack of dementia services in the public health care system is also common. As a result, families play an essential role in caring for the elderly. They suggest that unpaid family caregivers are essential for caring for persons with dementia worldwide (1).

Caring for a person with dementia can be physically and emotionally demanding. It can have a significant impact on the family caregiver's social, psychological, and physical well-being.

According to the literature, the caregiver's low quality of life is often associated with both a diminished quality of life of the person with dementia and some high costs of care (3).

Although the term "quality of life" is frequently used throughout the literature, there is no consensus on how to define and assess the quality of life of dementia caregivers. The World Health Organization (WHO) defines it as an individual's assessment of their position in life, based on the culture and value systems in which they live, in terms of objectives, expectations, standards, and worries. The general quality of life includes many aspects, such as psychological state, physical health, level of independence, personal beliefs and spirituality, social relationships, and the environment. It is related to health and refers to components that are directly and indirectly affected by health, disease, disorder, and injury and, therefore, often overlap with the concept of health (4).

More precise tools created to measure the quality of life of both carers and patients with dementia have been published in research during the last ten years. There are a small number of studies in the literature on the correlations between psychiatric symptoms (depression, hypnotic disorders), somatic comorbidities, socio-familial support, caregiver training, and the quality of life of both patients and their families (4).

The following goals are proposed for this study:

O1. Identifying possible differences in terms of personal factors (gender, level of depression, number of interactions, level of functioning and cognitive impairment, marital status), but also in terms of environmental factors (type of institutionalization, type of tax and fee-based fee, number of visits) depending on the quality of life perceived by patients diagnosed with dementia in Alzheimer's disease.

O2. Identify possible differences in quality of life depending on the patient's perspective and their relatives.

O3. Identification of potential effects of personal characteristics (gender, marital status, interactions, level of depression, functioning, cognitive impairment) and socio-demographic factors (kind of institutionalization, type of tax, tax rate) on the quality of life of the patients with dementia in Alzheimer's disease

MATERIALS AND METHODS

Between March 2018 and April 2019, data were taken from the caregivers of 145 beneficiaries institutionalized in the Care Centre for the Elderly in Arad and the Residential Center Casa Seniorilor Arad with free consent to participate in the study, signing the informed consent according to Helsinki Declaration.

The diagnosis was established according to DSM 5 criteria (5).

The patients' personal and environmental factors were noted, and their quality of life was assessed on a multidimensional but also on an individual basis, with particular focus paid to:

- Environmental factors (type of institutionalization, tax, type of tax contribution, number of visits of members);
- Personal factors (level of depression, associated diagnoses, characteristics such as level of schooling, marital status, gender, number of social interactions).

The information was converted into a series of binary variables.

The degree of urbanization was used to code the site of residence, which was divided into

two categories: urban areas (population > 5000, according to national legislation) and rural areas (population 5000, according to national legislation).

A general clinical examination, as well as psychiatric, neurological, and psychological evaluations, were performed on all patients. Additional investigations included blood tests, EKGs, and neuroimaging studies (CT).

Statistical analysis of the data was performed using IBM SPSS Statistics Version 22 software (IBM Corp for Windows, Armonk, NY), JASP software and JAMOVI. Multinomial regression models were applied to test for relationships between variables such as patient - and caregiver -perceived quality of life and level of depression or number of interactions, type of institutionalization. The Fisher Exact Test was applied to assess differences in quality of life perspective based on criteria such as: type of institutionalization, fee contribution, fee, residence, gender, marital status, functional level, and level of cognitive impairment.

Ethical approval for the study was obtained from the local research ethics committee. Patients or legal guardian (where applicable) signed a written consent for inclusion in this study as stated above.

TOOLS

The following tools were used in this study:

MMSE 2 - Mini-Mental State Examination, Second Edition, is an instrument that measures cognitive impairment (6). It was adapted for the Romanian population in 2013. Grades of the severity of cognitive impairment are based on patient scores as follows: initial cognitive impairment 24-27 points, mild cognitive impairment 21-23 points, moderate cognitive impairment 18-20 points, marked cognitive impairment 15-17 points, severe cognitive impairment 12-15, significant cognitive impairment ≤ 10.

The Clock Drawing Test is a short technique that is used to check for early dementia, such as Alzheimer's disease. The test involves drawing a clock on a piece of paper with numbers, clock hands, and a certain time. A person's inability to perform the task strongly indicates mental decline (7).

GAFS - Global Assessment of Functioning Scale is well known internationally and widely used for scoring the severity of illness in psychiatry (8).

The Reisberg Scale - Global Cognitive Impairment Scale was developed for the assessment of primary degenerative dementia and the delineation of its stages (9).

Cornell Scale - This scale was created to examine the signs and symptoms of significant depression in dementia patients. Because some dementia patients are unable to offer accurate reports, this scale relies on information from the patient and a caregiver/informant. The emphasis is on depressive symptoms that occur in the week leading up to the interview. First, the caregiver should be interviewed, then the patient. On a scale of 0 to 2, the severity of the items is scored (0 = nonexistent, 1 = mild or intermittent, 2 = severe). The results are totaled. A score of six or less indicates the lack of depressive symptoms; scores of ten or more suggest the possibility of major depression, and values of thirteen or more indicate major depression (10).

The QOL-AD / Quality of Life in Alzheimer's Disease Scale - Patient and Caregiver Forms is a 13-item measure specifically intended to assess the patient's quality of life from both the patient and the caregiver's perspective. It

was created for people with dementia with the help of patients, caregivers, and experts to ensure construct validity. The measure focuses on areas of quality of life that are significant to older adults with cognitive impairment. The total score is the result of adding all of the components together. Low-quality-of-life ranges of 13-26, medium-quality-of-life ranges of 27-39, and high-quality-of-life ranges of 40-52 are also possible (11).

Because this scale was not calibrated on the Romanian population and, at the same time, in order to respect the methodological norms, the scale was translated, adapting it to the specifics of the Romanian language, then a pilot study was performed on 30 people with Alzheimer's. Cronbach Alpha's fidelity had a value of 0.88, which means that the test measures precisely what it intended. Furthermore, it is necessary to mention that the adaptation to the specific Romanian language was carried out in the following way: a doctor, a psychologist, and a translator independently translated the scale, then, according to the observations of each of them, the best decision was taken. Subsequently, the scale, together with informed consent, reached patients.

The Cronbach's Alpha reliability index for the first study was 0.91 and for the second was 0.94, indicating that the test measures what it set out to measure.

PATIENTS

The study included 145 patients diagnosed with Alzheimer's disease dementia, 65 male and 80 female, aged 65 to 91 years, with a mean M=75.1 and a standard deviation SD=6.03. All participants had anti-dementia medication. 73 of the participants were from urban areas and 72 from rural areas.

Regarding marital status, in the figure and tables VI-VIII, we can see that most patients (66) were widowed, and 35 of them were female (Table VI-VIII). 33 of the participants were single, and 26 were married. Out of the unmarried participants, most were female (19), and the M:F ratio within the married group was equal (13 women and 13 men, ratio 1:1).

96 of the patients are admitted to private centers and 49 to state centers. 96 of the participants paid a contribution fee of 3000 lei, and 37 of the participants paid 60% of their pension +/- percentage from their caregivers, while for 12 patients, the fees were paid by the Local Government Authorities. At the same time, 96 of the participants contributed partly from their own income and had financial support from their caregivers, while 18 of them paid the full fee themselves, and 20 of the participants had the fee paid in full by their caregivers.

We also noticed that among the patients admitted to private centers, most of them, i.e., 18, can pay the full fee of 3000 lei from their own income, and 20 have the fee paid by their caregivers. 37 of the patients in the state centers have the fee paid 60% of their own income, and the rest is borne by the Local Administration.

In terms of scores on the scale measuring depression in dementia, the Cornell Scale, patients scored between 5 and 34 points, and 86 of the patients also had a major depressive episode, 51 were only suspected of having a major depressive episode, and 8 of the patients did not comply with the criteria of a major depressive episode.

Patient scores on the MMSE show that most patients, i.e., 58, had severe cognitive impairment, 30 moderate, and 24 severe.

Cognitive impairment in 56 participants is also evidenced by patients' Clock Test scores.

60 of the participants had a GAFS score between 21 and 30, and 57 scored between 31 and 40. 26 of the participants had scores between 41 and 50. All of this demonstrates the high need of patients for care.

In addition, the results of 97 of the participants illustrated severe cognitive decline on the Reisberg scale and moderate-severe decline for 25 of them.

On the other hand, 92 of the study participants receive less than 2 visits per month from caregivers, 34 of them receive more than 4 visits per month from caregivers, and 19 patients receive more than 2 visits per week.
In terms of quality of life, from the patients' perspective, scores range from 13 to 51. 88 patients say their quality of life is low, 51 say it is moderate, and 9 patients see their quality of life as good.

From the perspective of caregivers, however, scores range from 13 to 51, but 59 say that patients have a moderate quality of life and 51 say that parents/grandparents with Alzheimer's have a high quality of life.

RESULTS

In processing the information obtained from caregivers and patients, we used both numerical variants of the variables and also the transformation of numerical variables into ordinal ones, depending on the purpose of each hypothesis. Our approach is complex and therefore involves several steps.

Thus, we first tested for statistically significant differences in personal factors (gender, background, level of schooling, level of depression, number of interactions, level of functioning and cognitive impairment, marital status) and environmental factors (type of institutionalization, type of fee and fee contribution, number of visits) in the perceived life quality of patients diagnosed with Alzheimer's disease.

For this, we transformed all variables into ordinal variables and then applied the Fisher Exact test (Table I) whose results revealed statistical significance for: level of functionality, level of depression, number of interactions, visits, type of institutionalization and charge (F level of functionality = 10,280, F depression in dementia = 18,804, F visits = 16,858, F type of institutionalization = 14,496, F charge = 11,136, F interactions = 19,768, $p<0.05$).

Table I Fisher Exact Test

Value	Sig.
F gender = 0,180	0,084
Average F of origin = 1,019	0,091
F marital status = 4,258	0,067
F tuition = 3,263	0,122
F functionality level = 10,280	0,021
F cognitive decline = 0,423	0,355
F depression in dementia = 18,804	0,001
F visits = 16,858	0,001
F type institutionalisation = 14,496	0,036
F fee =11,136	0,033
F contribution fee = 3,9890	0,233
F interactions = 19,768	0.0001

We can conclude that a good level of functionality, a relatively normal number of interactions with others, a number of visits from caregivers so that patients feel cared for, financial independence of the patient from the family, and the type of institutionalization contribute to a medium to a high quality of life.

Another step in our scientific approach is to verify statistically significant differences in quality of life according to the perspective of the patient and the caregivers.

For this, the quality of life variable was used in the form of an interval-report.

Table II's findings revealed that the statistical data reinforces this hypothesis (U=5622, p<0,0001).

Table II Mann-Whitney U test

		Statistic	**p**
Quality of life	Mann-Whitney U	5622	< .001

Table III also shows that the averages of the two groups are different, i.e., 25,2 and 34, respectively. Thus, for a real improvement in the quality of patients' lives, a balance between the two perspectives is necessary. This way, the needs of our patients can be met promptly. It is important to see what the

expectations of the two parties involved, the patient and the caregiver, are in terms of quality of life and then to make an intervention plan that addresses all parties involved.

Table III Descriptive statistics of the two groups

	Group	N	Mean	Median	SD	SE
Quality of life	patient	145	25.2	25.0	8.48	0,704
	caregiver	145	34.0	33.0	10.6	0,882

Last but not least, we tested whether personal factors (gender, marital status, interactions, level of depression, level of functioning, and level of cognitive impairment) and socio-demographic factors (type of institutionalization, type of fee, fee contribution) have an influence on the perceived level of quality of life of the Alzheimer's patient.

For this step, too, we used the ordinal version of the research variables.

Thus, table IV shows that the chosen regression model is statistically significant, R2=0,65, p<0,001).

Table IV Model Fit

				Overall Model Test		
Model	**Deviance**	**AIC**	**R^2_{McF}**	**χ^2**	**df**	**p**
1	79.7	156	0,658	153	36	< .001

At the same time, the Omnibus Test (Table V) illustrates that all variables included in the model have an effect on the criterion variable (p<0,05).

Table V Omnibus Likelihood Ratio Tests

Predictor	**χ^2**	**df**	**p**
Gender	1,05	2	0,023
Marital status	15,81	6	0,015
Cognitive decline	6,67	4	0,045
Depression in dementia	1,27	4	0,046
Interactions	121,43	4	< .001
GAFS	22,10	8	0,005
Type of institutionalisation	-7,01e−7	2	1,000
Duty	-6,78e−7	4	1,000
Membership fee	4.43	6	0,018

Going further with the analysis, in the table VI, we can see that an influence on the moderate and low levels of quality of life perceived by the patient are: the level of functionality, the type of institutionalization, the contribution from the fee borne by the Local Public Administration, moderate level interactions ($p<0,05$).

Table VI Coefficients - QOL.AD.Patient

QOL.AD.Patient2	**Predictor**	**Estimate**	**SE**	**Z**	**p**
medium level - low level	Intercept	309,675	57,985	5,341	< .001
	Gender:				
	F – M	-0,196	0,623	-0,316	0,752
	Marital status:				
	married - single	-0,546	1,225	-0,446	0,656
	divorced - single	0,883	0,943	0,936	0,349
	widower - single	0,406	0,791	0,513	0,608
	Reisberg scale:				

Table VI Coefficients - QOL.AD.Patient

QOL.AD.Patient2	Predictor	Estimate	SE	Z	p
	Severe cognitive decline - Moderately severe cognitive decline	0,192	0,785	0,244	0,807
	Severe cognitive decline - Moderate severe cognitive decline	-0,173	1,060	-0,163	0,871
	Depression in dementia2::				
	≥ 10 possible major depressive episode -	-0,556	1,448	-0,384	0,701
	>18 major depressive episode -	-1,219	1,458	-0,836	0,403
	interactions:				
	moderate - normal	-508,628	100,505	-5,061	< .001
	deficient - normal	-1036.609	NaN	NaN	NaN
	GAFS:				
	50-51 – 60-51	75,763	19,339	3,918	< .001
	40-31 – 60-51	74,369	19,336	3,846	< .001
	30-21 – 60-51	76,242	19,335	3,943	< .001
	20-11 – 60-51	75,633	1,89e0-9,	4,00e+10,	< .001
	Type: institutionalisation:				
	private center - state center	61,164	11,605	5,270	< .001
	Fee:				

Table VI Coefficients - QOL.AD.Patient

QOL.AD.Patient2	Predictor	Estimate	SE	Z	p
	60% of pension +/- percentage from the caregivers - borne by Local Government Authorities	124,500	23,208	5,364	< .001
	3,000 RON - borne by Local Public Administration Authorities	61,164	11,605	5,270	< .001
	Membership fee:				
	Partial contribution from own income and financial support from caregivers - Full contribution from own income	0,234	1,425	0,164	0,870
	Total contribution borne by the caregivers - Full contribution from own income	1,001	1,582	0,633	0,527
	Contribution borne by the Local Government - Full contribution from own revenue	124,011	23,210	5,343	< .001
high level - low level	Intercept	467,350	158,753	2,944	0,003
	Gender:				
	F – M	-120,022	84,635	-1,418	0,156
	Marital status:				
	married - single	62,509	84,658	0,738	0,460
	divorced - single	308,279	0,268	1150.452	< .001
	widower - single	-99,178	239,392	-0,414	0,679
	Reisberg scale:				

Table VI Coefficients - QOL.AD.Patient

QOL.AD.Patient2	Predictor	Estimate	SE	Z	p
	Severe cognitive decline - Moderately severe cognitive decline	-33,638	43,490	-6,138	0,007
	Severe cognitive decline - Moderate severe cognitive decline	-213,037	4,827	-4,328	< .001
	Depression in dementia2::				
	≥ 10 possible major depressive episode -	-120,233	4,423	-27,181	< .001
	>18 major depressive episode -	-134,769	169,732	-0,794	0,427
	interactions:				
	moderate - normal	-1301.961	0,268	-4858.728	< .001
	deficient - normal	-932,317	6.07e-10,	-1,54e−12	< .001
	GAFS:				
	50-51 – 60-51	-63,952	324,061	-0,197	0,044
	40-31 – 60-51	372,854	80,618	4,625	< .001
	30-21 – 60-51	126,092	84,693	1,489	0,037
	20-11 – 60-51	11,031	0,000	Inf	< .001
	Type: institutionalisation:				
	private center - state center	9,564	81,836	0,117	0,007
	Fee:				

Table VI Coefficients - QOL.AD.Patient

QOL.AD.Patient2	Predictor	Estimate	SE	Z	p
	60% of pension +/- percentage from the caregivers - borne by Local Government Authorities	203,845	83,710	2,435	0,015
	3,000 RON - borne by Local Public Administration Authorities	119,564	81,836	10,117	0,007
	Membership fee:				
	Partial contribution from own income and financial support from caregivers - Full contribution from own income	-182,311	79,961	-2,280	0,023
	Total contribution borne by the caregivers - Full contribution from own income	-93,171	51,709	-5,310	< .001
	Contribution borne by the Local Government - Full contribution from own revenue	253,941	24,294	0,783	0,034

High quality of life is influenced by marital status, cognitive decline, number of interactions, and low level of depression ($p<0,05$).

CONCLUSIONS AND DISCUSSIONS

In conclusion, our results partially overlap with the results in the literature.

Söylemez and colleagues (12) published results similar to those of our study regarding the influence of education and functional level on the quality of life. An educated person will be able to appreciate his quality of life in the optimal parameters as long as he has a high level of functionality.

Functional impairment of the patient will result in low QoL scores for both patients and their relatives. Functionality, as stated by Martyr et al. (13), is related to the quality of life. Excellent functional status is indicated by high QoL-AD scores. Functionality is one of the most vital components of existence. The result of the current relationship is logical because the need for functional support generally comes from the presence of multiple functional deficiencies, and the patient's perception of their own health is strongly influenced by it.

Patients with excellent functional status should anticipate having high QoL scores. It has been observed that individuals with high functionality have a high quality of life score. A caregiver who sees his or her loved one suffering from multiple functional impairments is normally expected to assess the patient's QoL more negatively (14). In the present study, depression was one of the predictors of quality of life, as in the study by Chan et al. (15). They previously reported a link between depression and the scores of patients and caregivers in QoL-AD in a study of 111 patients with Alzheimer's dementia with a poorer quality of life seen in patients with depression.
A number of additional research have discovered a relationship between depression and poor quality of life in dementia individuals with Alzheimer's disease, regardless of whether QoL AD was self-reported or assessed by others (14).

Depression was the most significant factor affecting the patient's reported quality of life, with the highest coefficient (compared to polypharmacy and anxiety). In terms of the caregiver's assessment, depression was discovered to have a considerable impact on quality of life, with a coefficient of the same size as the caregiver's burden (16). As a result, the findings of our study highlight the necessity of recognizing and treating depressive symptoms in Alzheimer's patients.

However, detecting depression can be difficult, as some depressive symptoms can be confused with symptoms of dementia, such as apathy or decreased energy. Therefore, both healthcare professionals and the patient's immediate entourage should pay special attention to these types of symptoms. Antidepressants can help older people with depression; however, they can cause side effects due to comorbidities and drug-drug interactions in polypharmacy (17).

For these reasons, the elderly receive lower doses of antidepressants than recommended or are treated for a short period. Non-pharmacological therapies such as psychotherapy (cognitive-behavioral and interpersonal psychotherapy) and exercise therapy have been demonstrated to be useful in managing mild to moderate depression in studies (17). However, insufficient studies have been conducted to verify the efficacy of these techniques in patients with severe dementia.

At the same time, there were disparities in perspective between the patient and the caregiver regarding the quality of life in both our study and other studies in the literature. When the patient can no longer self-assess, caregiver assessment can still be utilized to guide illness management.

As a result, we discovered in our research that the following factors have an impact on the patient's perception of moderate and low quality of life: level of functionality, type of institutionalization, fee contribution paid by the Local Public Administration, moderate level of interactions ($p<0.05$).

High quality of life is influenced by marital status, cognitive decline, number of interactions, and low level of depression ($p<0,05$).

Elements of originality lie in the fact that we have chosen to look at quality of life multi-dimensionally, involving both personal factors (gender, background, level of schooling, level of depression, number of interactions, level of functioning and cognitive impairment, marital status) and environmental factors (type of institutionalization, type of fee and fee contribution, number of visits). In addition, we have translated and adapted to the Romanian language essential scales for the assessment and self-assessment of patients diagnosed with Alzheimer's.

The possible finiteness of this study is the small and non-homogeneous sample. We did not have an equal number of participants on each level of cognitive impairment signaled by the MMSE.
In the future, we plan to conduct longitudinal studies that reflect the predictors of the quality of life of these patients and implement psycho-pharmacological intervention plans designed to improve both the patient's well-being and provide an improvement in the management of these patients this condition.

ACKNOWLEDGEMENTS AND DISCLOSURES
The authors declare that they have no potential conflicts of interest to disclose.

REFERENCES

1) Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 2012;4(5):40.
2) Angeles RC, Berge LI, Gedde MH, et al. Which factors increase informal care hours and societal costs among caregivers of people with dementia? A systematic review of Resource Utilization in Dementia (RUD). Health Econ Rev 2021;11:37.
3) Lasrado R, Bielsten T, Hann M, et al. Designing and Implementing a Home-Based Couple Management Guide for Couples Where One Partner has Dementia (DemPower): Protocol for a Nonrandomized Feasibility Trial. JMIR Res Protoc. 2018;7(8):e171.
4) Wang J, Xiao LD, He G-P, De Bellis A. Family caregiver challenges in dementia care in a country with undeveloped dementia services. J Adv Nurs. 2014;70(6):1369-80.
5) American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
6) Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev. 2016;(1):CD011145.
7) Park J, Jeong E, Seomun G. The clock drawing test: A systematic review and meta-analysis of diagnostic accuracy. J Adv Nurs. 2018;74(12):2742–54.
8) Aas IM. Global Assessment of Functioning (GAF): properties and frontier of current knowledge. Ann Gen Psychiatry. 2010; 9 (1):20.
9) Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry.1982;139(9):1136–9.
10) Cornell Scale for Depression in Dementia (CSDD) [Internet]. [cited April 6, 2022]. https://instruct.uwo.ca/kinesiology/9641/Assessments/Psychological/CSDD.html
11) Torisson G, Stavenow L, Minthon L, Londos E. Reliability, validity and clinical correlates of the Quality of Life in Alzheimer's disease (QoL-AD) scale in medical inpatients. Health Qual Life Outcomes. 2016; 14 (1):90
12) Felekoğlu E, Özalevli S, Yakut H, et al. Investigation of the Factors Affecting Quality of Life in Patients with Mild to Moderate Alzheimer's Disease in Terms of Patients and Caregivers. Medicina (Mex). October 2021;57(10):1067.
13) Martyr A, Nelis SM, Quinn C, et al. Living well with dementia: a systematic review and correlational meta-analysis of factors associated with quality of life, well-being and life satisfaction in people with dementia. Psychol Med. 2018;48(13):2130–9.
14) Zucchella C, Bartolo M, Bernini S, et al. Quality of life in Alzheimer disease: a comparison of patients' and caregivers' points of view. Alzheimer Dis Assoc Disord. 2015;29(1):50-4.

15) Chan IW-P, Chu L-W, Lee PWH, et al. Effects of cognitive function and depressive mood on the quality of life in Chinese Alzheimer's disease patients in Hong Kong. Geriatr Gerontol Int 2011;11(1):69-76
16) Nikmat AW, Hawthorne G, Al-Mashoor SH. The comparison of quality of life among people with mild dementia in nursing home and home care--a preliminary report. Dement Lond Engl. 2015;14(1):114–25.
17) Kok RM, Reynolds CF. Management of Depression in Older Adults: A Review. JAMA.2017; 317(20):2114–22

Correspondence:

Chiriță Roxana,
M.D., PhD, Professor of Psychiatry Grigore T Popa University of Medicine and Pharmacy, Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași, d.stigma@gmail.com

Submission: 28 apr 2022
Acceptance: 04 jun 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Mental anorexia – medico-legal psychiatric risks

Călin Scripcaru, Diana Bulgaru Iliescu, Silvia Spac, Andrei Scripcaru

Călin Scripcaru- MD, PhD, Institute of Forensic Medicine Iasi
Diana Bulgaru Iliescu - MD, PhD, professor, Grigore T. Popa University of Medicine and Pharmacy Iasi
Silvia Spac - MD, Institute of Forensic Medicine Iasi
Andrei Scripcaru - MD, PhD stud, Grigore T. Popa University of Medicine and Pharmacy Iasi

ABSTRACT
Mental health is not a destination, but a process. It Is about "how you drive, not where you go". In a broad sense, anorexia is an eating disorder, which consists in the voluntary decrease in food intake, which can reach most extreme cases with the cessation of feeding. In the context of this mental illness analysed by this material, it can be concluded that the implications are from small to most serious, even reaching catastrophes, irreversible trauma and even causing the death of the victim.

