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The image on the first cover represents the main building of "Socola” Institute of Psychiatry Iași

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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.

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Editorial contact: contact@buletindepsihiatrie.ro

Publisher contact:

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Editorial

Covid-19 – the last wave

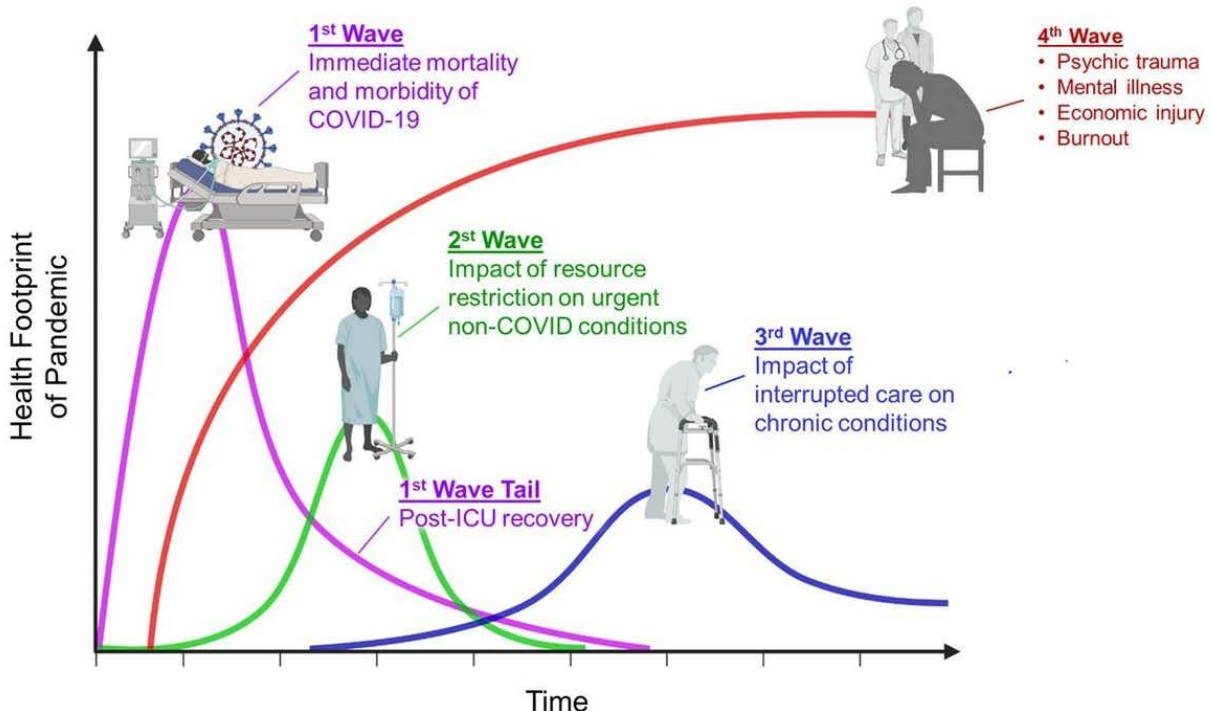
Matei Palimariciuc, Roxana Chiriță

Matei Palimariciuc - M.D., PhD student, Assistant Professor, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Romania

Roxana Chiriță - M.D., PhD., Professor, senior psychiatrist, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Romania, „Socola” Institute of Psychiatry Iași, Romania

It seems that in our corner of the world the threat of the pandemic has smothered, at least for now, with lower numbers of new cases being reported every day. This is of course the result of the coordinated efforts of the vaccine campaign, of people understanding the importance of social distancing and unfortunately of the sheer number of people actively immunized by being infected. The latter is estimated by

unofficial sources to be in the millions, outnumbering the doses of vaccines administered in Romania. The scientific community’s consensus cannot rule out the occurrence of a fourth wave but even in such an event we could somewhat rest assured based on the experience gained from the first three. There is however a different kind of fourth wave coming illustrated in the image below.

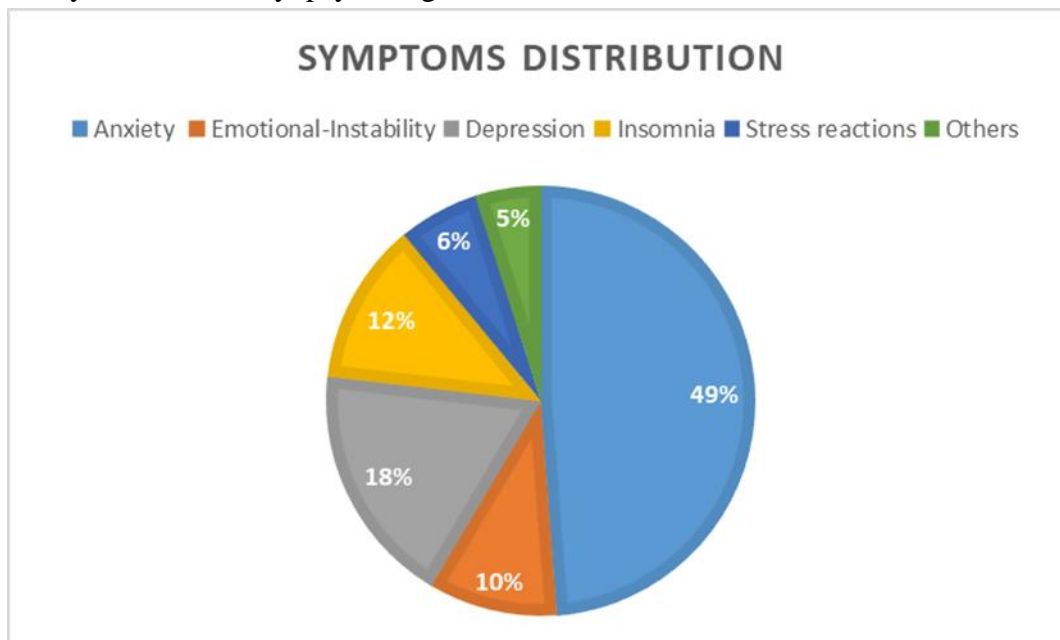


This image was first popularized by M.D. Victor Tseng on Tweeter in March, 30th 2020. The X and Y coordinates are not based on any scientific data as the author himself mentions, it is though the perfect conceptual framework for the health cost projection of the pandemic. In Romania as much as we can see we are recovering from the third wave depicted in this image with hospitals beginning to open toward chronically ill patients.

Addressing the fourth wave of psychic trauma our hospital and university alike, piloted Covid-19 psych support health lines in which professional psychiatry health care workers offered their services to medical students and health care workers affected by the pandemic. These support lines, popularized through the official web pages of the hosting institutions were formed in response to observational data coming from all around the world which indicated that health care workers and students are most prone to experience psychic distress during the pandemic.

The university support line comprised of academics working in the “Socola” Institute of Psychiatry and university psychologists

saw a discrepancy of addressability between psychiatrists and psychologists, in favour of the latter. This preference for psychologists can be explained by at least two factors: the stigma associated with psychiatry and psychologists proximity due to them working within the student campus. Less than one percent of students solicited assessment from one of the psychiatrists included in the program. One might think that this is a good result and consider that it is the outcome of students not developing distress symptoms but this contradicts statistics around the globe stating that between a third and a half of students experienced significant amounts of distress during the pandemic. Of course, not all require professional attendance and not all who solicited support did so through our services but we can’t logically exclude the fact that there is a significant proportion of students who would and can still require psychological support and that through different reasons hesitated in doing so. From what we have seen so far, students who did call for support experienced symptoms ranging from mild anxiety and insomnia to severe depression and Post-Traumatic Stress Disorder as depicted in the following chart.



With these results in our minds, we have to move forward and lay out the design of a national response strategy to the so-called Fourth Wave of Psychic Trauma and Mental Illness. The Romanian Health Ministry has already laid down the cornerstone establishing a national psychological support line for people affected by the Covid-19 pandemic. The line is staffed by more than 40 volunteer psychotherapists and it is open Monday through Saturday from 12 am to 8 pm.

At “Socola” Institute of Psychiatry there are currently more than one hundred psychiatry residents in training, doctors whose potential is not fully utilized at this time due to the hospital’s strategy in fighting the pandemic. Many feel like time is passing by and that they do not have the proper environment to develop the attributes needed to practice psychiatry. Many wish to

have the ability to practice the caring nature of medicine and to do their part in the fight against the pandemic.

In conclusion, we hereby submit for analysis the possibility of establishing a 24/7 psychological support line staffed by on-call psychiatry residents from every training centre. The service could be included in the mandatory training module entitled Community psychiatry and performed by doctors who have completed the Psychotherapy training module in the third year of residency. Based on international guidelines and by using an agreed upon triage algorithm the residents could offer supportive psychotherapy to those experiencing mild to moderate distress caused by the pandemic and refer those with severe and continuous symptoms to standard mental health consult.

Articles

Using Mate20 in improving the number sense in case of students with specific learning disabilities with impairment of mathematics

Petru – Marian Călinescu

Petru-Marian Călinescu - PhD Student, Psychology and Education Sciences Faculty, Alexandru-Ioan Cuza University of Iași

ABSTRACT

The primary cause for the specific learning difficulties with impairment of mathematics seems to be the weakness of the number sense, defined as the ability to non-verbally represent and manipulate numerical quantities. Performance on additions and subtractions of natural numbers is seen as a measure of the number sense. But above mentioned performance is negatively influenced by the maths anxiety. An intervention based on educational games is susceptible to improve the numerical skills. Mate20 was specially designed to improve the number sense, acting on both arithmetic knowledge and math anxiety. The aim of the present study is to measure the effectiveness of the intervention based on Mate20 program. 55 students with specific learning disabilities with impairment of mathematics participated in a controlled clinical study. The experimental group received for 2 weeks, 15 – 20 minutes per day, an intervention based on the use of Mate20 educational program. The control group benefited from a classic intervention during support hours. A non-standardized test containing 76 items and Abbreviated Maths Anxiety Scale were applied before and immediately after the interventions. The number of correct answers, respectively of errors were statistically processed. After the intervention based on Mate20, participants recorded significantly less errors, concomitantly with a significant improvement of the number sense. More than that, participants of the experimental group registered significantly fewer errors and an significant improvement of the number sense compared to the control group. No correlation between math anxiety level and improvement of the performance were outlined. Future research will evaluate the persistence of gained results over time.

KEYWORDS:

Number sense, specific learning disabilities with impairment in mathematics, math anxiety, Mate20.

INTRODUCTION

Mathematics and number sense. Mathematics is a language whose first aim is to represent and to model the reality (1). Learning mathematics is synonymous with acquiring this new and complex language, and this approach intensely requests the attention and the memory resources. The primary source of learning difficulties in mathematics seems to be the impairment of the "number sense". According to Dehaene (2), the number sense is "the ability to non-verbally represent and manipulate numerical quantities". Brain neuroimaging has located the extraction of numbers from sets of objects and the reversible transitions from quantities to numerical symbols in the intraparietal sulci of both hemispheres (3). No agreement was reached in the question if the difficulties of learning mathematics are the consequence of

- a) a misrepresentation of numerical quantity itself or
- b) a poor connection between understanding quantity and symbolic representation of number(4).

However, learning mathematics can also be impeded by deficits in attention, language, memory, or by poor visual-spatial ability, lack of sequential organization or cognitive inadequacies (5).

Jordan, et. al., (6) states that a battery for assessment of the number sense has to include tasks of numerical quantities comparisons, counting, identification of numbers and simple arithmetic operations. But, due to the hierarchical structure of mathematical knowledge, testing the addition and subtraction might be sufficient, since the above mentioned operations include counting, identifying numbers and comparing them.

Improving the number sense through gaming. Neurocognitive systems provide only a framework for basic numerical skills (7), in the form of fundamental, general principles, which will be further developed through practice. Therefore, engaging in various games or activities with a formal or non-formal educational content helps to form

numerical skills. In general, math problems raise difficulties, for both normal students and special educational needs students (8). Games have the advantage to generate a positive emotional state and thus to increase students' motivation for learning. Phillips et. al. (9), analyzing 58 qualitative studies, reported a decrease in anxiety and an increase in motivation in students who were involved in educational games. Takeuchi and Vaala (10) conducted a study of more than 700 teachers in the USA and reported an improvement in math learning in 71% of cases of digital game users meant to support learning. Highly personalized and engaging games help to form the so-called 21st century specific skills: increased motivation, communication efficiency, critical thinking, perseverance. (11). Students who play serious games become more involved in learning, and the results obtained are easier quantifiable (12). Despite all these evidences, meta-analyses conducted by various authors have often led to contradictory results (13).

The impact of the intervention on math anxiety in terms of performance. The public humiliation of the student is considered to be the main cause of math anxiety installation. Teachers' hostility and embarrassing situations are potentially generating math anxiety. In turn, students suffering of math anxiety avoid the situations where it is necessary to use mathematical knowledge (14), and choose a scholar and professional route as far as possible from mathematics (15). In consequence, an effective remedial plan for the students with specific learning disabilities must include a therapeutic intervention on math anxiety. Math anxiety affects also the person's memory resources. Through its characteristic intrusive thoughts, math anxiety consumes the resources of working memory (16), which leads to an increase in both the time needed to solve tasks and the probability of appearance of the mistakes (17). Decreasing anxiety is expected to free up additional resources of working memory, which translates into increasing performance.

Mate20 and improving the number sense. The educational software Mate20 was designed to intensify the educational intervention on students with specific learning disabilities affecting the mathematical field, on the one hand, by increasing students' involvement in learning perceived as a game situation, and on the other hand by increasing the number of students the teacher simultaneously can work with. The intervention is focused on ameliorating the number sense, taking into account the limited effort resources of special educational needs persons. The intervention was designed in a similar way to the Program for training students in order to access the positions of mathematics teachers, offered by Khan Academy (18).

Mate20 gamifies learning (19), in order to improve the innate number sense. Mate20 is organized on three levels with increasing degrees of difficulty: performing comparisons, additions and subtractions of natural numbers in the intervals 0 - 10, 0 - 100; respectively 0 - 1000. The transition from one level of the game to the next one is marked by a counting exercise of moving objects. If the player gives the correct answer, he or she receives a feedback consisting of a suggestion meant to influence math anxiety and the dysfunctional beliefs about learning mathematics. In case of a wrong answer, a tutorial is displayed on the screen in order to exemplify the forward and backward counting, or to explain to the student how to make a correct addition or subtraction. The three codes of representation of numbers: verbal, symbolic and concrete are simultaneously used. The transition from units to tens is marked by a specific sound and the reversible replacement of ten 1-penny coins with a 10-penny coin. Also, the placement of the coins on the tablet respects the division into classes of units, tens, respectively hundreds.

After completing the first level, consisting of simple operations with natural numbers up to 10, students were asked to perform more complex calculations and those with passing over the order in a classical way using pen and paper, and then to introduce the final

results in the game box. During the calculations, students were encouraged to use their fingers anytime they had doubts about the outcome of an operation. Although appreciated as an artifact in the acquisition of knowledge (20), the use of fingers during counting has proven its effectiveness due to the role of semiotic mediation that this behavior possess (21).

OBJECTIVES

The objective of the current research was to verify, in a controlled clinical study, the effectiveness of the intervention using Mate20 software on the numerical sense of students with specific learning disabilities with impairments of mathematics.

Hypothesis 1: the participants who benefited from educational intervention with the help of the Mate20 game will register at the end of the intervention stage several correct answers, respectively a smaller number of errors compared to the moment before the intervention.

Hypothesis 2: participants who benefited from educational intervention with the help of the Mate20 game will record at the end of the training more correct answers and fewer errors compared to students in the control group, who benefited only from the classical intervention during support hours.

MATERIAL AND METHODS

The participants in the study were 55 students with adapted curriculum, aged 9 - 15 years, whose scores on the arithmetic subscale of Wechsler Intelligence Scale for Children situated with at least two standard deviations below the expected score according to the chronological age. Participants with non-verbal and verbal scores with more than one standard deviation below the expected score according to chronological age were excluded from the research, in order to avoid possible interference with other potential sources of influence on the data obtained (22). 30.91% of the participants were female, and 47.27% of them came from rural schools.

After distributing the participants in the two groups (the equivalence was partially

achieved, for practical reasons, while it was necessary to take into account the access in the schools of the teacher who applied the intervention), a non-standardized test was applied. The 76 items consisted of additions and subtractions of natural numbers whose results are also in the set of natural numbers. The Abbreviated Maths Anxiety Scale, translated and validated for the Romanian school population, was applied also. The participants in the experimental group received for 2 weeks an intervention program consisting of playing the Mate20 game for 15-20 minutes each day, assisted by the teacher. Participants in the control group benefited only from the usual intervention during support hours. After two weeks, the test was applied again and the results were quantified in terms of:

- (a) number of correct answers provided;
- (b) number of lacking items;
- (c) number of errors, as follows: e1 - mistakes in performing additions up to 10; e2 - mistakes in making subtractions up to 10; e3 - mistakes in performing additions up to 20; e4 - mistakes in making subtraction up to 20; e5 – when the student did not pass ten further to the neighboring higher rank; e6 – when the student did not borrow 10 from the neighboring higher rank; e7 - when the

student enters parasitic digits; e8 – when the student omits digits; e9 – when the student does not respect the ranks of the numbers; e10 - when the student reverses the low with the subtractor; e11 – when the student confuses the addition and subtraction operations; e12 - when the student performs the operations from left to right.

The first four types of errors were considered to evaluate the number sense, the other types of errors being rather a measure of proficiency in using rules and arithmetic calculation algorithms.

RESULTS

In order to test the first hypothesis, the normality of the distribution of the data recorded before, respectively after the educational intervention, was verified. The Kolmogorov-Smirnov test indicated that the data have a distribution close to normal for the variables the number of initial correct answers (KS $z = 0.143$, $p = 0.168$) and the number of final correct answers (KS $z = 0.166$, $p = 0.055$). The paired samples t test indicated that the final number of correct answers is significantly higher than the initial number of correct answers ($t(27) = -3,094$, $p < 0.01$, see Table 1)

Table I: Comparing initial correct answers with final correct answers using paired samples t test. Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 Initial correct – final correct	-4,704	7,854	1,511	-7,810	-1,597	-3,112	26	0,004

Given that the total number of erroneous answers depends not only on the total number of correct answers, but also on the number of omitted items, a comparison between the initial total number of erroneous answers and the final number of erroneous answers was conducted. Data distribution, in the case of the final number of errors, deviates

significantly from a normal distribution (KS $z = 0.172$, $p < 0.05$). As a consequence, the comparison was performed using the nonparametric Wilcoxon test. The final number of errors was significantly lower than the number of errors initially recorded ($z = -3,258$, $p < 0.01$, see Tables 2 and 3)

Tabel II: Descriptive statistics of the variables initial number of errors, respectively, final number of error.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
total initial errors	33	29,64	18,102	0	71
total final errors	26	24,19	15,789	5	69

Tabel III: Value of the Wilcoxon test.

Test Statistics

	total initial errors total final errors
Z	-3,258 ^b
Asymp. Sig. (2-tailed)	,001

- a. Wilcoxon Signed Ranks Test
- b. Based on positive ranks.

In order to measure the influence of the Mate20 training strictly on the number sense, the initial number of errors, respectively the final number of errors attributed to the deficient number sense, according to the formula $e_1 + e_2 + e_3 + e_4$, was computed. The test of normality showed that both variables deviate significantly from a normal

distribution (KS $z = 0.217$, $p < 0.01$, respectively $z = 0.222$, $p < 0.01$), therefore the Wilcoxon nonparametric test was used. The results indicated a significant decrease in the total number of type 1, 2, 3 and 4 errors ($z = -2,803$, $p < 0.01$, see Tables 4, 5).

Tabel IV: Descriptive statistics for the variables initial number sense, respectively, final number sense.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Initial number sense	25	12,64	11,273	0	48
Final number sense	26	7,08	7,429	0	37

Tabel V: Value of the Wilcoxon test.

Test Statistics

	Initial number sense Final number sense
Z	-2,803 ^b
Asymp. Sig. (2-tailed)	,005

- a. Wilcoxon Signed Ranks Test
- b. Based on positive ranks.

Another point of interest of the study was the relationship between math anxiety and the evolution of participants after the intervention with the help of the game Mate20. The correlational analysis did not indicate a link between the level of math anxiety and the effects of the intervention (Spearman $\rho = -0.313$, $p = 0.104$). The analysis of the correlation between the level of mathematical

anxiety and the improvement of the number sense did not reveal, again, a link between these two variables (Spearman $\rho = -0.184$, $p = 0.379$).

When the effectiveness of the Mate20 program was compared with the classic intervention, the results indicated that although the average of the correct answers

recorded by the students who benefited from the intervention with the Mate20 program was higher than the average of the correct answers recorded for the students who benefited from classical intervention, the differences were not statistically significant ($z = -1.433$, $p = 0.152$, see Table 11). However, there were significant differences between the decrease in the number of errors in the non-standardized test produced as a result of the

intervention with the Mate20 game and the decrease in the number of errors as a consequence of the classic intervention ($z = -2.064$, $p < 0.05$, see Table 6). There were also significant differences in that more significant improvement in numerical sense in the Mate20 experimental group compared to participants in the control group were registered ($z = -2.792$, $p < 0.01$, see Table 6).

Table VI: Values of the Mann-Whitney test for the variables improvement of performance 1 (increase of the number of correct answers), improvement of the performance 2 (decrease of the total number of errors), respectively, improvement of the number sense (decrease of the type 1, 2, 3 and 4 number of errors)

Test Statistics

	improvement of performance 1	improvement of the performance 2	improvement of the number sense
Mann-Whitney U	293,000	245,000	203,500
Wilcoxon W	699,000	596,000	609,500
Z	-1,433	-2,064	-2,792
Asymp. Sig. (2-tailed)	,152	,039	,005

a. Grouping Variable: mate20

DISCUSSION

The data indicated a positive evolution of the participants in the intervention program based on the use of the Mate20 game, in the sense that they recorded a higher number of correct answers, as well as a lower number of errors in the non-standardized test requiring arithmetic operations. There was also a decrease in the number of errors in the addition and decrease of natural numbers to 20, considered to be an indicator of improving the number sense. The short duration of the intervention, 2 weeks only, once again supports the ability of the Mate20 game to provide a targeted, focused and effective intervention, designed to improve the numerical sense of students suffering from specific learning disabilities in mathematics. Moreover, a meta-analysis by de Boer, Donker and van der Werf (23) indicated a low influence of the duration of the intervention program and the intensity measured in number of hours per week on its effectiveness, in the sense that an increase in duration over 10 weeks and the intensity of more than 2 hours per week causes a slight increase in the performance of program participants. However, interventions that are too short or too intense can cause a small effect on participants, although the authors cite interventions that have yielded results even after only one week of training. Intervention in children with specific learning disabilities in mathematics may focus on underdeveloped components, the search for bypass techniques (such as using the Calculator application), or the management of neurodevelopmental dysfunctions (5), but training the number sense is a first action in recovering students with a specific disorder of the mathematical field. These because the number sense is the one that strongly correlates with the acquisition of subsequent arithmetic and mathematical skills.

