ROMANIAN JOURNAL OF GERONTOLOGY AND GERIATRICS

Prof. Acad. Ana Aslan M.D.

"ANA ASLAN" NATIONAL INSTITUTE OF GERONTOLOGY AND GERIATRICS

1952

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Cuprins

EVOLUTION OF THYROID FUNCTION IN OLDER PATIENTS WITH HASHIMOTO'S THYROIDITIS AND RELATED CONDITIONS – PART 1

Dan **Perețianu**[1], Mihaela **Stanciu**[2]

[1]*Medical Center "Povernei", Bucharest, Romania*
[2]*Department of Endocrinology, Faculty of Medicine „Victor Papilian",
University "Lucian Blaga", Sibiu, Romania*

Corresponding Author: Dan Perețianu, danperetianu@yahoo.com

Abstract. Aim of the study was to establish if there are differences in the evolution of thyroid function in older patients with Hashimoto's thyroiditis and related conditions as compared to younger counterparts. We investigated a total of 4.668 patients, 2.034 being diagnosed with Hashimoto's thyroiditis (HT). Thyroid function was assessed by thyroid hormone free thyroxin (FT4) and by hypophyseal/pituitary thyroid stimulating hormone (TSH). Patients with Hashimoto's thyroiditis had a higher prevalence of euthyroidism (46.51%) than with hypothyroidism (40.86%). In older patients the prevalence of euthryoidism (45.59%) and hypothyroidism (45.8%) was the same at the time of admission. Patients with hyper-AGT (T-ATG) thyroiditis were even more euthyroid (71.26% vs. 22.47% hypothyroid) than those with Hashimoto's (classical) thyroiditis; p<0.01. In older patients the prevalence is different; more hypothyroidism: 56.25% vs. 35.41%, p<0.01. Only 4% of patients with euthyroidism and T-ATG become hypothyroid. In older patients the evolutional pattern is preserved: only 2% (NS). After more than 20 years of observation, in cases of Hashimoto's thyroiditis, respectively 5 years, in those with hyper-ATG thyroiditis, no changes in thyroid function are observed. This suggests that most patients with euthyroidism will remain euthyroid all their lives. The older patients have the same pattern. Patients with T-ATG and hyperthyroidism (6.3%) appeared to be associated with Graves-Basedow's disease in much lower prevalence than the phenomenon observed in TH: only 50% had TRAB positive. The older patients with this association reach a prevalence of 8.33%, no statistical difference. Almost all patients with hyperthyroidism became normothyroid under the antithyroid treatment. In 5 years only 5 relapses were registered. In older patients hyperthyroidism was under control, no relapse. About 3% of the hyperthyroid patients became spontaneous hypothyroid. Older patients with Hashimoto's thyroiditis and related conditions demonstrate some specific patterns of evolution if thyroid function that warrant further investigation.
Keywords: autoimmune thyroiditis, Hashimoto's thyroiditis, hypothyroidism, hyperthyroidism, older patients

Rezumat. Scopul studiului a fost de a stabili dacă există diferențe în evoluția funcției tiroidiene la pacienții mai în vârstă cu tiroidita Hashimoto și afecțiunile asociate, în comparație cu omologii mai tineri. Am investigat un total de 4.668 de pacienți, 2.034 fiind diagnosticați cu tiroidita Hashimoto (HT). Funcția tiroidiană a fost evaluată prin tiroxina liberă de hormoni tiroidieni (FT4) și prin hormonul de stimulare a tiroidei hipofizar/hipofizar (TSH). Pacienții cu tiroidita Hashimoto au avut o prevalență mai mare a eutiroidismului (46,51%) decât cu hipotiroidism (40,86%). La pacienții vârstnici prevalența eutiroidismului (45,59%) și a hipotiroidismului (45,8%) a fost aceeași la momentul internării. Pacienții cu tiroidită hiper-AGT (T-ATG) au fost chiar mai eutiroidieni (71,26% vs 22,47% hipotiroidă) decât cei cu tiroidită Hashimoto (clasică); p<0,01. La pacienții în vârstă prevalența este diferită; mai mult hipotiroidism: 56,25% vs 35,41%, p<0,01. Doar 4% dintre pacienții cu eutiroidism și T-ATG devin hipotiroidieni. La pacienții mai în vârstă se păstrează modelul evolutiv: doar 2% (NS). Dupa mai bine de 18 ani de observatie, in cazurile de tiroidita Hashimoto, respectiv 5 ani, la cei cu tiroidita hiper-ATG, nu se observa modificari ale functiei tiroidiene. Acest lucru sugerează că majoritatea pacienților cu eutiroidism vor rămâne eutiroidieni toată viața. Pacienții mai în vârstă au același model. Pacienții cu T-ATG și hipertiroidism (6,3%) au părut a fi asociați cu boala Graves-Basedow cu o prevalență mult mai mică decât fenomenul observat în TH: doar 50% au avut TRAB pozitiv. Pacienții mai în vârstă cu această asociere ajung la o prevalență de 8,33%, fără diferență statistică. Aproape toți pacienții cu hipertiroidism au devenit normotiroidieni sub tratamentul antitiroidian. În 5 ani s-au înregistrat doar 5 recidive. La pacienții vârstnici hipertiroidismul a fost sub control, fără recidivă. Aproximativ 3% dintre pacienții hipertiroidieni au devenit hipotiroidieni spontan. Pacienții mai în vârstă cu tiroidita Hashimoto și afecțiunile asociate demonstrează unele modele specifice de evoluție dacă funcția tiroidiană necesită investigații suplimentare.
Cuvinte cheie: tiroidita autoimuna, tiroidita Hashimoto, hipotiroidism, hipertiroidism, pacienți vârstnici

DEFINITIONS

A. Syndrome vs. disease

In endocrinology, the modification of the function of a certain hormone/gland, evaluated according to the admitted models, does not represent a disease, but it represents a syndrome. In terms of function, any kind of endocrine secretion can have only three expressions: within the limits of normality, called eu-….-ism, lower than normal, called hypo-….-ism, or higher than normal, called hyper-… -ism.