This paper tries to highlight the medico-legal and social risks of this condition, even if it is a rare but constantly growing mental disorder due to the challenges that adolescents are currently going through. From the analysis of the practical cases briefly exposed in the chapter dedicated to this analysis, we have exemplified with two cases examined at European legislative level.

KEYWORDS:
Anorexia, nutrition, risks.

MOTTO:
"If we begin to be honest about our pain, anger and deprivation instead of pretending that it does not exist, then maybe we will leave the world a better place than we found it." Russel Wilson

PURPOSE OF THE PAPER
In a narrow sense, mental anorexia is a mental problem in the category of eating disorders. Also called nervous anorexia, it is characterized by an abnormal reduction in body weight accompanied by deformation of the image of one's own body, with the prevailing, persistent fear of fattening.

The essential elements of mental anorexia are the following(1):

- restriction on the consumption of food necessary to maintain a minimum normal body weight;
- fear of gaining weight;
- significant deterioration in the perception of conformation or dimensions of the body.

A typical case of the onset of mental anorexia usually involves a teenager or young adult of normal weight or a little overweight; thus, he begins a diet accompanied by physical exercise, loses weight, is encouraged and praised for his performance and the physical appearance achieved by the entourage, arriving without realizing to this type of medico-legal risk that makes its mark in a very harsh way, sometimes irreversible on the mental health.

In addition to the intense fear of not gaining weight, the distorted perception of the body image closely related to self-esteem and severe weight loss lead to the appearance of depressive mood, irritability and insomnia.

Consequently, it is a complex syndrome of psychological, biological and social factors, found mainly among women and adolescents.

The appearance of mental anorexia during puberty led to the issuance of the theory that by controlling the consumption of food and body weight, one tries to compensate for the lack of autonomy and development of the self.

Against this background, cases of nervous anorexia have been reported in twins and triplets, which suggests an increased genetic predisposition, of 50-80% similar to that for bipolar disorder and schizophrenia.

Among the most common factors in practice, predisposing for mental anorexia, are:
-female gender;
-family history of eating disorders;
-perfectionism;
-difficulties in expressing negative emotions;
-difficulties in resolving conflicts;
-low self-esteem.

Also, in the analysed context, it is important to note and to highlight the prominent obsessive-compulsive elements which reveal that the people affected by this medical risk are preoccupied with ideas in relation to nutrition, other associated elements being inflexible thinking, perfectionism, extremely restricted emotional expression, affective lability, excessive alcohol consumption or drug abuse.

Neurobiologists have hypothesized that disorders in the serotonergic and dopaminergic pathways in the brain mediate the evolution of mental anorexia and are the basis for the increased presence of other associated psychological disorders.

From a medical point of view, the malnutrition characteristic of mental anorexia produces disturbances in the laboratory data, the most common being:
-hypercholesterolemia;
-anemia;
-leukopenia;
-low values of thyroxine (T3) and triiodothyronine (T4).

Other signs and symptoms of mental anorexia are: constipation, abdominal pain, intolerance to cold, lethargy or excess of energy, peripheral edema, bradycardia.

An essential medical element in relation to this condition is amenorrhea by lowering the

level of estrogens which is an indicator of the physiological dysfunction in mental anorexia.

The onset of mental anorexia can be associated with a stressful life event around the age of 14-18, with the majority of affected people being women.

When you experience one or more of the following states or behaviours, it can be a sign of early warning of a mental anorexia problem(2):
-you think you no longer have any purpose and you experience strong feelings of guilt;
-you feel helpless or hopeless;
-you feel that nothing matters to you anymore, you are indifferent;
-you have lost interest in hobbies or other pleasant activities;
-you weep a lot, for no particular reason;
-you begin to isolate yourself from others;
-you feel a state of confusion, you often forget, you feel as if you are at the limit;
-you have a lot of energy;
-you continually repeat thoughts and memories in your mind, which you cannot control;
-feel a state of very strong worry, panic or fear;
-you have too much energy, you can't concentrate and you have difficulty following a plan;
-you are irascible, you get easily angry, you scream, you are hostile or violent;
-you suddenly move from one mood to another, which causes relational problems;
-you hear voices or see images that others don't perceive.
-you think others are conspiring against you;
-you feel unable to cope with daily problems and activities;
-important changes have occurred in the habits of nutrition and sleep;
-you have unexplained pain;
-smoke, drink more than usual, use drugs;
-you want to hurt yourself or someone else;
-you are thinking about death or intending to commit suicide.

To define the various types of mental illness, specialists use the term *"disorder"*, a term found in two of the most important reference works in the fields of psychology and psychiatry: *"Diagnostic and statistical manual of mental disorders"* (DSM) of the American Psychiatric Association and *"Classification of mental and behavioural disorders"* (DCI) of the World Health Organization, where the disorder represents a set of clinically recognizable symptoms or behaviour,s associated in most cases with discomfort or interference in the functioning of the person. *(3)*

Mental disorders affect behaviour, mood and thinking, in a way that makes it difficult to carry out activities and life habitually. A person becomes mentally ill when he no longer accepts himself or others, when he has an excessive preoccupation with his own body and person, when he loses contact with reality by retreating into his own world, and can no longer adapt to social, occupational and cultural norms.

The main ways to prevent but also combat this type of mental illness - anorexia, are (4):
-appreciate yourself, treat yourself with kindness and respect and avoid self-criticism, make time for your favourite hobbies and projects, and broaden your horizon of knowledge; take care of your body, make sure:
-you regularly do a physical activity;
-consume nutritious foods;
-you have a sufficient and restful sleep;
-drink enough water;
-do not smoke or consume alcohol in moderation.

-connect with other people, people who have strong family or social connections are generally the healthiest.
-give, so give of your time and energy to help someone else, you will feel better when you do something tangible to help someone in a difficult situation.
-learn how to be resilient to stress, learn that things in life do not always happen in your favour and adapt to the situation, stay positive with the hope that you will find a solution, even if not in the moment;
-calm your mind, spend time in nature, meditate, do relaxation exercises, pray;
-set realistic goals, decide what you want to do academically, professionally and personally, and set the steps you need to achieve your goals.
-be creative, make small movements of rhythm and activities that will break and enliven monotony;
-avoid alcohol and other drugs;
-get professional help when you need it.

Practical aspects related to the medico-legal implications (risks) of mental anorexia or other disorders associated with this condition

The European Court of Human Rights has repeatedly ruled that the detention of a sick person may raise problems under Article 3 of the Convention [European Convention on Human Rights, which prohibits inhuman or degrading treatment] [...] and that the absence of adequate medical treatment may constitute treatment contrary to that provision [....]

In particular, the assessment of the compatibility or incompatibility of specific detention conditions with the standards laid down in Article 3 must, in the case of persons with mental disorders, take into account their vulnerability and inability, in some cases, to complain or to complain in a consistent manner about how they are affected by a given treatment [...]

There are three special elements to be taken into account regarding the compatibility of a complainant's state of health with his detention:

(a) the medical situation of the person deprived of liberty,

(b) the adequacy of the care and medical care provided in detention, and

(c) the appropriateness of maintaining the custodial measure, having regard to the state of health of an applicant. (5)

Aerts v Belgium (6)
30 July 1998

The complainant, who had attacked his ex-wife with a hammer, was arrested in November 1992 for committing an assault following which the victim was declared unfit for work. He was placed under preventive arrest in the psychiatric ward of a penitentiary.

In particular, the applicant complained about the detention conditions in the psychiatric ward, for detentions for longer periods of time, for people who needed psychiatric treatment.

The European Court of Human Rights has ruled that article 3 (prohibition of inhuman or degrading treatment) of the European Convention on Human Rights has not been violated. It observed that it was not disputed that the general conditions in the psychiatric ward in question were unsatisfactory and that they did not favour the effective treatment of detainees.

The European Committee for the Prevention of Torture (CPT) considered that the standard of care provided to patients placed in psychiatric wards was below the minimum ethically and humanitarianly acceptable level and that the prolongation of their detention in

that section for long periods of time entailed an undeniable risk of deterioration of their mental health.

However, in the present case there was no evidence of a deterioration in the applicant's mental health and the living conditions in the psychiatric ward did not appear to have had such serious effects on his mental health as to fall within the scope of Article 3 of the Convention. Indeed, it was not reasonable to expect a person with serious mental illness to give a detailed or coherent description of the suffering endured during detention. However, even in accepting that the applicant's state of anxiety was caused by the conditions of detention, and even in view of his possible difficulty in describing how he had been affected by those conditions, it has not been conclusively established that the applicant had been subjected to treatment that is classified as inhuman or degrading.

Raffray Taddei v. France (7)
December 21st, 2010

Suffering from a number of medical conditions, including anorexia and Münchausen syndrome (a psychiatric disorder characterised by the need to simulate a disease), the applicant complained about being kept in detention and not receiving treatment in accordance with her health problems.

The Court ruled that Art. 3 (prohibition of inhuman or degrading treatment) of the Convention had been violated, finding in particular that the fact that the national authorities did not take sufficient account of the need for specialized treatment in an appropriate unit, as required by the applicant's state of health, combined with her transfers (made despite her particular vulnerability) and with the prolonged uncertainty that followed her requests for postponement, was likely to cause her suffering that exceeded the inevitable level of suffering inherent in detention.

CONCLUSIONS

In the context of this mental illness analysed by this material, it can be concluded that the implications are from small to the most serious, reaching catastrophes, irreversible trauma and even causing the death of the victim.

From the assessment of the practical cases briefly set out in the chapter dedicated to this analysis, I have chosen to present two cases analysed at European legislative level.

Mental anorexia is therefore the consequence of eating disorders at the onset of the disease, manifested by complex disorders that require the intervention of specialists from several fields.(8)

Although, at a first analysis from a general, psychological, psychiatric and medical perspective, mental anorexia begins and presents itself as a physical disease, the main reason and causes that aggravate the phenomenon is related to mental disorders.

From the legal point of view, the consequences/risks are of the most serious, given that a person suffering from mental anorexia no longer has discernment over his actions, being in a permanent predisposition to commit acts punished by the criminal law, of the most serious ones.

The above aspect is certainly confirmed by the diversity of cases in which such persons with mental illness commit serious and particularly serious crimes, without being aware of this aspect.

From a legal point of view, in such cases, there are causes of non-imputability, i.e. of exemption from criminal legal liability, but I consider that this aspect is not of paramount importance, as essential for the case are the ways of discovering the causes of this and preventing them in all possible legal and human forms.

Among the most adequate methods of detecting, preventing and combating the phenomenon analysed from a social and legal perspective, there are: nutritional counselling, family therapy, congnitive-behavioral therapy, treatment of other conditions associated with anorexia, family support, resorting to specialized services of professional psychologists and psychiatrists.(9)

Concluding, we can state to the issue analysed in the way of perceiving and combating the subject, the fact that "no matter how hard the past is, we can always start again".

ACKNOWLEDGMENTSAND DISCLOSURE
The authors declare that they have no potential conflicts of interest to disclose.

REFERENCES

1. https://magnanews.ro/2015/06/anorexia-nervoasa-sau-frica-intensa-de-kilograme/
2. www.e-psihiatrie.ro
3. Diagnostic and statistical manual of mental disorders of the American Psychiatric Association
4. https://www.reginamaria.ro/articole-medicale/sanatatea-mintala-ce-este-si-cum-ne-dam-seama-cand-avem-nevoie-de-ajutor
5. Dute J. ECHR 2009/8 Case of Slawomir Musial v. Poland, 20 January 2009, no. 28300/06 (Fourth Section). Eur J Health Law. 2009 Jun;16(2):193-6.
6. www.scj.ro, www.echr.coe.int.
7. www.scj.ro, www.echr.coe.int.
8. Beumont P.J.V., Touyz S.W.What Kind of illness is Anorexia Nervosa? European child and teenager psychiatry.2003:12(1).
9. Lock J, Fitzpatrick K.K. The Evidenced -based Treatments for Children and Teenagers with Eating Disorders: Family Therapy and Family-facilitated Cognitive-Behavioral Therapy.Journal of Contemporary Psychotherapy.2007:53.

Correspondence:

Călin Scripcaru,
MD, PhD, professor, Institute of Forensic Medicine Iasi, calinscripcaru@yahoo.com

Submission: 19 apr 2022
Acceptance: 02 jun 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Melotherapy in stress-related illnesses

Bogdan M Tarcău, Miruna L Bîtcă, Marcel A Găină, Ioana A Halip, Adriana I Pătrașcu, Otilia A Petcuță, Laura Stătescu, Alina Stîncanu, Dan Vâță, Laura Gheucă Solovăstru

Bogdan Marian Tarcău – MD, PhD student, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania. Dermatology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania
Miruna Lorelai Bîtcă – MD, Dermatology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania
Ioana Alina Halip – MD, PhD, assistant professor, Department of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iasi, Romania
Marcel-Alexandru Găină – MD, PhD, assistant professor, Department of Psychiatry, "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iasi, Romania
Adriana Ionela Pătrașcu – MD, Dermatology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania
Otilia Andreea Petcuță – MD, Endocrinology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania
Laura Stătescu – MD, PhD, associate professor, Department of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iasi, Romania.
Alina Stîncanu – MD, Dermatology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania
Dan Vâță – MD, PhD, associate professor, Department of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iasi, Romania.
Laura Gheucă Solovăstru – MD, PhD, professor, Department of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iasi, Romania. Dermatology Clinic, "Saint Spiridon" County Hospital, Iasi, Romania

ABSTRACT

Music has proven to be more efficient than just for entertainment purposes, as music therapy has emerged as a clinical method in targeting different diseases of the mind and body. In this current review of the literature, we focus on the effects of music therapy on stress-related illnesses, such as substance use disorder, post-traumatic stress disorder, dementia, menopause, psoriasis and neurodermatitis. Addressing the psychological stress factor could prevent, alleviate, or even cure but is often overlooked in the therapeutic scheme focused on more pragmatic and rapid-acting treatments. Patients may consider psychological stress as expected in the modern era. Still, we must inform them about the long-term adverse effects of

stress and propose stress-reduction techniques. Even though counselling, cognitive behavioural therapy, hypnosis and even meditation have proven their effectiveness, music therapy appears to be a more pleasant and readily-accessible technique.

KEYWORDS:
Music therapy, stress, substance use disorder, post-traumatic stress disorder, dementia, menopause

INTRODUCTION

Music therapy, also known as melotherapy, is the clinical and evidence-based use of music in addressing different psychological and somatic disorders. It has its roots deep down in the history of humanity and is based on the ancient multicultural beliefs that listening to music could heal not only the mind but also the body. Despite its long existence, it was just the end of the nineteenth century when solid scientific evidence of the efficacy of medicine and psychology was reported and developed—the base on which melotherapy eventually and very slowly has been acknowledged as having healing properties. Everett Thayer Gaston, an American psychologist, is regarded as the "father" of music therapy through his fundamental contribution to the scientific recognition of this form of therapy during the 1940s - 1960s (1).

There is no consensus on which type of music offers the best healing results in a specific clinical setting. Several models of music therapy have been used: analytical music therapy (2), the Bonny Method of Guided Imagery and Music (3), Benenzon (4), Nordoff-Robbins (5), community music therapy (6), neurologic music therapy (7) and vocal psychotherapy (5).

Most of the clinical trials focused on the outcome of the intervention, and therefore less is known about the physiological mechanisms of melotherapy. Koelsch et al. reported five modulation factors that could explain the benefits of music therapy: attention modulation in reducing anxiety and pain during surgical procedures; emotion modulation related to affecting disorders; cognition modulation in managing Alzheimer's disease; behaviour modulation and communication modulation (8).

Studies using Positron Emission Tomography (PET) offered more scientific data to detect cerebral blood flow changes in subjects listening to different types of music. In a study from 1999, Anne Blood and colleagues (9) examined the brain responses of 10 participants who were asked to listen to music stimuli that were perceived as more or less pleasant. The suitable parahippocampal gyrus activity increased while listening to unpleasant music stimuli while listening to pleasant music stimuli correlated with increased activity in the frontopolar and orbitofrontal cortex (9). Blood and Zatorre used pleasant music stimuli until achieving "shivers down the spine", which correlated to increased brain activity in regions associated with rewards and emotion, such as the insula, orbitofrontal cortex, ventral striatum and ventral medial prefrontal cortex. In contrast, decreased brain activity was noted in the amygdala and the hippocampus (10). Amygdala dysfunction is involved in affective disorders, such as depression and pathologic anxiety (11, 12).

METHODS

This review of the literature will present the results of melotherapy on stress-related illnesses in the fields of psychiatry, neurology, endocrinology and dermatology until April 2022. The search was conducted on PubMed Central, Scopus and EMBASE databases. The information presented includes evidence from peer-reviewed journals. Due to the scarcity of scientific knowledge on melotherapy, our search included controlled trials and cohort and case-control studies, reports, systematic reviews, and meta-analyses. All patients diagnosed with substance use disorder, post-traumatic stress disorder, dementia, menopause, psoriasis and neurodermatitis were eligible, regardless of age, sex or comorbidities. We searched for articles reporting music therapy interventions without other complementary approaches, which could alter the results. Outcomes were not included as eligibility criteria. Only articles written in English were reviewed.

MELOTHERAPY AND SUBSTANCE USE DISORDERS

Substance use disorders (SUD) are a common concern in modern society, given the wide availability of alcohol, tobacco and illegal drugs on the black market. Chronic alcohol consumption was associated with a lower socio-economical level (13). However, among 468 Romanian medical and law students, 19.3% of the males and 16.2% of the females were considered heavy drinkers (5+ drinks at least twice a week) (14). A 2019 study of the general population of Romania reported the following rates of drug abuse: new psychoactive substances 6.3%, cannabis 6.1%, cocaine 1.6%, medical drugs without prescription 1.5%, ecstasy 1.0%, heroin 0.9% and LSD 0.5% (15). Stress is a well-established risk factor for the onset of SUD and contributes to its relapse (16). Given the low compliance of patients diagnosed with SUD, music therapy could prove an efficient treatment method.

According to the American Music Therapy Association (AMTA), a 2020 workforce analysis reported 160 music therapists working with patients with substance use disorders (17).

Short and Dingle (18) examined 19 patients (52.6% males; avg. age 31.1) with SUD (95% polydrug, 42% alcohol, 32% amphetamine, 11% cannabis, 5% heroin) and 19 age- and gender-matched controls who were exposed to one session of listening to sad, happy and relaxing songs. Outcomes were measured using the 7-point Scale and the Geneva Emotions in Music Scale (GEMS-9). All three types of songs were rated equally by the experimental group (EG), while the happy and relaxing songs were rated as more pleasant by the control group (CG) ($p < .01$). The arousal ratings were uniform in the EG, while in the CG, the happy songs were more arousing than the others ($p < .05$). Per the GEMS-9 ratings, the happy songs had a more powerful increase in the joyfulness of the CG vs EG ($\eta^2_p = 0.28$, $p < .01$). This study is limited by the low sample size and the lack of intervention and outcome repetition.

Out of 49 patients diagnosed with SUD and mental illnesses who were subjected to music therapy, 51% showed a decrease in anxiety, 10.2% an increase in anxiety, 42.9% decrease in anger, 2% increase in anger, 65.2% decrease in sadness, 6.1% increase in sadness – according to a 7-point visual analogue scale (19).

Hohmann et al. (20) reported in a 2017 systematic review 67% positive effects on locus of control and over 50% higher

perceived helpfulness for the intervention. Melotherapy had no benefits regarding motivation, enjoyment, depression, withdrawal and coping skills. Data on anxiety, medical symptoms and anger were insufficient evidence of efficacy.

Stress was identified as an eligibility criterion or outcome measure in only one study on 42 alcohol addicted patients, which reported decreased stress levels, depression, anxiety and anger post-intervention ($p < .01$) (21). Almost all studies are limited by reduced intervention time and lack of follow-up evaluation.

MELOTHERAPY IN VETERANS AND WAR VICTIMS

In military services, music has been used to entertain, stimulate and raise morale and reports of musicians playing to injured soldiers date back to the American Civil War (22). In a 2017 study on 5826 American veterans, 12.9% suffered from post-traumatic stress disorder (PTSD), while the PTSD rates in the American general population average 6.8% (23).

In a 2019 scoping review, Gooding et al. reported that PTSD, shell shock, traumatic brain injury, military sexual trauma, moral injury, stress and physical injuries were addressed through music therapy (24). The interventions were primarily represented by active music-making, especially drumming, but music listening, therapeutic singing, group music-making and Guided Imagery in Music techniques were also used.

Seventeen patients with significant PTSD symptoms who did not respond to cognitive behavioural therapy were divided into an EG (n=9) and a CG (n=8) (25). The EG was assigned to a 10-week group music therapy intervention. The symptoms were assessed at the beginning and end of the intervention through the Impact of Events Scale-Revised and Beck Depression Inventory-II. After the intervention, the EG recorded a significant reduction in the severity of PTSD symptoms (-20.18; 95% confidence interval [CI]: [−31.23, −9.12]). Regarding depression, only a marginally significant reduction was recorded (−11.92; 95%CI: [−24.05, 0.21]) (25). The results are limited by the low sample size, the study's unblinded nature, and the lack of post-intervention follow-up.

Individual reports of successful music therapy delivered through telehealth systems could address the insufficient number and overall availability of trained music therapists, especially in war zones (26).

Beck et al. (27) conducted a randomized controlled trial on 74 danish refugees who have PTSD who were allocated either to music therapy sessions (n=39) or psychological treatment (n=35). Western classical music, new age music and music from the subject's cultural backgrounds were used. Trauma symptoms were measured by the Harvard Trauma Questionnaire (HTQ), well-being by WHO-Well being index (WHO-5) and somatoform and psycho form dissociation by the Dissociative Symptoms Scale (DSS-20). Regarding the trauma symptoms, music therapy proved to be significantly non-inferior to the psychological treatment, not only at the end of the study (PP analysis difference 0.07; CI -.29; .15) but also at six months follow-up (PP analysis difference 0.16; CI -.07; .38). At six months, 12 subjects reported remission of PTSD, 10 in the music group and 2 in the psychological group (p=.185). The music group also recorded a significant decrease in mean values

of DSS-20 and an increase of WHO-5 at the end of the intervention (p=.005) and follow-up (p=.004) (27).

MELOTHERAPY AND MEMORY DISORDERS

Dementia represents the loss of cognitive functioning to such an extent that it interferes with a person's daily life and activities. There are several different forms of dementia, including Alzheimer's disease, the most common type of dementia (28). Worldwide 36 million people are estimated to live with dementia, and this number is rapidly increasing (29).

There is a range of symptoms known as „behavioural and psychological symptoms of dementia" (BPSD) that can affect up to 90% of patients with dementia during the disease course (30). BPSD include many different behaviours such as screaming, restlessness, repetitive questions, wandering and apathy. Although there is no effective treatment or proven prevention for Alzheimer's and related dementias, in general, taking care of your mental health may help lower one of the risk factors that have been associated with these diseases: chronic stress (30).

According to the 2018 AMTA Member Survey and Workforce Analysis, the work settings with the highest number of music therapists are geriatric facilities (31).

In a study by Satoh et al. (32), ten patients with Alzheimer's disease (mean age 78.1 years) participated in music therapy once a week for six months, and another ten patients were part of the CG. Before and after the intervention, each patient was assessed with neuropsychological batteries, and functional magnetic resonance imaging (fMRI) was performed. In the EG, the subjects completed the Japanese Raven's Colored Progressive Matrices significantly faster (p= .026), and the results obtained from interviewing the patients' caregivers revealed a significant decrease in the Neuropsychiatric Inventory score (p= .042) and a prolongation of the patients' sleep time (p= .039). The fMRI study revealed increased activity in the right angular gyrus and the left lingual gyrus (32).

Sung et al. (33) studied the effects of group music therapy in elderly patients diagnosed with dementia. A selection of songs familiar to the patients was used for the 30 minute-music therapy sessions, twice a week for six weeks. Participants in the control group received routine care. Results indicated that music intervention significantly reduced anxiety (p= .004) (33).

Svansdottir and Snaedal (34) investigated the effect of music therapy in a case-control study in a sample of 38 patients diagnosed with dementia and reported significant improvement in aggressiveness and anxiety. The active intervention consisted of 18 music therapy sessions (30 minutes/ session, x3/ week, six weeks). The authors concluded that music therapy significantly reduced agitation and anxiety (p=.02) in moderate and severe dementia (34).

Music therapy can be considered a non-pharmacological intervention that has the potential to reduce cognitive decline, improve neuropsychiatric symptoms, and enhance the quality of life in dementia patients.