Also, compared to the control group, the participants who benefited from the educational intervention with the help of the Mate20 game, registered a significantly higher evolution in terms of decreasing the number of errors, as well as improving the number sense, even if the increase of the total correct answers did not significantly vary compared to that measured after the classical

intervention. Students with specific learning disabilities with impairment of mathematics show frequent relapses in terms of the maximum level reached, the main causes being memory and attention deficits, as well as limited abilities to properly use the computational algorithms. Mate20 acts mainly on the sense of number, respecting the pedagogical principles derived from a constructivist approach: the proposed goals make sense for the learner, motivates the student in the direction of learning, provides useful and fast feedback without causing negative emotions and avoidance behaviors; motivates readjustment of the mode of action to achieve the proposed goal (24). Mate20 proposes an effective solution for a short time intervention, such as those in the pandemic conditions, although its effective application can only be achieved with the physical presence of students.

Further research will have to determine, on the one hand, to what extent the results obtained are due to the intervention on math's anxiety, and, on the other hand, how long the changes produced with Mate20 persist in case of adapted curriculum pupils.

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Correspondence

Petru-Marian Călinescu,

PhD Student, Psychology and Education Sciences Faculty, Alexandru-Ioan Cuza University of Iași,
arterapiaudio@gmail.com

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An update on the neuropsychiatric complications of COVID-19

Ioannis Mavroudis, Eleni Karantali, Symela Chatzikonstantinou, Florin Petriș, Alin Ciobîcă, Adrian Cantemir, Dimitrios Kazis

Ioannis Mavroudis – PhD, Neurology Department, Leeds Teaching Hospitals, NHS Trust, Leeds, UK

Eleni Karantali - PhD, Third Department of Neurology, Aristotle University of Thessaloniki, Greece

Symela Chatzikonstantinou – PhD, Third Department of Neurology, Aristotle University of Thessaloniki, Greece

Alin Ciobîcă - PhD, Faculty of Biology, “Alexandru Ioan Cuza” Iași University, Romania, Academy of Romanian Scientists, București, Center of Biomedical Research, Romanian Academy, Iași

Adrian Cantemir - MD, PhD, assistant of professor, “Grigore T. Popa” University of Medicine and Pharmacy Iași, Romania

Florin Petriș - MD, PhD, professor, “Grigore T. Popa” University of Medicine and Pharmacy Iași, Romania

Dimitrios Kazis - PhD, professor, Third Department of Neurology, Aristotle University of Thessaloniki, Greece

ABSTRACT

SARS-CoV-2 is a single-stranded RNA coronavirus predominantly causes a respiratory disease, however increasing evidence has shown that it is also related to several neurological complications. The underlying mechanisms of SARS-CoV-2 neurotropic action is not yet clearly understood; however, it is believed that the virus can enter the central nervous system either through the haematogenous route, or through neuronal anterograde dissemination. The main neurological manifestations of patients positive for SARS-CoV-2 can be categorized to parainfectious, post-infectious and cerebrovascular complications. In the present study we describe the main neurological complications as they have been described in the most recent literature.

KEYWORDS:

COVID-19, SARS-CoV-2, neuropsychiatric manifestations.

INTRODUCTION

SARS-CoV-2 is a single-stranded RNA coronavirus that has been classified at the genus of Betacoronavirus, subgenus Sarbecovirus and is the seventh member of the coronavirus family that can infect humans (1, 2). SARS-CoV-2 causes a respiratory illness; however, increasing evidence has shown that it is also related to a number of neurological complications. The underlying pathophysiological mechanisms of SARS-CoV-2 related neurological manifestations are not yet clearly understood, however having other viruses' neurotropic mechanisms as a reference, there are two main routes that a virus can enter the central nervous system (CNS), the hematogenous and the neuronal retrograde dissemination (3, 4, 5). It is thought that SARS-CoV-2 infects endothelial cells of the blood-brain-barrier, allowing direct passage into the CNS (6). In addition to that, it has been found that the virus can infect monocytes and macrophages to migrate through the blood-brain-barrier (7). Another major route is thought to be the peripheral or cranial nerves, while SARS-CoV-2 can use axonal transportation to enter the CNS (3 -5).

Experimental evidence has shown that SARS-CoV-2 enters the brain of hACE2 mice through the olfactory bulb, resulting in rapid, transneuronal spread to related areas of the brain (8). Furthermore, multiple reports have shown that the virus can affect the CNS indirectly by triggering a cytokine storm, which can result in a BBB breakdown without direct viral invasion, and can be responsible for an acute necrotizing encephalopathy or polyradiculopathy (9 -12).

NEUROLOGICAL COMPLICATIONS

Encephalitis

The term encephalitis usually describes an immune-mediated inflammation of the brain

parenchyma. It is characterized by pleocytosis in the cerebrospinal fluid (CSF), focal abnormalities in the electroencephalogram (EEG), and certain neuroimaging findings. Since the beginning of the COVID-19 pandemic, there are several cases of COVID-19 related encephalitis. Their neurological symptoms started up to 17 days after the respiratory illness, and in at least one of the cases, neurological symptoms preceded the respiratory ones (13). Amongst clinical symptoms, irritability, confusion and reduced consciousness, occasional seizures, neck stiffness, psychotic symptoms, ataxia, oscillopsia, hiccups, and bilateral facial palsy were the more frequent (14-17). The CSF showed pleocytosis, mainly lymphocytic, but was normal in at least one case. Brain imaging was normal in most cases, but in the minority of cases, it showed high signal lesions in the temporal lobe, the cerebellum, and into spinal cord (15). EEG showed generalized slowing, focal abnormalities, and on one occasion, non-convulsive status epilepticus (16-19). Although there is no specific treatment for COVID-19 encephalitis, corticosteroids might be useful.

Encephalopathies

A retrospective study from Wuhan, China, in 214 patients with COVID-19, described symptoms from the central nervous symptoms in 25% of them, including dizziness (17%), headache (13%), and impaired consciousness (7%) (20). Another series from France on 58 patients with COVID-19 described neurological complications in 84% of patients in intensive care, including encephalopathy (67%) with corticospinal tract signs. CSF showed no pleocytosis in a small percentage of patients. About one-third of patients (33%) had a dysexecutive syndrome (21). Further cases of necrotizing encephalopathy and a fatal case with viral particles in endothelial

cells and neural tissue have been described (21). Children with COVID-19 have developed seizures, with paroxysmal episodes consistent with seizures in two infants with no respiratory symptoms but positive SARS-CoV-2 nasopharyngeal swab (22, 23). A small percentage of children hospitalized with COVID-19 also developed seizures (23).

Parainfectious encephalopathy with psychosis

Paterson et al. described a case of a 55-year-old female patient without a previous history of neurological or psychiatric issues who was admitted with fever, cough, muscle aches, breathlessness, anosmia, and hypogeusia. The patient required minimal oxygen treatment and was discharged three days later, but the following day she developed confusion and odd behavior, with disorientation. She described visual hallucinations and developed auditory hallucinations, persecutory delusions, and a Capgras type psychotic episode. Her brain MRI, EEG, and lumbar puncture were normal, and her clinical course improved with haloperidol, followed by risperidone (24).

Acute disseminated encephalomyelitis and myelitis

ADEM typically occurs after an infection and presents with focal neurological symptoms, usually encephalopathy and multifocal degeneration (25). Two case reports in middle-aged women with positive SARS-CoV-2 swabs who developed acute disseminated encephalomyelitis have been described so far (26, 27). Amongst the symptoms, dysphagia, dysarthria, and encephalopathy were the most common ones (27), while seizures with reduced consciousness, headaches, and myalgia were also described (28). Both patients had normal CSF and typical findings on MRI for ADEM. They improved with intravenous

immunoglobulin and steroids. A case of myelitis in a man aged 66 years in Wuhan, China, has also been described with fever, fatigue, acute flaccid paraparesis, and incontinence. His neurological examination revealed hyporeflexia and sensory level at T10, and the patient was treated with dexamethasone, intravenous immunoglobulin, and was discharged with rehabilitation (28).

Paterson et al. also described a case of ADEM with hemorrhage in a critically ill patient and a case of the acute hemorrhagic leukoencephalopathy form of ADEM in a 47-year-old patient that required decompressed craniotomy (24).

Peripheral nervous system

A number of patients with Guillain-Barre syndrome (GBS) or its variants and COVID-19 have been reported (25). The main neurological symptoms started around seven days after the respiratory symptoms, and some patients also developed febrile illness seven days after the onset of GBS (29, 30). The majority of patients developed weakness of all four limbs with or without sensory loss (30-35), while a small number of patients developed the paraparetic variant with leg weakness only (29, 32, 36), lower limb paresthesia facial nerve involvement, dysphagia, respiratory failure, and autonomic nervous system complications (32). Neurophysiology showed demyelinating disease in the majority of cases and axonal in about 30%. Case reports with the Miller-Fisher variant, with ophthalmoplegia, ataxia, and areflexia, have also been described (37, 38), while a case of an acute vestibular syndrome with horizontal nystagmus and oscillopsia has been reported (39). Lumbar puncture showed albuminocytological dissociation in most patients. Patients were treated with IVIG, and some of them required ventilatory support (34, 35).

Headaches

Huang et al., in an early study in 41 SARS-CoV-2 positive patients in Wuhan, China, described non-specific headaches in 8% of patients (40).

Muscle pathology

Myopathy with raised creatinekinase and rhabdomyolysis has been described in 11% of patients in the Wuhan series (41).

Olfactory dysfunction and hypogeusia

Olfactory dysfunction, anosmia, and ageusia have been described in most patients with COVID-19 (82-86%) (42, 43), and they are the most common self-reported initial symptoms amongst patients (44, 45). A neuropathological study of human olfactory bulb tissues infected with SARS-CoV2 did not reveal viral infection or injury to the neural tissue (46). These are thought to be related to epithelial damage (47).

Tremor and ataxia

Diezma-Martín et al. have described a case of parainfectious ataxia with marked bilateral action and postural tremor in a 70 years old patient with a previous history of COPD but no additional symptoms. The patient developed progressive tremor on all four limbs, voice tremor, and an orthostatic element. Brain MRI and lumbar puncture were normal. The patient was treated with clonazepam with slight improvement (48).

Cerebrovascular complications

Cerebrovascular complications of COVID-19 have been reported for 6% of patients in

Wuhan series, including ischemic stroke (5%), intracerebral hemorrhage (1%), and cerebral sinus venous thrombosis (1%). Another retrospective study in Italy reported that 2% of patients who were admitted to neurology with laboratory-confirmed SARS-CoV-2 had a cerebrovascular event, including ischemic stroke, hemorrhagic stroke, and transient ischemic attacks (49). Other studies also described cerebrovascular events in relation to COVID-19 infection in small percentages of patients (2%) (50). The majority of cerebrovascular events includes ischemic events, and hemorrhagic incidents concern only a small percentage of patients. Most patients were older than 60 years and also had known risk factors for cerebrovascular disease; however, younger stroke patients have also been described (51, 52). Cerebrovascular symptoms started about 10 (0-33) days after the onset of the respiratory illness. In one case, the stroke preceded respiratory symptoms, and a small number of patients had only cerebrovascular symptoms with no respiratory illness (52-55). The most common laboratory findings for these patients include raised blood D-dimer, positive lupus anticoagulant, anticardiolipin, and anti- β 2-glycoprotein-1 antibodies (56).

COVID-19 is known to increase the risk of thrombotic episodes, hence immediate anticoagulation with low-molecular-weight heparin has been recommended (57); however, this approach should always be balanced against the risk of intracranial hemorrhage.

DISCUSSION

COVID-19 is manifested by several symptoms, ranging from asymptomatic/mild symptoms to severe illness and death. It is mainly linked to respiratory symptoms and complications; however multiple studies since the beginning of the pandemic have reported certain neurological complications, including encephalitis, encephalopathy, anosmia and ageusia, headaches, acute disseminating encephalomyelitis, cerebrovascular events, and Guillain-Barre syndrome. The

underlying neurotropic mechanisms of SARS-CoV-2 are not yet clearly understood; however, it is thought that there are two main routes for the virus to enter the CNS, haematogenous, or through the peripheral nerves. The percentage of neurological patients is small compared to respiratory system illness; however, given that the pandemic is currently one the second wave, more patients will present neurological complications. Additional evidence will give new insights into our understanding of SARS-CoV-2 mechanisms and related diseases and conditions.

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Correspondence:

Ioannis Mavroudis,
PhD, Neurology Department, Leeds Teaching Hospitals, NHS Trust, Leeds, United Kingdom,
i.mavroudis@nhs.net

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The impact of orthorexia nervosa on bone health

**Luana Andreea Macovei, Ioana Brătoiu, Patricia Richter,
Alexandra Burlui, Anca Cardoneanu, Elena Rezuș**

Luana Andreea Macovei - Lecturer, MD, PhD, “Grigore T. Popa” University of Medicine and Pharmacy – Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

Ioana Brătoiu - MD, PhD student, “Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

Patricia Richter - MD, PhD student, “Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

Alexandra Burlui - Assistant Professor, MD, PhD, “Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

Anca Cardoneanu - Assistant Professor, MD, PhD, “Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

Elena Rezuș - Professor, MD, PhD, “Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist Rheumatology Clinic

ABSTRACT

Dietary recommendations are meant to optimize bone health and prevent bone resorption and osteoporosis when dietary intakes do not maintain normal serum levels of calcium, phosphorus, and magnesium. The current healthy eating trend is verified in association with its effects on bone density, with particular attention to some practices: vegetarianism, lactose-free diet, alkaline diet and dietary supplements. A plant-based diet may inhibit intestinal calcium absorption, due to the impact of oxalates and phytates. Lactose was suggested to enhance calcium absorption and lactose intolerant individuals have a lower calcium intake than healthy controls. The alkaline diet, with foods associated with neutral or alkaline urine thought to be beneficial for the skeleton, is based solely on findings from patients with renal

impairment, where alkaline salts, such as calcium phosphates, are released from bones in order to provide an optimal acid-base balance. Excessive vitamin and mineral consumption limits the absorption efficiency and induce detrimental structural changes in bone morphology.

A healthy diet with protective effects on bone should be focused on diversification, instead of restrictions and excess.

KEYWORDS:

Nutritional status, orthorexia nervosa, healthy diet, obsessive-compulsive disorder.

INTRODUCTION

Various dietary factors contribute to positive changes in bone turnover and there is a general belief in diet-controlled diseases. An online survey conducted in Canada in 2018 on 1108 osteoporosis patients reported the need for recommendations on nutrition in 68% of respondents(1). The role of nutrition for the osteoporosis prevention in women, in whom menopause is the main risk factor, has been shown to be based on calcium and protein intake, vitamin D, potassium, phosphorus and other nutrients. Calcium and vitamin D insufficiency is common among women of all ages, due to inadequate nutritional habits. Only protein intake is lower in older female age groups who are prone to osteoporosis, fall risk, fractures and fragility. The menopause-induced osteoporosis risk can be reduced by adopting a healthy lifestyle that includes adequate levels of dietary calcium, vitamin D and protein, regular physical exercise, smoking cessation and reduced alcohol use (2).

In individuals with orthorexic tendencies, dieting does not achieve solely a therapeutic goal, but rather it becomes a lifestyle. That is why orthorexia is not yet considered pathological and not recognized as a medical diagnosis in international classifications. Orthorexia, the obsession with the quality of food eaten and the tendency to incriminate some foods as dangerous, has been described in literature since 1997. In cases in which over-concern about food leads to lifestyle changes aimed at suiting eating patterns, orthorexia was linked to obsessive-

compulsive disorder (3), especially because it is difficult to strictly control diet for years. Health, aesthetics and disease prevention are related to orthorexia, whereas animal welfare, politics, religion and ecology are not within its scope.

Orthorexia is considered a means of controlling body fat and body weight, with less regard to bone health. Body image issues lead many anorexic female patients in their twenties to suffer from premenopausal osteoporosis of the spine, with a rapid progression of skeletal degeneration, with a BMD loss of 2.5% per year, due to malnutrition and depressed ovarian estrogen synthesis (4, 5). When adhering to a restrictive diet, orthorexic individuals are not motivated by body image issues, but orthorexia nervosa could be a residual symptom of eating disorders, such as anorexia nervosa, where patients convert from food quantity to food quality, as a means of dieting in a socially acceptable manner. Malnutrition has been reported even in dietitians and a lower body mass is often related with symptoms of orthorexia nervosa (6).

Healthy eating, which discourages sodium consumption and recommends potassium intake, by focusing on fresh fruits and vegetables helps bone health and may be beneficial. However, when carried to extreme and meat safety anxiety prevails, orthorexia nervosa can lead to protein-energy malnutrition and osteoporosis. Nutritional deficiencies in orthorexia could be a major risk factor for bone fragility.

VEGETARIANISM

A healthy diet is often seen as a vegetarian diet, due to health benefits such as a decreased risk of metabolic syndrome, ischemic heart disease or cancer, and due to concerns about possible use of hormones and antibiotics in animals. The high fat or cholesterol content of calcium-rich foods are thought to cause weight gain and cardiovascular disease. Vegetarian diets include several variants: lacto-vegetarianism, which adopts also dairy products, ovo-vegetarianism, with egg consumption and veganism, when flesh, dairy, egg and even honey are avoided. The extent to which an orthorexic diet could be considered healthy remains to be measured by the effects of a meat-restrictive diet, which causes nutritional deficiencies in vitamin D, iron, calcium and zinc. Proteins provide the structural matrix of bones and account for approximately half of bone volume and about a third of bone mass. Proteins stimulate IGF-I, a hormone that increases calcium and phosphorus absorption in the gut and the rate of phosphate reabsorption from the kidney.

Even if protein consumption is important for preventing bone fractures, the excess in protein intake leads also to higher urinary calcium excretion. However, this increased calciuria is counterbalanced by the hypocalciuria triggered by meat, which is rich in phosphorus and by increased calcium absorption due to higher serum levels of insulin-like growth factor 1. That is why high-protein diets are associated with reduced hip fractures. The protective role of foods rich in proteins has been associated with an adequate calcium intake (7,8). Insufficient protein intake may be also responsible for secondary hyperparathyroidism, which causes bone loss (9).

The plant-based sources of calcium, such as legumes and nuts, contain significant amounts of calcium, but its bioavailability is dependent on the levels of phytate and oxalate present in the food. Oxalates and phytates inhibit calcium absorption. Oxalates from spinach and legumes are the strongest inhibitors of calcium absorption. Phytates from seeds form

insoluble salts with calcium cations, which can be released through yeast fermentation. For that reason, high fiber foods rich in calcium, such as beans, spinach, chard and rhubarb, impair calcium intestinal absorption due to their phytate and oxalate content. The bioavailability of calcium in soy juice (tricalcium phosphate) is only 75% of that corresponding to cow's milk (10). However, dairy product intake is richer in calcium, protein, magnesium, potassium, zinc and phosphorus than any other food. By way of comparison, 3 to 4 portions of dairy are the equivalent of up to 24 servings of vegetables or 48 servings of grain foods (2).

The recommended moderate intake of meat beneficial for bone health could be provided by the Mediterranean diet, which is characterized by the intake of vegetables, legumes, fruits, fish, unrefined cereals, unsaturated lipids (olive oil), dairy products (cheese and yogurt), with small portions of meat and alcohol (red wine) (11).

LACTOSE-FREE DIET

The lactose-free diet was intended to provide an optimal calcium intake in individuals with lactose intolerance. However, avoiding dairy products, due to abdominal symptoms post-consumption, is linked to a recent trend in healthy lifestyle, the lactose-free and low-fat movement.

It has been reported that in a group of lactose intolerant adolescents there was a lower Ca and Vitamin D intake than in the control group, even if the lactose-free cow's milk has all the properties of regular cow's milk, including the presence of bioactive components such as the insulin-like growth factor 1, that may facilitate bone growth (12). This may be explained by the fact that lactose intolerant individuals tend to consume less dairy products than the controls but also by the beneficial role of lactose in calcium absorption, as it has also been shown by the comparative study of lactose-containing formula and lactose-free infant formulas, with a fractional and total calcium absorption significantly higher in the presence of lactose (13). Therefore, lactose is thought to stimulate mineral and especially calcium absorption.

ALKALINE DIET

The deterioration of bone integrity was first observed in patients with severe chronic renal failure who also have a low urinary pH. It was suggested that alkaline salts, in the form of calcium phosphates, are released from bones so that the systemic pH could be preserved. The acidity retained in the body could be neutralized by bicarbonates (calcium bicarbonate) coming from the dissolution of carbonate impurities found in hydroxyapatite crystals. It is highly doubtful that acid neutralization is induced via bone demineralization, due to the fact that it would take up to 8 years and about 50 % of bone mineral density to achieve that (14).

In acidity related to renal insufficiency, bone demineralization is caused by renal mechanisms instead of nutritional factors, such as calcium intestinal absorption. Acidosis inhibits the renal tubular reabsorption of calcium, leading to an increased urinary calcium excretion and hence to bone resorption.

Animal experiments dating back in the nineteenth century have shown that, when eating meat, the alkaline urine of rabbits became clear and acidic, like the urine of carnivores. The degree of urinary acidity varies according to the type of consumed foods. This well documented scientific fact gave rise to the alkaline diet craze, which incriminates the Western diet, the consumption of meat, dairy products and cereals and promotes foods rich in alkaline potassium salts, such as fruits and vegetables, which might have, among other benefits, a protective effect against bone resorption and osteoporosis. Nevertheless, the human body, whose digestive system is supported by hydrochloric acid, has coping mechanisms capable of neutralizing the excess of acidity, with the result of an increased release of carbon dioxide, which is then eliminated by the respiratory system. The renal system regulates the acid–base balance through the renal tubular system. Even if the kidneys play an essential role in maintaining an extracellular pH of 7.35, no association has been found between osteoporosis and age-

related renal diseases (14). So far, there is no evidence that bone instead of kidney could maintain acid-base homeostasis.