For example, when the level of the cortisol hormone is higher than normal, the syndrome is called "hypercorticism" or "hypercortisolism". If it is smaller, then it is either "hypocorticism" or "hypocorti-solism". When we want to refer to blood concentrations, the suffix "... emia" is used. Hyperprolactinemia, for example, is not a disease and is not a syndrome, too. It is only an observation that there is more prolactin in the blood. From a syndromic point of view, it would be hyperprolac-tinism, an expression not yet in use.

Therefore, related to the thyroid, there is no disease called hyperthyroidism, as there is no disease called hypothyroidism. These are syndromes. A thyroid disease can develop with both hyperthyroidism and hypothyroidism, obviously in its different observation moments, as we will present in the current analysis. For example, although Graves Basedow's disease is known to occur most often with hyperthyroidism, there are cases of Graves-Basedow's disease with spontaneous (spontaneous, i.e., non-therapeutic) hypothyroidism.

Although Hashimoto's thyroiditis has been described (and is) related to the syndromic hypothyroidism, there are quite a few cases of Hashimoto's thyroiditis with sponta-neous hyperthyroidism.

Related to the syndrome, there is a "subclinical hyperthyroidism", as well as there is a "subclinical hypothyroidism". However, in the current stage of medicine development, even the "clinical" syndrome does not express something "clinical", but also a biological analysis. When hypothyroidism is clinical, the notion refers to the FT4 level and not to the clinical aspect of the patient.

B. On thyroiditis

Immune thyroiditis is characterized by thyroid inflammation associated with specific immune mechanisms. Defining thyroiditis as Hashimoto's thyroiditis has gone through a historical process.

Initially, Hakaru Hashimoto (1881-1934) described in 1912 [1] a form of thyroid disease with thyromegaly with follicular inflammation and hypothyroidism different from the hypothyroidism with thyroid atrophy, then called "myxedema" or "thyroiditis of Ord" (Ord's thyroiditis). William Miller Ord (1834-1902) described the thyroid atrophy with thyroid inflammation as early as 1877. Subsequently, in our times, the pathogenesis of the thyroid injury was recognized as immunological and thus received the name of "lymphocytic", "chronical", and/or "autoimmune".

Under the clinical spectrum, it has been observed that patients with thyroiditis may also be normothyroid (euthyroidism), not necessarily hypothyroid, as initially described by Hashimoto.

Investigating the pathogenesis of this disease, it was observed that it is generated by an antibody called "antimicrosomal", because it affects certain intracellular organisms of the thyroid, i.e. microsomes. To the "antimicrosomal" antibody was then discovered the antigen: thyroperoxydase. Thus, the name of antimicrosomal antibody has been changed, the antibody becoming "anti-thyroperoxydase" (ATPO). Then, Ord's thyroiditis was shown to occur through the same antibodies.

Thus, Hashimoto's thyroiditis became from thyroiditis with myxedema and thyromegaly that thyroiditis with anti-thyroperoxydase antibodies. In this chronic and lymphocytic inflammation of the thyroid, the autoantibodies behave in a specific way, generating a specific immune mechanism. This mechanism was describes as *antibody dependent cellular cytotoxicity* (ADCC) [2]. Thus, in defining the disease, the size of the thyroid does not appear, nor its functionality.

The existence of a strictly individualized immune mechanism makes the broader notion of "thyroid immune/autoimmune disease" meaningless. In this broad context, some believe that Graves-Basedow's disease, Hashimoto's thyroiditis, postpartum thyroiditis or other silent forms of immune thyroid disease represent a single disease or a continuous spectrum of disease [3]. However, the isolation of specific mechanisms must lead to the change of conceptions and must lead to the assertion "a mechanism - a disease" [4].

In addition, other diseases have other immune mechanisms of the disease, and they are identified and clearly specified [5]. Because it presents as a disease with strictly localized pathogenesis, thyroiditis has been included in the category of „organ-specific" immune diseases [2].

The fact that the thyroid is large (thyromegaly or, inappropriately "goiter") or small (thyromicria) has no relevance to the diagnosis: the disease is the same. Some researchers and authors [6] make the inadequate distinction between *Hashimoto's thyroiditis* (thyroiditis with "goiter", i.e., with thyromegaly) and *chronic lymphocytic thyroiditis* (thyroiditis without goiter). This distinction is not based on the correct understanding of thyroid pathogenesis, due to the phenomena associated with ATPO.

The presence of other antibodies, such as antithyroglobuline (ATG), creates problems of nosological taxonomy. But, as ATGs are oriented towards another antigen and because the immune reaction is different, i.e., it is realized through complement, not by cells [2], by adopting the concept of "a mechanism - a disease", it becomes obvious that thyroiditis with ATG is another kind of thyroiditis. Obviously this is true if we accept the concept that Hashimoto's thyroiditis is that thyroiditis due to ATPO.

Another problem arises when Hashimoto's thyroiditis is said to be "sero-negative" [7] because the diagnosis was morphopathological and in the serum there was no known type of antihyroid antibody present. By adopting the concept of "a thyroid immune mechanism - a thyroid immune disease" it is clear that "sero-negative" thyroiditis is or should be not Hashimoto's thyroiditis. It will become another form of thyroiditis, when the antibodies and antigens involved will be discovered.

INTRODUCTION

Thyroid function has been frequently investigated in thyroid autoimmune diseases including in patient cohorts or in specific communities [8-13]. Most studies focus on the evolution from subclinical hypothyroidism to clinical hypothyroidism. Our study was realized to show whether there is an evolution from euthyroidism to hypothyroidism in patients with Hashimoto's thyroiditis. Furthermore, we have correlatively investigated thyroid function together with the evolution of antithyroid antibodies. To date, such an approach has not been described in the literature. Only two studies investigate the level of ATPO in patients with Hashimoto's thyroiditis: in one it is stated the decrease of the level during the treatment [14], in another one it affirms "fluctuating" evolution [8].