MELOTHERAPY AND MENOPAUSE

Menopause is the permanent cessation of menstrual periods that occurs naturally or is artificially induced through chemotherapy,

surgery or radiation (35). Due to the hormonal changes, menopause is accompanied by several physical burdens. The vasomotor symptoms are the most common and distressing, causing hot flashes, cold sweats and night sweats (36). The menopause symptoms were aggravated in frequency and severity by psychological stress (37). However, the exact underlying pathophysiological mechanisms are unclear (38).

In a small comparative study, Bhave et al. (39) investigated the effects of music therapy on 30 menopausal women who scored at least 13 on the Cohen-Perceived Stress Scale (CSS). The music therapy sessions consisted of alpha wave music, sounds of rippling water and acoustic songs, delivered for 30 minutes/ session, three sessions/ week, eight weeks in total. Distress in subjects was assessed through the CSS and the Quality of Life Scale (QoLS). Pre-intervention mean CSS was 17.7 ± 2.08 SD vs 12.03 ±1.90 SD post-intervention, resulting in a significant difference in CSS of 5.67 ($p < .0001$). The difference between pre-and post-intervention QoLs means was 19.1 ($p < .05$) (39). This study has a significant statistic level but lacks a control group and follow-up evaluation.

Koçak and Varışoğlu (40) carried out a randomized-controlled study on 48 postmenopausal women (21 EG and 27 CG). The intervention group was assigned to a music therapy programme of 18 sessions over six weeks. Data were collected using the Beck Depression Inventory (BDI) and Menopause Rating Scale (MRS). The authors reported a significant decrease in BDI and MRS in the EG ($p=0.036$) (40).

Twenty-three menopausal women were assigned to a music therapy intervention (60 minutes/ session, three sessions/ week, two weeks) and evaluated pre-and post-intervention through the Menopause-Specific Quality of Life questionnaire (MENQoL) (41). Pre-test MENQoL was 23.57 ± 4.35 SD vs post-test 16.00 ± 2.57 SD, with a significant mean difference of 7.56 ± 2.93 SD ($p < .001$). This study has a significant statistic level, but the music intervention is insufficiently described, and it lacks a control group and follow-up evaluation of the effects of the intervention.

Mo and Jang (42) measured the effects of a music therapy intervention on 25 peri-menopausal women. The subjects were asked to listen to 10 classical music pieces and two preferred songs for 30 minutes before going to bed at least five times/week for four weeks. The authors performed pre-and post-intervention assessments of depression through the Center for Epidemiologic Studies Depression Scale (CES-D) and quality of life using the Quality of Life Scale. The EG recorded a decrease in the depression score from 1.34 to 0.92 ($t=6.84$, $p<.001$) and an increase in the quality of life score from 2.49 to 3.09 ($t=10.57$, $p<.001$), while no difference was recorded in the CG (42).

MELOTHERAPY IN PSORIASIS AND NEURODERMATITIS

Psoriasis is a common chronic inflammatory skin condition characterised by a high physical and psychological burden with 20% suicidal ideation (43). Psychological stress is a well-established risk factor for the onset, aggravation and relapse of psoriasis (44).

Neurodermatitis (lichen simplex chronicus) is a neurological localised skin disorder characterised by chronic itching and

scratching, highly influenced by psychological stress (45).

Lazaroff and Shimshoni (46) investigated the effects of Medical Resonance Therapy Music on 28 neurodermatitis and 20 psoriasis patients. In comparison, the CG consisted of 10 neurodermatitis and ten psoriasis patients who were instructed to relax by any means. After 14 days of music therapy, the degree of the sickness of the psoriasis EG was reduced by 65% (vs 20% CG), while in the neurodermatitis EG a decrease of 41% was recorded (vs 12% CG). The urge to scratch was reduced by 86% in the psoriasis EG (vs 29% CG) and 59% in the neurodermatitis EG (vs 14% CG). Lower heart rate and blood pressure were recorded post-intervention in both study populations (46).

This is the only study of music therapy on psoriasis or neurodermatitis; Its scientific value is highly arguable due to the lack of statistical data, standardized disease severity assessment scores, inconsistent experimental vs control groups, and low sample size and no follow-up.

CONCLUSIONS

The scientific evidence behind music therapy is slowly growing as we acknowledge the critical role of psychological stress in different physical and mental illnesses. In western Europe and the United States of America, music therapy is well-established as an alternative method in the holistic treatment of the patient, and more effort should be put into promoting it in Romania. However, the efficacy of music therapy varies from one disease to another, and more qualitative research is needed.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors declare that they have no conflicts of interest to disclose.

REFERENCES

1. Gaston, E. Thayer. Music in Therapy. New York: Macmillan, 1968.
2. Bruscia, Kenneth E. Defining Music Therapy (3 ed.). University Park, IL: Barcelona Publishers, 2014. p.230.
3. Wheeler, Barbara L. "Part II: Orientations and approaches". Music Therapy Handbook. New York: The Guilford Press, 2017. pp. 129–132.
4. Knight, Andrew; LaGasse, Blythe; Clair, Alicia. Music therapy: An introduction to the profession. Silver Spring, 2018. pp. 56-62.
5. Wheeler, Barbara L. "Part II: Orientations and approaches". Music Therapy Handbook. New York: The Guilford Press, 2016. pp. 129–170.
6. Stige, Brynjulf. "Community Music Therapy". In Wheeler, Barbara L. (ed.). Music Therapy Handbook. New York: The Guilford Press, 2017. pp. 233–245.
7. Hurt-Thaut, Corene P.; Johnson, Sarah B. "Neurologic Music Therapy". In Wheeler, Barbara L. (ed.). Handbook of Music Therapy. New York: The Guilford Press, 2017. pp. 220–232.
8. Koelsch, S. A Neuroscientific Perspective on Music Therapy. Annals of the New York Academy of Sciences, 1169(1), 2019. 374–384.
9. Blood, A. J., Zatorre, R. J., Bermudez, P., & Evans, A. C. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nature Neuroscience, 1999. 2(4), 382–387.
10. Blood, A. & R.J. Zatorre. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc. Natl. Acad. Sci. USA, 2001. 98: 11818–11823.
11. Stein, M.B., A.N. Simmons, J.S. Feinstein & M.P. Paulus. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am. J. Psychiatry, 2007. 164: 318–27.
12. Drevets, W.C., J.L. Price, M.E. Bardgett, et al. Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. Pharmacol. Biochem. Behav. 2002. 71: 431–447.

13. Collins SE. Associations Between Socioeconomic Factors and Alcohol Outcomes. Alcohol Res. 2016. 38(1):83-94.

14. Nasui BA, Popa M, Popescu CA. Drinking Patterns and Behavioral Consequences: A Cross-Sectional Study among Romanian University Students. Zdr Varst. 2015. 55(1):59-66.

15. National Antidrug Agency Romania, „Prevalenţa consumului de droguri în România. Principalele rezultate ale studiului în populaţia generală 2019.", 2019, available at: http://ana.gov.ro/wp-content/uploads/2020/09/GPS-2019.pdf.

16. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 2008. 1141:105-130.

17. American Music Therapy Association. „2020 workforce analysis". 2020. Available at https://www.musictherapy.org/assets/1/7/2020Wor kforceAnalysis.pdf.

18. Short AD, Dingle GA. Music as an auditory cue for emotions and cravings in adults with substance use disorders. Psychol Music. 2015. 559–573.

19. Gardstrom SC, Bartkowski J, Willenbrink J, Diestelkamp WS. The impact of group music therapy on negative affect of people with co-occurring substance use disorders and mental illnesses. Music Ther Perspect. 2013. 31: 116–126.

20. Hohmann L, Bradt J, Stegemann T, Koelsch S. Effects of music therapy and music-based interventions in the treatment of substance use disorders: A systematic review. PLoS ONE, 2017. 12(11): e0187363.

21. Hwang E-Y, Oh S-H. A comparison of the effects of music therapy interventions on depression, anxiety, anger, and stress on alcohol-dependent clients: A pilot study. Music Med. 2013. 5: 136–144.

22. Sullivan, J. M. Music for the injured soldier: A contribution of American women's military bands during World War II. Journal of Music Therapy, 2007. 44, 282– 305.

23. Müller J, Ganeshamoorthy S, Myers J. Risk factors associated with posttraumatic stress disorder in US veterans: A cohort study. PLoS One. 2017;12(7):e0181647.

24. Gooding, L. F., & Langston, D. G. Music Therapy With Military Populations: A Scoping Review. Journal of Music Therapy, 2019.

25. Carr, C., d'Ardenne, P., Sloboda, A., Scott, C., Wang, D. and Priebe, S, Group music therapy for patients with persistent post-traumatic stress disorder – an exploratory randomized controlled trial with mixed methods evaluation. Psychology and Psychotherapy: Theory, Research and Practice, 2012. 85: 179-202.

26. Vaudreuil, R., Langston, D. G., Magee, W. L., Betts, D., Kass, S., & Levy, C.. Implementing music therapy through telehealth: considerations for military populations. Disability and Rehabilitation: Assistive Technology, 2020. 1–10.

27. Beck BD, Meyer SL, Simonsen E, Søgaard U, Petersen I, Arnfred SMH, Tellier T, Moe T. Music therapy was noninferior to verbal standard treatment of traumatized refugees in mental health care: Results from a randomized clinical trial. Eur J Psychotraumatol. 2021 Jul 6. 12(1):1930960.

28. Fang, R., Ye, S., Huangfu, J., Calimag, D. Music therapy is a potential intervention for cognition of Alzheimer's disease:a mini review. Translational Neurodegeneration, 2017. 6:2.

29. Alzheimer's Disease International: World Alzheimer Report 2012. Available at https://www.alzint.org/u/WorldAlzheimerReport2012.pdf.

30. National Institute on Aging: What is Dementia? Available at https://www.nia.nih.gov/health/what-is-dementia.

31. American Music Therapy Association, Inc. (2018). Member survey and workforce analysis. Available at https://www.musictherapy.org/assets/1/7/18WorkforceAnalysis.pdf

32. Satoh M, Yuba T, Tabei K, Okubo Y, Kida H, Sakuma H, et al. Music therapy using singing training improves psychomotor speed in patients with Alzheimer's disease: a neuropsychological and fMRI study. Dement Geriatr Cogn Dis Extra, 2015. 5:296–308.

33. H.-C. Sung, W.-L. Lee, T.-L. Li, and R. Watson, "A group music intervention using percussion instruments with familiar music to reduce anxiety and agitation of institutionalized older adults with dementia," International Journal of Geriatric Psychiatry, vol. 27, no. 6, 2012. pp. 621–627.

34. H. B. Svansdottir and J. Snaedal, "Music therapy in moderate and severe dementia of Alzheimer's type: a case–control study," International Psychogeriatrics, vol. 18, no. 4, 2016. pp. 613–621.

35. WHO. Research on the menopause in the 1990s. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1996: 866: 1–107.

36. Avis NE, Brockwell S, Colvin A. A universal menopausal syndrome? Am J Med. 2005;118 Suppl 12B:37–46.

37. Arnot M, Emmott EH, Mace R. The relationship between social support, stressful events, and menopause symptoms. PLoS One. 2021;16(1):e0245444.

38. Falconi AM, Gold EB, Janssen I. The longitudinal relation of stress during the menopausal transition to fibrinogen concentrations: results from the Study of Women's Health Across the Nation. Menopause. 2016;23(5):518–27.

39. Bhave, Devika, et al. "Effect of Yoga and Music Therapy for Stress Management in Menopausal Women: a comparative Study.", Internation Journal of Yoga and Allied Sciences, Vol.7, 1; 2018

40. Koçak, Derya Yüksel; Varışoğlu, Yeliz. The effect of music therapy on menopausal symptoms and depression, Menopause: January 24, 2022

41. Deshpande, Shruti, et al. "A Community Survey on Effect of Step Aerobic Exercises and Music Therapy on Mental Health in Menopausal Women." Journal of medical pharmaceutics and allied sciences. 2021. 10 (4), p. 1306.

42. Mo, Moon-Hee, and Hee-Jung Jang. "Effect of the Music Therapy for Peri–menopausal Women.". International Journal on Consulting Psychology for Patients. 2018.

43. Krueger G, Koo J, Lebwohl M et al. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patientmembership survey. Arch Dermatol 2001. 137: 280–284.

44. Rousset L, Halioua B. Stress and psoriasis. Int J Dermatol.2018. 57:1165-72

45. Nagarale, Vivekkumar Ashok, et al. "Psoriasis and neurodermatitis: comparing psychopathology, quality of life and coping mechanisms." International Journal of Advances in Medicine. 2017. 4.1: 238.

46. Lazaroff I, Shimshoni R. Effects of Medical Resonance Therapy Music on patients with unipsoriasis and neurodermatitis--a pilot study. Integr Physiol Behav Sci. 2000 Jul-Sep; 35(3):189-98.

Correspondence

Otilia Andreea Petcuță,

MD, Endocrinology Clinic, “Saint Spiridon” County Hospital, Bd. Independentei, nr. 1, Iasi, Romania, otilia.petcuta@yahoo.com

Submission: 29 mar 2022

Acceptance: 30 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Recent developments in Parkinson's disease psychosis: a systematic review

Ovidiu Alexinschi, Emanuel-Andrei Sirițeanu, Cristina Elena Nedelcu

Ovidiu Alexinschi - MD, PhD, senior psychiatrist, Institute of Psychiatry "Socola", Iasi, Romania.
Emanuel-Andrei Sirițeanu - residency training in psychiatry, Institute of Psychiatry "Socola", Iasi, Romania.
Cristina Elena Nedelcu - clinician psychologist, Institute of Psychiatry "Socola"

ABSTRACT

Parkinson's disease represents a chronic neurodegenerative process that impairs the dopaminergic neurons in substantia nigra pars compacta and the nigrostriatal tracts. This causes a hypodopaminergic status responsible for the motor symptoms of Parkinson's disease (tremor, rigidity, akinesia, postural instability and gait difficulty). Clinicians have also observed non-motor symptoms of Parkinson's disease (psychotic disorders, neurocognitive disorders, affective disorders, anxious disorders, sleep disorders). Psychotic features of Parkinson's disease are a prominent prognostic factor which can affect the patients' quality of life. Visual hallucinations are the most common symptom, followed by minor hallucinations, illusions, auditory hallucinations, olfactive hallucinations, tactile hallucinations and gustatory hallucinations. Delusions, albeit rare, contribute to the severity index of Parkinson's disease psychosis. Therapy must follow some general rules, with treatment of comorbidities, reduction of antiparkinsonian drugs and usage of antipsychotics. The first FDA approved antipsychotic for Parkinson's disease psychosis is Pimavanserin. It is a highly efficient drug that reduces psychotic symptoms without exacerbating motor symptoms and relatively few side effects. Other options are represented by atypical antipsychotics such as Clozapine and Quetiapine, each with its own clinical attributes and limitations.

KEYWORDS:
Parkinson's disease, psychosis, treatment

INTRODUCTION

First described as the shaking palsy („Paralysis agitans") by James Parkinson at the beginning of the 19th century, Parkinson's disease (PD) represents a chronic neurodegenerative disease that was initially presumed to be strictly comprised only of

motor symptoms (1). This disorder progresses unappeasable, damaging the dopaminergic neurons in substantia nigra pars compacta and the nigrostriatal tracts, thus diminishing the levels of dopamine. This hypodopaminergic status is liable not only for the conventional motor symptoms of PD, but also for a collection of symptoms called non-motor (Tab. 1) (2,3,4). Non-motor features of PD consist of psychotic symptoms, neurocognitive disorders, affective disorders, anxious disorders, sleep disorders, delirium, and impulse control disorders (2).

Tab. 1 Motor and non-motor symptoms of PD

Motor symptoms	**Non-motor symptoms**
Tremor	Psychotic features
Rigidity	Neurocognitive disorders
Bradykinesia/Akinesia	Sleep disorders
Postural instability with gait difficulty	Autonomic dysfunction

There isn't a well-defined consensus regarding Parkinson's disease psychosis (PDP) diagnostic criteria. Standard ICD 11 and DSM-V-TR evaluation would appoint it under the Secondary Psychotic Syndrome (6E61). In 2007, Ravina et al. designated the diagnostic criteria for PDP through the joint NINDS-NIMH (The National Institute of Neurological Disorders and Stroke and National Institute of Mental health) work group as the presence of psycho-productive phenomena (hallucinations, delusions, illusions and minor hallucinations with false sense of passage or presence) for one month or recurrent symptoms, with the exclusion of other possible etiology (5,6,7).

MATERIAL AND METHODS

This article aims at appraising the clinical symptoms, risk factors and treatment for PDP, making a critical analysis of the most frequent features and treatment documented for this disorder. For this study, we have assessed a number of 26 articles (systematic reviews) regarding the characteristics of PDP, published between 2014-2022 on PubMed and Embase. Key words include: Parkinson's disease, psychosis, hallucinations, delusion, antipsychotics, pimavanserin, clozapine.

RESULTS

Epidemiology

As the second most frequent neurodegenerative disorder after Alzheimer disease, it is estimated that there are over 10 million cases worldwide, 20% being diagnosed under the age of 65. This draws a heavy toll on the health department, with expenses of billions of dollars each year (2, 3, 8).

Up to 60% of patients with PD may develop psychotic criteria (3,8). PD dementia may also be associated with psychotic features (up to 75% of patients) (8).

PDP has a significant impact on the quality of life of patients, considerable health care costs and a higher risk of care home placement (5,9). These subjects are prone to depression and major neurocognitive disorder, earlier institutionalization, with increased morbidity and mortality rates (10, 11). The family also suffers alongside the patient, chronic stress

leading to anxiety and unipolar mood disorders (10).

From a neurological (motor) point of view, there are two major clinical phenotypes in PD, tremor dominant and non-tremor dominant (12). The non-tremor dominant phenotype (postural instability disorder with gait difficulty, rigid-akinetic, dyskinetic) is more frequently associated with psychotic features and neurocognitive deterioration (6,13).

The classic positive symptoms described in psychotic disorders can also be observed in PDP and are associated with a poor prognosis and a higher risk of morbidity and mortality (4,8). Sleep disorders and hyposmia have been observed as prodromal symptoms, even before the motor symptoms emerge (14). Life expectancy is a decisive factor for the escalating incidence of PD. It is estimated that over half of the patients diagnosed with PD will develop over the course of the illness hallucinations (especially visual), illusions, thought disorders and delusions (9,15).

Etiology, risk factors and rating scales

It is rather difficult to ascertain the precise etiology of PDP. The natural course of PD is marked by a neurodegenerative process that involves the deposition of α-sinuclein and a loss of dopamine neurons (16). This mechanism presumably coupled with PD medication and other diseases (including psychiatric co-morbidities) can be responsible for the development of psychotic features (Fig. 1) (17).

Since antiparkinsonian drugs act as D_2 agonists, they may reveal an underlying psychotic event (18). The first step that must be taken into account is the dose reduction of antiparkinsonian drugs. The clinician must be aware that this will aggravate the motor symptoms (15).

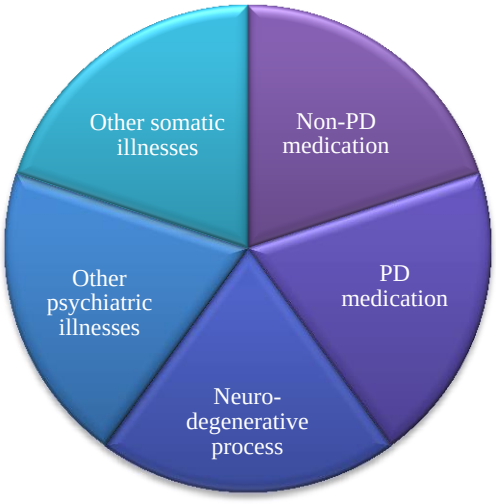

Fig. 1 Etiology of PDP (after Martinez-Ramirez et al., 2016)

Some etiologies are reversible (metabolic, infectious, traumatic, medication side effects, psychoactive substances), hence the clinician should actively evaluate the patient and treat accordingly to the cause (5). Risk factors associated with PDP are depicted in Table 2.

Tab. 2 Risk factors for PDP

Antiparkinsonian drugs
Severe/long term PD
Neurocognitive impairment
Visual impairment
Hyposmia
Sleep disorders (including REM sleep disorder)
Depression/anxiety
Postural instability with gait difficulty
Autonomic dysfunction
Elderly
Females
Polypharmacy
Negative life events

The severity of PDP is appraised with different rating scales, most often MDS-UPDRS I (Movement Disorder Society's Unified PD Rating Scale section I), NPI (Neuropsychiatric Inventory), SEND-PD (Scale for Evaluation of Neuropsychiatric Disorders in PD) and PPQ (Parkinson's Psychosis Questionnaire). MDS-UPDRS section I item 1.2 ask specifically about hallucinations and psychosis, while the other three sections represent and area of interest for neurologists (19).

Psychotic symptoms in PDP consist of visual hallucinations (the most frequent psychotic symptom recognized in PDP), minor hallucinations, auditory hallucinations, olfactory hallucinations, tactile hallucinations, gustatory hallucinations and delusions (Tab 3) (11).

Visual hallucinations are connoted to be generated by a low activation of DAT seen in the ventral striatum and the right caudate nucleus (9).

Tab. 3 *Psychotic features of PDP*

Hallucinations	Minor
	Visual
	Auditory
	Olfactory
	Tactile
	Gustatory
Delusions	Persecutory
	Grandiose
	Cotard Syndrome
	Capgras Syndrome
	Othello Syndrome

Minor hallucinations consist of passage and presence hallucinations, hallmarks of PDP (11). Visual hallucinations are on a continuum of psycho-productive phenomena with minor hallucinations (20).

Delusions are not specific for PDP, but suggest a poor prognosis with a higher severity index (8,21). Most often, delusion are non-bizarre (10).

Tab 4 Prevalence of hallucinations

Hallucinations	**Prevalence (%)**
Minor	25.5-72
Visual	22-38
Auditory	22-48
Olfactive	~10
Tactile and Gustatory	Limited cases, very rare.

Antiparkinsonian drugs can trigger or exacerbate visual hallucinations. This symptom can impact the patients' quality of life, with an elevated risk of care home placement and mortality (20).

General treatment measures of PDP

Treatment must follow six essential steps. First the clinician and the patient must ensure a stable environment, with normal level sensory stimulus, a proper diet and sleep hygiene. Afterwards, any comorbidity must be attended before changing medication. There are categories of drugs that must be discontinued in order to prevent the emergence of psychotic features, for example anticholinergics and sedatives (11). PD medication must be reduced in a specific order, as presented in Table 5. If the step down in antiparkinsonian drugs is not sufficient, judicious use of antipsychotics must be considered (3). Neuroleptics have been demonstrated to pose a higher risk of mortality when used by PD patients (22).

Tab 5 General treatment approach

General measures	Sleep hygiene, exposure to normal level sensory stimulus, psycho-protective environment
Treatment of co-morbidities	Infection, dyselectrolytemia, trauma, SuD
Non-PD medication	Discontinue anticholinergics, antidepressants, sedatives
PD medication	Reduce in this order: 1. Anticholinergics 2. Amantadine 3. MAO-B-Inhibitors 4. Dopamine Agonists 5. COMT-Inhibitors 6. L-DOPA Retard 7. L-DOPA NonRetard
CheI for neurocognitive impairment	Rivastigmine, Donepezil
Antipsychotics	Clozapine, Pimavanserin, Quetiapine

CheI, cholinesterase inhibitors; COMT, catechol-ortho-methyltransferase; MAO-B, monoamine oxidase B; SuD substanse use disorders

Antipsychotics

The first FDA approved (29 April 2016) antipsychotic targeted for PDP is Pimavanserin as a first line drug (5,15,23,24). The mechanism of action is represented by partial inverse agonist and selective antagonist at 5-HT_{2A} and 5-HT_{2C} , with no affinity for adrenergic, muscarinic, or histaminergic receptors (5, 15, 21, 23, 24). No D_2 antagonism has been observed (2). AC-279 (the active metabolite of Pimavanserin) has a half time of 200 hours (24). There have been reported less side effects compared with the atypical antipsychotics, but it takes up to 6 weeks for Pimavanserin to make noticeable improvements psycho-productive phenomena (15). It has a high efficacy in reduction of hallucinations, delusions and thought disorder (8,23). A trial of a minimum of 4 weeks of Pimavanserin must be assessed before changing to another neuroleptic (Quetiapine or Clozapine) with a dose of 17-34mg/day for a proper assessment of efficacy (Black, 2017). If the side effects are tolerable and the price manageable, Pimavanserin should be continued. Pimavanserin can be associated with Quetiapine for a higher antipsychotic efficacy in case of resistant PDP, but QTc must be evaluated (23). About 30% of patients treated with Pimavanserin need augmentation with another antipsychotic (8). Pimavanserin has a high efficacy and relatively low side effects, with no exacerbation on movement disorders (1, 21, 22, 24).