The Framingham Osteoporosis Study has also shown that there is no relationship between nutritionally induced variations of urinary acid excretion and calcium balance, bone metabolism and the risk of osteoporotic fractures, by reporting that the subjects with the highest protein intakes in this study had the highest bone mineral density. The Framingham Offspring Study showed that yoghurt intake showed a protective effect against hip fracture, while no other dairy groups showed a similar positive impact (9).

VITAMINS AND MINERALS IN EXCESS

Plant extracts or synthetic vitamin and mineral supplementation in the form of powders, liquids, tablets and capsules have become an obsession and are thought to complement a perfect diet.

Calcium and vitamin D supplementation associated with long term use of alkaline salts raise concern about toxicity and the risk of vascular calcification, due to calcium deposition in soft tissues. Calcium supplements, particularly when used in the absence of vitamin D, were linked to an increased risk of myocardial infarction. High calcium intakes can also impair zinc absorption. Potential adverse effects of excessive calcium intake are hypercalcemia, vascular or other soft tissue calcification, kidney stones, prostate cancer, interactions with other minerals such as iron and zinc, and constipation. For vitamin D, excessive intake may lead to vitamin D intoxication, marked by hypercalcemia and hypercalciuria.

Excessive zinc consumption limits the size of hydroxyapatite crystals. Chronically high phosphorus intake may contribute to elevated plasma phosphate, which can lead to hyperparathyroidism and subsequent high bone turnover, and is also associated with vascular calcifications and cardiovascular death, particularly in people with chronic kidney disease (15).

Excessive vitamin A intake through supplementation have been associated with low body mass density and fracture risk, and excessive vitamin A intakes are associated with poor bone mineralization.

In minerals such as calcium, magnesium, and zinc, absorption efficiency decreases as the nutrient intake increases. This explains why smaller doses divided throughout the day may lead to more efficient absorption than a single large dose.

Food sources of calcium pose no risk of cardiovascular events, with benefits on bone density and prevention of fractures. Therefore food sources of macronutrients and micronutrients are preferable for maintaining bone health.

Current evidence has shown that calcium and vitamin D supplements are not required in healthy individuals and in patients receiving drug treatment for osteoporosis with an adequate vitamin D status and a normal calcium intake (16).

DISCUSSION

Sun exposure has an important role in preventing osteoporosis, as shown by data suggesting that, when comparing Scandinavian to Mediterranean populations, urban to rural dwellers and Caucasian race to other races, the latter groups are less prone to bone fracture (7). Genetic factors, gender and race determine differences in calcium retention after similar dietary calcium intakes, with black and Asian individuals retaining higher amounts of calcium than whites and men with higher intestinal calcium absorption and lower urinary calcium excretion than women.

A calcium daily intake below 400 mg is linked to an increased risk of osteoporosis, but during menopause, calcium supplementation cannot slow down bone loss. However, various factors, including dietary patterns contribute to changes in bone turnover.

A balanced nutrition plan is more useful for preventing bone damage than for reversing

the effects of bone fragility. Diet involvement in preventing osteoporosis is mainly associated with calcium intake, which maintains bone density, but also with nutrients containing vitamin D, protein, fat, magnesium, phosphorus, zinc, iron, copper, manganese, vitamin C, vitamin K, the B-vitamins, vitamin A, potassium and dietary estrogen (phyto-oestrogens), even if the latter has little effect on bone metabolism. They are found in dairy, meat, beans, fruits and vegetables, nuts and seeds, fish and seafood. Tobacco and alcohol use, coffee and tea drinking, diet drinks, mineral water, eating according to religious practices such as halal, kosher or fasting are beyond the scope of our interest.

Foods rich in calcium are milk and dairy products (yogurt, cheese, ice cream), bread, some species of fish (sardines, anchovies), foods fortified with calcium (soy and almond milk) or fruits and vegetables (figs, almonds, hazelnuts, kale, beans, sesame) (7,8). Vitamin D is present in meat, fatty fish, liver, mushrooms, eggs and foods fortified with vitamin D (dairy products and cereals) (7,17). Dietary sources of vitamin D are less known to the public at large. Minerals such as potassium, magnesium, vitamin C and vitamin K are found in fruits and vegetables (18). A safe moderate protein intake (meat, fish) also improves bone health through amino acids and trace minerals, such as copper, manganese and zinc, which are important for the synthesis of the bone matrix and bone growth.

Dietary calcium compensates for calcium demand or loss through skin, hair, nails, sweat digestive secretions and urine. A calcium daily intake below 400 mg is linked to an increased risk of osteoporosis, but during menopause calcium supplementation cannot slow down bone loss, which is, however, slower in overweight women, who have a higher calcium absorption efficiency than their slimmer counterparts, due to nutritional abundance, a more intense mechanical stimulus on bones and higher estrogen levels, as estrogen is also involved in the pathogenesis of obesity (19,20). That is why

dietary interventions in osteoporosis are not aimed at reducing calorie intake and do not encourage dieting (21).

Beyond their ingredients, foods release their nutrients based on how they were cultivated, raised and cooked. The current practice of adding lime to acidic soils leads to a decreased magnesium content in plants. Unleavened bread without yeast may cause zinc deficiency.

Osteoporosis and osteopenia attributable to poor nutrition have been associated with nutrient deficiencies that occur during childhood and teenage years and are apparent in bone health only in the fifth or sixth decade of life (16). It is prudent that parents do not expose their children to the current vegan mania. Moreover, higher intake of calcium-rich foods during pregnancy tends to result in a higher bone mineral density of children at later ages (2).

CONCLUSIONS

Healthy eating should not be shaped by the marketing strategies of food companies. Any food restriction can easily turn into food deprivation and malnutrition, with severe damage to bone quality and mental health. Current research remains inconclusive as to which dietary pattern is most beneficial for bone health and the excess of some vitamins and minerals has also been shown to be harmful for bone health. Therefore, healthy eating should be understood as a guideline for a non-restrictive and non-repetitive diet, rather than a lifestyle and a short-lived trend. Physical exercise and an active lifestyle should complement any dietary approach.

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Correspondence:

Luana Andreea Macovei,
Lecturer, MD, PhD, “Grigore T. Popa” University of Medicine and Pharmacy - Iasi, Romania,
Faculty of Medicine, Department of Medical Specialties (II), Clinical Rehabilitation Hospital – Ist
Rheumatology Clinic, luanam77@yahoo.com

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Correlations between the SARS-COV-2 pandemic and increased aggressive behaviour to self and others

**Laura Elena Bucur, Amira Chehab, Mirona Letiția Dobri,
Codrina Moraru, Petronela Nechita**

Laura Elena Bucur - Second Year Medical Resident in psychiatry, “Socola” Psychiatry Institute, Iași, Romania

Amira Chehab - Second Year Medical Resident in psychiatry, “Socola” Psychiatry Institute, Iași, Romania

Mirona Letiția Dobri - Fourth Year Medical Resident in psychiatry, “Socola” Psychiatry Institute, Iași, Romania

Codrina Moraru- Third Year Medical Resident in psychiatry, “Socola” Psychiatry Institute, Iași, Romania

Petronela Nechita - MD, PhD, Senior psychiatrist, “Socola” Psychiatry Institute, Iași, Romania

ABSTRACT

The current times are facing an unprecedented phenomenon for our generations. The pandemic outbreak with SARS-CoV-2 rapidly and profoundly changed the aspect of the world we live in. The insecurity, the social isolation and its consequences, the fear of infection and the economic collapse are only a few of the elements that the current pandemic introduced in most lives. While the impact on physical health was immediately observed, the impact on mental health is gradually revealing itself and threatens to persist long-term. The socio-economic and psychological imbalances seem to leave a significant mark by triggering or enhancing mental disorders such as anxiety, depression, sleep disorders and posttraumatic stress disorder. All these are associated with an increased risk of aggressive behaviour to self and others, amplifying an already existing public health problem: suicide. Being defined as a self-harming behaviour based on the intention of ending one’s life, suicide is responsible for approximately 800000 deaths worldwide every year. Multiple social, economic and psychological factors are involved in this huge phenomenon and many of them are highly influenced by the current pandemic. Therefore raising awareness of the way pandemic-related changes might lead to suicide could be useful as a first step in elaborating prevention measures and avoiding tragedies.

KEYWORDS:

COVID-19, suicide, domestic violence, social isolation.

INTRODUCTION

Aggressive behaviour is defined as a social conduct based on the intention of harming someone and it can be directed against others, being defined as hetero-aggressive behaviour, or against oneself, defined as auto-aggressive behaviour. The most severe form of self-aggression is suicide, constituting a current public health problem that affects all regions of the world, being a global phenomenon with a higher preponderance in the low- and middle-income countries. According to World Health Organization (WHO) in 2016 suicide was the second leading cause of death among 15-29 years old, with approximately 800000 cases worldwide every year. (1) Numerous risk factors are involved in the suicidal behaviour. While some of them, such as family history of suicide or preexisting psychiatric disorders cannot be modified, most risk factors can be highly influenced by external events, like the current SARS-CoV-2 pandemic, that started in December 2019 in Wuhan, China. Being one of the most challenging phenomena facing our world, the pandemic has led to several changes in multiple areas of our lives, and has had a high impact on socio-economical structure and both physical and mental health. Therefore it is very likely that the risk factors for suicide will be influenced by the current pandemic context and an impact over suicide rates and aggressive behaviour is expected. (2).

The aim of this paper is to raise awareness on how the current pandemic might intensify the risk factors for suicidal behaviour and domestic violence. Therefore we search to identify and describe the economic, social and psychological triggers of mental disorders that are associated with aggressive behaviour to self and others in the current pandemic context.

THE PSYCHOLOGICAL IMPACT OF THE PANDEMIC ON MENTAL HEALTH AND THE ROLE OF MASS

MEDIA

The widespread growth of the COVID-19 cases and the fact that the outbreak was rapidly declared a pandemic had a major psychological impact on the population: the fear of getting through the disease or of contracting and transmitting the virus, the social stigma that surrounded not only the infected but also the suspected ones, were often amplified by the media and social networks. The concern that grew along with the number of cases worldwide was overwhelming for some people, leading them to extreme gestures. A study conducted in China by Wang et al. at the beginning of the pandemic suggested that half of the participants rated their psychological impact as moderate to severe. 16.5% reported moderate to severe depressive symptoms, 28.8% reported moderate to severe anxiety symptoms, and 8.1% reported moderate to severe stress levels. (3, 4)

Multiple cases of COVID-19 related suicides were reported starting from February 2020. The first case was reported in India, where a man who was returning to his village decided to hang himself in order to avoid spreading the virus throughout the village. Afterwards some other pandemic-related suicides were reported all over the globe. A 36-year old man in Bangladesh who presented fever killed himself while being prejudiced by his neighbors who were convinced that he had the virus. The tests performed postmortem revealed he was negative for SARS-CoV-2. (5) As a conclusion to these cases we can notice that the excessive fear of spreading the disease, sustained by the social stigma attached to those who might have COVID-19, can be a real and dangerous trigger for an altruistic suicide.

On the other hand, the overwhelming fear of the disease and its consequences might be a destabilizing element for some individuals. We support this statement with numerous examples of suicide cases that

have happened all over the globe in the past few months. In England, a 19-year old girl took her life driven by unbearable concern regarding the impact that social isolation might have. In Saudi Arabia a Chinese student who was quarantined on suspicion of being infected with the coronavirus had committed suicide by jumping from the third floor of a hospital. (6) A 66-year old man with throat cancer hanged himself in a New York City hospital after testing positive for the novel coronavirus. An extreme example is the one of a man in Illinois who feared that his girlfriend contracted the virus and fatally shot her. Then he committed suicide. They both tested negative for COVID-19. (5) We highlight the fact that all these deaths were not caused by the viral infection itself, but directly by its psychological impact. The anxiety, the misinformation and the panic that grew along with the spread of the virus played a key role in the disproportional response of some individuals, who eventually found death more bearable than pandemic-related stress.

Both media and social networks generally play a key role in the public perception and they have a certain capacity of influencing people's behaviour. Despite being useful in informing the population about the current pandemic, media often proved itself imprudent. The exaggerated news reports and their continuous display often led to panic, distress and anxiety. Another study conducted in China by Dong and Zheng tried to evaluate the public perception over the COVID-19 news. It revealed that most people labeled the news as being exaggerated and overwhelming, suggesting that a better control over the circulating information is needed. (7) Moreover, the social networks were particularly involved in transmitting fake news, often leading to confusion and misinformation. The uncertainty, mistrust, the feeling of helplessness and indignation, together with a sense of losing control over their own lives were all intensified by contradictions

and misleading information spread on several networks. All these brought their contribution to the imbalances everyone experiences nowadays, but they might have had a devastating impact on those with an already fragile emotional structure.(8) Therefore we cannot emphasize enough the importance of an ethical way of sharing pandemic-related news, considering that they might indirectly influence vulnerable categories, which are more prone to resort to extreme gestures such as suicide.

Another essential aspect that we should take into account when evaluating the impact of SARS-CoV-2 on suicide is that there is a high probability for survivors of severe forms of infection to be especially at risk of suicidal thoughts and behaviour. Because they experienced major stressors such as learning the diagnosis, the fear of transmitting the virus to their loved ones, the severe symptoms of infection, the hospital or even intensive care admission, these patients might be at high risk of developing depression and posttraumatic stress disorder. (4, 9) A study conducted in China by Bo et al. evaluated the mental state of patients infected with COVID-19 and it revealed that 96,2% of them had symptoms of posttraumatic stress disorder which are correlated with higher risk of suicidal thoughts and behaviour (10). Besides the psychological stress that infected patients are experiencing there is also a physio pathologic mechanism that is involved in the development of neuropsychiatric disorders. SARS-CoV-2 has tropism for central nervous system and the infection might lead to neurological disorders such as: ischemic stroke, seizures, encephalitis, dizziness, headache, ataxia and chronic pain. This is of high importance for our subject as these conditions are also correlated to a higher long-term suicide risk. (11) As a consequence, it is essential that we raise awareness over the importance of a proper support for these patients and of a higher

vigilance on the possible display of psychiatric disorders associated with suicidal thoughts.

THE SOCIAL ISOLATION AND ITS CONSEQUENCES

Social distancing and isolation have become imperatives of our world since the SARS-CoV-2 outbreak. In order to limit the spread of the virus, the authorities worldwide recommended and even imposed a massive reduction of social contacts. Through direct measures such as the interdiction of gathering in large groups or even leaving the house during the lockdown, and indirect measures such as closing most of the public places where people had a chance to hang out, the authorities restricted more and more the social contact. This particular aspect is a double-edged sword. While from an epidemiological perspective these measures proved to be a highly effective method of limiting the spread of the virus, from a psychological point of view they might have a negative impact. In his iconic book, "Suicide", written in 1897, the sociologist Emile Durkheim emphasizes the major role of social factors, besides the psychological ones, in the mechanism of the suicidal act. He states that the absence of social integration of an individual is a key element in one's motivation of committing suicide.

A decrease in social cohesion and isolation will amplify the feeling of alienation and disconnect with subsequent depression, anxiety and eventually suicide (12). A study conducted by Stravynski et al., that followed the relation between loneliness and suicide attempts, proved there existed a strong connection between them. Defining an objective loneliness as for the ones who live alone, and a subjective loneliness as the feeling of alienation that one might feel, the study revealed that both of them are correlated with a higher prevalence of suicidal thoughts (13). From this perspective, we appreciate that the

quarantine enforced by the current pandemic is associated with both types of loneliness: the objective one for those who live alone and also a subjective one through the affective echo that isolation from family and friends can have. Multiple studies have shown a higher prevalence of depression and anxiety among those who have experienced quarantine comparing to those who have not. As a parallel, during the SARS epidemic in Hong Kong in 2003, the social distancing played a role in the increasing suicide rates, for one third of the victims' experienced social confinement before taking their lives (5, 14). Although it is premature to evaluate the suicide prevalence related to the current pandemic, we think it might be useful to consider some aspects that might be correlated with a higher risk. Therefore Xiao et al. conducted a study including people who were under lockdown in the current pandemic context and it revealed that they had high levels of stress and anxiety and additional sleep disorders. We have previously mentioned the relationship between depression, anxiety and suicidal behaviour. In addition to that we highlight that insomnia and a poor quality of sleep are per se risk factors for suicidal thoughts. That is why an early and effective diagnosis and treatment of such disorders might save lives and a special attention should be given to them in the current context. (4, 15) Moreover staying in contact and maintaining the communication with family and friends through various means such as telephone might be an effective way of fighting loneliness and its terrible consequences as it might have a beneficial impact on those who are under lockdown.

SELF-AGGRESSIVE BEHAVIOR IN RELATION TO HETERO-AGGRESSIVE BEHAVIOR IN THE CONTEXT OF SOCIAL ISOLATION

A less discussed aspect of the isolation is that regarding an already vulnerable group: the victims of domestic violence. Domestic

violence is defined as an abusive behaviour occurring in a family. According to the World Health Organization (WHO) it can take various forms, such as physical, psychological, economic or sexual violence. There is a multitude of behaviours that an aggressor can manifest and there is a “scale of violence”, often beginning with intimidation, followed by isolation and devaluation of the victim and ending up in full-blown abuse. Therefore the isolation of the victim plays a key role in the display of domestic violence. Taking into account that the current pandemic context enforces social isolation in order to prevent the spread of SARS-CoV-2, an increase in the number of domestic violence cases is expected. (16) An explanation for this phenomenon also lies in the exacerbation of the risk factors and a decrease in the protective factors of domestic violence during lockdown. The forced and prolonged proximity between family members enhances the risk of domestic conflicts and an aggressive behaviour. Furthermore unemployment, financial difficulties and psychological distress due to pandemic may amplify the anger and hetero-aggressive impulses, exposing even more the victims. In the meantime a decrease of the protective factors is also a favorable element for manifestation of abuse. Isolation from family, friends and community will additionally increase the risk for victims while a more restricted access to the institutions that could support the abused ones will eventually condemn them. (17)

In France, the Minister of Interior reported a 30% raise of domestic violence during confinement since March 2020. This seems to be a global phenomenon as many countries reported a higher addressability to domestic violence hotlines since the pandemic outbreak: Spain reported a 20%, England 25%, Cyprus 30% and Brazil up to 50% increase in the solicitations of hotlines. In addition, USA, Germany and Canada reported increasing cases of

domestic violence. (18) A diametrically opposed phenomenon is witnessed in Italy, where a drop in the reported cases of domestic violence was registered during the lockdown. The decrease though does not reflect a real reduction in violent incidents, but a dangerous situation in which the abused ones encounter increased difficulties in asking for help from the community, while the aggressor gains more control over the victim. (16)

The impact that abuse can have over mental health is not at all neglectable. A study conducted by Brown and Seals, using data from the Kentucky Violent Death Reporting System from 2005-2015, reveals a strong correlation between domestic violence and suicide, reporting that 30% to 43% of suicides were committed after an abuse came from the partner (19). Also domestic violence is a trigger for some mental disorders such as mood disorders, anxiety, posttraumatic stress and addictions, all of them being associated with a higher suicidal risk. A highly affected group is composed of children, who are extremely susceptible to the tragic impact that abuse has on mental health. The trauma haunts them in their adult lives, predisposing them to several mental disorders, to social isolation, low self-esteem and suicidal behaviour (20). That is why facilitating access to institutions able to help victims during the lockdown should be a priority in order to avoid tragic consequences on short and long term.

THE IMPACT OF AN ECONOMIC CRISIS

The restrictive measures enforced since the pandemic outbreak have had a major impact on the global economy. In order to limit the widespread of the virus numerous activities have been suspended. Auto isolation of both consumers and service providers, the closing of restaurants, limiting the artistic and cultural activities at the online environment are only few of

the multiple reasons for which millions of people worldwide lost their jobs. Based on multiple observational studies the European Psychiatric Association (EPA) elaborated in 2016 a guidance paper which shows there is a strong connection between high unemployment rates and high suicide rates (21). The major financial crisis that the world has faced over time made the individuals liable to mental disorders such as depression, anxiety and suicide (5). For example during The Great Depression that USA faced during the '20s and '30s, the massive economic collapse led to an increasing number in deaths by suicide (22). More recent data registered during the economic crisis between 2008 and 2010 sustain the connection between the two phenomena; studies showed that suicides committed out of financial reasons exceeded by 10000 the expected number for that period of time. (23)

Moreover a meta-analysis of prospective observational studies conducted by Kim and von dem Knesebeck, revealed that not only unemployment, but also the perceived job insecurity, the financial uncertainty associated with harsh times such as current pandemic may determine depression, anxiety, sleep disorders and alcohol abuse, eventually leading to suicide in many

cases. (24) We cannot deny that nowadays uncertainty has become one of the most prevalent elements, and for many workers in various domains there persists a real threat of losing their jobs sooner or later. The distress generated by the constant and prolonged insecurity is not neglectable as it is a significant favorable factor for both auto-aggressive behavior and hetero-aggressive behavior. In March 2020 The International Labor Organization estimated that a 5.3 to 24.7 million job loss increase is expected due to COVID-19. According to Kawohla and Nordta the unemployment rate is expected to register a raise of 4.936% to 5.644%. These statistics can be translated by an increasing number of suicides of 2135 up to 9570 cases per year. (6, 25)

These being said it is expected that the economic collapse that might come after the pandemic will have a major impact on the mental health causing depression, anxiety and eventually suicide in vulnerable individuals. Giving the fact that this is an adjustable and preventable factor we insist on the importance of elaborating efficient strategies that would facilitate the burden of poverty on the population and therefore lower the risk of deaths by suicide.