We did not find on *pubmed.gov* a study that takes into account, at the same time, the thyroid function correlative with

antibody evolution, especially ATPO, as an essential element of pathogenesis, the direct cause of the disease known as Hashimoto's thyroiditis [15]. As a particularity of the fact that ATPO are considered necessary and sufficient element in the diagnosis of Hashimoto's thyroiditis [4], in our previous research we observed ultrasound characteristics of thyroiditis [16] with normal levels of ATPO. Some patients had high levels of anti-thyroglobulin (ATG) antibodies. We considered these patients non-thyroiditis Hashimoto's, but thyroiditis with hyper-ATG.

The study was retrospective, cohort-specific, and shows the evolution of thyroid function and anti-thyroid antibodies in Hashimoto's thyroiditis, hyperATG thyroiditis (T-ATG) and idiopathic myxedema, correlative with Graves-Basedow disease data.

Nowadays patients with thyroiditis live more. There are many patients with this disease over 65 years, considered as conventional criterion for elderly people. We identify a single study which emphasized the evolution in elderly patients with thyroiditis [8].

Therefore, we stressed on this topic: the evolution of thyroid function corroborated with thyroid autoantibodies in patients over 65 years old with thyroiditis.

MATERIALS AND METHODS

This project/study started more than 20 years ago, when both ultrasound machine

and laboratory tests were available in the same time at one patient, for corroboration data. If there were earlier data available in the same format, we used them.

A. The diagnostic

• The diagnostic of the disease.

Hashimoto's thyroiditis (HT) was considered if the patient had: ATPO antibodies above the conventional cut-off of 34 IU/ml; and ultrasound appearance of hypoechogenic, pseudonodular, nonhomogeneous thyroid [16].

If the ATPO level was normal, but the modification was at the level of the anti-thyroglobulin (ATG) antibodies and the ultrasound aspect was for thyroiditis, then anti-thyroglobulin (T-ATG) thyroiditis was considered. The cut off level for ATG normality was also considered at 34 IU/ml.

If a patient was diagnosed with hypothyroidism but he or she did not have elevated levels of ATPO or ATG, as well as no changes (increases) in TRAB antibodies (which define Graves-Basedow disease), and no other clinical cause known to alter thyroid function (e.g., cervical irradiation for lymphoma), then the diagnosis was considered "idiopathic myxedema".

When a patient presented with increased levels of ATPO concomitant with increased levels of TRAB, regardless of thyroid function, two concomitant diagnoses were considered, namely the association between Hashimoto's thyroidditis and Graves-Basedow's disease,

according to the "one mechanism- one disease" theory [4].

For all laboratory analyses, commercial kits were used in approved laboratories from Bucharest in the health public system. If the standard curves used different values for normality, the transformation was performed by the simple 3 rule. ATPO and ATG were analyzed by ECLIA-type electrochemiluminescence. TRAB were determined by binding analysis of some immunoglobulin inhibitors in Brahms technique. The cut-off for TRAB was considered 1 IU/l.

Five patterns were observed regarding the evolution of the thyroid autoantibodies: "undulating", "increasing", "decreasing", "unmodified" and "normalized". It was considered that the ATPO/ATG level did not change if the value was not greater/ lower than 15 IU/ml. We considered ATPO/ATG "normalization" when their level fell below the cut-off limit and thus remained as so at the last observation.

• The diagnostic of the syndrome – functional diagnostic

Normal thyroid function was considered to be when TSH level was between 0.4 and 4 mU/ml, associated with a free thyroxine level (free T4 - FT4) between 10 and 20 pmol/l. When TSH was greater than 4 mU/ml and FT4 was normal, subclinical hypothyroidism was considered. When TSH was lower than 0.4 mU/ml and FT4 was normal, subclinical hyperthyroidism was considered.

B. Patients

We investigated a total of 4.668 patients, 2.034 being diagnosed with Hashimoto's thyroiditis (HT), 19.52% being over 65 years-old. Only 253 have been diagnosed with thyroiditis with only antithyroglobuline autoantibodies (T-ATG). Diagnosis of "idiopathic myxedema" was encountered in 142, 35.21% of patients being over the age of 65 years.

We recorded the patients in time, as they were presented in our clinics/offices. Patients were differentiated according to the diagnosis of disease, corresponding to the level of ATPO, ATG, and according to the diagnosis of the syndrome, corresponding to the level of TSH and FT4. The control patients were specifically registered.

The moment of the last recorded consultation was the moment when the material was sent for publication. All patients were informed according to the Helsinki Declaration 1975 and gave their consent.

C. Statistical analysis

Statistical analysis was performed by the Student t test, the X^2 test, the Fisher test (z test), and the linear correlation test, depending on the context. A "P" value <0.05 was considered to indicate significant differences between the groups under analysis. An Excel 2007 file from a Windows 7 or 10 System was used to perform the calculations.

RESULTS

Using the above criteria, we recorded the following data (Tab. I):

1. Hashimoto's thyroiditis: 2034 patients. From these, 397 (19.52%) were over 65 years old.

2. Thyroiditis with hyper-antithyro-globulinemia (T-ATG): 253 patients. From these, 48 (18.97%) were over 65 years old. No difference in prevalence for patients over 65 years old between HT and T-ATG (z=0.2; p=0.83).

3. Idiopathic myxedema: 142 patients. From these, 50 (35.21%) were over 65 years old. There is an important difference between this nosological entity and HT/T-ATG. The prevalence of older patients is very high (z>-4.4; p<0.001).

4. In the Control group we registered 2125 patients, of which 567 (26.68%) were over 65 years old. In this group, there are also older patients that in HT/T-ATG (z=-5.4; p<0.001).

a) Age

Age at first diagnosis in Hashimoto's thyroiditis is slightly older than the age in T-ATG thyroiditis, but statistically insignificant. In contrast, the first diagnosis in idiopathic myxedema is rather late; age was significantly higher than in other forms of thyroiditis (p<0.001). However, in the group of patients with idiopathic myxedema, we also recorded 7 children aged 6-15 years (see standard deviations of the groups). The control patient's age was also a little higher than that of thyroiditis.