Tab. 6 Antipsychotics used for PPD

Antipsychotic	**Mechanism of action**	**Dose (/day)**	**Efficacy**	**Motor symptoms**
Pimavanserin	Partial inverse agonist /antagonist 5-HT_{2A}, 5-HT_{2C}	17-34 mg	High efficacy	Not exacerbated
Clozapine	Antagonist D_4>D_2, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, $M_{1,3}$	6,25-150 mg	High efficacy	Not exacerbated / minimum
Quetiapine	Antagonist 5-HT_2, $D_{1,2}$, α_1, H_1, $M_{1,3}$, partial agonist 5-HT_{1A}	25-150 mg	Relative efficacy	Exacerbated
Olanzapine	Antagonist D_2, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1,	2,5-15 mg	Low efficacy	Exacerbated

Clozapine can be used in low doses (25-50mg/day) for PDP (24). Usually there are no exacerbation of motor symptoms with Clozapine, with a good response in diminishing hallucinations and delusions (3,15,23). Because of the risk of agranulocytosis (0,3-1,3%) and ensuing infections, a complete blood count must be checked weekly for the first six months, and monthly afterwards (1,23,24). Clozapine has proved to be superior antipsychotic in comparison to Pimavanserin and Quetiapine, although with an increased risk of adverse effects (15). Some authors consider Clozapine as the best antipsychotic in terms of reduction

of psychotic symptoms, with minimum impact on motor disturbance (15,21).

Quetiapine is the most frequently used antipsychotic for PDP. Due to its low antagonism at D_2, there are secondary benefits on the long term (22). Quetiapine dose range from 25-150 mg, but can increase up to 600 mg/day (1). If there are no clinical improvements in the trial with Quetiapine, Clozapine should be considered. Quetiapine does not influence UPDRS and has a positive outcome on visual hallucinations (23). It is a well tolerated psychotropic drug, with no to minimum motor exacerbation, but not as efficient in diminishing psychotic symptoms (21).

Olanzapine is not a preferred choice for PDP because of the relative low efficacy as an antipsychotic in this population, elevated risk of motor symptoms and cardiometabolic repercussions. Other antipsychotics (Aripiprazole, Risperidone, Ziprasidone) have not been observed as effective in PDP, and they usually exacerbate motor symptoms (15,23).

Antipsychotics side effects

As with other psychopharmacological drugs, a risk-benefit ratio must be appraised.

Reported side effects of Pimavanserin are postural instability, oedema, sleep disorders, sedation, nausea, QTc prolongation, worsening parkinsonism, confusion, headaches, with no metabolic or haematologic influence (2,3,8,23).

Atypical antipsychotics can have a negative outcome the motor symptoms because of D_2 antagonism, and they pose a high risk of development of metabolic syndrome (obesity, diabetes mellitus, arterial hypertension and dyslipidemia) (5).

Clozapine, although an effective treatment for PDP has an controversial safety profile with the risk of agranulocytosis, hypotension, sedation, metabolic syndrome, myocarditis, sialorrhea (3,21).

Quetiapine can cause orthostatic hypotension, sedation, insomnia, headache, increased risk of falling, but it has a better tolerability profile than Clozapine (22,23).

Treatment adherence can be an issue. Patients on Quetiapine tend to have a low compliance because of side effects reported, whilst patients on Pimavanserine declare that the efficacy is not adequate (22).

Major neurocognitive disorder

One vital risk factor for PDP is neurocognitive impairment and vice-versa (since PDP predisposes patients to dementia) (6,8). There have been observed impairments in the executive, attention, memory, visuospatial and visuoperceptual functions in major neurocognitive disorder associated with PDP (Tab 7) (6).

Most curious, the perceptual distortions in PDP (hallucinations) have been linked to neurocognitive decline. Such correlation has not been demonstrated in the case of delusions (11).

Tab. 7 Neurocognitive impairment in PDP

Attention and memory deficits (language, visual and verbal memory)
Visuospatial and visuoperceptual dysfunction
Executive dysfunction

A characteristic of Lewy Body Dementia is the presence of visual hallucinations, as a consequence of low levels of acetylcholine in the temporoparietal cortex. Such neurobiochemical alterations have not been noted in PD, even though the same symptom is prominent in PDP (25).

Patients with Parkinson's disease dementia or Lewy Body dementia must be treated with Cholinestarese Inhibitors (Rivastigmine, Donepezil, Galantamine) as first line treatment. This class of drugs has proven to be effective not only for delaying the neurodegenerative process, but also for the reduction of psychotic symptoms. Antipsychotics can also be used (Quetiapine, Pimavanserin, Nelotanserin) (2, 22).

There is an elevated risk of mortality in the elderly population diagnosed with major neurocognitive disease associated with psychotic symptoms under treatment with antipsychotics (3).

CONCLUSIONS

In synthesis, Parkinson's disease psychosis can have a negative impact on the quality of life and socio-occupational functioning of the patient. It also poses an increased risk of mortality for this category. It is difficult to prove the exact etiology of Parkinson's disease psychosis, most frequently involved being the continuous neurodegenerative process with deposition of α-sinuclein and antiparkinsonian drugs.

Nevertheless, further studies must be realized in order to determine the precise pathophysiology underlying this disease and optimal therapy.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors declare that they have no conflicts of interest to disclose.

REFERENCES

1. Black, K. J. (2017). Treatment of Parkinson's disease psychosis. Medicina Internacia Revuo, 27(109), 266–271.
2. Doral Fredericks, P., James C. Norton, P., Carolyn Atchison, Ms., Robert Schoenhaus, P., Michael W. Pill, P. (2017). Parkinson's Disease and Parkinson's Disease Psychosis: A Perspective on the Challenges,Treatments, and Economic Burden. https://www.ajmc.com/view/parkinsons-disease-and-parkinsons-disease-psychosis-a-perspective-on-the-challenges-treatments-and-economic-burden-article
3. Zhang, H., Wang, L., Fan, Y., Yang, L., Wen, X., Liu, Y., Liu, Z. (2019). Atypical antipsychotics for Parkinson's disease psychosis: A systematic review and meta-analysis. Neuropsychiatric Disease and Treatment, 15, 2137–2149.
4. Dominic H. Ffytche, Dag Aarsland. (2017). Psychosis in Parkinson's Disease | Elsevier Enhanced Reader.
5. Dashtipour, K., Gupta, F., Hauser, R. A., Karunapuzha, C. A., Morgan, J. C. (2021). Pimavanserin Treatment for Parkinson's Disease Psychosis in Clinical Practice. Parkinson's Disease, 2021, 2603641.
6. Lenka, A., Hegde, S., Arumugham, S. S., Pal, P. K. (2017). Pattern of cognitive impairment in patients with Parkinson's disease and psychosis: A critical review. Parkinsonism Related Disorders, 37, 11–18.
7. Ravina, B. et al (2007). Diagnostic criteria for psychosis in Parkinson's disease: Report of an NINDS, NIMH Work Group. Movement Disorders, 22, 1061–1068.
8. Sellers, J., Darby, R. R., Farooque, A., Claassen, D. O. (2019). Pimavanserin for Psychosis in Parkinson's Disease-Related Disorders: A Retrospective Chart Review. Drugs Aging, 36(7), 647–653.
9. Dave, S., Weintraub, D., Aarsland, D., ffytche, D. H. (2019). Drug and Disease Effects in Parkinson's Psychosis: Revisiting the Role of Dopamine. Movement Disorders Clinical Practice, 7(1).
10. Naasan, G., Shdo, S. M., Rodriguez, E. M., Spina, S., Grinberg, L., Lopez, L., Karydas, A. et al. (2021). Psychosis in neurodegenerative disease: Differential patterns of hallucination and delusion symptoms. Brain, 144(3), 999–1012.
11. Taddei, R. N., Cankaya, S., Dhaliwal, S., Chaudhuri, K. R. (2017). Management of Psychosis in Parkinson's Disease: Emphasizing Clinical Subtypes and Pathophysiological Mechanisms of the Condition. Parkinson's Disease, 2017, 3256542.
12. Vascellari, S., Melis, M., Palmas, V., Pisanu, S., Serra, A., Perra, D., Santoru, M. L., Oppo, V. et al(2021). Clinical Phenotypes of Parkinson's Disease Associate with Distinct Gut Microbiota and Metabolome Enterotypes. Biomolecules, 11(2), 144.

13. Hinkle, J. T., Perepezko, K., Bakker, C. C., Broen et al(2017). Onset and Remission of Psychosis in Parkinson's Disease: Pharmacologic and Motoric Markers. Movement Disorders Clinical Practice, 5(1), 31–38.
14. Brigo, F., Erro, R., Marangi, A., Bhatia, K., Tinazzi, M. (2014). Differentiating drug-induced parkinsonism from Parkinson's disease: An update on non-motor symptoms and investigations. Parkinsonism & Related Disorders, 20(8), 808–814.
15. Iketani, R., Furushima, D., Imai, S., Yamada, H. (2020). Efficacy and safety of atypical antipsychotics for psychosis in Parkinson's disease: A systematic review and Bayesian network meta-analysis. Parkinsonism & Related Disorders, 78, 82–90.
16. Hijaz, B. A., Volpicelli-Daley, L. A. (2020). Initiation and propagation of α-synuclein aggregation in the nervous system. Molecular Neurodegeneration, 15(1), 19.
17. Martinez-Ramirez, D., Okun, M. S., Jaffee, M. S. (2016). Parkinson's disease psychosis: Therapy tips and the importance of communication between neurologists and psychiatrists. Neurodegenerative Disease Management, 6(4), 319–330.
18. Waddington, J. L. (2020). Psychosis in Parkinson's disease and parkinsonism in antipsychotic-naive schizophrenia spectrum psychosis: Clinical, nosological and pathobiological challenges. Acta Pharmacologica Sinica, 41(4), 464–470.
19. Lenka, A., Herath, P., Christopher, R., Pal, P. K. (2017). Psychosis in Parkinson's disease: From the soft signs to the hard science. Journal of the Neurological Sciences, 379, 169–176.
20. O'Brien, J., Taylor, J. P., Ballard, C., Barker, R. A., Bradley, C., Burns, A., Collerton, D. et al. (2020). Visual hallucinations in neurological and ophthalmological disease: Pathophysiology and management. Journal of Neurology, Neurosurgery, and Psychiatry, 91(5), 512–519.
21. Frei, K., Truong, D. D. (2017). Hallucinations and the spectrum of psychosis in Parkinson's disease. Journal of the Neurological Sciences, 374, 56–62.
22. Horn, S., Richardson, H., Xie, S. X., Weintraub, D., Dahodwala, N. (2019). Pimavanserin versus quetiapine for the treatment of psychosis in Parkinson's disease and dementia with Lewy bodies. Parkinsonism Related Disorders, 69, 119–124.
23. Kyle, K., Bronstein, J. M. (2020). Treatment of psychosis in Parkinson's disease and dementia with Lewy Bodies: A review. Parkinsonism Related Disorders, 75, 55–62.
24. Aubignat, M. (2021). Clozapine-related immunodeficiency: Implications for Parkinson's disease psychosis in the context of the COVID-19 pandemic. Revue Neurologique, 177(8), 849–851.
25. Haider, A., Spurling, B. C., Sánchez-Manso, J. C. (2022). Lewy Body Dementia. In StatPearls. StatPearls Publishing.
26. Patel, R. S., Bhela, J., Tahir, M., Pisati, S. R., Hossain, S. (2019). Pimavanserin in Parkinson's Disease-induced Psychosis: A Literature Review. Cureus, 11(7), e5257.

Correspondence

Emanuel-Andrei Sirițeanu,
residency training in psychiatry, Institute of Psychiatry "Socola", Iasi, Romania,
siriteanu.andrei@gmail.com

Submission: 10may2022
Acceptance: 04 jun 2022

BPI Bulletin of Integrative Psychiatry
Buletin de Psihiatrie Integrativă

Humanistic Contributions

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Taking traditional customs to town. A Romanian dynamic

Adina Hulubaş

Adina Hulubas - PhD, Senior Researcher, Romanian Academy - Iasi Subsidiary

ABSTRACT

The article discusses data gathered in two research projects and compares them to argue that folk practices continue to be transmitted and performed in urban settlements. This is due to the recent urbanization process that allows active folk beliefs to be enacted and witnessed frequently. The rites of passage are presented both in Romanian towns and in urban settlements from Western Europe, revealing a significant attachment to traditional ways. Calendar customs complete the image on cultural preservation in the midst of the city, even despite regulations. Romanian urbanites and immigrants maintain folk convictions they learned about in childhood or before leaving the country, with positive reflection results.

KEYWORDS:

Intangible cultural heritage, migration, urbanites, customs.

Population flow has direct consequences on economic, political and social levels, but it also influences a more elusive segment of life: cultural practices and their psychological function. Leaving the rural home in search for a better life does not imply oblivion of the intangible cultural heritage. On the contrary, displacement often triggers an emotional response towards all childhood elements that built a feeling of security: food, ritual practices, family gatherings.

Two projects on internal and international migration of Romanians allowed me to analyse the dynamics of customs in changed environments. The first consisted in a postdoctoral research on childbirth customs from Moldavia, which is a North-Eastern region of Romania (the fieldwork was conducted from 2011 to 2014), while the second is an on-going research entitled *Migration and identity in the Romanian cultural milieu*. The latter implied research interviews with citizens from the Republic of Moldova, too, since the two countries share a common language, history, and culture.

Migrants bring more than statistics to their host societies. The semi-directive interviews with 53 subjects from destination countries

together with 23 more, recorded in Romanian towns reveal that host communities overcome possible adverse sentiments once they can witness cultural practices. On the other hand, villages become depopulated and the transmission of folk knowledge is in true danger. Romania is the second largest provider of immigrants after Syria, and internal migration has recently reached a new record according to The National Institute of Statistics.

The method of research implied a semi-directive interview (with 82 inquiries in the case of childbirth customs, and a 60 question one for Romanian immigrants living in Italy, Spain and Greece), and participant observation. I spoke with fourteen men, while the rest of the subjects are women. The age varies from 23 to 80, with just two informants in their twenties. Only 24 subjects benefited from college education, the majority of them being from The Republic of Moldova.

It is safe to say that the recent urbanization process from Romania preserved traditional knowledge to a greater extent than in countries from Western Europe, where industrialization started two centuries and a half ago. Some of the experts on this process consider that there are three phases of the development: an urban-industrial growth (by a significant rural to urban migration) and a concentration of population in metropolitan areas; a sub-urbanization, determined by changes in occupational structure and a decline of industry; total decentralization, focused on the development of non-metropolitan zones or on *counter-urbanization*1.

According to this theory, Eastern European countries are still in the first phase of urbanization, Western Europe experiences the second one, and U.S.A. are already in the third stage. The criteria of labelling a country for one of these phases are given by the starting point of urbanization, the level of industrialization and technology development, and by the number of generations that have succeeded in the urban environment. While in the last three decades counter-urbanization became a common trend in the developed world 2 , it actually means that at least a century of urbanization has passed and three to four generations of town dwellers brought their contribution to this cultural process.

Most of the urbanites forced by the communist modernization politics to leave their villages in the 1960's now celebrate the maturity of their children, which means that the first generation of urban inhabitants is of adult age. Hence, it is predictable to witness a strong rural dimension of their demeanour for at least two more decades, a prognosis that follows the steps of American urban sociologists who came to this conclusion as early as a hundred years ago: "the city is rather a state of mind, a body of customs and traditions, and of the organized attitudes and sentiments that inhere in these customs and are transmitted with this tradition"3.

From a rural country, as it was before 1938, Romania becomes a heavily industrialized and allegedly modernized country, like other countries from the region. Large masses of rural people were moved away in the new towns, which often lacked any industrial or even economic history. These populations –

[1] Dorel Abraham, *Introducere în sociologia urbană* , București, Editura Științifică, 1991, p. 41.

[2] Charambos Kasimis *et al.*, „Gaining from Rural Migrants: Migrant Employment Strategies and Socioeconomic Implications for Rural Labour Markets", in *Sociologia Ruralis*, no. 50(3), 2010, p. 258-259.

[3] Robert E. Park, Ernest W. Burgess, *et al*., *The City*. With an introduction by Morris Janowitz, The University of Chicago Press, 1967, p. 1.

ceasing to be rural only by residence[4] were indeed observed in cities like Belgrade, described as a "living laboratory"[5] fifty years ago. The same phenomenon takes place in Ukraine[6] or Russia, where "people often considered pagan rituals and beliefs to be Christian and experienced difficulty in differentiating one from the other", despite state efforts to eliminate such mentality[7].

In the following sections, customs performed in the public eye by Romanians who left their home villages or country are presented to argue that cultural heritage is reinforced by a psychological need of self-expression. The comparison between urbanites and immigrants is relevant for the persistency of cultural reactions towards life changes or calendar events.

Rites of passage

Customs addressing the major family events are mostly performed indoors, with selected witnesses that share a "collective consciousness" – "through it, the group periodically renews the sentiment which it has of itself and of its unity; at the same time individuals are strengthened in their social natures" [8]. Several rites disclose the ontological passage publicly, according to the principle identified by Arnold Van Gennep: the circles separating the neophyte enlarge gradually, until the whole community reintegrates the individual in his new, superior social status[9].

Childbirth customs are especially representative for this ritual constraint that loosens after specific periods of time: seven days the parturient woman keeps herself from cooking, forty days she and her new-born need to stay inside the house, after a year the baby can receive the first haircut[10]. For Romanians, the Christian Orthodox baptism signifies a spiritual birth of the child, and it usually takes place before the baby turns forty days. The second day after this event, a social birth is added to the previous biological and religious ones.

The Godmother comes to the child's house and gives him a ritual bath containing several elements intended to provoke contagious magic: the milk will make her/ his skin white, the bread will turn her/ him into a kind person (according to the Romanian saying, a person is "as good as the fresh bread" when she/he proves to be a humanitarian), honey and sugar are intended to give a "sweet" character – meaning that the child will grow up to be a very sociable individual and so on[11]. Holy water is also poured in the bath water, for the child to stay safe from diseases and other unseen dangers. As a consequence, when the washing is done, the water cannot be simply flushed down the drain, since it has gained magic properties. The Godmother carries the baby bathtub outside with the help of an appointed midwife (60 years ago the wives

[4] Augustin Ioan, Ciprian Mihali, *Dublu tratat de urbanologie*, Cluj-Napoca, Idea Design & Print, 2009, p. 62.

[5] Andrei Simić, *The Peasant Urbanites. The Study of Rural-Urban Mobility in Serbia*, New York, Seminar Press, 1973, p. 2.

[6] Inna Golovakha-Hicks, *The Life of Traditional Demonological Legends in Contemporary Urban Ukrainian Communities*, „Folklore", no. 40, p. 37.

[7] Ekaterina Belousova, *The Preservation of National Childbirth Tradition in the Russian Homebirth Community*. „Folklorica. Journal of the Slavic and East European Folklore Association", no. VII (2), 2002, p. 50.

[8] Émile Durkheim, *The Elementary Forms of the Religious Life*, New York, The Macmillan Company, 1915, p. 375

[9] Arnold Van Gennep, *The Rites of Passage*. Translated by Minika B. Vizedom, Gabrielle L. Caffee. Introduction by Solon T. Kimball. The University of Chicago Press, 1960, p. 13.

[10] See Adina Hulubaș, *Obiceiuri de naștere din Moldova. Tipologie și corpus de texte*, Iași, Editura Universității „Alexandru Ioan Cuza", 2012.

[11] Idem, *Credințe despre naștere în contextul urban din Moldova. Memoria tradițională*, Iași, Editura Universității „Alexandru Ioan Cuza", 2014, p. 123-127.

were assisted by traditional birth attendants; the role is merely ceremonial today, since women give birth in hospitals), and accompanied by other women who took part in the washing.

This exposure to the public space is not shy at all, since women shout and sing throughout the entire time. The water is poured to a fruit tree and urbanites never consider skipping this rite: M.D. declared that "you cannot throw the water down the drain, it is mandatory to pour it on a tall fruit tree, for the baby to grow tall and to bear fruit, to have offspring". E.B. stated that the child will be "beautiful like the tree", while G.M. added that the future adult will have a dignified posture.

Romanian immigrants continue to obey this traditional rule, too. G.D. was in Rome, Italy when she had her relatives and guests carry the water down four stories. A tangerine tree or an orange tree were not inappropriate for E.G. and M.N. (despite the fact that such trees do not grow in Romania). As for the case of R.Z., the fulfilment of the ritual needed the intervention of the Italian house owner. He actually bought him an olive tree especially for this occasion, and had it planted there, because previously there were no trees in front of the property.

The water for the first bath of the new-born used to be taken to a tree in rural settlements, both by Romanians[12] and Bulgarians: "the water from a baby's first bath was often emptied under a fruit tree, so that the child would 'grow as the tree grows' "[13]. The urban reactions to this after baptism rite is positive in host countries, as G.I. indicated, or simply tolerant, like the Spaniards who watched the event but did not stare at performers, according to F.F., who had her children baptized in Alcañiz. In Greece, A.G. even insisted that the neighbours must see 'our tradition' and had her women group shout out loud. The Greeks 'came out and watched' the entire rite, that included a magic contagion: a childless woman was pushed to sit on the bathtub turned downwards, so that she would get pregnant, too. Apparently, it worked for A.G.'s friend - she was with child four months later.

Weddings come to a point when the magic gestures have to performed out in the open air. Before going to church, the bride is dressed by her sponsor. She also has to break a ritual bread called *colac* over the head of the bride, right in front of her house, prior to leaving for religious service. The custom was used to be performed in U.K.[14] where barley or wheat scones were broken over the bride's head for good fortune. A.G. celebrated her union in this particular country, but her mother brought her *turta miresei* (the ritual bread also called *colac*) from Romania. She recalls her weeding day: 'when I left the building I lived in, the sponsor broke the bread in four pieces over my head and said *In the name of the Father, the Son and the Holy Spirit*. I threw them to four directions'. The witnesses hurry to grab a piece, for it is believed that it brings good luck and good health to have them.

In Spain, this bridal bread was provided likewise by family in the case of F.F. Her sister baked her a *colac* (the word is Slavic; it exists in many neighbouring countries – Bulgarian: колач, Ukrainian: калач or колач, Serbian: колач / kolačs) and the rite was

[12] Idem, *Obiceiuri de naștere*, p. 203.
[13] Mercia MacDermott, *Bulgarian Folk Customs*, Jessica Kingsley Publishers Ltd., 1998, p. 80.

[14] Phoebe Parke, *Kate Moss' wedding cake baker's 7 sweetest secrets*, in „CNN Wire Service", Atlanta, the 26th of August, 2015.

carried on under the eyes of the people passing by. Such urban continuations of traditional practices are not singular, as Andrei Simić identified the phenomenon in Belgrade, half a century ago: "more contemporary and affluent couples speed to their wedding festivities in Fiats bedecked with plastic flowers and towels (towels are tied on the hood just under the windshield) in the same manner that horse-drawn fiacres are decorated for village weddings"15. The roots of this common ritual in the Balkans go as far back as the Roman Antiquity, when the scenario was identical16.

Ritual bread is not only used for family events, Romanian immigrants bake it whenever they gather, to recreate the environment of home with the help of familiar smell and taste, as an attempt of 'returning to the whole'17.

A second exposure of wedding rites in public places consists in a post-liminary rite, when the mother of the groom certifies her acceptance of the new couple. Originally, it was in her own house that she would pull the newlyweds over the threshold with the help of a loom woven towel. Thus, the guardians of this sacred space from home were announced that a new member of the family is placed under protection. Sometimes a small waist belt was used or even a horse rein 18, to suggest future common efforts in achieving life goals.

F.D. used a table cloth to bring her son and his wife inside, but it was a restaurant doorway from Rome that hosted this old practice. The practical use of the gift (woven towels are no longer used on daily basis) modified the initial form of the rite. The change, however, is not as dramatic as performing this integration gesture in a public, impersonal place instead of honouring the household gods who were once associated with the threshold in numerous old civilizations. Although there are no family tutelary spirits under the door step, the coerciveness of the gesture remains and it should be placed in relation to the taboo of touching the threshold when you are a stranger. The familiar practice of carrying the bride over this entrance place initially avoided bringing an offence to threshold deities19.

Funeral rites could be observed in Romanian towns, too. The folk conviction that a lit candle has to be near a person in the moment of death is built on an old imaginary that considers the world of the dead to be pitch dark. Hence, in all the villages from Moldavia subjects believe that such a light needs to be placed in the hand of the moribund, otherwise he will not find his way to the eternal resting place20. Urbanites cannot react otherwise to this tragic event, and they even put pressure on the medical staff to assure a last candle to their patients.