CONCLUSIONS

The SARS-CoV-2 pandemic is an unprecedented phenomenon for our generation and it brought rapid and profound changes in the socio-economic structure. For many people, it had a remarkable psychological impact, affecting not only the physical but also the mental health. The fear inspired by the infection with COVID-19, social distancing and isolation, unemployment and financial insecurity are some of the pandemic related changes that might precipitate or trigger mental disorders such as depression, anxiety and posttraumatic stress disorder. By leading to suicidal behaviour these conditions threaten to exacerbate this already existing health issue that affects hundreds of thousands of people worldwide. In addition, the social isolation, the high unemployment rates and the distress caused by the SARS-CoV-2 pandemic may increase the number of domestic violence cases by triggering aggressive behaviour within the family, and also by limiting the access to support for victims. Violence within family has long term consequences, predisposing the abused ones to self-aggressive behavior. Hence it is a priority to raise awareness on a large scale over the mechanisms and risk factors that can determine suicide and aggressive behaviour in the current pandemic context, in order to avoid further tragedies.

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Correspondence:

Petronela Nechita,

MD, PhD, Senior psychiatrist, "Socola" Psychiatry Institute, Iași, Romania,

craciunpetronela@yahoo.com

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Drug interactions associated with psychotropic medication and COVID-19

**Valentin Oprea, Nicolae Bacinschi,
Anastasia Caracas**

Valentin Oprea - MD Ph.D. Associate professor, Chair of psychiatry, narcology and medical psychology, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chișinău, Republic of Moldova

Nicolae Bacinschi - MD Ph.D. Professor, Department of Pharmacology and Clinical Pharmacology, "Nicolae Testemițanu" State University of Medicine and Pharmacy Chișinău, Republic of Moldova

Anastasia Caracas - Resident, Department of Pharmacology and Clinical Pharmacology, "Nicolae Testemițanu" State University of Medicine and Pharmacy Chișinău, Republic of Moldova

ABSTRACT

SARS CoV-2 infection or COVID-19 disease has triggered a global pandemic and requires a complex approach, given the multisystemic impairment and lack of specific etiological treatment. The diversity of drug groups, used for non-specific, pathogenetic, and symptomatic treatment, may expose the patient to a significant risk of developing drug interactions. The long-term treatment of a psychiatric patient may predispose to an increased risk for side effects, especially in the association of chronic somatic pathologies that require the administration of specific preparations. Psychotropic drugs are associated with adverse effects on the cardiovascular system (cardiotoxicity, QT prolongation), central nervous system (convulsions), and hematopoietic system (neutropenia, agranulocytosis, lymphopenia), which may overlap with concomitant use with other groups of drugs. Drug interactions in these cases may have an increased incidence with unpredictable manifestations. The elucidation of the mechanisms underlying drug interactions and the possibility of anticipating the occurrence of clinically relevant interactions is extremely important for clinicians.

KEYWORDS

Drug interactions, psychotropic medication, SARS CoV-2, COVID-19, side effects.

INTRODUCTION

The SARS CoV-2 pandemic has led to a reorganization in the health system, an extraordinary mobilization of scientific research in many areas of medicine to develop specific drugs (antivirals, vaccines, etc.), and anti-epidemic measures. At the same time, the coronavirus revealed a series of pathological changes from organs and systems that required a review of treatment tactics, including in psychiatry, of patients with those pathologies infected with SARS CoV-2. In this context, the number of groups and preparations used simultaneously increased significantly, which further raised the issue of drug interactions (1).

People with mental disorders are more vulnerable to the novel coronavirus COVID-19 than the general population due to the risk of infection (including pneumonia), barriers to timely access to healthcare facilities because of their isolation in the psychiatric ward, and the fear, anxiety and depression accompanying the pandemic process. The long-term side effects of psychotropic drugs (metabolic syndrome, extrapyramidal symptoms, electrolyte imbalance, etc.), physical health problems (obesity, gynecomastia, sexual dysfunction, etc.), substance use disorders (nicotine, alcohol, marijuana, etc.), and medication non-adherence are other important problems in the fight against COVID-19. Risky combinations and drug–drug interactions (DDIs) occur as a

result of COVID-19 treatment concomitant with psychotropic drugs, which are indispensable in chronic mental disorders (2). Preparations with fixed combinations, along with drug combinations, are increasingly used in the treatment of many diseases and represent an important risk factor for the occurrence of drug interactions, including clinically relevant changes in the efficacy or safety of a drug therapy (3). Drug interactions can occur on a pharmacokinetic level (absorption, distribution, metabolism, elimination) and pharmacodynamic level (receptors, tissues, organs, systems) with synergistic or antagonistic consequences, sometimes unpredictable (4).

Psychotropic preparations (antipsychotics, anxiolytics, antidepressants, antiepileptics, psychostimulants, thymoleptics, etc.) may interact with the drugs metabolized by hepatic cytochrome P450 isoenzymes (CYP 2D6, 2C9, 2C19, and 3C19), and with their inducers or suppressors. Drug interactions that can occur during concomitant use of psychotropics with other drugs with similar properties may cause a rise in serious adverse reactions, lack of efficacy, or clinically significant tolerability issues. The clinical relevance of many drug interactions is slightly underestimated because detection is difficult and possible outcomes can vary widely (5) (fig.1).

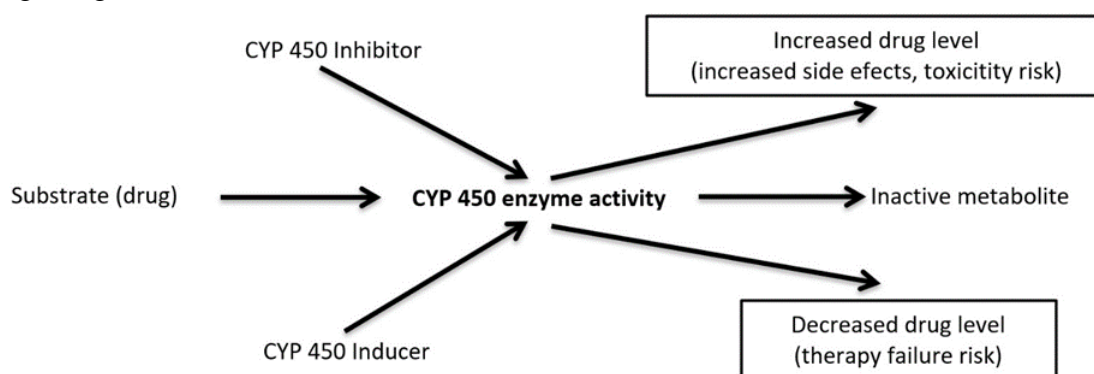


Figure 1. Effects of CYP450 inducers and inhibitors on CYP450-metabolized drug substrates (6)

DRUG INTERACTIONS

It is necessary to analyze and specify the drug interactions that may occur when using drugs for the treatment of COVID-19 and psychotropic drugs, widely used in psychiatric practice. Elucidation of the mechanisms of pharmacokinetic and pharmacodynamic interactions may be essential to prevent the occurrence of relevant drug interactions and to optimize therapy in patients with psychiatric pathology and COVID-19.

Azithromycin

Azithromycin does not interact significantly with the hepatic cytochrome P450 system and it does not produce its induction or inhibition due to which pharmacokinetic drug interactions are not relevant. Azithromycin is known to be a P-glycoprotein (P-gp) inhibitor and, in case of co-administration with P-gp substrates (e.g. digoxin, colchicine), it has been reported to result in increased serum levels, requiring monitoring. Psychotropics are not known to be P-gp substrates, and do not interact with azithromycin at this level (7, 8).

Pharmacodynamic interactions were found due to QT prolongation, when azithromycin was co-administered with psychotropics, a characteristic effect of macrolide, antipsychotics and antidepressants, which require careful use and/or electrocardiogram monitoring. Azithromycin presents a major risk for QT prolongation when is combined with citalopram, escitalopram, amisulpride, ziprasidone, clozapine, pimozide, haloperidol and thioridazine, and a moderate risk when is combined with amitriptyline, clomipramine, trazodone, imipramine, aripiprazole, chlorpromazine, olanzapine, paliperidone, perphenazine, quetiapine, risperidone and lithium. Also, it is necessary to take into account the side effects of azithromycin, such

as catatonia, delirium, agitation, anxiety, psychotic depression, and drowsiness, when combined azithromycin with psychotropics. A potential adverse effect of azithromycin is myelosuppression, and some psychotropic drugs may cause also neutropenia or agranulocytosis (especially clozapine and carbamazepine), with an increased risk of inhibiting hematopoiesis (7, 8, 9).

Clozoquine and hidroxiclozoquine

Both preparations, due to the prolongation of the QT interval and their torsadogenic potential, have an increased risk of interactions with psychotropic drugs. Despite not being formerly contraindicated, co-administration of hydroxychloroquine and the drugs that prolong the QT interval is not recommended (10).

CYP enzymes (CYP2C8, CYP3A4, CYP2D6 and CYP1A1) catalyze the dealkylation of chloroquine and hydroxychloroquine to pharmacologically active metabolites. The combination of chloroquine and hydroxychloroquine with psychotropic drugs that inhibit CYP3A4 may cause side effects due to elevated levels of antimalarial drugs. CYP3A4 inducers (carbamazepine, oxcarbazepine) may lower chloroquine or hydroxychloroquine levels. Hydroxychloroquine is an inhibitor of CYP2D6. Several psychotropic drugs (fluoxetine and paroxetine) are potent inhibitors of CYP2D6 and may increase hydroxychloroquine levels. In turn, HCQ can inhibit CYP2D6 and increase the levels of aripiprazole, atomoxetine, paroxetine, risperidone, venlafaxine, vortioxetine and several tricyclic antidepressants. Cardiac side effects of chloroquine and hydroxychloroquine (QT prolongation, atrio-ventricular block) should be monitored when are prescribed in combination with psychotropic drugs that prolong the QT

interval. In addition, clinicians will need to be vigilant for the emergence of drug induced psychosis. Chloroquine may antagonize the antiepileptic effect of carbamazepine (9, 11, 12).

Chloroquine and hydroxychloroquine have not been shown interactions with lamotrigine, valproic acid and clonazepam. Hydroxychloroquine may reduce the seizure threshold, and when combined with some antipsychotics (clozapine, chlorpromazine, risperidone, bupropion, etc.) and antidepressants (clomipramine, maprotiline, etc.) may increase the risk of seizures. It should be noted that a history of seizures, CNS damage, metabolic disturbances, concurrent use of other drugs that lower the seizure threshold and drug metabolism may increase the probability that an antipsychotic drug may induce seizures (13, 14).

Sertraline is metabolised by CYP2D6, CYP3A4, CYP2B6, CYP2C9, CYP2C19 and inhibits CYP2D6 with less potency than fluoxetine and paroxetine. Sertraline may increase the risk of hypoglycaemia when is co-administered with chloroquine and hydroxychloroquine (15).

Citalopram increases the QT interval in a dose-dependent manner, and may precipitate the occurrence of torsade de pointes. A European decision has contraindicated the use of citalopram (and its isomer escitalopram) with any other potentially torsadogenic drugs, including hydroxychloroquine. However, this is easily manageable in the context of COVID-19. Indeed, as the maximum recommended duration of hydroxychloroquine treatment is 10 days, the interruption of citalopram or escitalopram for such a short period should not expose the patient to the risk of recurrence of depression. Switching to another serotonin reuptake

inhibitor (SSRI) is possible, as the pharmacodynamic effect immediately replaces that of the preceding SSRI, even if the pharmacokinetic equilibrium of the new antidepressant may take some time (10).

The combination of chloroquine and hydroxychloroquine with lithium preparations, antidepressants (amitriptyline, clomipramine, citalopram, escitalopram, trazodone), antipsychotics (chlorpromazine, clozapine, haloperidol, pimozide, quetiapine, zuclopenthixol, ziprasidone) and anxiolytics (hydroxyzine) require medical attention due to prolongation of QT interval. Antidepressants (sertraline, reboxetine, milnacipran, agomelatine, bupropion) and antipsychotics (aripiprazole, amisulpride, asenapine, olanzapine, paliperidone, perphenazine) have lower side effects and fewer interactions with hydroxychloroquine and chloroquine (9).

Famotidine

Famotidine is considered a weak CYP1A2 inhibitor and may lead to substantial increases in blood concentrations of CYP1A2 substrates. Whilst there are no reports, theoretically, co-administration can lead to increased levels of clozapine, olanzapine and agomelatine as they are predominantly CYP 1A2 substrates. Famotidine may cause QTc prolongation. Theoretically, coadministration with other agents that can prolong the QT interval may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. In general, the risk of an individual agent, or a combination of these agents, causing ventricular arrhythmia in association with QT prolongation is largely unpredictable but may be increased by certain underlying risk factors such as congenital long QT syndrome, cardiac disease and electrolyte disturbances. In addition, the extent of drug-

induced QT prolongation is dependent on the particular drug involved and dosage of the drug (7).

Lopinavir / ritonavir

Lopinavir is metabolized extensively by the hepatic cytochrome P450 system, almost exclusively by CYP3A. Ritonavir is also noted to be extensively metabolized by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Ritonavir is a potent CYP3A and CYP2D6 inhibitor, and is given with lopinavir to increase plasma levels of lopinavir. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19, thereby increasing the biotransformation of some drugs metabolized by these pathways. This may result in decreased systemic exposure of these agents and therapeutic failure (7, 16).

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is metabolized by N-demethylation, mediated by CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Fluoxetine and its active metabolite (norfluoxetine) markedly inhibit CYP2D6, moderate CYP2C9, weak to moderate CYP2C19 and CYP3A4, and weak CYP1A2 increase the Area Under The Curve (AUC) of the ritonavir without significant changes in other pharmacokinetic parameters.

This relatively low drug-drug interaction does not need dosage adjustment. On the other hand, there is a possibility of serotonin syndrome in concomitant use of ritonavir with SSRIs (15).

Serotonin syndrome is one of the important adverse drug reaction (ADRs) associated with the use of drugs affecting serotonin reuptake, caused by excessive activation of postsynaptic serotonin receptors. In one study, the incidence of this adverse reaction in ICU was

estimated to be 39%. This syndrome can occur due to overdose with single serotonin agents, but most of the severe cases are because of interaction between two or more drugs increasing serotonin transmission. (17) Citalopram and escitalopram are metabolized by CYP3A4, CYP2C19, and CYP2D6. They both have a weak inhibitory effect on CYP2D6, so it does not appear to cause significant changes in ritonavir levels. Ritonavir inhibits CYP 3A4 but the interaction with these antidepressants is not clinically significant (15).

Quetiapine is a CYP3A4 substrate and concomitant treatment with ritonavir and other protease inhibitors can increase its serum concentrations. For this reason, FDA recommends reducing the dosage of quetiapine to 1/6th and to monitor for quetiapine related adverse effects. Combination of the oral solution of Ritonavir / Lopinavir, which contains 42.4% ethanol alcohol, with disulfiram may trigger reactions characteristic for acetaldehyde dehydrogenase inhibitor. Ritonavir/Lopinavir may exacerbate metabolic adverse reactions, also caused by second-generation antipsychotics, but this is not of great significance as COVID-19 approved drugs are given only for short term (3, 18).

A clinically significant drug interaction may occur when risperidone is co-administered with protease inhibitors. A number of case reports have documented the occurrence of ADRs such as extrapyramidal symptoms, reversible coma, neuroleptic malignant syndrome, and late-onset angioedema in patients receiving risperidone associated with ritonavir/indinavir, presumably due to inhibition of risperidone metabolism (3).

Severe infections are usually manifested with signs of generalized inflammation including

fever and serum C-reactive protein (CRP) elevations secondary to the cytokines released that can inhibit several CYPs. Inflammation can increase serum clozapine concentrations. More limited is the information on olanzapine, which is also metabolized by CYP1A2, and on the antipsychotics CYP3A4 metabolized. This specific DI, caused by inflammation-released cytokines, may be relevant for clozapine use, because of the narrowest therapeutic index of all atypical antipsychotics. This may explain why in a study of the ADRs reported to the FDA, clozapine ranked as the third most lethal drug with 3277 deaths. Decreasing the clozapine dosage during infections with systemic inflammation may be necessary. Cases of clozapine intoxication are starting to be described during pneumonia associated with the COVID-19 disease (3).

In patients with symptoms of COVID-19, they suggested rapid antigen testing as well as complete blood count testing, to distinguish COVID-19-related symptoms from side-effects of clozapine. They recommended continuation of clozapine in patients with COVID-19 infection, and only dose adjusting if necessary, preferably as guided by plasma levels of clozapine. Another recommendation was to initiate vitamin D supplementation in all patients taking clozapine, considering the high rates of low vitamin D in patients with schizophrenia and some possible protective effects in decreasing the likelihood of COVID-19 respiratory infection (19).

The use of lopinavir/ritonavir is contraindicated with medications that include pimozide, midazolam, and triazolam due to increased drug levels and potentiation of adverse effects. Therefore, is recommended to use benzodiazepines not metabolized by CYP enzymes (lorazepam, temazepam, or oxazepam). Owing to CYP450 enzyme or

glucuronidation-inducing effects, ritonavir-boosted protease inhibitors also have been shown to lower concentrations of some psychotropics (e.g., bupropion, methadone, lamotrigine, and olanzapine), thus leading to increased dose requirements of these medications. Other potential nonpsychiatric side effects that may have implications for psychiatrists include Stevens Johnson syndrome, diabetes mellitus, QTc prolongation, pancreatitis, neutropenia, hepatotoxicity, and chronic kidney disease (8, 9).

Tocilizumab

Tocilizumab has no direct inducing or inhibitory effects on cytochrome P-450 enzymes. Increased IL-6 during the cytokine storm inhibits the activity of CYP3A4, CYP2C19, CYP2C9 and CYP1A2 with reduced metabolism and increased exposure to their substrate drugs. The preparation, by removing IL-6-induced suppression of cytochrome P-450, will require dose adjustment (16, 20).

Caution should be exercised when tocilizumab is co-administered with myelotoxic medicinal preparations such as clozapine or carbamazepine due to the potential additive effect on hematological toxicity. No clinically significant effect was found on the QT interval in healthy subjects (12).

Tocilizumab might cause vascular disorders (hypertension), and nervous system disorders (headache, demyelinating disorders, leukoencephalopathy with cognitive impairment, and peripheral neuropathy). A serious adverse effect reported with tocilizumab is increasing the risk of fungal and bacterial infections which should be considered in COVID-19 patients (20).

Antipsychotics have been associated with immunosuppressive properties, such as decreased pro-inflammatory cytokine levels, blood dyscrasias, and altered production of antibodies. The risk of neutropenia is about 1% for clozapine (3% in the elderly) and 0.1% for phenothiazines, while for other medications data are limited. Furthermore, both first- and second-generation antipsychotics have been associated with a higher risk of pneumonia in observational studies. Data from randomized trials

including mostly second-generation antipsychotics showed a higher risk of infections. Apart from immunity abnormalities, multiple mechanisms may contribute, including reduced clearance of the airways (related to central sedation and inhibition of cough), impaired chest movements and swallowing due to extrapyramidal symptoms, and sialorrhea (1).

CONCLUSIONS

1. Drug interactions associated with the administration of psychotropic drugs and reprofiled drugs for Covid 19 are on pharmacokinetic and pharmacodynamic level.
2. QT prolongation is a clinically relevant adverse event, characteristic for psychotropic drugs and drugs for Covid 19 (azithromycin, chloroquine, hydroxychloroquine, famotidine, etc.), which require monitoring due to possible cardiovascular complications.
3. Immune disorders during SARS-CoV-2 infection may promote the development of psychotropic (neuroleptic) side effects, such as the risk of developing infections, myelosuppression.
4. Cytochrome P450 microsomal enzymes inhibition and/or induction of concomitantly administered drugs cause important pharmacokinetic interactions. Increasing the concentration of the drug may induce the development of toxicity, and decreasing the concentration reduces the therapeutic effect of the drug. Comprehension of metabolic pathways and possible drug interactions would allow the anticipation of unwanted complications.
5. Overlapping of side effects of drugs used in Covid 19 and symptoms of psychiatric pathology are a problem in clinical practice and require rigorous monitoring.

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Correspondence:

Valentin Oprea,

MD Ph.D. Associate professor, Chair of psychiatry, narcology and medical psychology, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chișinău, Republic of Moldova,
valentin.oprea@usmf.md

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Anxiolytic, anti-depressant and metabolic effect of *Salvia* spp. essential oil on a rat model of schizophrenia

Samson Guenné, Prosper T. Kinda, Radu Lefter, Daniel Timofte, Adama Hilou, Adrian Cantemir, Martin Kiendrebéogo

Samson Guenné - Laboratory of Applied Biochemistry and Chemistry (LA. BIO. C. A), University Joseph KI-ZERBO, Burkina Faso

Prosper T. Kinda - Laboratory of Applied Biochemistry and Chemistry (LA. BIO. C. A), University Joseph KI-ZERBO, Burkina Faso, Laboratory of Forensic Sciences, General Direction of National Police, Burkina Faso;

Radu Lefter - Center of Biomedical Research, Romanian Academy, Iași, Romania

Daniel Timofte - MD, PhD, professor, “Grigore T. Popa” University of Medicine and Pharmacy Iași, Romania

Adama Hilou - Laboratory of Applied Biochemistry and Chemistry (LA. BIO. C. A), University Joseph KI-ZERBO, Burkina Faso

Adrian Cantemir- MD, PhD, assistant of professor, “Grigore T. Popa” University of Medicine and Pharmacy Iași, Romania

Martin Kiendrebéogo - Laboratory of Applied Biochemistry and Chemistry (LA. BIO. C. A), University Joseph KI-ZERBO, Burkina Faso

ABSTRACT

An essential oil is a concentrated, hydrophobic liquid of volatile aromatic (odoriferous) compounds of a plant. Plants from *Salvia* genus are rich in essential oils that have an activity on the nervous system. The aim of this study was to evaluate the effect of essential oil from *Salvia* genus plants on the rat model of schizophrenia. L-methionine was used to create the animal model of schizophrenia. Schizophrenic animals were exposed to *Salvia* essential oil for 21 days. Elevated plus maze and forced swim test were used for the anxiolytic and anti-depressant effects of the *Salvia* spp. essential oil. Our results show that *Salvia* spp. essential oil significantly reduced the depression and decreases slightly the anxiety level created by L-methionine in rats. These medicinal plants could be used to delay the onset of schizophrenia and treat people with this disorder by reducing their anxiety and depression.