That means that the symptomatology in thyroiditis is easier to be recognized by a doctor or by patient herself/himself, and the patient consult earlier an endocrinologist for establishes the problem/the diagnostic.

b) Gender

In classical thyroiditis the ratio Female/ Male = 14.13, with 7.18% men. In the T-ATG, the ratio F/M is slightly lower = 12.31, with 8.12% men (no statistical difference, p=0.5). In the idiopathic myxedema we have the ratio F/M = 4.26, with more men, 23.48%; the statistical significance is z=-8.3, p<0.001. The sex/gender ration in older patients (over 65 years) did not differed comparing with the entire thyroiditis group (7% vs. 6.5%; 8% vs. 6.5%; 23.5% vs. 22%). Even in the control group the ratio is not statistical significant (15% vs. 18%).

c) Autoimmune associations

An important feature of patients with autoimmune diseases is that they associate one or more such diseases. In earlier analyses, we described these associations in Hashimoto's thyroiditis, ATG thyroiditis and idiopathic myxedema, as well as the difference from control patients (for TH, T-ATG and idiopathic myxedema, the test $X^2>24$, p<0.001) [4]. Thyroid diseases investigated have a 2-fold higher prevalence of immune associations than the presence of immune/autoimmune impairment in control patients.

In HT, the prevalence of immune association for patients over 65 years old are slightly lower than in adult patients (18% vs. 27%, p=0.054, NS).

In idiopathic myxedema the prevalence of immune association in patients over 65 years old were double than in adult patients (44% vs. 22%, p=0.08). The association with another autoimmune disease was observed in 32 cases (22.54%), with 14 patients over 65 years old (43.75%). The prevalence for all idiopathic myxedema was slightly lower than in HT and T-ATG, but without major significance. On the other hand, the prevalence of an immune association is very high in patients over 65 years old.

In the control group, the immune association prevalence in patients over 65 years old is slightly higher than in adult patients (19% vs. 12%, NS).

The prevalence of an immune/autoimmune association in T-ATG (no. 61, 24.11%) is not different from clastic thyroiditis, or idiopathic myxedema. In the patients over 65 years old, this association had a lower prevalence (no=18, 13.11%); p=0.0016, z=3.17.

d) Thyroid volume and nodularization

Hashimoto described in 1912 a nosological thyroid disease with hypothyroidism and thyromegaly. However, in HT there are also thyromicria.

For all patients with classical TH, the volume of the thyroid, measure by ultrasound, was recorded as follows:

- Normal thyroid volume: 1268 patients (62.34%);

- Small thyroid, named also thyromicria: 107 patients (5.26%). All patients with thyroid disease were registered with hypothyroidism! The prevalence of thyromicria in patients over 65 years old was higher: 9% vs. 5%; z=-2.9, p<0.001.

- High thyroid volume, named also thyromegaly: 659 patients (32.4%). The prevalence of thyromegaly in patients over 65 years old was reduced, only 20%; z=4.8, p<0.001.

Therefore, in elderly patients with HT there is the trend to decrease the volume of thyroid.

In patients with T-ATG, the thyroid volume was as follows:

- Normal: 242 patients (95%), a higher prevalence that in HT p<0.001, z=-7.9);

- High (thyromegaly): 5 patients (1.58%), a lower prevalence that in HT (p<0.001, z=5.86);

- Small (thyroid disease): 6 patients (2.37%), a lower prevalence than in classical thyroiditis (p=0.04, z=4.4).

From the point of view of the thyroid volume, there is no difference between elderly patients vs. younger ones with T-ATG.

In all patients with idiopathic myxedema, the thyroid volume was registered, as follows:

- Normal thyroid volume: 126 patients (62.34%);

- Thyromicria: 22 patients (15.49%). Is an important difference from other thyroid entities, especially with HT, z=-7.1, p<0.001. From these, only 3 patients (13.64%) were over 65 years old

(difference nonsignificant). These results are hard to interpret.

- Thyromegaly: 0 patients. This phenomenon is very interesting, and dissociates idiopathic myxedema from HT and T-ATG.

Some patients presented a/more thyroid nodule association.

The elderly patients with HT had a higher prevalence of this association than the entire patients with this entity (14.86% vs. 10.57%; z=-2.47, p=0.013).

T-ATG is more associated with a thyroid nodule than HT (27.67% vs. 10.57%; z=-7.7, p<0.001). However, in T-ATG, the prevalence of thyroid nodules in elderly is the same as in all patients with this nosological entity (27.14% vs. 27.67%).

In idiopathic myxedema the number of patients with nodules are lower (9.15%), but the prevalence of nodules among elderly was very high (38.46%; z=-3.15, p=0.0019).

In control group there were many patients with thyroid nodule (41.69%), since this group was made especially from patients with thyroid disorders not registered as thyroiditis. The prevalence of thyroid nodules among elderly patients was high, too (45.15%).

In our patients it seems that nodularization increases with age.

The data related to the structure of thyroid from the control group could not be used to compare with the thyroid entities described above, because the control group was quite inhomogeneous: patients with thyroid nodules, normal, patients with radio-

intervention on the chest and neck. Therefore, a common analysis of these patients was inappropriate.

CONCLUSIONS

After more than 20 years of observation, in cases of Hashimoto's thyroiditis, respectively 5 years, in those with hyper-ATG thyroiditis, no changes in thyroid function are observed. This suggests that most patients with euthyroidism will remain euthyroid all their lives. The older patients have the same pattern. Patients with T-ATG and hyperthyroidism (6.3%) appeared to be associated with Graves-Basedow's disease in much lower prevalence than the phenomenon observed in TH: only 50% had TRAB positive. The older patients with this association reach a prevalence of 8.33%, no statistical difference. Almost all patients with hyperthyroidism became normothyroid under the antithyroid treatment. In 5 years only 5 relapses were registered. In older patients hyperthyroidism was under control, no relapse. About 3% of the hyperthyroid patients became spontaneous hypothyroid. All these data suggests that an autoimmune association should be a factor to trigger the attention on the thyroid disorder, conducting the patient earlier to the doctor and conducting the doctor to make an earlier diagnosis.