O.S. is a doctor in Iași, and her husband works as a paramedic. She told me that very often families call to ask if their relative, the person taken by the ambulance, died with a lit candle. "To die without a light" imposes a specific set of magic and religious measures that will save the departed from damnation. Therefore, paramedics included a box of matches and a candle in their CPR kit, to be

[15] Andrei Simić, *op. cit.*, p. 70-71.
[16] Carol Wilson, *Wedding Cake: A Slice of History*, in „Gastronomica", no. 5 (2), 2005, p. 69–72.
[17] David E. Sutton, *Remembrance of Repasts: An Anthropology of Food and Memory*. Berg, 2001, p. 82.
[18] Silvia Ciubotaru, *Vitralii,* Iași, Editura Presa Bună, p. 81.
[19] James George Frazer, *Folklore in the Old Testament*, Oxford, Hart Publishing Inc. 1975, p. 317.
[20] Ion H. Ciubotaru, *Marea trecere. Repere etnologice în ceremonialul funebru din Moldova*, București, Editura „Grai şi Suflet – Cultura Naţională", 1999, p. 47.

able to offer this last compensation to the grieving families21. This mix of scientific and cultural services is created by a society with a significant common cultural heritage, on top of human empathy.

Funeral processions when the family and friends walk slowly after the hearse are no longer allowed in towns, according to Law 102 from 2014. Despite this regulation we can still observe this traditional manner of saying good-bye to the deceased on the roads. Moreover, the convoy stops at each crossroads for a specific religious service while the family throws around numerous coins believed to reach the other world and to help the departed pay her/ his passage (Rom. *vămile*). On the other hand, participants pick up these coins because they bring good luck, in a similar logic that we saw in the case of bridal crumbs from the ritual bread. Living in a town does not change the spiritual response to life events, on the contrary, turning to cultural heritage provides efficient strategies of copying with significant change.

International migration seems to accentuate such reactions in the attempt of building a feeling of security in a heterogeneous environment. Immigrants "would have an interest in maintaining their own cultural repertoire, as values of tradition could help to reinforce their cultural identity and give them a feeling of belonging"22. Hence, various holidays that follow throughout the year cannot be spent otherwise than in a traditional manner.

Calendar customs

The most important calendar dates for Christian Romanians are represented by Easter and Christmas. The first is rather secluded from the public eye, while the latter is necessarily accompanied by various practices intended to function as a ritual sacrifice and apotropaic strategies.

On the 20st of December, Saint Ignatius is celebrated according to the canon. However, calendar customs managed to preserve a pre-Christian practice that consists in slaying a pig as part of this solstitial moment. The root of the word *Ignat* indicates an evolution from the Proto-Indo-European *h_1n̥g^{w}nis ('fire'), also suggesting a link with the solar flame that seems to be extinguishing in December and needs urgent help. The sacrificed blood reinforces the power of the sun both due to the chromatics of the offering and to the symbolism of the chosen animal. The pig used to be associated with agrarian rites by Greeks, Egyptians and Phrygians who sacrificed such animals for Demeter and Persephone, Osyris or Attys to magically assure the fertility of the crops in the year to come23.

Romanians raise one or more pigs during the year to slay it in this day and prepare various dishes from all its meat and organs. Somehow, buying pork from the supermarket fails to serve this function and even though they live in a town now, many Romanians continue to follow the ritual practice that also involves getting pig blood on the face for good health. Each December the newsfeed is flooded with at least one such example of people killing pigs behind their blocks of flats. G.H. told me that in 2019 a firm from Craiova organized a meeting where business partners were invited to join the slaying and to eat the 'alms of the pig' (Rom. *Pomana porcului*). This name of the meal cooked from

[21] Adina Hulubaș, *Credințe despre naștere…*, p. 18.

[22] Bobowik M. et al., *Personal Values and Well-Being among Europeans, Spanish Natives and Immigrants to Spain: Does the Culture Matter*, în „Journal of Happiness Studies", no. 12, 2011, p. 405.

[23] Silvia Ciubotaru, *Obiceiuri nupțiale din Moldova. Tipologie și corpus de texte*, Iași, Editura Universității „Alexandru Ioan Cuza", 2015, p. 20.

the fresh meat is anthropomorphic, since we only give alms for people. The sacred nature of the slaughtered pig is thus revealed, no other animal that is killed throughout the year receives a ritual meal.

The rural demeanour in an urban, work context is similar in the case of the rites of passage. D.M. is an engineer in a private company and he spontaneously organized a meal for his late father in his office, in August 2014. The reason for these alms was that he dreamt about him a night before, and according to traditional knowledge such dreams occur when the departed needs something from this world. D.M. comes from an intellectual family and holds a top position in his company, but he did not hesitate to obey folk codes. Moreover, nobody from his team was surprised by his *ad-hoc* almsgiving, since traditional knowledge is still in common use.

Host countries are not accustomed to cultural purposes of animal sacrifice and legal complications follow immediately afterwards. In Chicago, SWAT troops were called in by the neighbours in 201024, and the scenario repeated itself in 2019, in Anzio25, Italy. In the first case, the immigrants were acquitted thanks to a Romanian lawyer who invoked the lawful right to cultural freedom regarding traditional rituals, while in Italy the four migrants face jail and a significant fine for cruelty against animals.

The subjects I spoke with avoid such dangers in two ways: some manage to find pig farms were the slaughtering takes place in legal conditions and bring the pork at home where they prepare all the ritual dishes for Christmas, others receive it in packages from Romania, since 'the meat here [in Italy] doesn't taste [as good] as at home, obviously' (R.Z.). In some cases, Romanian immigrants benefit from the understanding of farm owners, like F.C. who lived in Spain: they don't do it in Romania as well as we do it here; we buy pigs and speak with the owner to let us stab it there, like we do it at home. We paint our faces with blood, we eat pork rind like in our home country. The only problem is that you cannot find hay to burn it, we have to do it with the flamethrower, otherwise it is the same as at home, the same sausages, the same haggis (Rom. *chișcă*, *caltaboș*).

The repeated observation that things take place following the traditional pattern implies a strong psychological need of constancy and identity expression. T.I. stressed that "you cannot tell it is Easter unless you eat lamb steak"; the same type of temporal mark defines Christmas. Even more so, a specific taste is achieved through ritual practice believed to assure the well-being of the family on a magic level.

Winter customs consist in Christmas carols and New Year's Eve masks dances. Romanian immigrants still perform them, although the ritual time is not always respected. A.M.G. lived in Greece for six years. At Christmas Eve, her group disturbed the neighbours and the police came, but she considered it mandatory to express her cultural heritage:

We just couldn't stop going carolling, we had friends, they dressed as bears and told the winter-solstice chants like we do it at home; we disturbed the peace, indeed, the locals

[24] http://www.bucharestherald.ro/front-page/front-page/152-most-interesting/18537-romanian-family-lifted-by-swat-troops-in-the-usa-for-slaughtering-the-pig-in-the-court-yard

[25] https://www.ilmessaggero.it/fotogallery/roma/anzio_denunciate_5_persone_maltrattamenti_di_animali_macellazione_clandestina_di_maiale_foto_luciano_sciurba-4203278.html

once called the police, whatever, we *had to* keep our tradition (she laughs).

The modal verb used in this confession reveals clearly the cultural pressure on people behaviour, so powerful that it often defies the law.

Romanian towns that host winter customs festivals become a stage for the groups that decide to go carolling on the streets. Once more, the initial purpose of auguring well to the household is forgotten, and the practice is perpetuated despite the change of environment.

In conclusion, the urban environment is enriched with steady traces of intangible cultural heritage that often provide missing links with the history of folk practices performed long before the industrialization of host societies. The apparent clash between the secular, pragmatic context and traditional imaginary is overlooked for the benefit of psycho-cultural comfort both by urbanites and immigrants. Quotidian activities are well adapted to the modern context, while important dates from life or of the calendar continue to be experienced in a ritual setting.

ACKNOWLEDGEMENTS AND DISCLOSURES

This work was supported by a grant of the Romanian Ministry of Research and Innovation, CCCDI – UEFISCDI, project number PN-III-P1-1.2-PCCDI-2017-0116, within PNCDI III.

REFERENCES

1. Dorel Abraham, Introducere în sociologia urbană , București, Editura Științifică, 1991, p. 41.
2. Charambos Kasimis et al., „Gaining from Rural Migrants: Migrant Employment Strategies and Socioeconomic Implications for Rural Labour Markets”, in Sociologia Ruralis, no. 50(3), 2010, p. 258-259.
3. Robert E. Park, Ernest W. Burgess, et al., The City. With an introduction by Morris Janowitz, The University of Chicago Press, 1967, p. 1.
4. Augustin Ioan, Ciprian Mihali, Dublu tratat de urbanologie, Cluj-Napoca, Idea Design & Print, 2009, p. 62.
5. Andrei Simić, The Peasant Urbanites. The Study of Rural-Urban Mobility in Serbia, New York, Seminar Press, 1973, p. 2.
6. Inna Golovakha-Hicks, The Life of Traditional Demonological Legends in Contemporary Urban Ukrainian Communities, „Folklore”, no. 40, p. 37.
7. Ekaterina Belousova, The Preservation of National Childbirth Tradition in the Russian Homebirth Community. „Folklorica. Journal of the Slavic and East European Folklore Association”, no. VII (2), 2002, p. 50.
8. Émile Durkheim, The Elementary Forms of the Religious Life, New York, The Macmillan Company, 1915, p. 375
9. Arnold Van Gennep, The Rites of Passage. Translated by Minika B. Vizedom, Gabrielle L. Caffee. Introduction by Solon T. Kimball. The University of Chicago Press, 1960, p. 13.
10. See Adina Hulubaș, Obiceiuri de naștere din Moldova. Tipologie și corpus de texte, Iași, Editura Universității „Alexandru Ioan Cuza”, 2012.
11. Idem, Credințe despre naștere în contextul urban din Moldova. Memoria tradițională, Iași, Editura Universității „Alexandru Ioan Cuza”, 2014, p. 123-127.
12. Idem, Obiceiuri de naștere, p. 203.
13. Mercia MacDermott, Bulgarian Folk Customs, Jessica Kingsley Publishers Ltd., 1998, p. 80.
14. Phoebe Parke, Kate Moss' wedding cake baker's 7 sweetest secrets, in „CNN Wire Service”, Atlanta, the 26th of August, 2015.
15. Andrei Simić, op. cit., p. 70-71.
16. Carol Wilson, Wedding Cake: A Slice of History, in „Gastronomica”, no. 5 (2), 2005, p. 69–72.
17. David E. Sutton, Remembrance of Repasts: An Anthropology of Food and Memory. Berg, 2001, p. 82.
18. Silvia Ciubotaru, Vitralii, Iași, Editura Presa Bună, p. 81.
19. Phoebe Parke, Kate Moss' wedding cake baker's 7 sweetest secrets, in „CNN Wire Service”, Atlanta, the 26th of August, 2015.
20. Andrei Simić, op. cit., p. 70-71.
21. Carol Wilson, Wedding Cake: A Slice of History, in „Gastronomica”, no. 5 (2), 2005, p. 69–72.
22. David E. Sutton, Remembrance of Repasts: An Anthropology of Food and Memory. Berg, 2001, p. 82.

23. Silvia Ciubotaru, Obiceiuri nupțiale din Moldova. Tipologie și corpus de texte, Iași, Editura Universității „Alexandru Ioan Cuza”, 2015, p. 20.
24. http://www.bucharestherald.ro/front-page/front-page/152-most-interesting/18537-romanian-family-lifted-by-swat-troops-in-the-usa-for-slaughtering-the-pig-in-the-court-yard
25. https://www.ilmessaggero.it/fotogallery/roma/anzio_denunciate_5_persone_maltrattamenti_di_animali_macellazione_clandestina_di_maiale_foto_luciano_sciurba-4203278.html

Correspondence

Adina Hulubas,
PhD, Senior Researcher, Romanian Academy - Iasi Subsidiary, Bld. Carol I nr.8, Iaşi, 700505, Romania, adina.hulubas@gmail.com

Submission: 04 mar 2022
Acceptance: 19 apr 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Didactogeny, Between delay and fatigue, overwork and demotivation

Mihai Șleahtițchi

Mihai Șleahtițchi- Doctor Habilitatus in Psychology,Doctor of Pedagogy, University professor,"Ion Creangă" State Pedagogical University, Chișinău, Republic of Moldova

ABSTRACT

Didactogeny is an expressive indicator of school maladaptation. As soon as it appears, as a result of the communication mistakes committed - voluntarily or involuntarily - by teachers, it puts undesirable pressure on their disciples, disorganizing their activity and relationships of all types. Since the phenomenon in question disrupts the training process by the pernicious energies which it possesses, calling into question its proper conduct, it is evident that the preoccupations appearing in such a case must concern - first of all and in particular - the learning capacity of the pupils or, more precisely, the manner and extent to which the targeted type of capacity is subjected to erosion. The data we have - we refer both to the findings we managed to extract from the specialized literature and to our own observations related to the inappropriate behavior of teachers - shows that, *ad extremum*, the detrimental influence that didactogeny has, as a pathological factor, over the ability to learn is expressed in at least three phenomenological situations: (i) occurrence of school delays, (ii) decreased ability to process information, and (iii) disrupted motivation to learn.

KEYWORDS:

Didactogeny, school delay, retake, school failure, fatigue, overwork, demotivation

As demonstrated in various contexts [26], didactogeny represents an expressive

[26] See, in this respect, Străchinaru, I. Didactogeny, in: S. Bârsănescu (coord.), Dicționar de pedagogie contemporană. București: Enciclopedic Publishing House, 1969, pp. 48-49; Platonov, K.K., Didactogenie, în: K.K. Platonov. Scurt dicționar al sistemului de concepte psihologice. Moscova: Editura Școlii Superioare, 1981, c. 35-40; Cuckier, J., Patologia de la didactogenia, in: Revista de Psicoanálisis, 1991, no. 47 (1), pp. 140-145; Poenaru, R., Sava, F. Didactogenia în școală. Aspecte deontologice, psihologice și pedagogice. București: Danubius Publishing House, 1998, pp. 25-30; Popovici, D., Greșeli în procesul de învățare – didactogenii, in: D.

parameter of school inadequacy. Once manifested, as a result of the voluntarily or involuntarily communication mistakes committed by the teaching staff, it puts undesired pressure upon its disciples, disorganizing their activity and relarions of all types.

As a matter of fact, in the opinion of specialists, the faulty pedagogic tact of teachers, their vulgar and irresponsible language may place the whole teaching-learning activity under the sign of an irrefutable *pathological condition*.

In this respect, D. Popovici mentions, in one of his studies [1], that didactogenies may be fully assimilated to what we call *pathological condition*. Or, children come to school wishing to learn, under the impulse of various internal and external factors. From the very beginning, the assumption made is that all pupils are characterized by normality, namely that their interpretors are suitable for the learning process. Principally, they are capable to solve, with normal efforts, the tasks they are confronted with at school, without any negative influences on their capacity of processing and assimilating information.

Pupils accommodation within the school background involves several hypotheses, obviously correlated among them. They are both active receivers of information, participating to the process (a situation in which they must comply with certain school norms) and possessors of a positive attitude with respect to the process they are part of. All such aspects are satisfactorily met with when pupils are characterized by a *normality state*. When didactogenies occur, this condition disappears, being replaced by a *pathological state*, which modifies their behaviour.

In fact, the pathological condition here discussed is but the revealing sign of an aggravating element which, according to the same D. Popovici [2], illustrates certain blockages of the processes directly involved in solving school obligations; by its manner of manifestation, it provokes failures, disillusions and numerous attitudes of morbid type which, considered either together or separately, are not to be found, obviously, in what characterizes normality (a situation in which they are – as already mentioned – active receivers of information, responsible participants to the learning process and possessors of a positive attitude with respect to the activity they are part of).

As, by the pernicious energies it possesses, didactogeny will pathologize the education process, thus questioning its proper development, it goes without saying that all preoccupations manifested in such a case should firstly and especially refer to pupils learning capacity or, more exactly, to the

---

Popovici, Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, pp. 98-100; Sava, F., Didactogenia – concept și evoluție, in: Șt. Boncu, C.Ceobanu (coord.). Psihosociologie școlară. Iași: Polirom Publishing House, 2013, pp. 210-211; Șleahtițchi, M., Despre amenințarea didactogenă, în termeni concreți, in: L. Pogolșa, N. Bucun (coord.), Școala modernă: provocări și oportunități. International Scientific Conference ”Școala modernă: provocări și oportunități” (Chișinău, November 5-7, 2015). Chișinău: Institute of Education Sciences (Cavaioli Typography), 2015, pp. 35-39; Șleahtițchi, M., Didactogenia, fenomenul care desfigurează învățământul, in: Psihologie. Pedagogie specială. Asistență socială: Revista Facultății de Psihologie și Psihopedagogie Specială a Universității Pedagogice de Stat „Ion Creangă”, 2015, nr. 3 (40), pp. 1-6 and/or Șleahtițchi, M., Burnout *versus* didactogeny: the reality of a pathologized connection, in: Bulletin of Integrative Psychiatry , New Series, Year XXVIII, no.1(92), March 2022, pp. 105-114 [ISSN 2393-2694; ISSN-L 1453 - 7257] [Journal B+ and Indexed IDB by CNCSIS, Index Copernicus International, DOAJ, Erih Plus, Gale Cengage, CEEOL, Crossref]. Available on: http://dev.buletindepsihiatrie.ro/bpi-nr-1-2022/

mode and extent to which the type of capacity becomes subject to erosion [3]. Or, facing the impossibility of adequately reacting to a large range of notions, definitions, rules, theories or case studies, those expected to ”burn the midnight oil” will ”stick in the mud”, uncapable of understanding the corresponding discoveries and assertions. Their – verbal, harmonic, figurative, etc. – interpretors will register low levels of cognitive functionality, a sign that things go in a wrong direction, being progressively heading towards abnormality [4].

Against such a background, the evolution of the process will not observe, any more, the existing rules, the result being installation of a reality hardly comparable to a *learning process* centered on ”the attainment of certain cognitive dimensions capable of supporting intentional modification at behavioural level” [5], or with a *learning product* strictly following school curricula (intellectual skills, cognitive strategies, logical information and cognitive attitudes) [6]. What is really happening in such a moment characterizes an acute crisis of educational nature, a huge disorder which – from one day to another – will render insignificant or even zerovalent the efforts made for the acquisition of ”knowledge, skills, strategies and cognitive attitudes” [7], up to becoming the faithful expression of some learning activities attained through either *contiguity* [8], *generalization* [9], *discrimination* [10], *insight* [11] or *significance* [12], or *problems solving* [13] and *stimulation of creative conducts* [14].

The data we rely on – both our own and those taken over from the literature of the field [15] – alongwith the observations made upon the inadequate behaviour and attitude of teaching staff representatives show that, *ad extremum*, the baneful influence exercised by didactogeny, manifested as a pathologizing element, on the *learning capacity* gets materialized in at least three aspects of phenomenological nature.

Firstly, an improper behaviour of the teachers, their non-observance of the norms of didactic communication may lead to *school retardation*, a condition in which learning regresses, or – in other terms – the normal rhythm of acquiring knowledge, skills and habits is lost. Compromising any endeavour of ”registering a higher performance of the instructive-educative activity, at the level imposed by the curricula and by the final objectives of the teaching process”, this type of retardation will cause, in the opinion of specialists [16], non-fulfillment of the mandatory requirements of school curricula, as well as a flagrant discrepancy among ”exigency, possibilities and results”. In its incipient moments, it is characterized by the occurrence of some problems related to the fulfillment of the school duties, while also evidencing the first voids in pupils' knowledge system, by a lower speed of information assimilation, comparatively with their mates, manifestation of the first symptoms of indifference for learning and/ or of a sense of futility [2]. If not catched in due time and not recovered in its initial stage, such a type of retardation will extend its energies, up to reaching a new phase, that of the *retake* as such. Now, it will be characterized by the accumulation of considerable deficit in pupil's knowledge system or by avoidance of any effort for an independent accomplishment of the task, by a manifest aversion for learning or even by its denial [3]. In the absence of a strict control and administration, the phenomenon will enter its final phase, that of the *formal school failure*. The pupils will now demonstrate their incapacity to ”meet school requirements, to acquire the competences established by curricula, to adapt themselves to the school life, to participate to evaluation tests” [17]. More than that, this could lead to *a second examination* or even *failure to get the remove*, namely two severe disciplinary sanctions susceptible of making inefficient not only the development of pupil's personality but even his/ her social integration.

Secondly, teacher's helplessness in maintaining an amiable relation with his/ her disciples affects considerably their *processing capacity*. In numerous situations, the impact is so huge that our capacity of response is

either ”forced beyond the normal possibilities”, or – even worse – it is brought ”in the situation of not functioning at all, any more” [18]. As a matter of fact, many of those obliged to acquire systematically solid knowledge and aptitudes are forced to observe, in a certain moment of time, that they *are tired* and have no force to face the existing school exigency. In this moment, in their blood and urine there appears – according to J. Scherrer [19] – an additional amount of adrenalin, which causes a higher psychosensorial and intellectual tension. One should not forget that such tensions, directly related to the activity of the neuronal systems localized in the midbrain (the brainstem), influence in a decisive manner the activity of the human organism. Against such a background, *homeostatic disequilibrium* will be sooner or later manifested, and coordination among the various functions and operations of the brain will be considerably – or even ultimately – disturbed. Accumulation of daily fatigue leads to *chronic wear* or, as defined by some authors [20], to *overwork.* In the opinion of P. Popescu-Neveanu [21], once overwork installed, the feeling of weakness gets intensified, becoming permanent, and not only during working activities. If, due to their communicational incapacity, teachers cause overwork of their disciples, things will worsen, up to most unpleasant consequences. Or, as repeatedly asserted, overwork induces pessimism, whichever the age of the suffering ones, who cannot enjoy any moment of their life, being overwhelmed by negative emotions, even in the absence of a real motivation. Concomitantly with this, their attention and concentration capacity dramatically decrease, while access of asthenia and anxiety are more and more frequently manifested. More than that – an especially alarming aspect – the number of individuals seeking salvation in smoking, consumption of alcohol, drugs or energizing drinks increases. Equally, the risk of self-medication is observed, namely utilization of drugs administered for coping with the working rhythm they cannot keep pace with [22].

Thirdly, when the representatives of the teaching staff display an inadequate professional conduct, so that their disciples are no longer able to achieve, in a satisfactory manner, the duties involved in the teaching-learning process, a significant – if not even dramatic – decrease of the *motivation for instruction* is to be observed. As known, such type of motivation includes the internal processes determining the activation, orientation and preservation of the behavioural attitudes focused on the acquisition of new information, skills and habits. Of either intrinsic (when pupils are interested in and pleased with the activity *per se*[27]) or extrinsic (when the scope of learning does not correspond to their nature [28]) expression, such processes may demonstrate their vivacity only when they are permanently accompanied by some rewarding gestures. More precisely, *informational/ verbal* compensations (compliments, encouragement, positive *feedbacks* to the demonstrated

[27] In such a case, motivation is to be found inside the learning activity and, equally, inside the person involved in such type of activity. Relevant examples in this respect are the *game* and/ or *active learning.* A question raised by many specialists – such as, for example, R.M. Ryan and E.L. [23] -, is: what can one observe in the manner in which children use to play? In their opinion, following children’ behaviour, it is simple to see that they seem to be ”born to learn” and ”to advance by what they are doing”. As a matter of fact, it is precisely within these paradigmatic intrinsic activities that ”one can directly observe the plenary manifestation of the inborn tendency toward self-determination”, a manifestation showing that, whichever their age, sex, race or social origin, people ”prefer to do mostly the activities for which they feel an intrinsic motivation”.

[28] To paraphrase the Romanian researcher D. Nastas [24], one can assert that, even if numerous pupils and students are intrinsically motivated for study, part of them do this for extrinsic reasons, such as: sense of duty, desire to advance socially, to develop a successful career, impulse to ”be the best”, to gain prestige, or simply habitude.

aptitudes, signs of affections, etc.), *unexpected* (surprising actions and/ or events, gestures provoking unforeseen satisfaction), in the case of intrinsic motivation and, respectively, *tangible/ material* compensations (prizes, gifts, money, diplomas, distinctions, special mentions, tokens, bowlines, etc.) or *contingent/ anticipated* ones (promises of possible praise, surprises, prizes, gifts, bonuses, etc.), in the case of extrinsic motivation [29] . In full agreement with the fundamental psychological needs – manifested, as known, in three distinct variants: *need of autonomy* (according to which, for attaining an authentic self-determination, the subjects should appreciate his conduct as coming from inside, as a manifestation of one's personal will), *need of competence* (assuming that self-determination will be achieved to the extent to which the individual feels that he/ she can follow a certain behaviour, that he/ she is capable of performing some activity) and *the need of networking* (involving the necessity of an emotional support, participation and sincere understanding from the part of the persons he/ she appreciates) – , the compensations here under analysis are the sources of psychomoral energy in whose absence a full involvement of the learning capacity is impossible or, at least hardly probable.