KEY WORDS:

Schizophrenia; *Salvia* spp.; anxiolytic; antidepressive.

INTRODUCTION

Schizophrenia, like other neuropsychiatric disorders, does not have well defined causes currently. The causes that contribute to this pathology installation involve from environmental to genetics by passing by chemistry (psychotropic drugs and receptors). This psychotic disorder is most often characterized by an altered sensory process (hallucination) and cognitive dysfunction (1, 2).

Hypotheses suggest a neuromodulator disorder in dopaminergic system also at other systems such as serotonergic, glutamatergic and GABA-ergic which are indexed to be responsible to the symptom observe in schizophrenia disorder (3, 4, 5). The real causes still not being well elucidated, the treatment of schizophrenia remains limited to its symptoms and not to the definitive cure. In this regard, researchers continue to make increasing use of medicinal plants, which contain an inexhaustible source of bioactive molecules (6). Traditionally, many plants from *Salvia* spp. genus have used for their neuropsychotropic properties such as *Salvia libanotica* (Boiss. et Gaill), *Salvia lavendulaefolia* Vahl, *Salvia divinorum* (Epling, Játiva-M), *Salvia multicaulis* Vahl, *Salvia cyanescens* Boiss and Bal (7, 8, 9). The aim of this study was to evaluate the effect of essential oil from *Salvia* genus plants on the rat model of schizophrenia.

MATERIALS AND METHODS

Plant material and essential oil extraction
Salvia spp. aerial parts were collected and dried away from sunlight, pulverized and weighed.

Essential oils of the dried powder of *Salvia* spp. were extracted by hydro-distillation with water vapor according to the method described by the 7th edition of European

Pharmacopoeia. The volume of the essential oil was measured and ranked for 100 g dry plant material.

Animals

Thirty female and male Wistar rats weighing respectively 238.40 ± 18.70 g and 310 ± 48.60 g at the start of the experiment were used. The animals were housed in a temperature and light-controlled room (22 °C, a 12 h cycle starting at 08:00 h) and were fed and allowed to drink water ad libitum. All behavioral evaluations were performed between 9 h and 16 h, respecting the current legislation for animal studies and indications of the local comities.

Chemicals

To carry out our research, we used methionine purchased from Sigma Aldrich.

Experimental design

Male rats were divided into four (4) groups (n=6) for the experiment performed: (1) control group (0.9% NaCl), (2) methionine 500 mg/kg treated group, (3) methionine 500 mg/ kg + *Salvia* spp. volatile oil 1% group and (4) methionine 500 mg/ kg +*Salvia* spp. volatile oil 3% treated group. Inhalation method was used 60 min per day during 21 successive days for *Salvia* spp. volatile oil treated groups. These rats were treated for a week with L-methionine (750 mg/kg body weight twice daily) intraperitoneally.

Experiments training

Behavior in the elevated plus-maze (EPM) is also utilized to assess exploration, anxiety, and motor behavior. The EPM consisted of four arms, 49 cm long and 10 cm wide, elevated 50 cm above the ground. Two arms were enclosed by walls 30 cm high and the other two arms were exposed. 1h after *Salvia* spp. essential oil exposition, rats were placed at the juncture of the open and closed arms

and the amount of time spent on the open arms was recorded during a 5 min test, as previously described (10). After each assay, the maze was carefully cleaned with a wet tissue. The time spent on the open arms is an index of anxiety.

Forced swimming test (FST)

The antidepressant effects of *Salvia* spp. essential oil on rats were assessed, using the method described by Cojocariu (11) with some modifications. Firstly, rats were individually placed into cylindrical recipients (diameter 30 cm, height 59 cm) containing 25 cm of water at $24 \pm 1^\circ\text{C}$ during 2 min of training. After this session, the test was performed in a 6 min swim session. 1 h before the training, the rats had been exposed to *Salvia* spp. essential oil. During the test session, the following behavioral responses were recorded: (1) immobility (time spent

floating with the minimal movements to keep the head above the water) and (2) swimming (time spent with active swimming movements).

DATA ANALYSIS

All results were expressed as mean \pm standard error of the mean (S.E.M). Behavioral activities of rats were statistically analyzed with analysis of variance (one-way ANOVA). Tukey's test was used to determine level of significance of all results obtained on XLSTAT. Results were regarded as significant at $p < 0.05$.

RESULTS

Anxiolytic of *Salvia* spp. essential oil Numbers and time spent in open arms (figure 1) showed that L-methionine increased the rats anxiety level compared to untreated rats.

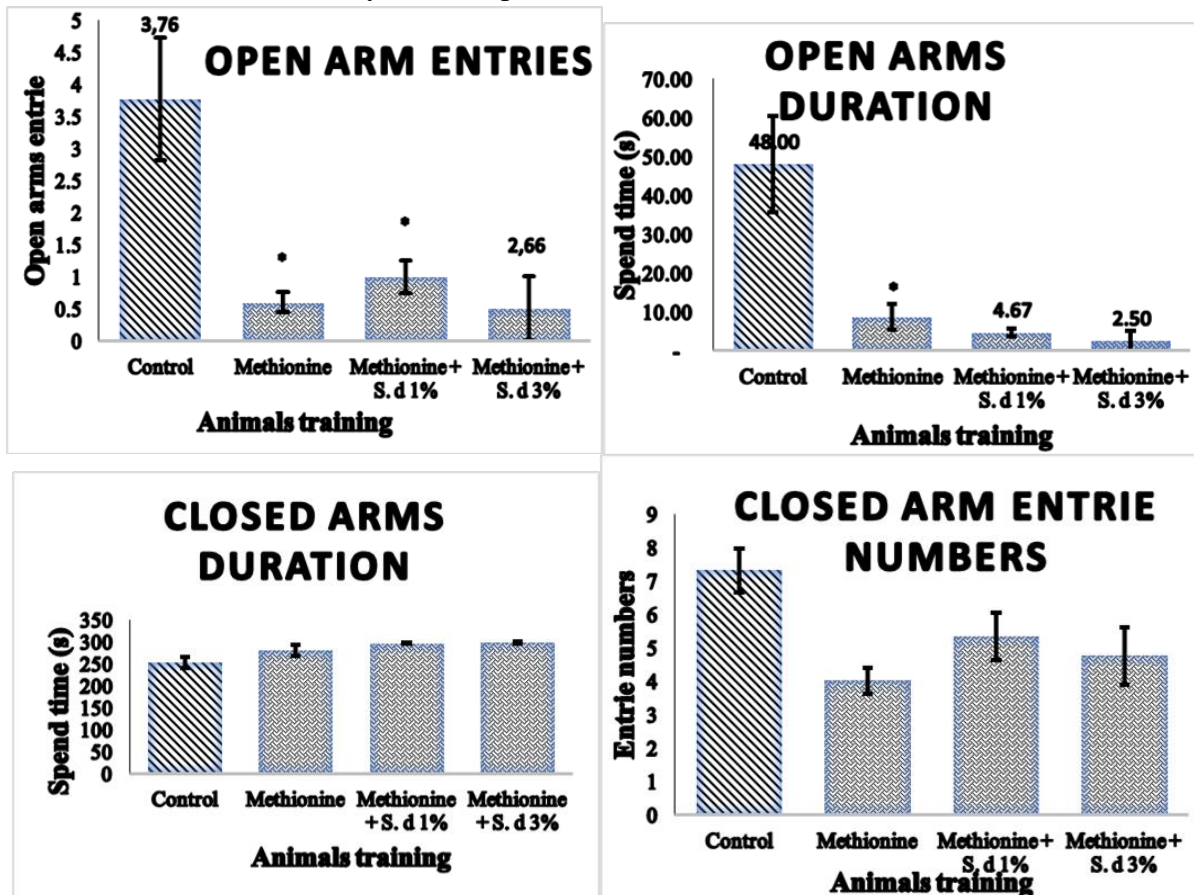


Fig. 1 *Salvia* spp. essential oil effect in elevated plus maze

The values are mean ± S.E.M. (n=6 per test).
 *p < 0.05 vs. control.

level of anxiety in these rats compared to untreated rats.

The rats treated with L-methionine behavior (figure 2) have also indicated an increased

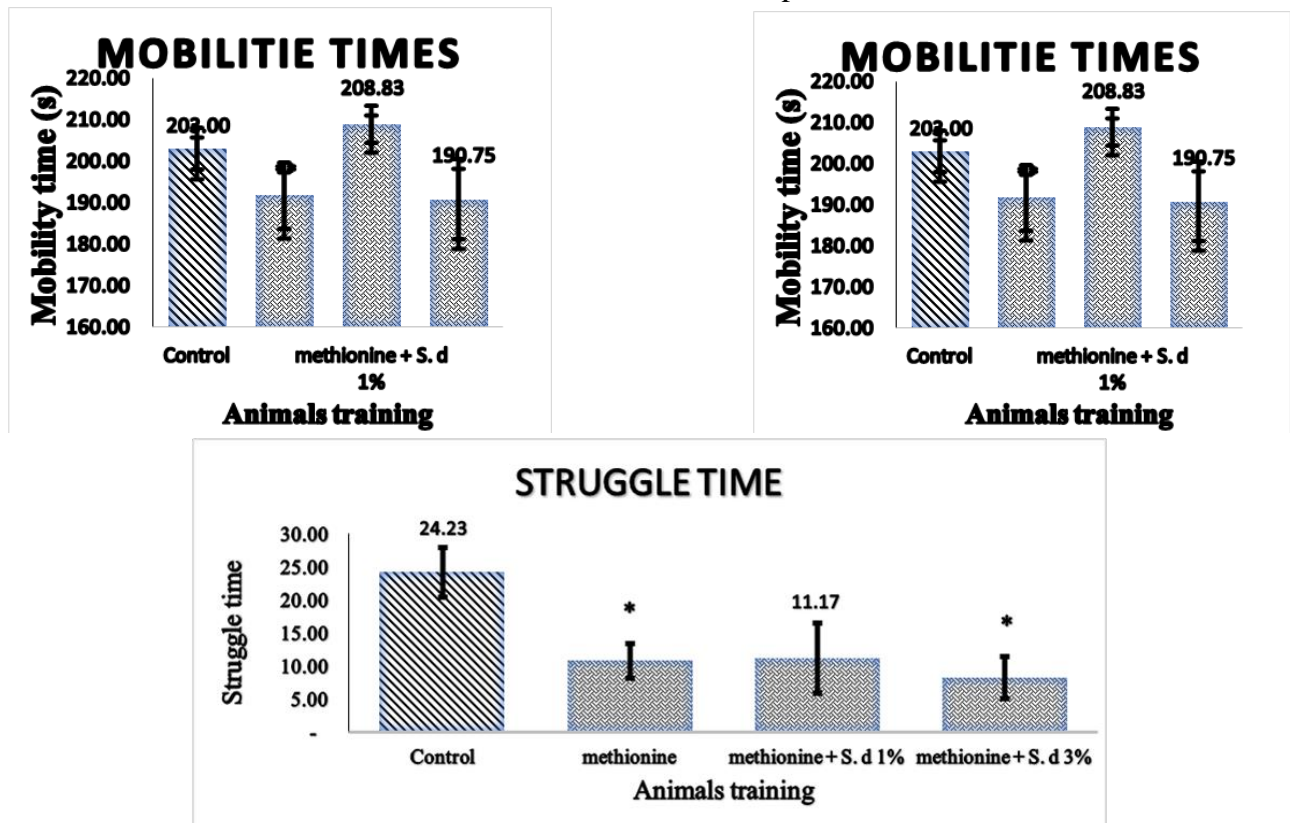


Fig. 2 *Salvia* spp. essential oil effect in elevated plus maze

The values are mean ± S.E.M. (n=6 per test)
 *p < 0.05 vs. Control.

By analyzing immobility times, our study showed that L-methionine creates depression in rats compared to untreated rats. However, *Salvia* spp. essential oil significantly reduced this depression.

Anti-depressant activity of *Salvia* spp. essential oil



DISCUSSION

In the literature, the anxiety disorders present in schizophrenia are Obsessive-compulsive disorder, Panic disorder, Social phobia or the Posttraumatic stress disorder. Existing treatments are conventional (clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline) and act on the symptoms. These treatments are effective in varying percentages (12, 13, 14).

In our work, indeed L-methionine has caused a schizophrenia state in the rat which is more anxious than control rats. The results of EPM and Forced swim test showed this anxiety and depression in treated rats.

L-methionine has been used to induce in our study the animal model of schizophrenia. The role of this amino acid is to inhibit the action of glutamate on its N-methyl-D-aspartate (NMDA) receptor. Thus, rats treated with L-methionine have a disorder in their glutaminergic system causing a disturbance in their intelligence.

Schizophrenia is a neuropsychiatric disorder whose causes are not well defined. However, oxidative stress, microbial diseases, and the environment have a considerable influence on the genetic predisposition to this pathology of schizophrenia.

Many medicinal plants are known to have antioxidant, antimicrobial or immune-stimulant activities (15, 16, 17). This antioxidant property would fight against the installation of atheroma plaque, which would delay the installation of neuropsychiatric disorders such as schizophrenia. The

antimicrobial properties of these plants would allow the organism to resist also against the installation of these disorders in the nervous system which schizophrenia is a part (18).

These biological properties of plants are at the core of chemical compounds that these plants possess. As far as plants from *Salvia* genus are concerned, it is their essential oils that are targeted. These essential oils from *Salvia* genus plants, in addition to have properties on the central nervous system (like *Salvia divinorum* used in divination rites) have antioxidant and antimicrobial properties (19, 20).

All these data could also have an increased metabolic significance, considering the various metabolic disorders associated with the schizophrenic pathology (21, 22, 23), as well as the way the plant extract are affecting the general and specific metabolism in various disorders (24, 25) with special focus here in this report on schizophrenia

CONCLUSIONS

Plants from *Salvia* genus belong to the *Lamiaceae* family. These plants are well known for their effects on the nervous system through their essential oils. The morbidity of this disorder affects both the sick person and his relatives. In this research, we created an animal model of schizophrenia and used *Salvia* spp. essential oil to relieve depression and anxiety. Our results showed that exposure of schizophrenic animals to *Salvia* spp. essential oil for 21 days relieved the animals' state of depression and anxiety.

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Correspondence:

Daniel Timofte,

MD, PhD, professor, “Grigore T. Popa” University of Medicine and Pharmacy, 16th Universitatii Street, 700115 Iasi, Romania, dantimofte@yahoo.com

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A preliminary study on the possible effects of the acute zinc administration on the anxiety-like behaviour

Constantin Truş, Roxana Rosmary Enciu

Constantin Truş - Associate Professor, Department of Morphological and Functional Sciences, Faculty of Medicine, Dunarea de Jos University, Galaţi, Romania

Roxana Rosmary Enciu - MD, "Sf. Apostol Andrei" General and Emergency Hospital Galaţi

ABSTRACT

Zinc ions are trace elements in the human body with key regulatory role over numerous structural, transcriptional and enzymatic proteins essential for the correct function of the central nervous system. In the present work we were interested in determining the possible relevance of acute zinc administration on the anxiety-like behaviour. Our initial results described here show a promising relevance for zinc in anxiety-related context and advocate for further research, considering oxidative stress related mechanisms.

KEYWORDS:

Zinc, biotechnological, anxiety, oxidative stress.

INTRODUCTION

Zinc ions are some of the most abundant trace elements in the human body. Among many important functions, zinc ions regulate numerous structural, transcriptional and enzymatic proteins that play important roles in the correct function of the central nervous system (1,2,3). Therefore, zinc is considered to be essential for brain development function (3).

Up to date there is not a clear consensus regarding the effect of a zinc deficient diet on the brain. On one hand, zinc homeostasis in the brain is known to be strictly regulated by

the brain barrier system, and, therefore, is not easily affected by a zinc deficient diet (4,5). However, certain studies have demonstrated that some neuronal functions are impaired by a diet low in zinc (6).

For example, learning and memory are impaired before any decrease in zinc concentration can be observed in the brain of experimental animals fed a zinc-deficient diet. Specifically, one study showed that zinc concentration in the brain of rats did not decrease after a 4-week zinc deprivation, whereas a significant impairment in the learning behaviour of passive avoidance was

observed (7). Thus, the significance of zinc homeostasis in the brain neuronal function is still not fully understood.

Regarding the importance of zinc in a healthy diet and the possible negative outcomes of zinc deficient diet, approximately 50% of the world population does not get an optimal quantity of zinc, according to K. Brown et al. (8).

It has been demonstrated that zinc deficiency in children is a real nutritional and health problem in both developing and developed countries (10). This should raise serious concerns, especially when the evidence from animals experimental studies indicates that zinc deprivation during periods of rapid development critically impairs behaviour and brain function, in addition to brain development (11, 12).

One of the main behavioural symptoms of zinc deficiency is lethargy, characterized by reduced activity and responsiveness (13). Furthermore, zinc supplementation has been shown to improve neuropsychological behaviours in school-age children (14, 15).

However, the mechanisms underlying brain impairments in zinc deficiency are still unclear and further analysis on the relationship between neuropsychological behaviour and neuronal function in zinc-deficient animal models are necessary to a better understanding.

The possible correlation between zinc level and anxiety, could be implied by that the highest levels of zinc in the central nervous system are found in areas known to be important in anxiety, including the cerebral cortical part of the brain, the hippocampus, most amygdaloid nuclei and the lateral septum (16).

In addition, although zinc deprivation does not seem to influence brain zinc homeostasis, however zinc deprivation leads to alteration in behaviour, learning, mental function and may cause epileptic convulsions (18).

Several studies have indicated that zinc is also involved in the pathophysiology of depression and in the mechanism of antidepressants (19, 20, 21, 22). Animal models-based investigations have suggested that zinc produces similar effects to those of known antidepressants in various animal tests such as the forced swim test and the tail suspension test (23, 24, 25).

Furthermore, there are clinical data showing that zinc supplementation may present benefits for patients who suffer from unipolar depression (26, 27).

In the present study, we have investigated the effect of acute administration of zinc in rats in the elevated plus maze test.

MATERIALS AND METHODS

Animals and drug treatment

The experiments were performed on male Wistar rats (220–280 g). The animals were kept under a natural day/night cycle at room temperature (22–25°C), with free access to food and water. The design of our study had 5 experimental groups, consisting of 8 animals each: the control group and 4 groups of zinc-treated rats which received increasing zinc hydroaspartate doses of 8.125 mg/kg, 16.25 mg/kg, 32.5 mg/kg and 65 mg/kg respectively.

Experiments were conducted between 9:00 a.m. and 2:00 p.m. by an observer who was blinded to the treatment.

Zinc hydroaspartate dissolved in aqua pro injections or vehicle (control) was

administered intraperitoneally in a volume of 2 ml/kg, 45 min before the test.

These doses were selected based on previous data from literature (28, 29).

Rats were treated in accordance with the guidelines of the animal bioethics of the Act on Animal Experimentation and Animal Health and Welfare from Romania and all procedures performed in studies involving animals were in compliance with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Elevated plus maze test

The testing procedure was based on a method described by Pellow and File (30). The apparatus, consisted of two open arms (50 × 10 cm) and two closed arms (50 × 10 cm with 30-cm-high walls), arranged in a “+” shape, elevated to a height of 50 cm and made of durable, high-density, non-porous black plastic. The maze was placed in a darkened room, and the center of the apparatus was illuminated with a 25 W electric bulb hanging 100 cm above the maze. Each rat was gently placed in the centre of the plus maze, facing one of the closed arms, immediately after a 5-min adaptation period in a black plastic box (60 × 60 × 35 cm).

During a 5-min test period, the time in open arms was recorded. The ratio (%) of time spent in the open arms to total time spent in any arm was calculated as the standard anxiety index. After each trial, the maze was wiped clean.

RESULTS

Post hoc comparisons between all the 5 groups showed a significant difference regarding the percentage of time spent in the open arms, $F(1, 38) = 447.550$, $p < 0.001$.

Significant differences concerning the time spent in the open arms were also observed between the control group and the 8.125 mg/kg of zinc hydroaspartate group ($p = 0.044$), between the control group and the 16.25 mg/kg of zinc hydroaspartate group ($p = 0.011$), and between control and the 32.5 mg/kg of zinc hydroaspartate group ($p = 0.001$).

No significant difference regarding the time spent open arms was found between the control group and the group which received the maximum dosage of 65 mg/kg of zinc hydroaspartate ($p = 0.063$).

Furthermore, no other statistically significant differences were found between any possible pair of the experimental groups.

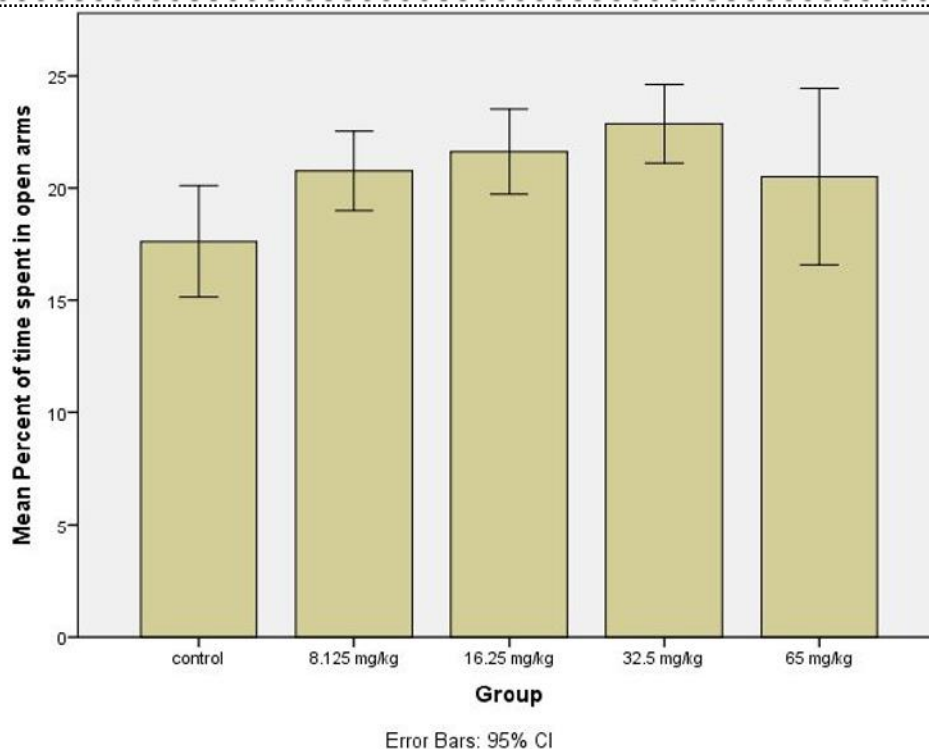


Figure 1. The differences regarding the time spent in open arms (in percent) between the 5 experimental groups. The results are displayed as means \pm SEM for $n=8$ rats for each experimental group.