Older patients with Hashimoto's thyroiditis and related conditions demonstrate some specific patterns of evolution if thyroid function that warrant further investigation.

tiroidei" (The immune diseases of the thyroid), ALL Publisher, Bucharest. And, of course to the publisher in chief, ms. Anca Salvador, director of ALL.

[1]Medical Center "Povernei". Bucharest, Romania; [2]Institute of Endocrinology "C. I. Parhon". Bucharest, Romania; [3]Department of Biophysics and Medical Physics. University of Medicine and Pharmacy „Gr. T. Popa". Iaşi, Romania; [4]CMI. Dr. Florentina Matei, Bucharest, Romania; [5]The Laboratory of Effort tests and fuctional diagnosis. National Institute of Sport Medicine "Ioan Drăgan". Bucharest, Romania; [6]Department of Endocrinology, Faculty of Medicine "Victor Babes", Timişoara, Romania.

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Tab. I Clinical and biological data from patients with Hashimoto's thyroiditis, thyroiditis with ATG (T-ATG), idiopathic myxedema, and control at diagnostic time

	Classical Hashimoto's thyroiditis (thyroiditis with hyper-ATPO-emia)		Thyroiditis with only hyper-ATG-emia (ATPO normal) (T-ATG)		Idiopathic myxedema (hypothyroidism with normal ATPO and normal ATG)		Control group	
	All patients	Patients over 65 years	All patients	Patients over 65 years	All patients	Patients over 65 years	All patients	Patients over 65 years
Number	2034	397 (19.52%)	253	48 (18.97%)	142	50 (35.21%)	2125	567 (26.68%)
Age								
Average	50.29		50.30		55.33		53.23	
Standard Deviation	15.63		15.56		20.62		17.46	
Median	51		51		60 (p < 0.01)		55	
ATPO								
Average	675.77	625	9.18		8.43		8.10	
Standard Deviation	1262	1139.5	7.64		6.60		6.98	
ATG								
Average	448.08	641	330.2	341.23	8.25		8.47	
Standard Deviation	1127.5	1539	886.7	768.2	8.16		9.61	
Gen								
Women	1888	373	234	45	115	41	1847	477
Men	146 (7.18%)	24 (6.43%)	19 (8.12%)	3 (6.66%)	27 (23.48%)	9 (21.95)	278 (15.05%)	90 (18.88)
Thyroid function								
Euthyroidism	946 (46.51%)	181 (45.59%)	181 (71.26%)	27 (56.25%)	0	0	1940 (91.29%)	499 (88%)
Hypothyroidism	831 (40.86%)	182 (45.8%)	57 (22.47%)	17 (35.41%)	142	50 (100%)	44 (2.07%)	14 (2.49%)
Hyperthyroidism	257 (12.64%)	34 (8.56%)	16 (6.3%)	4 (8.33%)	0	0	141 (6.64%)	54 (9.5%)
Thyroid nodule (>1 cm) associated	215 (10.57%)	59 (14.86%)	78 (30.83)	19 (27.14%)	13 (9.15%)	5 (38.46%)	886 (41.69%)	256 (45.15%)
Thyroid volume								
Thyromegaly	659 (32.4%)	80 (20.15%)	5 (1.98%)	3 (60%)	0	0		
Thyromicria	107 (5.26%)	36 (9%)	6 (2.37%)	2 (33%)	22 (15.49%)	3 (13.64%)		
Immune/Autoimmune association	555 (27.29%)	104 (18.7%)	61 (24.11%)	8 (13.11%)	32 (22.54%)	14 (43.75%)	259 (12.19%)	49 (18.91%)

HEART FAILURE WITH PRESERVED AND MILDLY REDUCED EJECTION FRACTION IN ELDERLY

Irina **Ispas**[1], Alice **Munteanu**[2], Andreea **Stoica**[3]

[1]*County Emergency Hospital "Dr. Pompei Samarian", Calarasi, Romania*
[2]*Central Military Emergency University Hospital "Dr. Carol Davila", Bucharest*
[3]*"Casa Suter" Palliative Care Center Bucharest, Romania*

Corresponding Author: Irina Ispas, aniri.irina@yahoo.com

Abstract. Heart failure (HF) is an important public health problem, with an increased prevalence both in the general population, but especially in people over 65 years, with high morbidity and mortality, with high hospitalization rate, with significant impact on functional capacity and quality of lives of patients, whose management involves high costs. The 2016 and 2021 ESC guidelines for heart failure introduced a third category of heart failure for ejection fraction of 41-49%, defined as heart failure with mildly reduced ejection fraction. The prevalence of heart failure with mildly reduced ejection fraction in the total population of patients with HF is 10–25%. This appears to be an intermediate clinical entity between heart failure with reduced ejection fraction and preserved in some aspects, but more similar to that with low ejection fraction in others, especially with respect to the high prevalence of ischemic heart disease in these patients. Heart failure with preserved ejection fraction is the most common form in the elderly. Heart failure with preserved and mildly reduced ejection fraction in the elderly is a challenge for the clinician, both in terms of diagnosis, prognosis and treatment. The clinical picture of heart failure is often atypical and may be masked by the presence of comorbidities. There are currently no evidence-based treatment guidelines for elderly patients, which makes managing heart failure an even greater challenge.
Key words: heart failure, ejection fraction, elderly