The results of several experimental investigations – such as, for example, those obtained by E.L. Deci [25,26], M.R. Lepper, D. Green and R.E. Nisbett [27] – confirm these ideas. Or, when analyzing them, one should stress the idea according to which, when a school behaviour is intrinsically motivated, *tangible* and *contingent* compensations should be avoided, and substituted prioritarily by the *informational* and *unexpected* ones. On the contrary, when we know for sure that some pupil is wholly devoid of any intrinsic motivation, we should resort, apart from the *informational* and *unexpected* compensations, to the *tangible* or *contingent* ones, as well. In the opinion of specialists [28], the latter ones will be put into practice for "gaining his/ her attention and interest, which could hopefully lead, by a gradual increase of competence and discovery of new aspects, to intrinsic motivation".

As motivation for learning and the compensations accompanying it represent decisive elements of school success, it goes without saying that, in the case of teachers lacking scruples and pedagogic tact, this will never happen, or they will have only a modest effect. The manner in which teachers organize interaction and communication in the classroom – centered on non-observance of the norms specific to the activities they perform – will undoubtedly have a negative impact upon the desire to study hard, to know as many things as possible about the world and about the mechanisms setting it in motion, to build up and achieve daring projects of research and self-fulfillment. By minimizing – or even reducing completely – the role of motivational compensations (from the *informational/ verbal* to the *unexpected* ones and from the *tangible/ material* to the *contingent/ anticipated ones*), these teachers do nothing but considerably disturb the teaching-learning process, which is therefore far from representing "a fundamental activity for adaptation to the social milieu and to the laws of psychobehavioural development, any more".

In the opinion of J. Reeve [29], which fully agrees with the above-mentioned observations, there exist at least three signs evidencing the mode in which didactogenic

[29] More information on these four types of compensations, in: Deci, E.L., Intrinsic Motivation. New York: Plenum, 1975; Deci, E.L., Ryan, R.M. Intrinsic Motivation and Self-determination in Human Behavior. New York: Plenum, 1985; Ryan, R.M., Deci, E.L., Promoting self-determined school engagement: Motivation, learning and Well-being, in: K.R. Wentzel, A. Wigfield (eds.), Handbook on motivation at School. New York: Routledge, 2009 and/or Nastas, D. Resorturi motivaționale ale învățării, in: Șt. Boncu, C. Ceobanu (coord.), Psihosociologie școlară (preface by C. Cucoș), Iași, Polirom, 2013, pp. 115-131.

educators endanger the idea of learning motivation.

In compliance with the first sign, they come to manifest, from one day to another, a sort of – in their own opinion – ”blockage”, interpreting facts and/ or phenomena exclusively from their own perspective, while neglecting the prospects of the pupils they have the duty to form.

The second sign brings into light the habit of interrupting their disciples during their speech, stressing their emotions or behaving in a specific manner.

Finally, the third sign reveals that the educator does not only deliberately interrupt his pupils but, even more, indicate them the manner in which they should think, feel, etc., as well as the line of conduct they should follow.

The conclusion reached by J. Reeve is that the main ways by which didactogenic educators exercise their influence are *intrusion* and *pressure*, ”frequently intervening in their thoughts, experience and line of conduct, forcing them to follow a certain manner of thinking, to grasp things in a certain manner and to adopt a precise behaviour”.

In this respect, J. Reeve proposes a list of didactic errors he observed which, in his opinion, block pupils’ cognitive capacities, thus seriously compromising the idea of learning motivation. Synthetically, such a list can include [30]:

- intense mechanicistic rigidity, manifested along the whole (or almost whole) learning process;
- absence of any explanation regarding the educational requirements had in view (pupils receive no illustration of the reasons and motivation for which they should do something);
- utilization of an insistent/coercive language (frequent formulation of the ”one must do this” and ”one must not do that”);
- impatience manifested when the pupil answers some question (brutal and frequent interventions for accelerating the formulation of answers, for identification of solutions or for reaching conclusions);
- refuse to tolerate any protest from the part of disciples (”no comments, please do your work!” is a frequent formula);
- monopolization of the materials of study (thus preventing pupils to discover by themselves some relevant aspects of the surrounding world or of their own world; such materials are not distributed, remaining hidden).

Characterized by insufficient attention, patience and/ or respect for learning activities, all those that may be labelled as didactogenic educators demonstrate that they consistently promote a professional conduct which – either deliberately or not – put into question or even annihilate the importance of learning[30].

[30] Once the annihilation stage reached, *demotivation* gets installed. As demonstrated on several occasions, demotivation produces one of the most noxious factors for any organization (including any education organization and, respectively, any person trained in such a structure). If such a phenomenon becomes reality, a thorough lack of energy may be noticed. Or, as asserted by specialists, this is the sign that ”one moves away one’s way, one invests in something which will help us grow and develop”. For further details, see, for example, Gorham, J., Christophel, D., Students’ Perception of teacher behaviors as motivating and demotivating factors in college classes, in: Communication Quarterly, 1992, no. 40, pp. 239-252; Gorham, J., Millete, D.M., A Comparative analysis of teacher and student perceptions of sources of motivation and demotivation in college classes, in: Communication Education, 1997, no. 46(4), pp. 245-261; Mayer, M.C., Demotivation – its cause and cure, in: Personnel Journal, 1978, no. 57, pp. 260-266; Rahman, F.U.N., Jumani,

One may therefore conclude that, considering the ruinous energies brought about by such communication errors – be they voluntary or involuntary –, educators induce undesired psychocognitive pressure on their disciples, thus seriously altering their assimilation capacity, making them lose contact with the normal rhythm of acquiring knowledge, skills and habits, wearing them up to manifesting a significant reduction of any motivation for study.

B., Basit, A., Motivating and demotivating factors among learners, in: International Journal of Academic Research, 2010, no. 2(1), pp. 206-212; Smith, M., Hepworth, M., An investigation of factors that may demotivate secondary school students undertaking project work: implications for learning infromation literacy, in: Journal of Librarianship and Information Science, 2007, no. 39(3), pp. 3-15; Andreeva, T., Yurtaykin, E. Why apples fall, or internal demotivation. în: "Top-Manager" magazine, 2002, no. 22, p. 14-21; Oak, G.V. Reasons for demotivation of students in foreign language lessons in higher education, in: Theory and practice of social development, 2012, no. 12, p. 170-172; Gataullin, R.G. Motivation - demotivation - remotivation. in: Herald Bashkir University, 2012, Vol. 17, No. 1, p. 121-129 and/or Prokina E.O. The main causes of staff demotivation and its consequences, in: Young scientist, 2015, No. 10, p. 768-771

ACKNOWLEDGEMENTS AND DISCLOSURES

The author states that he is no declared conflicts of interest regarding this paper.

REFERENCES AND NOTES

1. Popovici, D., Didactogenii posibile, in: D. Popovici. Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, pp. 104-105.
2. *Ibidem,* p. 105.
3. The idea according to which ”learning capacity” means that ”pupils are capable of attaining the objectives of the learning process” is agreed by several specialists in pedagogy. See, in this respect, Popovici, D., Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, p. 105 and/or Poenaru, R., Sava, F., Didactogenia în școală. Aspecte deontologice, psihologice și pedagogice. București: Danubius Publishing House, 1998, p. 37.
4. Specialists' opinion is that the learning capacity requires suitable (verbal, harmonic and/ or figurative) interpretors a pupil should activate. Obviously, when learning follows the principles and standards of the field, their development and functional progress may be observed. However, when normality gets altered, interpretors regress, which means that pupils are ”no longer capable” to fulfill their scholar tasks. See, for example, Popovici, D., Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, pp. 104-105.
5. In the literature of the field, this expression frequently helps elucidating the specific character of the *learning process*, its manner of manifesting itself. See, for example, Cerghit, I., Vlăsceanu, L. (coord.), Curs de pedagogie. București: Publishing House of the University of București, 1988, p. 111 and/ or Cristea, S., Dicționar de pedagogie. Chișinău – București: Grupul Editorial Litera Internațional, 2000, p. 201.
6. Once again, here mentioned is a formula through which the literature of the field expresses the quitessence of the *product of learning*. See also, Cristea, S., Dicționar de pedagogie. Chișinău – București: Grupul Editorial Litera Internațional, 2000, p. 201 and/or Manolescu, M., Procesul de învățământ ca relație predare-învățare-evaluare.
7. A formula taken over from the studies of S. Cristea is mentioned, again, referring to the *scope of the learning process*. See Cristea, S., Dicționar de pedagogie. Chișinău – București: Grupul Editorial Litera Internațional, 2000, p. 201.
8. *The law of learning through contiguity* asserts that ”a combination of stimuli accompanying an emerging movement tends to be followed by that movement”. By the manner in which it is formulated, this law goes beyond the Pavlovian theory of the conditioned reflexes, synthesizing the fact that a certain stimulus pattern attains its full associative strenght in the moment of its first pairing with a response. In other words, ”the first contact” of the pupil with a certain situation may instantaneously trigger a reaction capable of influencing any other subsequent reactions. Consequently, learning may become complete by *a single* experience, after a *single contact* with a *stimulus pattern*. See more in Guthrie, E.R., The Psychology of Learning. New York: Harper, 1952, pp. 25-30; Guthrie, E.R., Association by contiguity, in: S. Koch (ed.), Psychology: A study of a science. Vol.2. New York: McGraw-Hill, 1959, pp. 158-195; Prenzel-Guthrie, P. Edwin Ray Guthrie, Pioneer Learning Theorist, in: G.A. Kimble, C.A. Boneau, M. Wertheimer (eds.), Portraits of pioneers in psychology. Volume II. Washington DC: American Psychological Association, 1996, pp. 137-150 and/or Negreț-Dobridor, I., Pănișoară, I.-O., Știința învățării. De la teorie la practică. Iași: Polirom Publishing House, 2005, pp. 31-43.
9. In the case of *learning through generalization*, stress is laid on the establishment of some obvious similarities between two or more complexes of stimuli, based on some common characteristics of theirs. As T.S. Kendler used to say, the type of learning had in veiw will undoubtedly contribute to the instauration of some learning situations in which ”similar stimuli produce the same response as the original stimulus”. Se also Gluck, M.A., Bower, G.H., Evaluating an adaptive network model of human learning, in: Journal of Memory and Language, 1988, volume 27, pp. 166-195; Miller, J., Slomczynski, K.M., Kohn, M.L., Continuity of Learning-Generalization: The Effect of Job on Men's Intellective Process in the United States and Poland, in: American Journal of Sociology, 1985, no 3, pp. 593-615; Kendler, T.S., Basden, B.H., Bruckner, J.B., Dimensional dominance and continuity theory, in: Journal of Experimental Psychology, 1970, vol. 83 (2, pt. 1), pp. 309-318; Kendler, H.H., Kendler, T.S., Vertical and horizontal processes in problem solving, in: Psychological Review, 1962, no. 69, pp. 1-16: Kendler, T.S., Concept Formation, in: Annual Review of Psychology, 1961, vol. 12, pp. 447-472 and/ or Cristea, S., Dicționar de pedagogie. Chișinău – București: Grupul Editorial Litera Internațional, 2000, p. 202.
10. *Learning through discrimination* offers, as repeatedly mentioned, the possibility to make fine or extremely fine distinctions between the various elements from the surrounding world (beings, objects, situations, etc.). The already mentioned T.S. Kendler insists on stating that, as early as mid '60s - beginning of the '70s, such an organization of the

learning process assumes firstly ”updating of some basic notions which will differentiate the stimuli similar to the original ones, respectively of the stimuli which do not produce the same answer as the original stimulus”. See, in this respect Amitay, S., Irwin, A., Moore, D.R., Discrimination learning induced by training with identical stimuli. in: Nature Neuroscience, 2006, no 9, pp. 1446-1448; Feeney, M., An Examination of Discrimination Learning Patterns in Rats as seen through the Extensions of a Transpositional Paradigm. in: The Huron University College Journal of Learning and Motivation (London - Ontario), 2003, no 40, pp. 75-100; Hanggi, E.B., Discrimination learning based on relative size concepts in horses, in: Applied Animal Behaviour Science, 2003, no. 83 (3), pp. 201-213; Goldstone, R.L., Perceptual learning, in: Annual Review of Psychology, 1998, no 49, pp. 585-612; Kendler, T.S., The Development of discrimination learning: A levels-of-functioning explanation, in: H.W. Reese, L.P. Lipsitt (eds.), Advances in child development and behavior. New York: Academic Press, 1979, pp. 51-67; Kendler, T.S., Cross-sectional research, longitudinal theory and a discriminative transfer ontogeny, in: Human Development, 1979, no. 22, pp. 235-254; Kendler, T.S., Kendler, H.H., An ontogeny of optional shift behaviour, in: Child Development, 1970, no. 41, pp. 1-27 and/ or Cristea, S., Dicționar de pedagogie. Chișinău – București: Grupul Editorial Litera Internațional, 2000, p. 202.

11. Worth mentioning here is that *learning through insight* excludes any explanation based on *chance*, where ”the solution would result from recurrence of the elements which, in a certain moment of time, are accidentally brought together”. According to the specialistis – mainly E.R. Hilgard, G.H. Bower, J.R. Anderson and L. Dubé –, *insight*, as a manner of understanding ideas, phenomena and actions, is characerized by the occurrence of a specific cognitive moment, namely: *a sudden intimation of a possible favourable modification of the perceived existentialistic field.* Or, by this type of modification, ”perceptive configuration may acquire a new significance, a new function, a new meaning”. More details in Cocoradă, E., Introducere în teoriile învățării/ Preface by L.-M. Iacob. Iași: Polirom Publishing House, 2010, pp. 59-63; Anderson, J.R., Cognitive Psychology and its Implications. New York: Worth Publishers, 2000, pp. 240-245; Dubé, L., Psychologie d’apprentissage. Quebec: Presses de l’Université du Quebec, 1990, pp. 187-192 and/ or Hilgard, E.R., Bower, G.H., Teoriile învățării. București: Didactic and Pedagogic Publishing House, 1974, pp. 218-221.

12. From the moment in which it is mentioned in specialized sources – more precisley, the year 1969 – *learning through significance* is viewed as a performant pedagogic model, built up ”on the relations between the cognitive structure, the learning intentions, the contents to be assimilated and the modalities of transmitting information and knowledge”. Essentially, the type of learning here considered is conditioned by (*i*) the logic significance of the new knowledge, resulted from their associativity, (*ii*) the existence of some previous relevant ideas which will orient the material to be learned and (*iii*) the presence, in the mind of the disciple, of the intention of associating the ideas in a logical manner, of relating the new information to the old ones. Or, ”through relating the new, potentially significant material to the main ideas existing in the cognitive structure of the pupil, *meaning* occurs”. When this does not happen, learning becomes irrelevant, superficial, mechanic. See also Ausubel, D.P., Robinson, F.G., School learning: An introduction to educational psychology. New York: Holt, Rinehart & Winston, 1969; Ausubel, D.P., In defence of advance organizers: A reply to the critics, in: Review of Educational Research, 1978, no. 48, pp. 251-257; Ausubel, D.P., Novak, J.D., Hanesian, H., Educational psychology: A cognitive view. New York: Holt, Rinehart & Winston, 1978; Ausubel, D.P., Robinson, F.G., Învățarea în școală. O introducere în psihologia pedagogică. București: Didactic and Pedagogic Publishing House, 1981 and/ or Cocoradă, E., Introducere în teoriile învățării/ Preface by L.-M. Iacob. Iași: Polirom Publishing House, 2010, pp. 153-160.

13. *Learning through solving problems* expresses the type of cognitive activity which, as stated by D.P. Ausubel, ”practically involves the knowledge acquired for «filling in a void», thus facilitung a thorough study of the information received and skills improvement, as well as «endowing pupils with new information, abilities and skills»”. Whichever the form, place and moment in which a problem appears, it expresses a theoretical or practical aspect expected to be solved. It is manifesting when ”the subject intends to attain an objective or to react to a certain situation – a stimulus for which he/ she has no adequate response in his/ her mind”. As a matter of fact, solving of problems is the result of certain operations of cognitive type, which ”transform a condition of knowledge into another one”. More information on this topic in Hung, W., Theory to reality: A few issues in implementing problem-based learning, in: Educational Technology Research and Development, 2011, no. 59 (4), pp. 529-552; Barrett, T., The problem-based learning process as finding and being in flow, in: Innovations in Education and Teaching International, 2010, no. 47 (2), pp. 165-174; Negreț-Dobridor, I., Pănișoară, I.-O., Știința învățării: de la teorie la practică. Iași: Polirom Publishing House, 2005, pp. 191-219; Dochy, F., Segers, M., Bossche, P.V., Gijbels, D., Effects of problem-based learning: a meta-analysis, in: Learning and Instruction, 2003, no. 13, pp. 533-568; Norman, G., Schmidt, H., The psychological basis of problem-based learning: A review of the evidence, in: Academic Medicine, 1992, no. 67, pp. 557-565; Sweller, J., Cognitive load during problem solving: Effects on learning, in: Cognitive Science, 1988, no. 12 (2), pp. 257-285; Okon, W.,

Învățământul problematizat în școala contemporană. București: Didactic and Pedagogic Publishing House, 1978 and/ or Ausubel, D.P., Educational Psychology. A Cognitive Veew. New York: Holt, Rinehart & Winston, 1968.

14. *Learning of creative behaviours* expresses a complex form of learning, which ”finally achieves individual and collective behaviours mainly oriented towards searching and finding of the new, of the original and of the valuable aspects, defining the elements of creativity”. Centered on solving a special type of problems (= *problematic situations*), this type of learning is characterized by the fact that ”it urges the flexibility of thinking”, insisting on ”the application of the acquired knowledge in a new, original manner”, on ”the fulfillment of some recognoscible tasks” and on ”the manifestation of unexpected intuitions”. See also Guilford, J.P., Personality. New York: McGraw-Hill, 1959; Guilford, J.P., Factors that aid and hinder creativity, in: Teachers College Record, 1962, no. 63, pp. 380-392; Guilford, J.P., Intelligence, creativity and their educational implications. San Diego, CA: Robert R. Kmapp, 1968; Ausubel, D.P., Educational Psychology: A Cognitive View. New York: Holt, Rinehart & Winston, 1968; Mckinnon, D.W., Creativity and transliminal experience, in: Journal of Creative Behavior, 1971, no. 5, pp. 227-241; Mckinnon, D.W., IPAR’s contribution to the conceptualization and study of creativity, in: I.A. Taylor, J.W. Getzels (eds.), Perspectives in creativity. Chicago, IL: Aldine, 1975, pp. 60-89; Hilgard, E.R., Bower, G.H., Theories of Learning. New Jersey: Prentice - Hall, 1975 and/ or Moraru, I., Ştiinţa şi filozofia creaţiei, București: Didactic and Pedagogic Publishing House, 1995.

15. Brief mention will be here made of only part of the consulted studies, listed chronologically: Străchinaru, I. Didactogenia, in: Șt. Bârsănescu (coord.), Dicționar de pedagogie contemporană. București: Romanian Enciclopedic Publishing House, 1969, pp. 39-42; Poenaru, R., Didactogenia în școală. Pentru prevenirea și combaterea didactogeniilor în învățământ, in: Revista de pedagogie, 1980, nr. 9, pp. 51-53: Potolea, D., Stilurile pedagogice; dimensiuni structurale și incidențe în procesele de învățare la elevi, in: Revista de pedagogie, 1987, nr. 12, pp. 43-51; Cukier, J., Patologia de la didactogenia, in: Revista de Psicoanalisis, 1990, no. 47 (1), pp. 140-152; Sillamy, N., Didactogenia, in: N. Sillamy, Dictionnaire de la psychologie. Paris: Larousse, 1995, p. 100 (Romanian version: Sillamy, N. Didactogenie, in: N. Sillamy, Dicționar de psihologie. București: Enciclopedic Universe Publishing House, 1996, p. 101); Modrea, M., Didactogenia și condiția cadrului didactic, in: Tribuna învățământului, 1996, nr. 358, pp. 17-22; Poenaru, R., Sava, F., Didactogenia în școală. Aspecte deontologice, psihologice și pedagogice. București: Danubius Publishing House, 1998; Iancu, S., Psihologia școlarului. De ce merg unii elevi „încruntați” la școală? Iași: Polirom Publishing House, 2000; Popovici, D., Greșeli în procesul de învățare – didactogenii, in: D. Popovici, Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, pp. 98-111; Tarasov, S.V. Schoolchild in the modern educational environment. St. Petersburg: Education-Culture Publishing House, 2001; Weber, K., Martin, M.M., Patterson, B.R., Teacher behavior, student interest and affective learning: putting theory to practice, in: Journal of Applied Communication Research, 2001, no. 29 (1), pp. 71-90; Truța, E., Mardar, S., Relația profesor-elev: blocaje și deblocaje. București: Aramis Publishing House, 2007, pp. 125-135; Sava, F., Didactogenia – concept și evoluție, in: Șt. Boncu, C. Ceobanu (coord.), Psihosociologie școlară (preface by C. Cucoș). Iași: Polirom Publishing House, 2013, pp. 208-221 and/ or Piscunov, N., Piscunov, A., Factorii declanşatori ai didactogeniei şi impactul lor asupra elevilor, in: Perspectivele și Problemele Integrării în Spațiul european al Cercetării și Educației: Materials of the International Scientific Conference ”Perspectivele şi Problemele Integrării în Spaţiul European al Cercetării şi Educaţiei” (Cahul, Republic of Moldova, June 7, 2018), Cahul: ”Bogdan Petriceicu Haşdeu” State University, 2018 (Centrografic Printing House), pp. 120-126.

16. See, for example, Mitrofan, N., Rolul școlii și al familiei în cunoașterea și prevenirea unor fenomene de dezadaptare școlară, in: Revista de pedagogie, 1987, nr. 7, pp. 16-19 and/ or Popescu, V.V., Succesul și insuccesul școlar – precizări terminologice, forme de manifestare, cauze, in: Revista de pedagogie, 1991, nr. 12, pp. 17-25.

17. The formula belongs to the Romanian researcher M. Ștefan. Other information on the essence of school failure in Ștefan, M., Lexicon pedagogic. București: Aramis Publishing House, 2006, pp. 122-125.

18. The expressions belong to D. Popovici. See, in this respect, Popovici, D., Didactica. Soluții noi la probleme controversate. București: Aramis Publishing House, 2000, p. 106.

19. See also, Scherrer, J., Problèmes physiologiques posés par la fatigue, in: Le Travail Humain, 1962, vol.25, no.3/4, pp. 305-308 and/ or Scherrer, J. La Fatigue. Paris: Presses Universitaires de France, 1989, pp. 27-28 (Romanian version: Scherrer, J., Oboseala (translated by M. Boari). București: Humanitas Publishing House, 1993, pp. 32-33.

20. See, for example, Turcu, F., Turcu, A., Oboseală, in: F.Turcu, A. Turcu, Dicționar explicativ de psihologie școlară. București: Eficient Publishing House, 2000, p. 352.

21. See, in this respect, Popescu-Neveanu, P., Oboseală, in: P. Popescu-Neveanu, Dicționar de psihologie/ Scientific consultants: prof. dr. doc. S. Teodorescu and dr. doc. V. Săhleanu. București: Albatros Publishing House, 1978, p. 491.

22. Other details on overwork and its specific manifestations in the learning process in, for example, Andronic, C., Prevenirea surmenajului intelectual. București: Military Publishing House, 2007; Michie, S., Cockcroft, A., Overwork can kill, in: British Journal of Medicine, 1996, no. 312, pp. 921-922; Popescu-Neveanu, P., Surmenaj, in: P. Popescu-Neveanu. Dicționar de psihologie. București: Albatros Publishing House, 1978, p. 698; Schaffner, A.K., Exhaustion: A History. New York: Columbia University Press, 2016; Sillamy, N., Surmenaj, in: N. Sillamy. Dicționar de psihologie. Translation, preface and completations on the Romanian psychology by dr. L. Gavriliu. București: Enciclopedic Universe Publishing House, 1996, pp. 306-307; Rhoads, J.M., Overwork, in: Journal of the American Medical Association, 1977, no. 237, pp. 2615-2618; Teodorescu, S., Surmenaj, in: U. Șchiopu (coord.), Dicționar enciclopedic de psihologie. București: Babel Publishing House, 1997, p. 674; Kobyakov, V.D. Overwork of students and ways to prevent it, in: Problems of abnormal children and adolescents, psychocorrection of problem children. Kazan, 1997, p. 12-29; Kobyakov, V.D. Teaching without overwork, in: Principal, 1997, no. 5, p. 14-18; Magamedeminova, M.M., Korotkikh, V.M., Polyakova, S.R., Osokina, M.M. Signs of fatigue and overwork, their causes and prevention, in: Young scientist, 2020, No. 8 (298), p. 74-75 [URL:https://moluch.ru/archive/298/67584/] and/ or Zotova, F.R. Overwork of students and its prevention in the conditions of modern school. Kazan: Kazan State University Press, 2004.