Discussion

When we first started the study, the main goal of our research team was to discover if a zinc treatment for two weeks will influence the anxiety-like behaviour of rats in the elevated plus maze. Furthermore, we assumed that a decrease in the anxiety-like behaviour of the rats would be proportional with an increase in the dosage of zinc treatment. In addition, we also wanted to ascertain if an upper threshold exist, for the hypothesised improvement in the rats' anxiety related behaviour. In other words, we searched for the optimal zinc hydroaspartate dosage, equivalent to the maximum improvement in the time spent in the open arms.

The results from the statistical analysis showed that 3 out of the 4 dosages were efficient in reducing the anxiety-like behaviours in rats. More specifically, post hoc analysis showed that the rats from the control group spent significantly less time in the open

arms of the elevated plus maze compared to the rats which received the lower doses of zinc of 8.125 mg/kg ($p=0.044$), 16.25 mg/kg ($p=0.011$) and 32.5 mg/kg of ($p=0.001$). However, the maximum dosage of zinc hydroaspartate (65 mg/kg) did not improve significantly the time in the open arms in the treated rats when compared to the control group ($p=0.063$). These results suggest that a dose of 8.125 mg/kg of zinc hydroaspartate is sufficient for inducing significant improvements in anxiety-like behaviour of rats.

Increasing dosage of the zinc does not seem to significantly reduce the anxiety levels in rats. Furthermore, a high dose of 65mg/kg of zinc seem to have no significant effect on the anxiety related behaviour of the rats.

In addition, the assertion that a low dose of zinc is sufficient for optimal results in reducing anxiety levels in rats is also supported by our results that showed no

significant differences between the groups that received the lower dose of 8.125 mg /kg of zinc the groups receiving higher doses of 16.25 mg/kg and 32.5 mg/kg and the group that received the highest dose of mg/kg of zinc.

The results of our study are similar to those reported by previous studies on the possible correlation between anxiety and zinc supplementing in animal models, which demonstrated that zinc is involved in the pathophysiology of anxiety (31-33).

Also, the zinc supplementation has been demonstrated in preclinical studies to decrease anxiety-like behaviour.

Furthermore, two recent studies showed that a rodents fed a zinc deficient diet for a prolonged period of time exhibited a significantly higher rate of anxiety-like behaviours (34, 35).

Whereas the correlation between an optimal zinc level and a low level of anxiety has been

described, the mechanism responsible for the anxiolytic action of zinc is still unknown. Different authors have suggested various theories to support this correlation. Thus, J. Kotlinska (36) states that the beneficial action of zinc on anxiety may be related to the modulation of glutamate and GABA systems (36).

Examining the zinc antidepressant-like activity, other authors have speculated that the anxiolytic effect of zinc may be related to its antagonism to NMDA and mGluR5 glutamate receptors (37, 38).

A third theory suggests serotonergic receptors to play an essential role in the anxiolytic effect of zinc (39). Clearly, future studies are needed to elucidate the exact mechanisms that underlie this apparent anxiolytic effect of zinc, while these data could also exert an important scientific and possible therapeutically relevance.

CONCLUSIONS

These initial results described in the present study suggest a promising relevance for zinc in anxiety-related and also advocate for further theoretical research in this area considering oxidative stress related mechanisms.

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Correspondence:

Constantin Truş,

Associate Professor, Department of Morphological and Functional Sciences, Faculty of Medicine,
Dunarea de Jos University, Galaţi, Romania, dilconstantin@yahoo.com

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Risk factors for stroke and neurocognitive disorders: the role of pre- and post-stroke physical activity

**Bogdan Constantin Monac, Roxana Chiriță,
Dan Iulian Cuciureanu, Georgiana Mihaela Monac**

Bogdan Constantin Monac – M.D., PhD Student, Neurology fellow, Neurology department, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Romania

Roxana Chiriță - M.D., PhD, Professor, University of Medicine and Pharmacy ”Grigore T. Popa” Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași, Romania

Dan Iulian Cuciureanu – M.D., PhD, Neurology department, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Senior neurologist ”Nicolae Oblu” Emergency Clinical Hospital, 1st Neurological Clinic, Iasi, Romania

Georgiana Mihaela Monac – M.D., Gastroenterology fellow, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Romania

ABSTRACT

Stroke is one of the main problems for health systems, being a major cause of mortality and the second leading cause of DALYs. Through the development of medicine in recent years, mortality caused by cerebral vascular events and physical dysfunction tend to decrease. This turns mental dysfunction into the main cause of concern for the health systems and implicitly for society. Global cognitive decline after stroke is common, with a prevalence of approximately 44% in the first 6 months after the acute event. This has an effect on functional recovery abilities and increases the risk of developing major neurocognitive disorder. The long-term mortality is two to six times higher in patients with post-stroke dementia. Ten potentially modifiable risk factors are collectively associated with approximately 90% of the risks that can be attributable to the population for stroke. Physical activity decreased population attributable risk by about 53% in all types of stroke. Physical activity is associated with a decreased risk of stroke and mortality, as well as favorable results after stroke, which makes it a potential preventive measure against cognitive decline. An increased level of physical activity performed prior to stroke is independently associated with higher cognitive performance after stroke. The combined use of several measures with a vascular protective role, applied since middle age, could prevent several years of cognitive aging.

KEYWORDS:

Stroke, neurocognitive disorder, physical activity.

Stroke and neurocognitive disorders

Stroke is one of the main problems for health systems around the world, being a major cause of mortality and disability. According to the 2019 Global Burden Disease, Injuries and Risk Factors Study (GBD), stroke is the second leading cause of DALYs (Disability-adjusted life years) for both age group 50-74 years and for people over 75 years. (1)

The traditional definition of stroke is based on the sudden loss of neurological function due to infarction or hemorrhage in a relevant part of the brain, retina or spinal cord. According to an updated definition, stroke is an acute episode of focal dysfunction of the brain, retina or spinal cord that lasts more than 24 hours, or of any duration if there is an imaging lesion (CT, MRI) or at autopsy, which can justify the symptoms. (2)

The main symptoms of a stroke, regardless of etiology, are muscular weakness, expressive or receptive aphasia and cognitive dysfunction. Motor deficit along with language disorders are symptoms that alert the patient from the first moments of the vascular event and implicitly have the greatest psychological impact. Cognitive dysfunction does not have the same clinical resonance, it can have a long and silent evolution, which is why it alerts the patient or his entourage in late stages.

Through the development of medicine in recent years, both in terms of diagnosis with high-fidelity paraclinical explorations, and through topical treatments that allow rapid and successful interventions, mortality caused by cerebral vascular events and physical dysfunction tend to decrease. This turns mental dysfunction into the main cause of

concern for the health system and implicitly for society.

Cognition encompasses many aspects of intellectual functions and processes such as attention, knowledge development, memory and working memory, judgment and evaluation, reasoning and "calculation", problem solving and decision making, understanding and language production. Cognitive processes use existing knowledge and generate new knowledge.

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders abbreviated as DSM-5, published by the American Psychiatric Society in 2013, neurocognitive disorder is divided into minor neurocognitive disorder, major neurocognitive disorder and delirium. Minor neurocognitive disorder is manifested by a modest cognitive decline (compared to a previous level of performance), reported either by the patient, entourage, treating physician or by standardized neuropsychological testing, or, in their absence, by other clinical evaluations that can be quantified. This syndrome is characterized by impairment of one or more cognitive domains, such as complex attention, executive function, memory and learning, language, perceptual-motor function, or social cognition. Cognitive decline does not interfere with independence from complex daily instrumental activities, but requires greater effort, compensatory strategies, or accommodation in the conduct of daily activities, such as paying bills or administering medication. Also, this cognitive impairment does not occur exclusively in the context of delirium and is not explained by

another mental disorder, for example schizophrenia. (3)

Major neurocognitive disorder, corresponding to dementia, is manifested by a substantial impairment of one or (usually) several cognitive areas. The dysfunction must be sufficiently significant to interfere with independence from daily activities (excluding motor / sensory sequelae of a cerebral vascular event). (3)

Over time, there has been a significant evolution of the terminology that defines the cognitive syndrome associated with cerebrovascular risk factors and their manifestations, especially in terms of describing dementia. About 40 years ago, the term "multi-infarct dementia" (MID) was used to identify patients who developed dementia after multiple strokes. Subsequently, the expression "vascular dementia" (VaD - vascular dementia) was used, regardless of the pathogenesis of the vascular lesion, ischemic or hemorrhagic, single or multiple infarction. (4)

Global cognitive decline after stroke is common, with a prevalence of approximately 44% in the first 6 months after the acute event. (5) This has an effect on functional recovery abilities and increases the risk of developing major neurocognitive disorder.

Vascular cognitive impairment (VCI) are a heterogeneous group of neurocognitive disorders, the essential feature being that cognitive decline is mainly attributed to cerebrovascular disease. This group includes both vascular dementia and cognitive impairment that do not meet the criteria for dementia. (6,7)

The most severe form of cognitive impairment by vascular origin is vascular

dementia. Dementia is not always a direct consequence of cerebrovascular lesions, it can be degenerative, with onset and progressive course, even if it occurs after a stroke. Studies have shown that many patients hospitalized for stroke seems to have preexisting cognitive decline.

Dementia and neurocognitive disorders are important problems for health systems and a burden to society, with a significant impact as life expectancy increases. The autopsy and neuroimaging have shown that many cases of dementia are caused by pathological changes of vascular origin that occur in the brain (such as cerebral infarction, white matter lesions and microbleeds).

Dysfunction of the neurovascular unit and of the mechanisms that regulate cerebral blood flow are probably important components of the pathophysiological processes underlying VCI. Cerebral amyloid angiopathy appears as an important risk marker for Alzheimer's disease, microinfarction, microhemorrhage or macrohemorrhage of the brain and VCI. The pathogenesis of cognitive dysfunction in the elderly is generally a mixture of Alzheimer's disease and microvascular brain damage, which can cause, through overlap and synergy, an increased risk of cognitive impairment. In this regard, magnetic resonance imaging and other neuroimaging techniques may play an important role in the detection and definition of VCI, providing sufficient evidence that subcortical forms of VCI with white matter hyperintensities and small deep infarcts are common. (4)

Among patients who suffered a first stroke, post-stroke dementia (PSD) prevalence varies depending on the location, size of the infarction and the interval after the stroke. Generally, a stroke increases the risk of dementia by about 2 times. This is higher with

advancing age, lower education level, history of diabetes or atrial fibrillation and recurrent cerebral infarction. Patients with PSD have impaired functionality in varying degrees and high mortality rates. (4) After adjusting the demographic factors, associated cardiac pathology, cerebral vascular event severity and stroke recurrence, the long-term mortality is two to six times higher in patients with post-stroke dementia.

Risk factors for stroke and neurocognitive disorders

Risk factors were associated with an increased incidence rate of the disease, higher chances of developing the illness or determining the early onset of the disease, depending on the type of statistical analysis performed. By comparison, the protective factors are the opposite. An observed risk factor does not necessarily cause the disease, just as a protective factor does not prevent the disease and certainly does not treat the disease.

In many studies, a higher number of cardiovascular risk factors in middle age, along with vascular disease and diabetes are associated with a higher risk of dementia and cognitive decline. An important means by which cardiovascular risk factors can cause cognitive dysfunction is by causing cerebrovascular events (such as stroke or TIA). (8)

In the INTERSTROKE case-control study conducted between 11 January 2007 and 8 August 2015, on 26919 participants from 32 countries, it was shown that ten potentially modifiable risk factors are collectively associated with approximately 90% of the risks that can be attributable to the population (PAR - population attributable risks) for stroke, in every major region of the world, in ethnic groups, in women and men and in different age groups. (9)

History of blood pressure of 140 / 90mmHg or higher, physical inactivity, the ratio of apolipoprotein (Apo) B / ApoA1, diet, the waist / hip ratio, psychosocial factors, chronic tobacco use, cardiac causes, alcohol consumption and diabetes, have been associated with all types of stroke. Through an analysis that compared intracerebral hemorrhage with ischemic stroke (case-by-case analysis), hypertension was more strongly associated with cerebral hemorrhage, while smoking, diabetes, cardiac causes, and apolipoproteins were more significantly associated with ischemic stroke. (9)

Non-modifiable risk factors, also called risk markers, include demographic factors such as age, gender and race-ethnicity. In terms of age, generally, after the age of 65 there is an exponential increase in the incidence and prevalence of vascular origin dementia cases. Regarding sex, studies have shown a higher prevalence of stroke in women, this being justified by a higher life expectancy among them. Women are older at the onset of stroke compared to men (75 years compared to 71 years). Also, women between the ages of 45-84 have a lower risk of stroke compared to men, but this association is reversed after the age of 85, when women have a higher risk. (10) However, young women have a higher risk of stroke, which is correlated with pregnancy or postnatal status, hormonal changes and use of contraceptives.

In terms of race-ethnicity, studies have shown that black people have a double risk of stroke compared to their white counterparts, with a higher mortality associated with stroke. Latin Americans / Hispanics also have a higher risk. The disparity in the incidence of stroke is more prominent among young black people, in whom the risk of subarachnoid and intracerebral hemorrhage is substantially higher than whites of the same age. (11)

Modifiable risk factors are divided into those of a medical nature that can be modified by appropriate treatment: hypertension, diabetes, atrial fibrillation and dyslipidemia, or lifestyle factors: diet, obesity, alcohol and / or tobacco consumption and physical activity.

Modifiable medical risk factors

High blood pressure (hypertension), defined as systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg, is the most important modifiable medical risk factor for both ischemic and hemorrhagic stroke. Maintaining blood pressure values within normal limits can significantly decrease the risk of cerebral vascular events, so that patients with BP $<120 / 80$ mmHg have about half the risk of people with hypertension.

Diabetes mellitus is an independent risk factor, increasing the risk of stroke by about two times, with 20% of diabetics dying by stroke. (11) Hyperglycaemia is associated with functional changes in cerebral circulation, but which are reversible when good glycemic control is restored. Studies have suggested that cognitive function is affected more as the presence of diabetes is longer. (4)

Atrial fibrillation (AF) is the most common cardiac arrhythmia, the most important complication of which is stroke of cardioembolic etiology. It is a strong risk factor for the ischemic stroke, especially when not properly treated with anticoagulant, increasing the risk of stroke by two to ten times among all age groups. (12)

The relationship between dyslipidemia and the risk of stroke is complex, with an increased risk of ischemic stroke associated with high levels of total cholesterol, but with a lower risk for high levels of HDL-cholesterol. High cholesterol levels seems to

be more strongly associated with ischemic stroke involving large arteries compared to other types of ischemic stroke. However, total cholesterol is inversely associated with hemorrhagic stroke, the risk increasing as total cholesterol decreases. According to the 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack (a guideline from the American Heart Association/American Stroke Association) it is recommended that LDL-cholesterol levels be under 70mg /dl, to reduce cardiovascular events. (13)

Modifiable risk factors associated with lifestyle

Diet influences the risk of stroke, but also cardiovascular risk factors such as high blood pressure, diabetes and dyslipidemia. Salt intake, for example, is associated with a high risk of hypertension and stroke, while potassium intake is associated with a decreased risk of stroke.⁽¹¹⁾ Dietary guidelines for stroke prevention recommend reducing salt intake and increasing potassium intake, a diet rich in fruits and vegetables, or adopting DASH diet (Dietary Approaches to Stop Hypertension) or Mediterranean diet. (14)

Obesity increases the risk of stroke through multiple mechanisms, including hypertension, glucose intolerance, and changes in atherogenic serum lipids. Typically, body weight is divided into categories based on body mass index (BMI). (15) In recent years, abdominal obesity, as measured by the waist / hip ratio, proved to be a more important predictor of stroke. In the INTERSTROKE study, the body mass index had a lower association with stroke compared to the waist / hip ratio. (9)

Tobacco use remains a major risk factor for stroke, it doubles the risk compared to non-smokers. Smoking is also associated with a

two to four times higher risk of subarachnoid hemorrhage (HSA). (15) Smoking cessation is an essential component in the prevention of stroke⁽¹⁴⁾, with the risk of stroke being lower in people who have given up smoking compared to active smokers.

The effect of alcohol consumption on the risk of stroke is dependent on the amount of alcohol ingested and varies according to the type of stroke. Alcohol abuse can also affect other risk factors for stroke, leading to increased BP, higher rates of atrial fibrillation, coagulation disorders and reduced cerebral blood flow. However, moderate alcohol consumption can have beneficial effects by reducing platelet aggregation and plasma fibrinogen concentration, improving HDL-cholesterol and endothelial function. (15) There is evidence of a "J" form relationship between alcohol consumption and the risk of ischemic stroke, with low to moderate consumption having a protective effect against stroke, while abusive consumption is associated with an increased risk of ischemic stroke. (11) Current guidelines recommend moderate alcohol consumption, under two drinks per day for men and under one drink per day for non-pregnant women. (14)

Physical activity is the main subject of this article, being one of the factors that can bring significant benefits both on the risk of stroke, and on general health.

It is well known that physical inactivity or sedentary lifestyle is a predictor of cardiovascular disease and early mortality. Sedentary lifestyle is part of a vicious circle, and can easily cause obesity, dyslipidemia, atherosclerosis and arteriosclerosis, which will eventually lead to damage to all organs, all these changes causing difficulty or inability to perform physical activities. This

vicious circle has a significant impact both on the quality of people's lives and on society and health systems, leading to a decrease in work capacity and an increase in the costs of preventing and treating acquired diseases.

The effects of physical activity are manifested by decreased blood pressure values, improvements in glucose tolerance, weight loss, reductions in fibrinogen and plasma platelet activity, increases in HDL-cholesterol and control of other cardiovascular risk factors. (15) At the cerebral level, physical activity increases neurotrophins, such as brain-derived neurotrophic factor, improves cerebrovascular function and cerebral perfusion, decreases the stress response and increases brain plasticity through synaptogenesis and neurogenesis. (4)

Physical activity is associated with a decreased risk of stroke and mortality, as well as favorable results after stroke, which makes it a potential preventive measure against cognitive decline. (16) The mechanism underlying these changes is not well known, but it seems to be related to changes in traditional risk factors, including the reduction of inflammation, oxidative stress and capillary dysfunction after stroke. (17, 18, 19).

Although physical activity is recommended by both guidelines and international organizations in order to maintain physical and mental health, it is not so performed among the general population and stroke survivors. (20)

In the INTERSTROKE study conducted on 26,919 participants from 32 countries, physical activity decreased population attributable risk by about 53% in all types of stroke. (9)

A combined program of aerobic and endurance exercises applied to patients with residual motor deficit post-stroke, significantly improved MoCA scores and reduced by 44.5% the number of patients who met the criteria for mild neurocognitive disorder. (21)

Although there are few data of the influence of physical activity performed before stroke, on cognitive function after stroke, this seems to have a significant importance. In the TALOS trial (The Efficacy of Citalopram Treatment in Acute Ischemic Stroke), there was a substudy performed on 488 patients. On them were applied the PASE scale (Physical Activity Scale for the Elderly) to assess the physical activity in the last seven days before the stroke and the scales SDMT (Symbol Digit Modalities Test) applied at one month and six months after stroke, respectively

MMSE (Mini -Mental State Examination) applied 6 months after stroke, to assess cognitive performance. This substudy demonstrated that an increased level of physical activity performed prior to stroke is independently associated with higher cognitive performance after stroke, measured by SDMT (16). This finding is consistent with previous findings that participation in physical activity and leisure is associated with better cognitive function after stroke (22).

The results obtained by these studies can assign to physical activity the role of protective factor. This makes it even more important to follow the stroke prevention guidelines, which recommend that healthy adults should perform moderate to intense physical activity for at least 40 minutes / day for 3-4 days a week. (14)

CONCLUSIONS

Conversion disorder has recently received attention in the psychiatric literature compared to other. In the context of increasing life expectancy and survival after stroke, neurocognitive disorder is one of the main consequences of stroke, with a particular importance for the population in terms of quality of life and implicitly for society and health systems, in terms of costs.

Measures taken to reduce the risk factors can prevent neurocognitive disorders, as they reduce the frequency of developing cerebrovascular disease. The combined use of several measures with a vascular protective role, applied since middle age, could prevent several years of cognitive aging. Regarding physical activity, there is ample evidence that it decreases the risk of stroke and the severity of complications that occur after it. However, studies on the relationship between physical activity performed before stroke, and cognitive performance after it, are relatively few, performed on small samples of participants but with encouraging results. This does not overshadow the benefit of physical activity on all cardiovascular risk factors and even offers the chance to conduct more extensive studies.

Therefore, according to international organizations, correlated with current medical guidelines, a healthy, balanced lifestyle is recommended in order to maintain biological constants within normal limits, which decreases the chances of developing cerebrovascular events that may impair cognitive function. However, in the event of a stroke, this lifestyle adopted both before and after the vascular event, can provide good functional results and improved cognitive performance during recovery.

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Correspondence:

Roxana Chiriță,

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

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Effects of Astaxanthin in patients with memory impairment

Alexandra Cristina Butunoi, Cristina-Maria Gavrilesu, Paloma Lascarache, Elena Cojocaru, Roxana Mihaela Barbu

Alexandra Cristina Butunoi - Specialist in Geriatrics - Gerontology, UMS Răducăneni, Romania.

Cristina-Maria Gavrilesu - Lecturer, MD, PhD, „Grigore T. Popa” University of Medicine and Pharmacy, Iași, Ist Medical Department, Senior in Internal Medicine, Specialist in Geriatrics, specialist în Clinical Pharmacology, Romania.

Paloma Lascarache - Lecturer, MD, PhD, „Grigore T. Popa” University of Medicine and Pharmacy, Iași, Ist Medical Department, Senior in Internal Medicine, Senior in Cardiology, Romania.