Rezumat. Insuficiența cardiacă (IC) reprezintă o problemă importantă de sănătate publică, având o prevalență crescută atât în populația generală, dar mai ales la persoanele peste 65 de ani, cu morbiditate și mortalitate ridicate, cu rată crescută de spitalizare, cu impact important asupra capacității funcționale și a calității vieții pacienților, a cărui management implică costuri ridicate. Ghidurile ESC din 2016 și 2021 pentru insuficiență cardiacă au introdus o a treia categorie de insuficiență cardiacă pentru fracția de ejecție de 41-49%, definită ca insuficiență cardiacă cu fracție de ejecție ușor scăzută. Prevalența insuficienței cardiace cu fracție de ejecție ușor redusă în populația totală a pacienților cu IC este de 10–25%. Aceasta pare a fi o entitate clinică intermediară, în unele privințe, între insuficiența cardiacă cu fracție de ejecție redusă și păstrată, dar mai asemănătoare cu cea cu fracție de ejecție scăzută în altele, în special în ceea ce privește prevalența ridicată a bolii cardiace ischemice la acești pacienți. Insuficiența cardiacă cu fracție de ejecție păstrată este cea mai frecventă formă la vârstnic. Insuficiența cardiacă cu fracție de ejecție păstrată și ușor redusă la vârstnic reprezintă o provocare pentru clinician, atât din punct de vedere al diagnosticului, al prognosticului, cât și al tratamentului. Tabloul clinic al insuficienței cardiace este adesea atipic și poate fi mascat de prezența comorbidităților. În acest moment nu există ghiduri de tratament bazate pe dovezi pentru pacienții vârstnici, ceea ce face ca managementul insuficienței cardiace să fie o provocare și mai mare.
Cuvinte cheie: insuficiență cardiacă, fracție de ejecție, vârstnici

INTRODUCTION

A clinical condition known as heart failure (HF) is caused by structural and /or functional heart defects, which lead to a decrease in cardiac output and /or higher intracardiac filling pressures at rest or exertion. With high prevalence and incidence rates, high morbidity and mortality, low functional capacity and quality of life, especially among the elderly, as well as substantial economic costs, HF is a significant public health problem. However, the incidence of HF has stabilized and appears to be declining in industrialized countries, but the prevalence is increasing due to aging population, ischemic heart disease that is better treated and patients live longer due to the availability of effective therapies that prolong life in patients with HF and after acute myocardial infarction [1, 2]. The prevalence of heart failure in adults is 1-2% and increases with age, reaching >10%

in people over 70 years. It is estimated that approximately 60% of patients with heart failure have a low ejection fraction, 24% have a mildly reduced ejection fraction and 16% have a preserved ejection fraction [3]. The left ventricular ejection fraction (FE), generally measured by echocardiography, remains the cornerstone of diagnosis, characterization, prognosis, patient triage, and IC treatment selection.

HF with low EF (HFrEF, defined as EF <40%) is well characterized and effective therapies are available for patients with HFrEF. In 2016, the European Society of Cardiology (ESC) introduced a new classification of heart failure, which was maintained in the guide in 2021, in three categories, depending on the value of the left ventricular ejection fraction. Thus, the current classification of heart failure includes HF with preserved ejection fraction (HFpEF characterized by EF >50%), HF with mildly reduced ejection fraction (HFmrEF, FE 41-49%) and with reduced ejection fraction (FE <40%) [3].

HEART CHANGES IN THE ELDERLY

The hallmark of cardiac aging is a decrease in the diastolic function of the left ventricle. Age-related diastolic dysfunction is responsible for the high prevalence of HFpEF, a disease that was previously called diastolic heart failure. Patients with HFpEF usually present with diastolic abnormalities, including delayed early relaxation, stiffening of the myocardium and myocytes, and changes associated with the dynamics of ventricular filling [4].

The systolic function of the left ventricle is affected by the aging process by reducing the cardiac reserve during exertion, decreasing myocyte contractile function and decreasing the maximum frequency of the ventricular heart rate that an elderly person can reach in case of physical exertion. However, the ejection fraction of the left ventricle is not affected by the aging process [4].

Regarding the cardiac excitoconducting system, the aging process is associated with a significant decrease in the number of pacing cells at the sinoatrial node. This causes an increase in the incidence of sinoatrial node dysfunction in the elderly, manifested by palpitations, dizziness, presyncopal status or syncope, fatigue and even confusing syndromes [4].

At the structural level, the most important phenomenon observed with age is the increase in the thickness of the left ventricular wall due to the increase in the size of cardiomyocytes. This phenomenon is often associated with dilation or hypertrophy of the left atrium, caused by increased intraventricular pressure. Structural changes are due to cellular changes. The most important cellular changes are the decrease in the number of myocytes and excitoconducting cells, responsible for the occurrence of ventricular hypertrophy and myocardial fibrosis, and amyloid deposition [5].

CLINICAL DIAGNOSIS

The most common etiologies of heart failure with preserved or mildly reduced ejection fraction in the elderly are hypertension and acute and chronic coronary heart disease. Other common etiologies are age-related diastolic dysfunction, valvopathies, pericardial pathology and non-ischemic heart disease caused by alcohol consumption, post-chemotherapy or inflammatory myocarditis. Triggers or aggravating factors of heart failure are chronic iron deficiency anemia or thiamine deficiency, hyperthyroidism, fever, some drugs, high-salt diet, endocrine diseases, chronic obstructive pulmonary disease, nonadherence to treatment, arrhythmias, renal failure, and pulmonary embolism [6]. The diagnosis of heart failure requires the presence of specific signs and/or symptoms, summarized in Tab. I, according to the ESC guideline and the objectification of heart dysfunction [3].

Tab. I Signs and symptoms of heart failure according to 2021 ESC Guideline

Symptoms	Signs
Typical	*More specific*
Breathlessness	Elevated jugular venous pressure

Orthopnea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	
Ankle swelling	
Less typical	*Less specific*
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitations
Palpitation	Pleural effusion
Dizziness	Tachycardia
Syncope	Irregular pulse
	Tachypnoea
	Cheyne-Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

Signs and symptoms of HF have low sensitivity and specificity in clinical diagnosis in elderly patients. Typical signs and symptoms are known to be less common in the elderly population due to the presence of other comorbidities, along with atypical manifestations such as confusion, drowsiness, anorexia and low activity, especially in patients with dementia. Dyspnea is the primary symptom of HF, the clinical expression of elevated lung pressure that can be underestimated in sedentary elderly patients and can be caused by other factors, such as chronic lung disease or anemia. On the other hand, fatigue, which is also a predominant symptom, may be related to hypoperfusion of skeletal muscle. Thus, if the patient complains of fatigue, this should not be considered a common symptom. Fine audible crackles at the base of the lungs may be common in the elderly due to prolonged bed rest and physical inactivity, and leg edema may be due to chronic venous insufficiency or malnutrition [1, 7].