23. Ryan, R.M., Deci, E.L., Self-determination theory and the facilitation of intrinsic motivation, social development and well-being, in: American Psychologist, 2000, no. 55, pp. 68-78.

24. See, in this respect, Nastas, D., Resorturi motivaționale ale învățării, in: Șt. Boncu, C. Ceobanu (coord.), Psihosociologie școlară (preface by C. Cucoș). Iași: Polirom Publishing House, 2013, p. 119.

25. Deci, E.L., The effects of externally mediated rewards on intrinsic motivation, in: Journal of Personality and Social Psychology, 1971, no. 18, pp. 105-115.

26. Deci, E.L., Intrinsic Motivation. New York: Plenum, 1975.

27. Lepper, M.R., Greene, D., Nisbett, R.E., Under-mining children's intrinsic interest with extrinsic rewards: A test of the "overjustification" hypothesis, in: Journal of Personality and Social Psychology, 1973, no. 28, pp. 129-137.

28. See Nastas, D., Resorturi motivaționale ale învățării, in: Șt. Boncu, C. Ceobanu (coord.), Psihosociologie școlară (preface by C. Cucoș). Iași: Polirom Publishing House, 2013, p. 125.

29. Reeve, J., How do I motivate others? The concept of motivating style, in: J.M.D. Gomez, E.G. Armas (eds.). Motivation y emotion: Investigaciones actuales. Laguna: Universidad de la Laguna, 2010, pp. 15-28.

30. Ibidem, pp. 27-28.

Correspondence

Mihai Șleahtițchi,
Doctor Habilitatus in Psychology,Doctor of Pedagogy, University professor,"Ion Creangă" State Pedagogical University, Chișinău, Republic of Moldova, msleahtitchi@yahoo.com

Submission: 10 apr 2022
Acceptance: 04 jun 2022

BPI Bulletin of Integrative Psychiatry
Buletin de Psihiatrie Integrativă

Case Reports

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Cerebrospinal fluid biomarkers for early and differential diagnosis of Alzheimer's disease

Bogdan Gireadă, Irina Dobrin, Silvia Onofrei, Cristina Elena Dobre, Iulia Sîrghie, Ilie Roșu

Bogdan Gireadă - M.D., Resident Psychiatrist, Institute of Psychiatry „Socola"
Irina Dobrin - M.D., PhD, lecturer, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania
Silvia Onofrei - M.D., Resident Psychiatrist, Institute of Psychiatry „Socola"
Cristina Elena Dobre – M.D., Institute of Psychiatry „Socola"
Iulia Sîrghie - M.D., Resident Psychiatrist, Institute of Psychiatry „Socola"
Ilie Roșu - M.D., Resident Psychiatrist, Institute of Psychiatry „Socola"

ABSTRACT

Biomarkers are likely to be important in the study of Alzheimer disease (AD) for a variety of reasons. A clinical diagnosis of Alzheimer disease is inaccurate even among experienced investigators and biomarkers might improve the accuracy of diagnosis. They might also serve as indirect measures of disease severity. While Alzheimer's disease classical diagnostic criteria rely on clinical data from a stablished symptomatic disease, newer criteria aim to identify the disease in its earlier stages. For that, they incorporated the use of AD's specific biomarkers to reach a diagnosis, including the identification of Aβ and tau depositions, glucose hypometabolism, and cerebral atrophy. These biomarkers created a new concept of the disease, in which AD's main pathological processes have already taken place decades before we can clinically diagnose the first symptoms. Imaging biomarkers including volumetric magnetic resonance imaging and positron emission tomography assessing either glucose utilization or ligands binding to amyloid plaque are also in use worldwide. Biomarkers are essential for an accurate identification of preclinical AD in the context of clinical trials with potentially disease-modifying drugs. A biomarker-based early diagnosis of AD offers great opportunities for preventive treatment development in the near future. Therefore, AD is now considered a dynamic disease with a gradual progression, and dementia is its final stage.

KEY WORDS:

Alzheimer's disease, amyloid, biomarkers, cerebrospinal fluid, dementia, diagnosis, cerebral atrophy, tau depositions, amyloid plaque.

THEORETICAL BACKGROUND

One of the great challenges faced by neuropsychologists over the past 50 years is to understand the cognitive and behavioral manifestations of dementia and their relationship to underlying brain pathology. This challenge has grown substantially over the years with the aging of the population and the age-related nature of many dementia-producing neurodegenerative diseases. In 1907, Aloysius Alzheimer carefully described the symptoms of a 51-year-old woman, Auguste Deter, who was under his care at the state asylum in Frankfurt Germany. Alzheimer's description of her symptoms is almost certainly the first neuropsychological characterization of the disease: *"Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When reading a test, she skips from line to line or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing she repeats separate syllables many times, omits others and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions ("milk-pourer" instead of cup); sometimes it is obvious she cannot go on. Plainly, she does not understand certain questions. She does not remember the use of some objects."*

When Auguste Deter died, Alzheimer used the then-new silver staining histological technique to examine her brain microscopically. When he did so, he observed the neuritic plaques, neurofibrillary tangles, and amyloid angiopathy that were to become the hallmarks of the disease that now bears his name. (1) It was also during this time that Eugen Bleuler in his study of schizophrenia coined the term "organic psycho syndrome" to refer to decrements in memory, judgment, perceptual discrimination and attention, emotional lability, and defective impulse control associated with chronic diffuse cortical damage. (1)

Over the past 20 years great progress was made in identifying in vivo biological markers of AD. Several investigators refined the ability to detect and measure cerebrospinal fluid levels of Aβ (the main constituent of the plaque) and tau protein (a constituent of the neurofibrillary tangle) that were indicative of AD pathology in the brain. When a clinician should discriminate AD from a non-AD dementia relying on (non-biomarker based) clinical diagnostic criteria, 16% are misdiagnosed and 16% of the patients have a doubtful AD versus non-AD diagnosis. (2) Therefore, it is important to increase the clinical diagnostic accuracy, which will even be harder at an early stage of the disease. Since biochemical changes are believed to take place and be detectable through biomarkers around two decades before clinical symptom onset [6], they will be important tools in the clinical setup for early and differential diagnosis of AD. (2) Also driven by the need of clinical trials to select 'pure' AD subjects early in the course of the disease, much effort has been put in developing biomarkers for AD during the past two decades. This has resulted in three core cerebrospinal fluid (CSF) biomarkers for AD diagnostics, namely the 42 amino acid long amyloid-beta peptide ($A\beta_{1-42}$), total tau protein (T-tau), and tau phosphorylated at threonine 181 ($P\text{-}tau_{181}$) (2). A biomarker should be readily accessible, accurately indicating a biological or pathological state and preferably inexpensive. In case of neurodegenerative biomarkers, the choice of CSF over blood biomarkers, at least in the case of $A\beta_{1-42}$, is mainly based on the fact that the central nervous system is secluded from the systemic circulation, which precludes direct translation of biomarker findings of the

brain to the periphery. (2) Tau on the other hand have shown more potential as a plasma or serum biomarker for the differentiation between AD and controls. Moreover, $A\beta_{1-42}$ has proven its potential to mirror the build-up of plaques, which is supported by the inverse correlation between the CSF $A\beta_{1-42}$ levels and the amount of amyloid plaques found at neuropathological examination of AD brains as well as the in vivo association with cortical amyloid load as measured by amyloid PET in patients with AD.

After Bruno Dubois' first step in including biomarkers as diagnostic criteria, in 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) defined new diagnostic criteria that separated the disease in three clinical stages, each one with its own diagnostic recommendation. First is the preclinical stage that presents pathologic brain changes, which may be in progress decades prior to disease, without evident clinical symptoms. In this stage, alterations can be seen in CSF and imaging biomarkers although, at present, they cannot predict which of these individuals will develop dementia. (3) The second stage is Mild Cognitive Impairment (MCI), which is marked by memory symptoms that are greater than normal for a person's age and education but that do not interfere with their independence and may or may not progress to Alzheimer's dementia. The final stage is Alzheimer's dementia, in which symptoms are significant enough to impair a person's ability to function independently. (3)

In early stages of AD, lower levels of Aβ appear in CSF, and it is considered a predictor of the evolution of MCI to AD and, in the same way, high levels of p-tau and t-tau in CSF can predict with good accuracy an incipient AD in patients with MCI. These parameter alterations appear even in cognitively normal subjects, where it is possible to detect abnormalities of Aβ and tau in CSF many years before MCI is diagnosed. (4)

With the advent of biomarkers came a conceptual change of the disease. We moved from a "static and defensive" view of the pathogenesis of AD to a "dynamic and compensatory" point of view. In the first viewpoint, the brain lesions that lead to neuronal and synaptic loss and finally to cognitive deterioration depend on the degree of external aggression and on the structural reserve that each person has. The current view considers an inter-individual variability in the response to these initial aggressions, as well as differences in the severity of the pathological process and in the efficiency and evolution over time of the cerebral compensatory mechanisms. Therefore, the idea that AD's main pathological processes have already taken place before we can clinically diagnose MCI has been established, and this is reinforced by the fact that these lesions begin even decades before the appearance of the earliest symptoms, when the subject is still cognitively normal. (6) Therefore, this change in perspective increasingly supports the need for early therapeutic action in order to compensate for those biological processes that are already compromised before the onset of the cognitive failure. In this progression, which may take years, biomarkers can anticipate the clinical manifestations of dementia and, as the new diagnostic criteria introduced biomarkers in a supporting role in AD's diagnosis, many laboratories world wide have already started using them. With this in mind, and based on determinations made in different populations, Jack and collaborators proposed a model for the evolution of AD over time, known as "the dynamic biomarker cascade model". In thus model each biomarker reaches its maximum

effect at a certain moment in the progression of the disease, and that happens in an orderly manner over time. Interestingly, the maximum levels can be detected in a person before any clinical symptom. In fact, several studies have shown that 20–40% of cognitively normal old present Aβ deposits in their cerebral tissue. (2, 3) Moreover, in post-mortem samples from non-demented elderly people, Aβ plaques were also present. Therefore, deposits of amyloid plaques alone, even in significant quantities, are not enough to produce dementia. Not only Aβ but also tangles may be present in subjects without cognitive decline. Nonetheless, in asymptomatic patients, the presence of neurofibrillary tangles tends to be limited to the entorhinal cortex (stages of Braak I–II), while in symptomatic subjects, tangles are much more widespread. (3) These studies are all in line with a final concept that this model postulates: the existence of a latent phase of variable duration between plaque formation and the onset of the neurodegenerative cascade. This could be due to differences in the processing of Aβ, to the capacity of resistance to pathological damage derived from the toxicity of Aβ and to compensatory mechanisms.

In recent years, new biomarkers have been described as related to other pathophysiological aspects such as vascular dysfunction, neuronal and synaptic integrity and neuroinflammation, to name a few. In this regard, neurofilament-light chain (NfL), an intermediate filament of the neuronal cytoskeleton, which is abundant in axons, has been recognized as a marker of neuronal damage, increasing in both CSF and blood as a result of different neurodegenerative diseases. Aside from their role in diagnosis, biomarkers could soon become indispensable tools for the development of future AD therapies. Currently, their use in clinical trials improves the classification of participants according to the underlying disease, allows staging the disease more precisely and also allows a better and earlier evaluation of treatment response. Based on all of the above, it seems clear that the biomarkers have improved the diagnosis of AD beyond clinical findings, and have shown that the preclinical stages of the disease may in fact last much longer than the symptomatic ones. (3)

If no disease-modifying drug is available, what is the point of applying biomarkers in clinical practice? Several papers have recommended their use in specific situations19. There is general agreement that in early-onset disease (under 65 years of age) as well as in atypical forms of AD, which often also present before 65, biomarkers could be useful. Less anosognosia is present in this age group, which is more concerned on diagnosis and still at very productive stages of life. Diagnostic confirmation would allow making life-changing decisions and improve differential diagnosis with other radically different types of disease. (5)

A major outstanding research question is why other tauopathies, including some forms of FTD and associated disorders like progressive supranuclear palsy, do not show increased P-tau concentration in the CSF, at least not as robustly as in AD. It is possible that disease-specific phosphorylation of tau occurs in these disorders, or that tau is processed or truncated in a way that is not recognized by the available assays. Another potential explanation for why increased CSF P-tau is specific to AD is that this particular pathological change is simply more extensive and severe in AD than it is in other tauopathies. CSF P-tau is currently considered to be the most specific biomarker for AD. Except for herpes encephalitis and superficial

CNS siderosis, no other condition features a systematic increase in this biomarker. (5)

Disease biomarkers have been developed into clinically available methods to detect tangle and plaque pathology in the CSF and brains of AD patients, and there are also promising biomarkers to detect synaptic loss and dysfunction. Tau and Aβ biomarkers can help to diagnose AD pathology in both the prodromal and the dementia stages of the disease. Moreover, a number of additional biomarkers have been identified that detect pathological changes common to AD and other neurodegenerative proteopathies, although reliable and accurate biomarkers for TDP-43 and Lewy body pathology remain to be identified. If identified in the future, such biomarkers could be employed in longitudinal studies to track the temporal development of different pathologies during neurodegenerative disease progression, and to assess how their interactions lead to clinical symptoms. (2) As multimorbidity appears to be common not only in AD but also in other neurodegenerative dementias, one potential future scenario is that these biomarkers could be used to subclassify the clinical syndromes in individual patients according to their pathological signature, allowing for personalized treatment.

GENERAL PRESENTATION OF THE CASES

Case A refers to a female patient aged 67 years, Romanian citizenship, who had complaints about short-term memory loss. Her relatives noticed her repeatedly asking the same questions. She had become insecure and started to double-check her own actions. A friend had to help her with administrative duties. Her complaints developed gradually over the last 1.5 years. She had a history of hypertension and osteoporosis. She smoked 20 cigarettes a day from the age of 15. Neuropsychological tests indicated significant cognitive decline, with a Mini Mental State Examination (MMSE) [23] score of 22 out of 30. Mainly semantic memory function, both verbally and visually, recognition and orientation in time and place were affected, while visuo-construction, attention, executive functioning and cognitive speed were normal. The subsequent MRI showed extensive white matter lesions (<25% of white matter), probably of vascular-ischemic origin, next to distinct atrophy with broadening of the ventricles, and hippocampal atrophy grade 1. Because of these MRI results and the patient's vascular risk factors, a diagnosis of possible Vascular Dementia was considered next to AD. A lumbar puncture and further neuropsychological testing were performed to help clarify the diagnosis. The CSF biomarker levels were: Aβ42 424 ng/l, t-tau 634 ng/l and p-tau 117 ng/l. The decreased level of Aβ42 with a significantly elevated t-tau and p-tau and, consequently, an Aβ42/p-tau ratio of 3.6, which is far below the cut-off ratio of 11.0 to discriminate Vascular Dementia from AD, supported the diagnosis of AD over Vascular Dementia, and therefore we diagnosed probable AD with cerebrovascular morbidity. Treatment with acetylcholinesterase inhibitors was initiated, which she tolerated well. 17 months after diagnosis the patient was stable without further deterioration in cognition, behavior or daily activities and no further vascular disease hallmarks developed, supporting our initial diagnosis.

Case B refers to a female aged 63 who visited our memory clinic with gradually increasing memory problems over the past 3 years. Her medical history revealed a subarachnoidal hemorrhage at the age of 33 due to an aneurysm of the anterior communicating artery, and excision of a frontal meningioma at the age of 54. After examination, we objectified both verbal and visual memory

dysfunction and disturbances in language, attention, visuo-construction and executive functions, which influenced her daily activities. Her MMSE score was 21 out of 30. We suspected a diagnosis of AD, but because of a complicated history and young age, we wanted to support this diagnosis with biomarker evidence. An MRI could not be performed because the patient had a metal clip on the cerebral aneurysm A CT-scan showed left-sided frontal atrophy and fronto-basal atrophy of both hemispheres. CSF analysis was done, showing an Aβ42 concentration of 431 ng/l, a t-tau concentration of 545 ng/l and a p-tau concentration of 118 ng/l. The decreased level of Aβ42 and elevated t-tau and p-tau confirmed our notion of the diagnosis as possible AD. Treatment with cholinesterase inhibitors was initiated. After 16 months, mild deterioration in memory function was seen, compatible with the diagnosis of AD.

DISCUSSIONS

These case reports illustrate that CSF analysis may be a valuable addition to the standard workup for AD. The first case shows the affirmative value of CSF biomarkers, when the combination of $A\beta_{42}$ and p-tau indicates that a diagnosis of AD with vascular disease is more likely than VaD.

The second case shows an example of a patient group in which MRI cannot be performed. Other conditions that exclude MRI scanning include having a cardiac pacemaker or claustrophobia. As an alternative a CT-scan can be performed to search for white matter lesions and to exclude a tumor, but the diagnostic value of CT-images is limited by the lower resolution and lower sensitivity for vascular lesions. Moreover, visualization of the temporal horn requires additional reconstruction, and CT more often leads to scatter artifacts. Therefore, CSF analysis is regarded as a better alternative, when a lumbar puncture is not contra-indicated, e.g. in case of structural lesions.

In certain cases, the CSF biomarkers can be of help in the differential diagnosis, both for confirming and excluding a diagnosis of AD. Due to practical and occasionally medical circumstances, CSF analysis is not suitable to be used as a primary diagnostic tool for all patients investigated at a memory clinic. However, neither the invasiveness of lumbar puncture nor post-puncture complaints are any longer a serious concern with modern techniques, especially in older patients.

CONCLUSIONS

AD had previously been defined based on Alois Alzheimer's original description of neuropathological findings in autopsy material. The diagnosis was based on the detailed presence, density and distribution of the characteristic lesions, namely extracellular amyloid plaque and intraneuronal neurofibrillary degeneration. These criteria were later refined and quantified in an attempt to include other lesions that usually coexist in the aging brain and affect cognition.

Diagnosis today is determined by detection of amyloid, T-tau and P-tau. It is not known whether these abnormal proteins actually cause the disease, but they are nevertheless their defining feature. Protein deposits make AD a unique and specific neurodegenerative disorder, separating it from other conditions causing dementia. This differentiation is key, since it allows examination of chronological events leading to clinically evident effects on cognition as a continuum, which includes intact subjects amenable to potential treatment strategies. In the not too distant future,

taxonomic consequences resulting from biomarker use are foreseeable, linking the nosology to an underlying molecular abnormality, which in turn, may become a potential objective for targeted therapies

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors state that they are no declared conflicts of interest regarding this paper.

REFERENCES

1. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's Disease: Past, Present, and Future. J Int Neuropsychol Soc. 2017;23(9-10):818-831.
2. Bjerke M, Engelborghs S. Cerebrospinal Fluid Biomarkers for Early and Differential Alzheimer's Disease Diagnosis. J Alzheimers Dis. 2018;62(3):1199-1209.
3. Lloret A, Esteve D, Lloret MA, Cervera-Ferri A, Lopez B, Nepomuceno M, Monllor P. When Does Alzheimer's Disease Really Start? The Role of Biomarkers. Int J Mol Sci. 2019;20(22):5536.
4. Chrem Mendez P, Surace E, Bérgamo Y, Calandri I, Vázquez S, Sevlever G, Allegri RF. Biomarkers for Alzheimer's disease. Where we stand and where we are headed. Medicina. 2019;79(6/1):546-551.
5. Zetterberg H. (2017). Review: Tau in biofluids - relation to pathology, imaging and clinical features. Neuropathol. Appl. Neurobiol.2017. 43, 194-199.
6. Tammaryn L. et al. Molecular biomarkers of Alzheimer's disease: progress and prospects. Disease models and mechanisms. 2018:11(5).

Correspondence:

Silvia Onofrei,
M.D., Resident Psychiatrist, Institute of Psychiatry „Socola", silvia_stx@yahoo.com

Submission: 02 apr 2022
Acceptance: 28 may 2022

BPI BulletinofIntegrative Psychiatry
Buletin dePsihiatrieIntegrativa

Munchausen Syndrome and post-traumatic stress disorder- a correlation

Roxana-Paraschiva Ciobanu, Codrina Moraru, Ionuț-Dragoș Rădulescu, Elena Albu, Petronela Nechita, Gabriela Rusu-Zota

Roxana-Paraschiva Ciobanu - student, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
Codrina Moraru - Fourth Year Medical Resident in psychiatry, "Socola" Psychiatry Institute, Iași
Ionuț-Dragoș Rădulescu - MD, Specialist in psychiatry, "Elisabeta Doamna" Psychiatry Hospital, Galați
Elena Albu - MD, PhD, Associate Professor, Department of Pharmacology – Algesiology, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
Petronela Nechita - MD, PhD, Senior psychiatrist, "Socola" Psychiatry Institute, Iași
Gabriela Rusu-Zota - MD, PhD, Lecturer, Department of Pharmacology – Algesiology, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

ABSTRACT
Munchausen Syndrome (MS) has been a medical entity since its discovery and has aroused curiosity in the medical world. The difficulty in diagnosing and treatment falls within the realm of severe psychiatric disorders. The individual simulates certain diseases in order to become a patient and to attract the attention and assistance of medical staff. The subject does not seek to obtain material or financial benefits. Its characteristic element is the repeated or exaggerated mimicry of the symptoms of an acute organic disease, as well as the falsification of laboratory tests in search of a treatment. The factual post-traumatic stress syndrome offers patients with MS a role as both a victim and a hero, and they receive understanding and respect from society. With the help of specific psychological tests, the clinician can determine if the symptoms are claimed or true, and finding an external motivation, such as financial motivation, makes it possible to differentiate the simulation from the true MS.
Key words: Munchausen Syndrome, post-traumatic stress disorder

KEY WORDS:
Munchausen Syndrome, post-traumatic stress disorder.

INTRODUCTION

Munchausen Syndrome (MS) is a category of factual disorders, in which there are intentional signs and symptoms for the purpose of receiving medical care, but without the desire for an external gain such as sick leave, financial reimbursement or prescribing drug treatment. This pathology is also found in the name of factual disorder imposed on the self (1). This syndrome was named by Dr. Richard Alan John Asher in 1951, by changing the name of Karl Friedrich Hieronymus, Baron of Munich (1720-1797). He is known for his false or exaggerated stories, inspired by his work as a soldier, hunter or sportsman. Dr. Asher noticed a correlation between the Baron of Munich and a category of patients who presented to the hospital with a false symptomatology and dramatization, a complex story in which they put a great deal of effort. He also noted that these patients have the tendency to return to the hospital on numerous occasions, hoping to meet new doctors willing to listen to them (2). Inspired by the speeches of the baron, Rudolph Erich Raspe (1737-1794) created in 1785 a series of stories that go beyond the limits of reality and whose main character is Baron Münchhausen, which have been a huge success over time (2). In one of these stories, the baron recounts an incident that portrays him as a prisoner during the Russo-Turkish war, and he is to be sold as a slave. As a result, he is given the daily task of caring for the sultan's bees, supervising them during the day in the field, and accompanying them back to their hives every night. One evening, the baron notices the loss of a bee, and after searching for it, he finds it endangered by 2 bears. To protect her, the baron wants to drive away the bears, so he throws his ax at them. Instead, the ax is thrown in the wrong direction and thus reaches the moon. Out of a desire to regain it, he plants a bean from which grows a twig that reaches the moon. By climbing it, Baron Münchhausen arrives on the moon and manages to retrieve his ax in a pile of straws. However, when he wants to go back down to earth, he notices that his bean stalk has been dried by the sun. Looking for a way to return, the baron came up with the idea of tying the straw he had found in such a way that he managed to form a string that he tied to one of the corners of the moon. During the descent, he falls from a considerable distance and at the moment of impact with the ground it forms a pit of at least 16 meters, from which it managed to get out without suffering any injury by digging with its bare hands a slope that brought it to the surface. Thus, the baron manages to get through all these extraordinary events and fulfill his mission, finally managing to regain his freedom (3).

In 1977, the term "Munchausen Syndrome by Transfer" or "Fact Intermediate Disorder" was introduced, which represents the production of false symptoms to another person, especially children. Most often, this syndrome is associated with parents presenting with their children in a medical unit. They present a false symptomatology or produced even by the parents, being subjected to various treatments, investigations and risky procedures without a real benefit (2).