Elena Cojocaru - Lecturer, MD, PhD, Department of Physiology „Grigore T. Popa” University of Medicine and Pharmacy, Iași, Senior in Laboratory Medicine, Romania.

Roxana Mihaela Barbu - MD, PhD, Department of Physiology, University of Medicine and Pharmacy „Grigore T. Popa”, Iași, Specialist in Clinical Pharmacology, Romania.

ABSTRACT

Introduction: Astaxanthin is used to treat a variety of cardiovascular, metabolic, ophthalmological, immune, degenerative, and psychiatric disorders. We aimed to perform a systematic review on the effects of astaxanthin in people with mental disorders. **Material and method:** Several medical databases were searched: PubMed, Embase, Cochrane, PMC to identify randomized studies for both humans and animals on the effects of this antioxidant on cognitive function. **Results and discussions:** Analyzed studies show that Astaxanthin is a carotenoid with strong antioxidant properties. It is useful as a supplement for the positive effects on the health of the cardiovascular system, immunity, but also on mental health. Due to the fact that Astaxanthin can cross the blood-brain barrier, it plays a very important role in everything related to the activity of the brain, protecting the nervous system from the harmful effects of the oxidative stress. Astaxanthin has direct effects on memory disorders present in young people as well as in the elderly, improving memory and ability to concentrate. **Conclusions:** This review of the data showed that astaxanthin has direct effects on the risk factors that trigger memory disorders. It reduces the risk of developing cardiovascular disease, but also protects directly and indirectly the activity of the brain, diminishing the harmful effects of the oxidative stress on the nervous system. It is a very useful natural supplement for memory disorders, helping mental health by improving

cognitive function. Further studies are needed to better understand the effects of astaxanthin on all human memory disorders, but it has been shown to improve memory and the ability to concentrate. Astaxanthin could be useful in treating Alzheimer's disease, Parkinson and for reducing the consequences of stroke.

KEYWORDS:

Astaxanthin; beneficial effects, memory disorders.

INTRODUCTION

Memory is defined as the brain's ability to retain and remember various information, experiences, procedures, abilities, and habits. There are factors that influence the normal activity of the brain, triggering various memory problems from senility, dementia or Alzheimer. Cognitive disorders are characterized by changes in brain structure and function that affect learning, orientation, judgment, memory and intellectual abilities. The normal functioning of the brain can be affected by various conditions or situations, which can lead to memory degradation, subsequently appearing memory disorders. Diseases that affect memory by damaging brain cells are: Alzheimer's, stroke, head trauma and other neurodegenerative conditions (1).

Alzheimer's disease is a progressive neurodegenerative disease, a type of progressive dementia that, correlated with the aging process, is characterized by memory loss, thinking disorders, speech, behavior and personality changes, affecting millions of people globally. It is known to be the most common cause of dementia in the elderly, causing major progressive deficits in cognitive function and memory. Currently, over 35 million people worldwide are affected by this disease. Memory problems are not just caused by injuries or disorders that occur in the brain. Environmental, psychological, and emotional factors can have a negative impact on memory, including storage, retention,

activation, subsequent retrieval, and the use of information or memories (2).

Regarding the factors that may contribute to the development of memory disorders, the literature indicates the following: genetics, aging, diet high in sugar or fat, sedentary lifestyle, disturbed chronobiology / sleep and excessive alcohol consumption. Pathogenesis is connected to reactive oxygen species , which play an important role in vascular biology and are harmful in high concentrations, aggravating stress and causing damage to all cellular components, leading thus to accelerated cellular aging (2, 3). Antioxidant defense decreases with age, so that we lose the ability to produce the high levels of antioxidants we need to cope with growing harmful environmental factors such as pollution, food processed, contaminants and stressors. In addition, with age, inflammation of the brain increases. The body's response is to release inflammatory compounds to aid in healing; but they can also destroy healthy cells - leading to irritation and tissue damage. Although memory loss can be an integral part of an aging brain, it is possible to slow the decline of mental abilities and maintain complete brain function in optimal conditions. The risk of developing neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or dementia, continues to increase alarmingly with age. These conditions are characterized by the progressive loss of neurons in the brain and can lead to memory

loss, confusion, tremor, agitation and anxiety. Numerous studies have shown that some supplements, such as astaxanthin, have benefits for the brain, helping to maintain cognitive function. In a study in mice, astaxanthin supplements increased the formation of new cells in the brain and improved the spatial memory of mice (4, 5, 6).

Astaxanthin (3,3'-dihydroxy- β -carotene-4,4'-dione, AXT) is a xanthophyll carotenoid commonly found in seafood and plants. Astaxanthin is found in the free state and in the form of an ester and also exists as a chromoprotein. Oxygen groups make ketocarotenoids relatively more polar, allow esterification and can lead to higher antioxidant activity. Astaxanthin is found in many organisms through food intake, but the primary producers of this carotenoid are limited; a number of microorganisms and plants, for example, bacteria, algae, fungi and members of the genus *Adonis* in higher plants. To date, green algae *Haematococcus pluvialis* (Chlorophyta, Volvocales) has the highest reported level of astaxanthin at 4% dry weight (7).

The main effects and benefits of Astaxanthin on the body are: decrease of reactive oxygen species, thus leading to protection of cells and cellular components against oxidative stress; decrease of TNF α , prostaglandin E₂, interleukin IL-1b; modulation of cyclooxygenase COX2 and COX1; anti-inflammatory effect; stimulation of antibodies production and strengthening of the immune system; protection of the brain, support to cognitive function and memory health; prevention of premature aging; reduction of pain and swelling at the osteoarticular, renal and gastrointestinal level; protection of the ocular system, improving capillary blood flow, acuity and visual accommodation at a

distance, reducing eye fatigue and loss of ability to focus nearby objects, protection of retinal photoreceptors against UV radiation aggression; increase of the metabolic, mitochondrial and cardiovascular health by reducing LDL peroxidation in the vascular wall; vasodilation; improve of skin elasticity and hydration, maintaining tone, reducing collagen degradation and wrinkle formation; support for the joint health by increasing physical endurance, decrease of joint and muscle pain after intense physical exertion by reducing the level of lactic acid caused by muscle overload (8, 9, 10).

MATERIALS AND METHOD

Several medical databases were searched: PubMed, Embase, Cochrane, PMC to identify randomized studies for both humans and animals on the effects of Astaxanthin on cognitive function.

RESULTS AND DISCUSSION

The articles were analyzed in order to find detailed analysis of the effects of astaxanthin supplementation in patients with memory disorders and provide an in-depth summary of the results of clinical trials addressing this issue primarily or indirectly. Astaxanthin is a relatively new antioxidant that has documented benefits for the human body. Almost unknown until recently, astaxanthin is a carotenoid with strong antioxidant properties. Extracted from a single-celled microalgae, it can be taken as a supplement with positive effects on the health of the cardiovascular system, on the eye system but also on mental health (8, 9). Astaxanthin has been shown to provide strong antioxidant protection and benefits for the whole body. Each type of antioxidant acts predominantly in certain organs having different functions of annihilation of oxidizing species specific to that organ. Astaxanthin mainly acts on small blood vessels, with positive effects on the

heart, brain, nervous system and eyes. Perhaps the most important antioxidant action of Astaxanthin is on the mitochondria, the engine of the cell. Compared to other antioxidants, Astaxanthin has the greatest ability to annihilate the free radicals with "singular oxygen". Because Astaxanthin can cross the blood-brain barrier, it plays a very important role in everything related to the activity of the brain, protecting the nervous system of the brain from the harmful effects of oxidative stress. Therefore, Astaxanthin is useful in treating Alzheimer's disease, Parkinson's disease, or reducing the sequelae caused by a stroke. (11, 12, 13) Because Astaxanthin easily reaches the small capillaries that supply the eye, it bring its benefits and also associate synergistically with lutein and zeaxanthin (14).

Clinical studies that have measured the effects of astaxanthin proved that supplements with this substance can reduce both markers of inflammation in the body and markers of oxidative stress. Another analysis suggested that astaxanthin could protect against atherosclerosis, a condition characterized by the accumulation of fat and cholesterol in the arteries, leading to loss of elasticity (3, 9, 10).When it comes to antioxidant coverage, Astaxanthin is in a class of its own because it reaches every cell in the body. Its unique lipophilic and hydrophilic molecular properties allow it to penetrate the entire cell body, with one part of the astaxanthin molecule protecting the fat-soluble part of the cell and the other part protecting the water-

soluble part of the cell. This phenomenon could be described as "an embrace of the whole cell" (11). Astaxanthin has also significant positive effects in cases of metabolic syndrome. Thus, in double-blind, randomized controlled trials, astaxanthin reduced oxidative stress in overweight and obese subjects, diabetics and smokers (3, 10, 12). It was proved that astaxanthin increases the level of adiponectin in the blood. Adiponectin is a hormone produced by adipose tissue, heart tissue, skeletal muscle and endothelium of blood vessels. Serum adiponectin levels tend to be significantly reduced in obese, diabetic, smoking subjects, in patients with coronary heart disease, and in patients with metabolic syndrome (12, 15).

Recent data show that patients with metabolic syndrome have a much higher likeliness to develop Alzheimer dementia compared to those without metabolic syndrome (16). The association between metabolic syndrome and dementia brings another argument for the positive role of astaxanthine for preventing dementia in patients with metabolic syndrome. Although some symptoms of dementia cannot be controlled, there are still strategies to improve memory capacity. Changes in diet, rest schedule, physical activity and routine are simple strategies for preventing and improving memory disorders. Remedies such as Astaxanthin help prevent memory problems, maintaining the harmony and systemic balance of the brain and nervous system, without side effects or sedation (12, 13).

CONCLUSIONS

This review of the actual state of knowledge showed that astaxanthin has direct effects on the risk factors that trigger memory disorders. It reduces the risk of developing cardiovascular disease, but also protects directly and indirectly the activity of the brain, diminishing the harmful effects of the oxidative stress on the nervous system. It is a very useful natural supplement for memory disorders, helping mental health by improving cognitive function. Further studies are needed to better understand the effects of astaxanthin on all human memory disorders, but it has been shown to improve memory and the ability to concentrate.

The proven properties of this substance are really numerous and remarkable, occurring from its main action as an antioxidant, slowing down the degenerative processes due to aging. Astaxanthin could be useful in treating Alzheimer's disease, Parkinson, or for reducing the sequelae caused by stroke.

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Correspondence

Cristina-Maria Gavrilescu,
Lecturer, MD, PhD, „Grigore T. Popa” University of Medicine and Pharmacy, Iași, Ist Medical
Department, Iași, Romania, Senior in Internal Medicine, Specialist în Geriatrics, Specialist în
Clinical Pharmacology, cristina.gavrilescu@umfiasi.ro

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Humanistic Contributions

A new beginning, a great challenge: metamodern psychology (Part II)

Mihai Şleahţichi

Mihai Şleahţichi - Doctor habilitat (docteur d'État) in Psychology, PhD in Paedagogy, Professor, Republic of Moldova

As the space of the present analysis does not permit discussion of other examples illustrating the perspectives of modern psychology(22), we shall propose in the following a synthetic view on its metamodern profile, being convinced that our approach – based on the information available in this moment – could represent a complex ideatic construction, capable of covering at least nine directions for its elucidation.

Firstly, we are convinced that the psychology of metamodernity will not leave aside "the great problems of the past", paying sufficient attention to the "hot topics" debated upon both in the modern and postmodern epoch. Paraphrasing, to some extent, P. Fraisse, we could say that metamodern psychology will follow, in various ways, the modern and postmodern one, so that "to be able to anticipate the domains and results to follow". Obviously, it goes without saying that, during metamodernity, the large variety of concepts, orientations and domains developed in modernity and/ or postmodernity will create difficulties related to the unification of

psychology. Accordingly, as already mentioned, and citing M. Richelle, the psychology of metamodernity will continue to be characterized by a sort of epistemological syncretism. In such a situation, the gathering effort should imply at least four essential traits: *a new reading of the theoretical approaches* ("not only for evidencing their common denominator, which would involve their devoiding of any substance, but also for revealing the issues to be faced, which they cannot solve, any more; it is only in this domain that all chances for attaining convergency and complementarity may be found"); *terminological explanations* ("in not few cases, the same idea is expressed in different words, or different things are referred to in the same words; to rediscover and identify things, one should leave aside the words"); *a radical modification of the main approach* ("instead of laying stress on explanatory – partial or totalitarian – models, more recommended is to re-establish the priority of issues, after which the theoretical models may be obtained"), and *a re-examination of the methods* ("study of some

aspect by several methods as, in too many cases, the method employed is selected precisely for checking the theory"). In all likelihood, distancing between the external and the internal observation, as well as the convergence between connex domains (for example, development of biotechnology has stimulated and will continue to stimulate biopsychological researches) will increase. Equally, cognitive psychology, the psychology of information processing, physiological and genetic psychology will advance.

Secondly, we are inclined to assert that the scientific psychology of the metamodern epoch will establish its own outlook regarding the human being. Under the new historical conditions, we repeat that "the postmodern culture of relativism" is doomed to fail, which means that it will be gradually substituted by a post-ideological condition centered on *involvement* and *affectation*. In such a context, most probably, the human being will be viewed as an *oscillating structure* susceptible of including "certainty and doubt, hope and melancholy, sincerity and irony, feeling and apathy, personal and impersonal attitudes, technicism and technology". On any occasion and under any circumstances, it will have to demonstrate that the philosophy of life it imparts, and also what it busily promotes, is based on a "pragmatic neoromanticism" (susceptible to create a symbiosis between two types of culture – that of utility and that of dignity), on a "new type of sincerity" (capable of denying both the ideological credulity imposed by the modern epoch, and also the cynical skepticism of the postmodern times), a "new rationalism" (centered on a consistent identification and promotion of the scientific truth), a "new type of hedonism" (ready to give priority to the present time, rendering to the most recent events adaptative positive significance), a

receptivity towards narrow social environment, on "the small cultural traditions" and territorial identities, on a "network logic" (prepared to approach the everyday life according to a complex thinking pattern), a lattice of interpreting reality adapted to "post-truth" (capable to fully develop critical thinking), a fully transparent code of manners (conferring visibility and distinctness to behavioral acts) and/ or a series of states whose name begins with "trans-", an element of pedantic composition, meaning "over" or "beyond (of)" (such as that of transgender or of transgression, trans-humanism or transmission). More than that, while strictly following "the spirit of the age", it will have to demonstrate that it is capable of decyphering the events and phenomena of the world to which it belongs based on data extracted from reality, that it may reconstruct itself by the organization and realization of inter-relational type communications, that it has the capacity to see things in all their depth and that it promotes an existential order in which all – small and big, common and less common – things express a unitary logic(23). As a result of the reinterpretations on the human being and his/ her role under the new historical conditions, we shall most probably witness an ample development of the psychological sciences (considering here mainly social psychology, cognitive psychology, introspective psychology, the psychology of communication, behavioural psychology and/ or pathological psychology) focused on the "psychic substance" of the human being – especially on his/ her affectivity and capacity of involvement – along with a decline of the psychological sciences which, in the past, neglected human's inner world (for example, behavioristic psychology).

Thirdly, it is quite possible that, in the years to come, the science of psychology will be

mainly and thoroughly devoted to the study of *self-organization* and *creative activism*. As already observed, metamodernity is interested in the intellectual strategies with "oscillating" nature, substituting the "or/ or" principle with the "and/ and" one, so that the necessity of *identifying the manner in which two or more contradictory conditions can be simultaneously experienced* might possibly appear. Or, in the case in which such "swingings" (namely, movements of the "come-and-go" type) play a determining part, establishment of a close connection between the significance of *decentralization at external level* and *self-organization at internal level*, a connection which will correlate personal *autonomy* with *civic responsibility* and its *moral maturity*, is highly expected. In such a context, it is not only selection of a certain "pole", but *grasping of the pulsating character of objective reality* that will constitute the essence of the knowledge and of social adaptation processes. Obviously, for facing the intellectual stress of such situations, each person will simply have to resort to various *syntheses of creative nature*, that will force him/ her to invent new things. Therefore, in one way or another, *self-organization* and *creativity* acquire defining characteristics of the metamodern individual and, respectively, metamodern psychology(24).

Fourthly, further evolution of psychology – preponderantly oriented to turning to good account epistemological constructions of *pragmatic type, self-reconstruction through inter-relational communication, capacity of involvement* or *affectivity* – will finally lead to the elaboration of some new concepts, of purely metamodern nature. In parallels with the notions invented and fully advanced either in the modern epoch(such as, for example, that of *social role* (proposed by F. La Rochefoucauld in 1655), that of *public*

opinion (proposed by J.-J. Rousseau in 1744), that of *aculturation* (proposed by W.H. Holmes, F. Bocs and W.J. McGee in the end of the XIXth century), that of *ambivalence* (proposed by E. Bleuler in 1910), that of *eros* (proposed by S. Freud in 1920) or that of *habit* (proposed by J. Dewey in 1922), or in the postmodern one(such as, for example that of *social representations* (proposed by S. Moscovici in 1961), that of *real conflict* (proposed by M. Sherif in 1966), that of *autopoiesis* (proposed by U. Maturana and F. Varela in 1975), that of *cript* (proposed by N. Abraham and M. Torok in 1978) that of *social impact* (proposed by B. Latané and S. Wolf in 1981), that of *sexism* (proposed by J.E. Williams and D.L. Bert in 1982) or that of *mcdonaldization* (proposed by G. Ritzer in 1993)) – which, undoubtedly, will remain strictly actual, a new series of previously unknown notions will appear, for example, the concept of *proteism* or that of *metaxypsychology*.

Discussing the essence of the concept of *proteism*, its author, M.N. Epshtein, considers that the state of mind prevailingly manifested in the beginning of the XXIst century may be described with expression "proto-", a fundamental linguistic element of pedantic composition, of Greek origin, meaning "the main", "the first", "the early". Using the term "proto-", says M.N. Epshtein, means to recognize that this century lays the foundations of an unknown civilization, in which all our previous knowledge represents only too few discoveries, comparatively with we ought to know in an epoch characterized by a massive presence of info- and biotechnologies. This notion is expected to express: (i) the human capacity of being oriented and, respectively, prepared to face a doubtful future, (ii) awareness upon the embryony-arhaic form of our present conduct (as, for the moment, each of us

represents both an embryo of the civilizations to come, and an immemorial relict of theirs), and (iii) openness towards transitivity (which agrees with the fundamental expression of the mythological Proteus), towards dynamicity and fluidity, towards everything existing and manifesting in either amorphous or polymorphous state (25).

The observation to be made about the second concept is that its author – A.A. Grebeniuk – starts from the idea that, in the metamodern epoch, "the exact science of the mind and of the human conduct" should be necessarily developed in the "metaxy" variant, which means that its specificity should be simply reduced to "a continuous movement between and outside some contradictory poles". Inspired by the studies of P. Friedlander, L. Herman and R. Eshelman, he states that such a new vision is actually expressing a critical reaction both against the contradictions present in the naive ideologies of the time and against the pseudo-scientific theories of postmodernism. Finally, *metaxypsychology* is expected to offer the necessary conditions for the development of non-ideologized and non-ironical scientific projects. With such a general objective in view, it will grant that the systematic study of human mentality and conduct will become organically related to art, imagination and creativity. More than that, while oscillating between the modern tradition of "searching of meaning" and the postmodernist trend of "neglecting the meaning", *metaxypsychology* will be responsible for creating some authentic representations of the human being, in his/ her quality of "behavioural entity endowed with perception, intellect and affectivity". Continuing to ceaselessly modify the tendencies of modernist and postmodernist origin, it will contribute to demonstrating that, for now, the ideas of the "our life is a game" type should not be taken seriously, any more,

being replaced by a wholly different postulate: "our life is a performance". Leaving aside the concepts of "good" and "evil", this assumption will show the way through which reality may be thoroughly reflected, providing an interpretation of events and facts in which interpretative dualism and uncertainty will be either hardly manifested or they will be absent. The form will follow the content, which means that things considered once as intricately, obscure and difficult to understand will become simple, distinct and easy understandable. In such a moment, the neoromantic character of *metaxypsychology* will find its expression as an oscillation between order and chaos, form and non-form, beautiful and ugly, sublime and horrible. Against such a background, self-therapeutical manifestations will become reality. Equally, it will be manifested as self-assertion and as creation of cronotopes capable of correctly and rapidly orienting one in extremely complicated contexts (26).

Oscillating between the epistemological poles of the modern and postmodern world, at a pace which will involve not only their "exploitation", but equally their "elevation", the new concepts will decisively contribute to a more thorough knowledge about the essential characteristics of the human species and also about its specific manifestations along the third millennium.

Fifthly, we make common cause with the observers who believe that, in an epoch deeply troubled by globalization – a complex phenomenon "whose result is that events occurring in some part of the world have more and more ample repercussions upon societies and issues from other parts of the globe" – the science of psychology will have to elaborate well-structured interpretative methods approaching the flows of persons (migration), of capital and of technology,

suprapopulation, fragmentation and weakening of social cohesion, modifications produced in technology and innovation, drastic fall of the cultural and national values under the pressure exercised by the progress of the new information and communication techniques, increased inequalities at both internal and external level, destruction of the classical system of values hierarchization, the possibility of an atomic war, spreading of infectious diseases (with special reference to the new types of pandemic virusi), sexism and rasism, ethnocentrism and ultranationalism, proliferation of arming and of transnational crime and/ or of international criminal organizations and therorist nertworks.

It stands to reason that, in the years to come, psychology will have to be correlated "with the great cahllenges of the time and with the possibility of achieving a long lasting international peace beyond the barriers of social policy"(27). Undoubtedly, this will bring about substantial modifications in the communication among psychologists all over the world. Or, as many of the specialists in this field – for example, Virginia Staudt Sexton(28) – anticipate, "the science and profession of psychology will develop if the psychologists of all countries will pay more attention to one another".

Sixthly, we may reasonably assume that, in the new historical conditions, when prevention or combat of the consequences of natural cataclysms(29) and technogenous type catastrophes(30) will play an extremely important part, psychology is expected to provide convincing answers about the behavioural strategies people should adopt in cases of "unexpected, tragic, disastrous events". Most probably, in such a context, studies devoted to the identifiiction and practical application of the strategies of psychological protection against (chemical,

radioactive, etc.) contaminations, (aviatic, maritim, railway, car, etc.) accidents, hurricanes, typhoons, earthquakes, tsunamis, volcanic eruptions, landslides, draught or floods, will be extremely actual.