PARACLINICAL DIAGNOSIS

The diagnostic suspicion of heart failure arises in the presence of specific signs and symptoms and is confirmed based on elevated serum BNP values and echocardiography.

Natriuretic peptide levels increase with age and may vary in the presence of comorbidities such as obesity, renal failure or atrial fibrillation. Accordingly, they should be interpreted in conjunction with clinical and echocardiographic findings. B-type natriuretic peptide (BNP) is an important marker for the prediction and prognosis of heart failure, its main secretion being from the left ventricle. The benefit of determining its plasma level in patients with dyspnea is well known, helping to differentiate the diagnosis between respiratory pathologies (COPD) and heart failure.[8] Serum BNP levels >100ng/L or NT-proBNP >300pg/L, associated with echocardiographic abnormalities support the diagnosis of heart failure [7].

Echocardiography (Tab. II) is crucial for identifying the type of HF (HFpEF, HFmrEF, HFrEF), cardiac structural damage (left ventricular hypertrophy and dilation of the left atrium), diastolic dysfunction, dilation of the vena cava and pulmonary hypertension and may help clarify the etiology of the disease (parietal kinetics abnormalities as an indirect sign of ischemic heart disease). Echocardiography is also important in diagnosis of treatable causes of heart failure, such as aortic stenosis or mitral valve regurgitation [7].

Tab. II Specifics of echocardiography in elderly heart failure patients

Most frequent echocardiographic abnormalities in elderly subjects with HF	Characteristics/main causes
Preserved LVEF	LVEF ≥ 50% Variables in favor of the diagnosis: LV hypertrophy; LA dilation; diastolic dysfunction
Diastolic dysfunction	At least three of the following criteria (if LVEF ≥ 50%): average E/e' > 14; septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s; tricuspid regurgitation velocity > 2.8 m/s; LA volume index ≥ 34 mL/m2
LV hypertrophy	LV mass > 95 g/m2 (women), > 115 g/m2 (men) Main causes: hypertension; aortic stenosis; cardiac amyloidosis
Mildly reduced LVEF	LVEF 41-49% Commonly in men, younger, and more likely to have coronary artery disease (CAD) Associated features: LV hypertrophy, LA dilatation, wall motion abnormalities
Reduced LVEF	LVEF < 40% Less frequent in elderly versus younger subjects with HF Associated features: LV dilation; wall motion abnormalities
LA dilation	LA volume index ≥ 34 mL/m2, LA diameter ≥ 40 mm Main causes: systolic or diastolic dysfunction; hypertension; valve diseases
Valve diseases	Aortic stenosis: most frequent valve disease in elderly patients with HF Severe aortic stenosis: area ≤ 1 cm2 (or ≤ 0.6 cm2/m2); aortic mean gradient ≥ 40 mmHg
Pulmonary hypertension	Systolic pulmonary artery pressure > 40 mmHg Main causes: heart disease; respiratory disease
Pericardial effusion	Main causes: bleeding (anticoagulant, cardiac surgery, and cardiac device); inflammation/infection; cancer; cardiac amyloidosis

The diagnosis of HFpEF requires the presence of signs and symptoms of heart failure, left ventricular ejection fraction >50% and evidence of increased filling pressure on the left side at rest or stress. Evaluation of biomarkers (increased serum levels of natriuretic peptides), cardiac structure (left atrium dilation, increased LV mass) and diastolic function (increased E/e' ratio at rest or during exertion and/or increased pressure in resting lung capillaries or with effort) are essential for the diagnosis of certainty [9].

The echocardiographic presence of concentric LV hypertrophy defined as an indexed LV mass >149 g/m2 in men and 122 g/m2 in women and a relative wall thickness >0.42 mm is associated with diastolic dysfunction. The volume of the left atrium indexed to the body surface area >34ml/m2 is one of the major morphological criteria for the diagnosis of HFpEF. It is also important to recognize that diastolic dysfunction is not the same with increased filling pressures. In general, if the mean e' is less than 9 cm/s and the E/e' ratio is greater than 13, the diagnosis

of HFpEF is favored in the context of the structural anomalies mentioned above. Other parameters that support the diagnosis are E/A >2, deceleration time <160ms, isovolumic relaxation time <60s and estimated systolic pulmonary arterial pressure >35mmHg. Importantly, if the suspicion of HFpEF is high and the resting echocardiogram is normal, exercise Doppler echocardiogram should be considered [10].

ADDITIONAL INVESTIGATIONS

In elderly patients, once the HF has been diagnosed, a multidimensional geriatric assessment should be performed to identify comorbidities and their risks for decompensation and functional consequences, to allow appropriate adjustment of treatments. A blood panel is made to identify the precipitating factors. A complete blood count (for anemia), a basal metabolic panel (for hyponatremia, indicating a poor prognosis, and hypokalemia or proarrhythmic hyperkalemia, which are responsible for conduction disorders) and

measurement of creatinine (for renal function; estimated glomerular filtration rate by Cockcroft-Gault formula) are essential. Hepatic impairment may be present (acute cytolysis indicates hypoxic liver in case of decreased cardiac output) [7].

An electrocardiogram provides information about the etiology of heart failure (atrial fibrillation, ischemia and myocardial hypertrophy), and regular electrocardiograms are needed to follow the patient.

A chest x-ray is not necessary for the diagnosis of HF, but is useful for the diagnosis of acute pulmonary edema, the presence of pleural effusion, or damage to the lung parenchyma.

COMORBIDITIES

The comorbidities associated with elderly patients with heart failure are multiple, including atrial fibrillation, ischemic heart disease, hypertension, stroke, chronic obstructive pulmonary disease (COPD), asthma, chronic respiratory failure, diabetes, obesity, malnutrition, dementia, depression, renal failure.