The importance of this pathology lies in the complexity of diagnosing and treating cases, often the patient being considered a medical mystery due to the inconsistency between symptoms and clinical and paraclinical investigations. Due to the possibility of presenting patients in all medical or surgical specialties, any doctor must be able to raise the suspicion of Munchausen syndrome. In the absence of diagnosis, the patient continues to go to the hospital and undergo multiple

procedures and prolonged hospitalizations. These have many negative effects both on the person concerned and on the health system, with a major impact on costs (1).

The etiology of MS is unknown, but certain psychosocial factors are associated with this diagnosis, including: traumatic childhood experiences, the death of a close family member at a young age, or abandonment. These experiences cause the patient to seek attention and care from the medical staff by fabricating a pathology (4). It has been observed that many of the patients suffered from childhood an important condition that required hospitalization. This early contact with the health system is considered to play an important role in the development of the disease. Also, a correlation was found between patients with personality disorders and those with MS, who have many common behavioral characteristics (5).

The incidence of MS is difficult to predict due to the difficulty with which the diagnosis is made. In some cases, it is possible for the patient to leave the medical institution once faced with inaccuracies in his hospitalization and to seek help and understanding in another hospital. An incidence of MS is estimated at approximately 6.8 cases per 100,000 patients (4).

The diagnosis of MS is a challenge for all medical specialties in terms of the variety of symptoms on presentation. The most common doctor's appointments include:

- chest or abdominal pain
- abdominal pain
- vomiting, diarrhea
- anemia
- hypoglycemia
- infections
- headache, weakness, seizures
- decreased visual acuity
- dermatological lesions
- arthralgia (4).

At any presentation in a medical service, the possibility of an MS should be discussed when there are some alarm signs and patients meet certain characteristics that have been observed to prevail in groups of patients with MS (6). Alarm signs that bring MS into question:

Typical characteristics of patients

- Atypical symptoms, which are not supported by clinical and paraclinical examination;
- Atypical symptoms that do not respond to treatment;
- Reports of numerous drug allergies;
- The appearance of new symptoms when the previous ones start to decrease in intensity;
- Lack of visitors during hospitalization;
- Extensive medical history, without being supported by diagnoses or medical interventions.
- Female sex;
- Age between 35 and 50 years;
- Unmarried;
- Job in the medical field;
- Previous diagnosis of depression.

DSM-5 criteria are used to diagnose patients susceptible to MS. These include, in the first instance, the identification of the deception by falsifying physical or mental symptoms or by one's own injury. Second, the patient presents himself to others as a sick, injured, or incapacitated person. Another criterion implies the lack of an external gratification, but also the lack of another mental disorder that would justify the behavior.

The differential diagnosis is made mainly with:

- Simulation

Malingering is a fabrication or exaggeration of symptoms for the purpose of external gain. Those who simulate a certain pathology can seek a financial reward, sick leave or compensation for accidents. Also, the military and detainees often simulate an illness in order to escape military service or imprisonment, respectively. Unlike simulation, in MS there is a psychological need to play the role of patient and to be cared for, without the need to gain an external advantage (7).

- Conversion disorder

Conversion disorder is a psychiatric condition characterized by signs and
symptoms of neurological impairment, without an existing organic cause. The symptoms are not deliberate and cannot be controlled by the patient, which causes a decrease in the patient's quality of life. Hearing aids include: psychogenic non-epileptic seizures, paralysis, tremors, inconsistent weakness, dystonia, myoclonus, sensory impairment, and impaired vision, hearing, and smell (8).

- Disorders with somatic symptoms

Disorders of somatic symptoms involve one or more somatic symptoms that persist over a long period of time and cause the patient to think excessively. These disorders are very similar to the conversion disorder, the difference being the patient's exaggerated response to the symptoms presented in the disorders with somatic symptoms. In order to differentiate a conversion disorder or a disorder with somatic symptoms from an MS, evidence must be found to show that the patient is deliberately trying to deceive the medical staff about his or her health, which is characteristic of the latter pathology.

- Borderline personality disorder

Borderline personality disorder is often found in patients with MS and is described as emotional instability, lack of impulse control, but also impaired interpersonal relationships and self-esteem. Clinically, patients are impulsive, nervous, prone to self-harm and suicide (9). Unlike MS patients, those who suffer from borderline personality disorder recognize the autolytic nature of the lesions and do not try to mislead medical staff.

MS treatment is difficult to initiate due to the patient's lack of acceptance of the diagnosis. He becomes hostile, denies his behavior, refuses treatment and leaves the medical unit to seek understanding elsewhere. A psychiatric consultation is absolutely necessary to diagnose and treat other conditions that may be present. It is important to take an empathic approach and create a trusting relationship between doctor and patient to increase the chance of adherence to treatment.

As a first step, long-term psychotherapy is recommended for all patients with MS. Drug treatment has been shown not to reduce the symptoms of the disease. However, a high percentage of patients with MS also have other psychiatric comorbidities, the proper treatment of which can improve the condition of patients. The most common psychiatric pathologies associated with MS are: depression, personality disorder (especially borderline personality disorder) or substance abuse (alcohol or drugs) (10).

The prognosis of patients with MS is poor, due to the low number of patients who accept the diagnosis and treatment. Among those who accept the start of psychotherapy, a significant percentage give up. However, those who continue long-term psychotherapy show favorable results. Patients who have

affective disorders or are addicted to certain substances have a better prognosis, unlike those with personality disorder (5).

Post-traumatic stress disorder (PTSD) is a chronic psychiatric condition, with important implications for the mental health of patients, which develops after experiencing a traumatic event such as: war, natural disasters, abuse or death of a loved one. Although the majority of the population who suffered an episode of this kind during their life show symptoms that have a resolute character within a period of a few weeks, a percentage of 10% -20% has a persistence of symptoms and a significant impairment of quality of life (11).

The prevalence of PTSD in the United States is 8.7%, and there is an increase in risk groups, including military veterans, firefighters, police officers, and emergency medical personnel. Also, people who have been abused or held captive in the past are at a much higher risk of developing PTSD. The prevalence of the disease is lower in the pediatric population, but the cause is considered to be a lack of adequate diagnosis and not a really low number of affected children (12).

The mechanisms that produce this pathology have not been fully discovered, but the implications of the immune and neuroendocrine systems have been suggested. Following the experience of a traumatic event, there is an activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis which causes an increased release of catecholamines and glucocorticoids that will have a proinflammatory effect. High levels of interleukin 1β (IL-1β) and interleukin 6 (IL-6) were found in these patients, as well as tumor necrosis factor alpha (TNF-α). They are considered to be a biological basis that acts on a pre-existing vulnerability to develop PTSD. In addition, the possibility of a genetic predisposition with encouraging results has been studied, which necessitate a deepening of future research (13).

Animal and human studies have shown that the brain regions associated with PTSD are the prefrontal cortex, the anterior cingulate cortex, the amygdala, and the hippocampus. The use of magnetic resonance imaging in patients with PTSD has shown a reduction in the volume of the hippocampus and anterior cingulate cortex. Magnetic resonance imaging has shown excessive amygdala activity and hypofunction in the anterior medial and cingulate prefrontal cortex in conditions of fear. However, the activity neuronal damage in the anterior cingulate cortex remains controversial, in terms of the analysis of other groups of patients who showed a higher level as opposed to those of normal people (14).

The diagnosis of PTSD is based on 8 diagnostic criteria (A-H) specified in the DSM-5, which are valid only for adults and children older than 6 years. For children under 6 years, criteria C and D are combined, the diagnosis being made with the help of 7 criteria (15).

Treatment guidelines recommend both psychological and pharmacological therapies for PTSD. These should be started as soon as possible after the trauma, and the choice of therapies is made according to the patient's preference and desire to participate, but also to the access to them. Psychological therapies include: exposure therapy, cognitive processing therapy, behavioral cognitive therapy, and EMDR therapy (desensitization and reprocessing by eye movement) (16).

Exposure therapy is based on the theory of emotional processing, which evokes the idea

that traumatic events are not emotionally processed when they occur. This is done in 8-15 sessions and includes psychoeducation about PTSD, common reactions to trauma, breathing exercises to help in stressful situations and two types of exposure: in vivo and imaginary. Repeated in vivo exposure helps patients to address the issues, situations, or fears that have caused the trauma suffered until there is a decrease in negative feelings. Instead, imaginary exposure helps the patient to analyze memories, thoughts, or emotions that are related to the traumatic event and that were avoided by him. Individuals who participated in this type of therapy showed a greater decrease in symptoms, as opposed to those who received supportive therapy or drug treatment (11).

Cognitive processing therapy is based on the assumption that reducing negative thoughts about the traumatic event will lead to a decrease in PTSD symptoms. This type of therapy is most often used for veterans and those working in the military. In cognitive processing therapy it is considered that there are certain blocking points that prevent recovery. These are negative thoughts about the cause or implications of the traumatic event, such as self-blame ("Trauma was my fault") or blaming others (17). The Socratic method is used, which tries to reduce the negative opinions related to trauma and the distorted thinking with balanced ones and which helps the cognitive restructuring and recovery of the person (18).

Cognitive behavioral therapy is similar to cognitive processing therapy and is based on cognitive reconstruction, behavioral change, and social support to determine symptom relief (19).

Drug therapy is recommended by one-third of the existing guidelines if the psychotherapy did not give the expected results. This recommendation comes as a result of a meta-analysis that compared the two means of treatment, showing the superiority of psychotherapy in creating beneficial effects for the individual with PTSD. However, certain categories of patients are recommended first-line pharmacological treatment, such as those in rural areas, those who cannot afford psychotherapy, those who prefer drug treatment, or people with other psychiatric comorbidities who would benefit from medication (such as depression) (20).

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors declare that they have no potential conflicts of interest to disclose

REFERENCES

1. Sousa Filho D, Kanomata EY, Feldman RJ, Maluf Neto A. Munchausen syndrome and Munchausen syndrome by proxy: a narrative review. Einstein (Sao Paulo). 2017; 15(4): 516-521.
2. Tatu L, Aybek S, Bogousslavsky J. Munchausen Syndrome and the Wide Spectrum of Factitious Disorders. Front Neurol Neurosci. 2018; 42:81-86.
3. Raspe RE. The surprinsing adventures of baron Munchausen. London: Lawrence and Bullen, 1895, 40-46.
4. Weber B, Gokarakonda SB, Doyle MQ. Munchausen Syndrome. 2021. In:StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
5. Carnahan KT, Jha A. Factitious Disorder. 2021. In: StatPearls.Treasure Island (FL): StatPearls Publishing; 2021. PMID: 32491479.
6. Abeln B, Love R. An Overview of Munchausen Syndrome and Munchausen Syndrome by Proxy. Nurs Clin North Am. 2018; 53(3):375-384.
7. Gelder M, Gath D, Mayou R. Tratat de psihiatrie Oxford. București: Asociația Psihiatrilor Liberi din România,1994.

8. Peeling JL, Muzio MR. Conversion Disorder. 2021. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. PMID: 31855394.
9. Storebø OJ, Stoffers-Winterling JM, Völlm BA et al. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2020; 5(5):CD012955.
10. Caselli I, Poloni N, Ceccon F et al. A Systematic Review on Factitious Disorders: Psychopathology and Diagnostic Classification. Neuropsychiatry. 2018; 8(1), 281-292.
11. Watkins LE, Sprang KR, Rothbaum BO. Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions. Front Behav Neurosci. 2018; 12:258.
12. Liriano F, Hatten C, Schwartz TL. Ketamine as treatment for post-traumatic stressdisorder: a review. Drugs Context. 2019; 8: 212305.
13. Miao XR, Chen QB, Wei K et al. Posttraumatic stress disorder: from diagnosis toprevention. Mil Med Res. 2018;5(1):32.
14. Yabuki Y, Fukunaga K. Clinical Therapeutic Strategy and Neuronal Mechanism Underlying Post-Traumatic Stress Disorder (PTSD). Int J Mol Sci. 2019; 20(15):3614.
15. Verbitsky A, Dopfel D, Zhang N. Rodent models of post-traumatic stress disorder: behavioral assessment. Transl Psychiatry. 2020;10(1):132.
16. Pary R, Micchelli AN, Lippmann S. How We Treat Posttraumatic Stress Disorder.Prim Care Companion CNS Disord. 2021; 23(1):19nr02572.
17. Dillon KH, Hale WJ, LoSavio ST, et al. Weekly Changes in Blame and PTSD Among Active-Duty Military Personnel Receiving Cognitive Processing Therapy. Behav Ther. 2020; 51(3):386-400.
18. Livingston NA, Berke D, Scholl J et al. Addressing Diversity in PTSD Treatment: Clinical Considerations and Guidance for the Treatment of PTSD in LGBTQPopulations. Current Treatment Options Psychiatry. 2020;1-17.
19. Li J, Li X, Jiang J, et al. The Effect of Cognitive Behavioral Therapy on Depression, Anxiety, and Stress in Patients With COVID-19: A Randomized Controlled Trial.Front Psychiatry. 2020; 11:580827.
20. Martin A, Naunton M, Kosari S et al. Treatment Guidelines for PTSD: A Systematic Review. J Clin Med. 2021;10(18):4175.

Correspondence:

Petronela Nechita,
MD,PhD Senior psychiatrist, "Socola" Institute of Psychiatry, Iasi, Romania, no.36 Str. Bucium,
craciunpetronela@yahoo.com

Submission: 09mar 2022
Acceptance: 27may 2022

Instructions for authors

The Bulletin of Integrative Psychiatry publishes blind peer reviewed articles, reviews, updates, meta analyses, original papers, case reports in the following fields of research: psychiatry correlated with philosophy, ethics, meta ethics, bioethics, aesthetics, economy, sports, nutrition, law, forensic medicine, political sciences, communication science ,sociology, social assistance, anthropology, cultural anthropology, literature, religion. The journal is published quarterly in English.
Articles are submitted to the discussions in meetings of the Editorial Board, being subjected to a blind peer review evaluation from two specialists in the field.
Evaluating the scientific value and originality of the article, as well as its layout, grammar and structure and the way in which the guidelines for publication have been observed, the final publication decision is made by the editor-in- chief and the advisory board. It is also required that the article admitted for publication should represent a substantial contribution in the field, and the data included are correct and pertinent.
There are no author fees and all articles are made free access on line.
In the Declaration of Interests, authors must indicate any financial and personal relationships with other people or organizations that could influence in an incorrect way their work.
Conflict of interests can refer to financial relationships and academic competition.
Authors should not submit articles that have been published or sent for publication to other journals.

Bulletin of Integrative Psychiatry, accept for publication the following types of works (articles): reviews, updates, meta analysis, original papers, case report

Fields of research: psychiatry correlated with philosophy, ethics, metaethics, bioethics, esthetics, economy, sports, nutrition, law, forensic medicine, political sciences, communicational sciences, sociology, social assistance, anthropology, cultural anthropology, literature, religion etc.

Manuscript Criteria and Information
Manuscripts and all attached files should be submitted in electronic form and on paper.
The electronic form should be submitted, either on compact disk or by e-mail (see at end). It is preferable that two copies (in English and Romanian) of the manuscript, printed on one side of A4 paper format, single-spaced, with 2 cm margins, be also submitted to the same address. The manuscript should be accompanied by a **cover letter** including the statement on authorship responsibilities form, the statement on ethical considerations and the statement on financial disclosure (For more information please see directions on website).

Authorship
All named authors should meet the criteria for authorship as stated in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" issued by the International Committee of Medical Journal Editors (www.icmje.org).

Ethical considerations

If the scientific project involves human subjects or experimental animals, authors must state in the manuscript that the protocol has been approved by the Ethics Committee of the institution within which the research work was undertaken. All authors are responsible for adhering to guidelines on good publication practice.

Financial Disclosure

The manuscript should be accompanied by a **cover letter** including the statement on financial disclosure. The statement on conflicts of interest will be published at the end of the paper. Please submit all requested signed documents by regular mail to the Secretariat. Scanned copies sent electronically and fax submissions are not acceptable.

Corrections

Scientific fraud is rare events; however, they have a very serious impact on the integrity of the scientific community. If the Editorial Board uncovers possible evidence of such problems it will reserves the right to take all steps it considers necessary for the elucidation of the situation, including possibility to publish errata, corrigenda, or retractions.

Copyright

The papers published in the Journal and protected by copyright. Their full or partial publication in other journal is allowed only with the written approval of the publisher.

Manuscript Preparation

- Romanian authors should send both the Romanian and English version of the article, including title, abstract and key words. Foreign authors should send the English version of the article.
- Manuscripts must be prepared in conformity to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" issued by the International Committee of Medical Journal Editors (www.icmje.org).
- Articles must be written in Microsoft Word, Style: Normal + Justify, Font: Times New Roman, size 12. All manuscripts must be typed single-spaced. Original source files (not PDF files), are required. In text editing, **do not use** spacing with spacebar, or paragraph mark, use only Enter or Tab key.
- Subheadings of the article should be left-justified, typed with capital letters, Font: Times New Roman, size 12.
- The abstracts and Key words must be written in Microsoft Word, Style: Normal + Justify, Font: Times New Roman, size 12.
- Use as few formatting commands as possible:
  - input your text continuously (without breaks);
  - do not use different types of fonts to highlight your text;
  - any word or phrase that you would like to emphasize should be indicated throughout the text by underlining;
  - use only the "Enter" key to indicate the end of the end of paragraphs, headings, lists etc.;
  - do not use the "Space Bar" to indicate paragraphs, but only the "Tab" key
- Figures must be cited in order in the text using Arabic numerals, (e.g., fig.2). Their width should be max. 13,5 cm. The figures have to satisfy the following conditions:

- Black and white photographs with good contrast, with recommended size;
- Scanned photograph with a resolution of minimum 300 dpi and edited on a computer, original file (*JPG);
- Illustrations (drawings, charts) created on a computer, cited in the text, original file (*XLS, *CDR). Every figure should be accompanied by a title and a legend.
- Tables, numbered consecutively with Latin numerals (e.g., Tab. II), should have a width of max. 13,5 cm. Every table should be also accompanied by a title and a legend. The distribution of tables and figures in the text should be balanced.
- Please do not import tables or figures into the text document, but only specify their insertion in text (e.g., Table No.III insertion). They have to be sent in separate files. Files should be labeled with appropriate and descriptive file names.
- Abbreviationsshall be avoid. If used, will occur preceded by the full term at their first apparition in text. A list of all used abbreviations shall be made at the end of the article,
- Separate pages:tables, graphics, pictures and schemes will appear on separate pages.
- You may use a common compression program: ARJ, RAR or ZIP.

Manuscript organization

Article title: titles should be short, specific, and descriptive, emphasizing the main point of the article. Avoid a 2-part title, if at all possible. Do not make a declarative statement in the title. Title length, including punctuation and spaces, ideally should be under 100 characters and must not exceed 150 characters.

Manuscript Size

- Original paper - 8 pages/3500 words;
- Review and update - 8 pages/3500 words;
- Case report - 4 pages/1700 words;
- Clinical notes - 3 pages/1300 words;
- Letters to editor, information scientific reunions - one page/450 words.

Author(s). First name, middle initials and surname of the authors, without any scientific, didactic or military degrees; (e.g., Mircea A Popescut, Aura Vasilescu, **not Popescu M.A., Vasilescu A.**).

Footnote that specifies the authors' scientific titles, professional title, name and address of their workplaces (institution and department) for each author; contact details of the corresponding author (full address, telephone number, fax number, e-mail address) and the address of the institution and department where the study has been carried out. Contact details will be published unless otherwise requested by the author.

Abstracts in **in English and Romanian,** should have max. 300 words. For original articles is advisable to include five paragraphs, labeled Background, Objective(s), Method(s), Result(s), and Conclusion(s).

Keywords maximum of 6 keywords (minimum of 3). Keywords should not repeat the title of the manuscript.

Original papers organized in:

- **Introduction** (no more than 25% of the text), material and methods, results, comments or discussions and acknowledgements.
- **Material and methods** have to be described in enough detail to permit reproduction by other teams. The same product names should be used throughout the text (with the brand name in parenthesis at the first use).
- **Results** should be presented concisely. Tables and figures should not duplicate text.
- **Discussions** should set the results in context and set forth the major conclusions of the authors.
- Information from the Introduction or Results should not be repeated unless necessary for clarity.

The discussion should also include a comparison among the obtained results and other studies from the literature, with explanations or hypothesis on the observed differences, comments on the importance of the study and the actual status of the investigated subject, unsolved problems, questions to be answered in the future.

- **Acknowledgements** section must disclose any substantive conflicts of interest in addition to the customary recognition of non-authors who have been helpful to the work described.

References. Referencesshould be numbered consecutively **in the order in which they are first mentioned in the text**. Identify references in text, tables, and legends by Arabic numerals in parentheses. The reference list will include only the references cited in the text (identified by Arabic numerals in parentheses, **not in square brackets and not bold).** All authors should be listed when four or less; when five or more, list only the first three and add "et al" (Popescu I, Popescu I, Vasile V. et al). The name of the Journals cited in the References should be abbreviated according to ISI Journal Title Abbreviations.

It is absolutely imperative that references to be entered in the text!!

Examples:

- **Reference to a journal publication:**

Amura SG.: Neurotransmitter transportor: recent progress. Ann Rev Neurosci 1993; 16; 73-93.
Tonis PJ, von Sandick JW, Nieweg OE, et al.: The hidden sentinel node,in breast cancer. Eur J Nucl Med 2002; 29: 305-311

- **Reference to a book:**

Ashcroft FM.: Ion channels and disease, San Diego, London: Academic Press,
2000, pp. 26-52.

- **Reference to a chapter in an edited book:**

Pandiom MR, Fischer DA. Immunoradiometric assays. In: Scabes CG, editor.
Handbook of Endocrine Research Techniques. New York, London: Academic Press, 1993, 26-52
The punctuation and the general aspect of the text format must comply with the rules mentioned above. This is a mandatory and eliminatory condition.

ACKNOWLEDGMENTS AND DISCLOSURE

Authors: an "author" is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications (1). An author must take responsibility for at least one

component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity.

We strongly encourage developing and implementing a contributor ship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.

Disclosure: The authors must declare if they have or not a potential conflicts of interest to disclose.

Acknowledgments: All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Authors should declare whether they had assistance with study design, data collection, data analysis, or manuscript preparation. If such assistance was available, the authors should disclose the identity of the individuals who provided this assistance and the entity that supported it in the published article. Financial and material support should also be acknowledged.

PEER REVIEW PROCESS

Although the practice of peer review started 300 years ago, only since 198s the process has been active to analyze if articles sent to journals are well-written, correctly edited and represent reliable sources of information.

All manuscripts intended for publication will be subject to blind peer-review by a committee of experts which assesses the scientific and statistical correctness of articles submitted. The committee receives the manuscripts without knowing the authors' name and proposes possible changes, which will be transmitted to the authors by the medium of Editorial Board. The authors have the obligation to oversee the text in English language with the help of a professional translator.

When submitting a paper, a confirmation email is automatically sent back to the author. It contains a unique registration number used as a referral in further correspondence.

Initially, the editorial team verifies whether the manuscript complies with the editing instructions. If the paper does not meet the necessary requirements, it is rejected and the corresponding author is notified to correct the errors. If all instructions for editing have been followed accordingly, the editor selects two reviewers that will independently evaluate the paper. They have high expertise in the "peer-review" system and are well-known specialists in the field. The reviewers have all academic affiliations and may be already accredited by the Journal or specifically contacted for certain papers. Their affiliation is usually different from the one of submitting authors.

The editor sends the paper in both electronic and printed format to each reviewer with the invitation to evaluate it within 15 days. The reviewers will analyze the paper from several perspectives such as clarity, objectivity of data, scientific quality and relevance. A scale from 1 to 5 is used, where 5 is excellent and 1 is poor. The reviewers score the paper accordingly and issue a recommendation.

The existence of a manuscript under review is not revealed to anyone other than peer reviewers and editorial staff. Peer reviewers remain anonymous and are expected to maintain strict confidentiality. After the review process has been completed, authors will be informed by mail of the Editor's decision.

Reviewers should inform the editor about suspected plagiarism.

Mandatory fill and send "Cover letter for submission of manuscript" and "Declaration of Interests and disclosure form", which you can download from the website of Bulletin of Integrative Psychiatry (www.buletindepsihiatrie.ro).

Ethical Considerations

Authors of articles should sign a statement assuming the responsibility for the originality, property rights and ethical implications of their work. Authors should obtain permission or copy right to publish figures, images or tables from other journals whose material they use.

A written consent must be obtained from patients when personal information or images of patients are included in the article. Authors must state that the protocol has been approved by the Ethics Committee of the institution where the research was conducted.

Address to send the manuscripts is:

Buletin de Psihiatrie Integrativa/ Institutul de Psihiatrie “Socola” Iasi

Lecturer Alexandra Bolos: Institutul de Psihiatrie “Socola” Iasi, Șos. Bucium 36, 700282, Iasi, jud. Iasi; E-mail: **contact@buletindepsihiatrie.ro**