Seventhly, we are prone to believe that metamodernity will favourize the infiltration of psychology in domains of activity previously neglected by it, either because they were not of interest or because, in general, they gave no "signs of life" (such as: international consulting, international organizational psychology, multiculturalism, mediation and negociation of interoganizational conflicts, international arbitration, etc.). Such an extension will require revisions both in the programs of psychologists' professional training and in the strategies and techniques of psychologic investigation.

Eighthly, the existing data shows beyond any doubt that, in metamodernity, the evolution of psychology will depend, to a considerable extent, on the progress registered in other domains of scientific research. In this respect, a special part will be played by the ecological and medical sciences, by electronics and technology of information, research of the cosmic space and of the individual, organizational, regional, national, planetary security. The impact will be rapid and intense and no one will have doubts as to the inevitable instauration of a new investigational frame. As part of an intense reaction of epistemological interpenetration, psychology will extend its sphere of interest, creating a new type of paradigms (such as, for example, ambiental psychology, psychoinformatics, psychobionics, psychobiotics, psychoaxiology and / or psychoanthropology). More than that, in the years to come, psychology will be obliged to thoroughly observe the "rules" of

transdisciplinarity. Or, the deeply contradictory character of the new daily reality will make it systematically resort to a manner of thinking combining the analytical perspective with the holistic expression. The *socialization* and *individualization* phenomena will create an *unifying antinomy* expected to explain that, in the new historical conditions, a full social affirmation involves individual resistance to the multiple disagreements manifested in such areas. As a matter of fact, in the metamodern epoch, most likely, psychology will propose investigation paths according to which the analyzes centered on the human being and on the manner in which he/ she advances in life will take into consideration the existing antinomies and the ideas strictly manifested on multiaspectuality, situationality, inter- and trans-disciplinarity(31).

Finally, *ninthly*, the existing data permits the assertion that, in the metamodern epoch, evolution of psychology will be highly influenced by the principles of market economy. In order "to keep pace with time", it needs a substantial financial support, whose obtaining will require full joining to a system in which "the decisions on the production and distribution of goods are relying on the demand-supply interaction". Along the historical period here analyzed, psychology will have to gain a large social approval, and a considerable social interest. In other words, as M. Zlate puts it(32), it will have "to consider much more people's social problems, to venture beyond the laboratory and the clinic, to approach the society – the social laboratory". As a matter of fact, this would involve promotion of the principles of psychology in the world of business, creation and large-scale approaching of managerial and enterprising projects capable of assuring maximum efficiency of all activities in the domain. Considerable efforts should be

undoubtedly necessary for the identification of new methods for staff recruiting and selection, for the promotion of *mentoring* and *coaching* policies, psychological consulting of both employers and employees, creation and development of managerial teams, prophylaxy and/ or reduction of professional exhaustion, establishment of objectives with motivational and ethic nature, etc. All these efforts will be felt in each domain, from banking, agriculture or IT&C up to pharmacy, outsourcing or FMCG. With the aim of raising the quality of people's economic behaviour, psychology will probably reach the conclusion that the great financial crisis (with which we came out postmodernity while entering metamodernity) occurred because the economic system had been built up on an erroneous vision about the human being. If, times ago – when the postulates of classical economy were preferred – the idea that "individuals are capable of performing exact economic calculations and of taking the most rational decisions about their money" was acknowledged, the premise now put forth was that "most of the individuals are irrational and self-destructive, they frequently take wrong decisions, always repeat the same mistakes, are naive and easy-to-handle, not knowing to calculate the risks and performing emotional economic operations". The *homo economicus* once established by Adam Smith will appear as only an elementary theoretical concept. This time, priority will be granted to the efforts made for integrating the most recent advances registered in psychology in "a more flexible and more realistic explanation of human economic behaviour". In other words, focus will be laid on the elaboration of an economico-behavioural paradigm capable of "considering all fluctuations of human rationality, which can be equally affected by emotions, by the herd effect, by the marketing techniques in use or simply by the

incompetency of making economic calculations”.

The conclusion of all these considerations is that, in metamodernity, psychology acquires a new contour. This time, it aims at playing a full spiritual part in an epoch which values pragmatism and involvement, the capacity of deciphering people' conduct on the basis of strictly realistic data and on the idea of self-reconstruction through inter-relational communication, on the ability of grasping things in all their complexity and on the objective of installing a new existentialistic order, in which each situation expresses a unitary logic.

In spite of its significant distancing from the experience accumulated in the postmodern epoch and, even more, from that of the

modern one, and if considering that metamodernity is an extension of modernity and postmodernity, metamodern psychology is not wholly detached from its previous manifestations, so that some assertions valid once will still be observed, such as: the existence of universal truths, the diversity and competition of paradigms, the presence of monolithic existentialistic factors, the importance of socio-cultural norms, of economic determinations and of arbitrary-linguistic conventions, etc. Therefore, metamodern psychology appears as a complex epistemological structure in whose composition originality matches ideally tradition, discontinuity – continuity, and classicism – full anchoring in contemporaneity.

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29. As generally known, natural cataclysms (hurricanes, typhoons, earthquakes, drought, floods, etc.) are caused not only by the nature of earth's surface, by the processes occurring in the atmosphere or by the mutations the biosphere is subjected to, but also by an exponential population increase, by its high concentration in certain regions of the globe, by the massive industrialization of the seacoast zones, by megaconstructions which drastically restricts the easily flooded areas of rivers and/ or by ecological involutions. In the last 20 years, approximately three million persons were victims of natural cataclysms, while more than 800 millions suffered severe consequences. In the year 2011, the material damages produced by natural cataclysms amounted to 380 billion dollars, comparatively with the annual average value recorded until then, of 75 billion dollars. The continuous industrial increase, along with urbanization, concentration of populations in zones with high natural risk (first, in seacoast areas, occupied by 44% of world's population, where 4/5 of the largest existing cities are placed) represent the main factors multiplying such type of risk. In recent years, the manifestation of dangerous natural phenomena has constantly increased. The risks of exceptional situations induced by the global modification of both climate and economic activities are huge for the population and, equally, for the economic objectives. In this respect, see also Catastrofele naturale. Available at: ro.wikipedia.org/wiki/catastrofa_naturala and/ or *Dezastre naturale*. Available at: www.storyboardthat.com/ro/lesson-plans/dezastre-naturale.

30. The technical-scientific progress – initiated in the middle of the XXth century, with the introduction, in productive activities, of large amounts of natural resources and with the utilization of complex technological systems – caused a substantial increase of technogenous type catastrophies. According to specialized opinions, such increase is first related to the application, in industrial and energetic domains, of a too high amount of chemical radiations and of technological processes with explosion risk. It has thus become obvious that the danger for people is generated by the environment he himself created. Data provided by the United Nations Organization shows that the incidents with technogenous character occupy the third position among all types of exceptional situations, concerning the number of human lives loss. The first place is held by hydrometeorological natural disasters (floods, tsunamis), and the second – by cataclysms of geological nature (earthquakes, landslides, volcanic eruptions, etc.). According to the data provided by the International Center Disaster Research, the mortality rate recorded by technogenous injuries produced between 1994-2007 was of 0.8 persons deceased at 1 million. Over the 2003-2006 period, the number of technogenous catastrophies increased several times, comparatively with the number of natural disasters. In the following years, the situation becomes even more critical. Thus, according to the data provided by the Schweizerische Rückversicherungs-Gesellschaft A.G. Swedish Insurance Company, between 2006-2013, 8,700 human victims were recorded, while the sum of material losses attained 4 billion dollars. In the last ten years, at world level, the technogenous disasters produced about 600,000 deceases, and about 2 billion persons were wounded. In the years to come, the specialists of such statistics estimate that no significant changes will occur, which means that the number of persons affected by technogenous phenomena will increase. For further details, see TĂBĂRȚĂ, V., CAPRĂ, G. Pericolul catastrofelor contemporane cu caracter tehnogen. Available at: <http://repository.utm.md/handle/5014/1004>; Catastrofele cu caracter tehnogen. Available at: <http://www.washprofile.org> and/ or Centre for Research on the Epidemiology of Disasters (CRED). Available at: <http://www.emdat.be>.

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Correspondence

Mihai Șleahțiți,

Doctor habilitat (docteur d'État) in Psychology, PhD in Paedagogy, Professor,
Republic of Moldova, mihai sleahitchi@yahoo.com

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Case Reports

Diagnostic challenges in shared delusional disorder (folie à deux). Case presentation

Ligia Vereșanu, Vasile Chiriță, Irina Dobrin,
Cristinel Ștefănescu, Roxana Chiriță

Ligia Vereșanu - M.D., residency training in psychiatry, Socola Institute of Psychiatry, Iași, Romania

Vasile Chiriță - M.D., PhD, Professor, Honorary Member of the Academy of Medical Sciences Iași, Romania

Irina Dobrin - M.D., PhD, lecturer, University of Medicine and Pharmacy "Grigore T. Popa" Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași, Romania

Cristinel Ștefănescu - M.D., PhD, Professor of Psychiatry University of Medicine and Pharmacy "Grigore T. Popa" Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași, Romania

Roxana Chiriță - M.D., PhD, Professor of Psychiatry University of Medicine and Pharmacy "Grigore T. Popa" Iași, Senior psychiatrist Socola Institute of Psychiatry, Iași, Romania

ABSTRACT

Psycho-social factors profoundly influence the meaning and nature of symptoms in mental disorders, therefore the cultural and family framework can correctly interpret behaviors and reduce diagnostic errors and diagnostic ambiguity in clinical situations. Abnormal beliefs are the main focus of delusional disorders, often finding paranoid symptoms in dysfunctional families. This paper presents the case of two brothers with a dysfunctional family, in which psychological stress and social isolation are the main important factors in the aetiology of shared delusional disorder, a rare psychiatric condition, characterized by uncritically accepting delusional beliefs of another person. This pathology has a chronic evolution because the people involved have an unusually close relationship and are isolated from the surrounding world from a cultural point of view.

KEY WORDS:

Shared delusional disorder, diagnostic, psychosocial factors.

INTRODUCTION

Regarding the social environment, recent studies show that psychiatric disorders occur

more frequently among disadvantaged people. Evolutionary theory highlights the role of social hierarchies that influence the social

choices and expectations of others regarding a person's behavior. The type of psychosocial information has a direct impact on physiological and psychological states: repeated negative information and behaviors can lead to deviant behaviors and vice versa (1, 4).

According to C.C. Hughes, family environment becomes a configuration of images and other symbolic elements (such as language) widely shared by its members, in which it serves as a matrix of communication and tends to coordinate and sanction behaviors. Thus, the family becomes a normative framework that defines normality and promotes preferred values and behaviors, while outlawing others, leading to healthy adaptation or preventing development by causing maladaptation (2, 4).

Induced (shared) delusional disorder or folie à deux was first described in 1877 by Lasegue and Falret as a rare clinical condition in which there are usually two protagonists. There are cases, in which delusion was shared by three or even more persons, sometimes the whole family, these persons being relatives or people who have a long-term intimate contact (two brothers, mother-child, father-child, husband-wife) (8).

A specific characteristic of the shared delusional disorder is the relationship of dominance and obedience, so the dominant partner is more affected, in terms of the severity of the disease and usually suffers from schizophrenia or another psychotic disorder, thus representing the origin of the delusion that passes to the other partner (inductive delusion). The recipient of delusions is not known as a psychotic patient in the records of the psychiatric network, the manifestations appearing after the onset of delusion in the dominant partner (induced

delusion). In the most common form, the individual who has the first delusion (the primary case) is often chronically ill and is typically the influential member of the intimate relationship with a more suggestible person (the secondary case) who also develops delusions. The secondary case is often less intelligent, more gullible, more passive, with low self-esteem. The most common delusion themes are persecutory, followed by hypochondria, grandeur and sexuality, all contributing to the hostile perception of the outside world which closes a vicious circle, the two partners isolating themselves, becoming even more interdependent and more motivated in developing delusions (3). The condition is usually chronic and both the dominant and submissive individual share the original delusions, which could be of any type (5).

CASE REPORT

We present the case of two brothers that meet the criteria for diagnosing Shared Delusional Disorder (secondary case), who underwent medical treatment and had an unfavourable evolution due to psychological stress inside their family.

- *Family health history*

The social family history of the two brothers revealed that their neuropsychic and psychiatric development in early childhood was normal. They have a dysfunctional family (their father has chronic alcoholism and their mother developed schizoid personality traits). They live in four bedroom house, located in the rural area, unmarried and childless. The older brother (the dominant case) graduated from the Faculty of Agronomy Iași in 2015, but never had a job because he retired on medical grounds, just like his brother did (the secondary case), who never went to high-school. The two brothers are occasional drinkers, non-smokers.

It is worth noting that their mother manifests an overprotective behaviour, the interdictions and associated fears incapacitating them to perform age-appropriate activities and isolating them from the outside world (she goes with them at the park or shopping). Their alcoholic father did not get involved in their education and therefore created an additional negative impact on the family.

- *Medical history – case 1 (the dominant case)*

It is a male patient, aged 33, with no pre-existing conditions, was diagnosed in 2014 with Acute Psychotic Disorder (treated with antipsychotic medication Risperidone 6mg/day oral suspension and Valproic acid 1000mg/day). He was admitted to the „Socola” Institute of Psychiatry in 2015, accompanied by his mother, for psychoproduktive symptoms. In 2016, he returned to the hospital, accompanied by his mother and brother for worsening symptoms and he was diagnosed with Paranoid Schizophrenia. He continued his initial treatment with Risperidone and Valproic acid and was also prescribed Clonazepam 2mg/day. Two years later, he was re-admitted to the hospital, along with his brother, due to non-adherence to treatment and his medication was switched to Olanzapine 20mg/day, Bromazepam 6mg/day and Valproic acid 1000mg/day. Once again, in 2020, his symptoms aggravated due to alcohol consumption and along his other medication, he is also prescribed Zopiclone 7,5mg/day. His latest admission to the hospital was earlier this year, accompanied by his mother and brother, for aggravated symptoms in a conflictual context and he presented psychomotor agitation, irritability, auditory hallucinations, suspiciousness, bizarre behavior, delusion of harm and persecution and interrupted sleep.

The psychiatric evaluation revealed a partially cooperating patient, dressed appropriately, with a suspicious attitude, good hygiene, low-pitched voice, detached look, less body language and facial expressions and unmotivated laughter. He had a tendency to depression, irritability, anhedonia and spontaneous and voluntary hyperprosexia. Regarding perception, auditory hallucinations were observed („I hear two people that judge me and criticize me because I am teaching my brother how to be strong”). His thinking is relatively consistent with the flow of ideas at an accelerated pace, with disturbances of content in the form of delusions of prejudice and persecution („Everyone wants to hurt me because I have the courage to educate my brother alone”). The consciousness of the disorder is absent, he is temporal and spatial oriented.

- *Medical history – case 2 (the obedient case)*

The other male patient, aged 30, with no pre-existing conditions, was diagnosed in 2015 with Acute Psychotic Disorder, after multiple admissions to the „Socola” Institute of Psychiatry (just two months after his brother’s onset of symptoms), for psychomotor agitation, irritability, auditory hallucinations („I hear two voices that criticize my behaviour and clothing when I go to church with my brother” , „Last night, there were patrol officers with dogs outside my window, ready to take me to the police station because I don’t know how to behave in society and because I protect my brother”), delusion of harm and persecution and interrupted sleep. He was prescribed Risperidone 6mg/day oral suspension and Valproic acid 1000mg/day. One year later, after many re-admissions to the hospital, he was brought in by his mother and brother (who was also admitted that day) for worsening psychotic symptoms due to lack of adherence to treatment. His

medication was switched to Amisulpride 600mg/day and Valproic acid 1000mg/day and Aripiprazole 30mg/day, but he stopped taking his medication on many occasions, therefore in 2020 his medication was switched again to Risperidone 6mg/day oral suspension, Valproic acid 1000mg/day, Trihexyphenidyl 4mg/day and Zopiclone 7,5mg/day. His latest admission to the hospital was earlier this year, accompanied by his mother and brother, for aggravated symptoms in a conflictual context and he presented irritability, irascibility, clastic behaviour, mixed insomnia and bizarre behaviour.

The psychological examination revealed a disharmonious configuration of paranoid personality in a delusional and hallucinating context and an integrative-relational deficit in the social and family environment.

The psychiatric evaluation revealed a cooperating patient, dressed appropriately, with a suspicious attitude, his body hygiene was in accordance with the hospital environment, low-pitched voice, detached look, less body language and facial expressions. Regarding perception, auditory hallucinations were observed („I hear a voice that threatens me and judges me for my actions”). His thinking is incoherent and at an accelerated pace, with disturbances of content in the form of delusions of prejudice and persecution („Some bad people want to steal my house and assets”). He had a tendency to depression and interrupted sleep. Clinical examinations, neurological evaluations and laboratory testing (blood tests, EEG, ECG, brain scan, toxicology screen, endocrine panel) did not reveal any pathological modifications for the two brothers.

The positive diagnostic criteria for SPD according to DSM-IV and induced delusional

disorder (IDD) according to ICD-10 are shown below. Guidelines for diagnosing SPD and IDD do not differ significantly.

- *ICD-10 Induced delusional disorder(6)*
 - A. A subject must develop a delusion or delusional system originally held by someone else with a disorder classified in F20–F23
 - B. The two people must have an unusually close relationship with one another, and be relatively isolated from other people;
 - C. The subject must not have held the belief in question prior to contact with the other person, and must not have suffered from any other disorder classified in F20–F23 in the past.

- *DSM-IV-TR Shared psychotic disorder(7)*
 - A. Delusion develops in an individual in the context of a close relationship with another person(s), who has an already-established delusion;

B. The delusion is similar in content to that of the person who already has the established delusion;

C. The disturbance is not better accounted for by another psychotic disorder (e.g., schizophrenia) or a mood disorder with psychotic features and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

DIFFERENTIAL DIAGNOSIS (THE SECONDARY CASE)

The differential diagnosis could be ruled out based on the history of the association between both partners. The onset of the condition usually precedes the onset of the shared delusions. The diagnosis of shared psychotic disorder should always only be made after ruling out any organic causes or substance induced.

• **Schizophrenia/Schizoaffective:** This could be differentiated if the case reported other findings that are not being influenced by the primary, hallucinations, disorganized speech, grossly disorganized or negative symptoms. In the case of schizoaffective, an affective component should be present.

• **Mood Disorder with Psychotic features:** This condition has a specific delusion which is mood congruent and not shared but expressed independently.

The prognosis of shared psychotic disorder is challenging to estimate, as it depends on multiple risk factors including the primary mental disorder and the secondary biopsychosocial predisposing factors. Taking into account the family environment and lack

of adherence to treatment, with multiple relapses, the long-term prognosis is reserved.

- Factors associated with a poor prognosis are:
 - Dysfunctional family;
 - Alcohol abuse;
 - Brother interdependency;
 - Presence of psychotic behaviours (hallucinations, delusions);
 - Lack of adherence to treatment.
- Factors associated with a good prognosis is:
 - Family with financial resources.

TREATMENT

- *Pharmacological treatment* – needed because of the severity of symptoms and it is individualised (tab 1).

Table 1. Pharmacological treatment for the two brothers

The primary case	The secondary case
Paliperidone 6mg/day Olanzapine 20mg/day Sodium Valproate 1000mg/day Bromazepam 3mg/day Zopiclone 7,5mg/day	Risperidone oral suspension 8ml/day Valproic acid 600mg/day Trihexyphenidylum 2mg/day Zopiclone 7,5mg/day

- *Psychotherapy*
The separation of the induced person from the dominant partner is essential, so the induced patient becomes accessible and rational, abandoning the delusional system.

Given that patients return to the same environment, other therapeutic measures are needed, including family therapy, based on the theory that this is a system that tries to maintain homeostasis. Therapy techniques include focusing on the family, not the patient who was identified as „ill”. These techniques include: re-framing and reformulating the problem in another context, trying to change maladaptive behaviors, understanding the

dynamics between generations, achieving a balance between individualization and cohesion, increasing direct communication. It also aims to develop activities and interests outside the relationship with the dominant partner.

The exact cause of shared delusional disorder is still unknown. However, certain risk factors associated with its development, include (5):

- *Length of a relationship:* Numerous studies highlight the role of the long relationship duration as an essential factor for developing this condition. It is crucial to understand that the attachment with the primary case

plays a key role in adopting the delusion.

- *Nature of the relationship:* The majority of cases reported were among family members. The commonest relationship was between married or common-law couples and the second most common group was between sisters.
- *Social isolation:* Most cases reported poor interaction with society. An individual who is confused and perplexed can undergo influence under frightening conditions in the absence of social comparison. This information received by the secondary individual is in harmony with what the primary individual felt. The conviction to certain ideas will eventually prevail as the only solution to maintain a mutual relationship.

- *Personality disorder:* Individuals usually show features of a personality disorder. The usual description for them is as neurotic, introvert and emotionally immature. Some case reports noticed features of premonitory personality disorders especially dependent (passive), schizoid and schizotypal type.
- *Life events:* Stressful life events that affect the relationship could influence the behavior in the individual to accept certain delusions or lessening the ability to resisting the feelings/emotions.
- *Communication difficulties:* Having difficulties in sharing ideas could be a reason for preferring isolation.

CONCLUSIONS

Psycho-social factors influence the evolution of psychotic symptoms, so exposure to harmful behaviours (alcohol consumption, hyperprotective mother) tends to increase the risk of long-term relapses. In this case, a psychological cause is possible, because it includes a socially isolated relationship, so delusion becomes a way of communicating with the partner, which compensates for the rupture with the external reality. The passive partner desperately seeks the care and acceptance of the dominating person, so for the moment, the delusion seems a compromise that allows him to continue a dependent relationship. The content of aberrant thinking, delusional ideas and themes seem to depend on the environment in which patients have developed and live and on their individual and social concerns. The delusional system entails poor social functionality and often the behavior occurs as a reaction to the beliefs of the parents, in the case presented, of the mother.

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Correspondence:

Irina Dobrin,

M.D., PhD, lecturer, University of Medicine and Pharmacy "Grigore T. Popa" Iași, Senior
psychiatrist Socola Institute of Psychiatry, Iași, Romania

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