Also, fragility syndrome, defined by decreased functional reserves, which increases the risk of death, hospitalization, falls and disability, has a negative impact on elderly patients by decreasing physical reserves and resistance to stressors. The link between fragility and heart failure is a complex one; the two can lead to a mutual aggravation. Some studies show that fragility is an independent risk factor in patients with heart failure. Psychiatric pathology in association with fragility syndrome and heart failure should be considered when it comes to therapeutic conduct and care of elderly patients to ensure a good quality of life [11].

NON-PHARMACOLOGICAL TREATMENT OF HEART FAILURE

Non-pharmacological treatment of HF includes an adequate sodium-restricted diet, modest alcohol consumption (less than two units of alcohol per day for men and one unit of alcohol per day for women), and smoking cessation [3]. It should be noted that in the elderly over 80 years the diet without sodium (<3 g/day) should be avoided due to age-related renal sodium reabsorption defects, which increase the risk of hyponatremia. Additionally, people who have experienced malnutrition are more likely to develop anorexia on a sodium-free diet. Therefore, sodium consumption must be adjusted (3-6 g/day), while also maintaining an adequate calorie intake, preserving the balance of other dietary recommendations, and incorporating it into a wider treatment strategy [6].

Physical activity is highly encouraged. Cardiac rehabilitation programs provide a unique tool to achieve good physical condition after the diagnosis of HF, but also to prevent the onset of HF. Rehabilitation programs are thus a multidimensional therapy with major benefits proven by avoiding hospitalizations due to HF and improving the quality of life, significantly in the elderly [1].

PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Although improvements have been noted for some particular phenotypes of individuals under the overall heading of HFpEF, no medication has been demonstrated to clearly reduce mortality and morbidity in patients with HFpEF to date. Treatment should focus on easing congestion symptoms using diuretics, in the absence of instructions for particular medications. Loop diuretics are preferred, although thiazide diuretics may be helpful in managing high blood pressure. Reducing body weight in obese patients and increasing exercise can improve symptomatology and exercise capacity and should therefore be considered in appropriate patients. It is important to identify and treat the underlying risk factors, etiology and comorbidities coexisting in HFpEF (eg, hypertension, ischemic coronary heart disease, amyloidosis, atrial fibrillation). Undoubtedly, the treatment of some of the basic phenotypes of HFpEF leads to improved results [3].

PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION

As with other forms of HF, diuretics should be used to control congestion. Substantial randomized prospective studies have not been performed exclusively in patients with HFmrEF. Some data can be collected from the subgroup analysis of studies for HFpEF, none of which met their primary endpoint. Although no strong recommendations can be made regarding specific therapies at this time, the ESC 2021 guideline for the management of heart failure recommends, with evidence class IIb, to reduce the risk of hospitalization and reduce mortality, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor II type 1 receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitor.

CONCLUSIONS

Heart failure with preserved and mildly reduced ejection fraction in the elderly is a challenge for the clinician, both in terms of diagnosis, prognosis and treatment. The clinical presentation of heart failure is often atypical and may be masked by the presence of comorbidities. Preserved ejection fraction heart failure is a common occurrence in elderly patients. The risk of morbidity and mortality for this type of heart failure is comparable to other classes of heart failure, for whom etiological treatment is the only one that brings significant benefits in terms of survival and quality of life. Heart failure with a mildly reduced ejection fraction is phenotypically similar to heart failure with a preserved ejection fraction, but etiologically and therapeutically similar to that with a reduced ejection fraction. Currently there is no clear evidence regarding the therapeutic benefits, being a subject that requires further studies. In elderly patients, a multidimensional geriatric assessment should be performed to identify comorbidities and their risks for decompensation and functional consequences, to allow for the proper adjusting of therapies.

Conflicts of interest
The authors declare no conflicts of interest.

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PHARMACOLOGICAL MANAGEMENT OF PAIN IN THE ELDERLY

Sorina **Capisizu**[1,2], Ruxandra **Mihalache**[1,2], Monica **Gidei** [1,2], Ana **Prada**[1,2], Costina Daniela **Gita**[1,2], Andreea **Zamfirescu**[1,2], Justin **Aurelian**[1], Sorina Maria **Aurelian**[1,2]

[1]*University of Medicine and Pharmacy "Carol Davila"*
[2]*Clinic of Geriatric and Gerontology - Chronic Disease Hospital "Sf. Luca"*

Corresponding Author: Sorina Maria Aurelian, sorina.aurelian@umfcd.ro

Abstract. Pain was originally defined as "a perception of an unpleasant sensory and emotional experience associated with, or described in terms of, potentially actual tissue injury". Pain syndromes have an increased prevalence in elderly patients and they should not be considered a normal consequence of aging, therefore the etiopathogenesis of this syndrome is not easy to establish in the elderly and especially frail people. Care is needed in the selection and administration of analgesics to avoid drug–drug or drug–disease interactions at the elderly. Changes in pharmacodynamics, physiological aging with changes in the body's homeostasis are taken into account in the decision to select drugs for the elderly. The perception of pain differs in geriatric patients because clinical status is frequently complicated by other conditions such as depression, psychosocial factors and cultural differences. Comorbidities, contraindications, and possible drug-disease and drug-drug interactions are considered for choosing an analgesic at the elderly.
Key words: pain, elderly, drug interactions

Rezumat. Durerea a fost definită inițial ca „o percepție a unei experiențe senzoriale și emoționale neplăcute asociată cu sau descrisă în termeni de leziuni tisulare potențiale reale". Sindroamele dureroase au o prevalență crescută la pacienții vârstnici și nu trebuie considerate o consecință normală a îmbătrânirii, de aceea etiopatogenia acestui sindrom nu este ușor de stabilit la vârstnici și mai ales la persoanele fragile. Este nevoie de grijă în selectarea și administrarea analgezicelor pentru a evita interacțiunile medicament-medicament sau medicament-boală la vârstnici. Modificările de farmacodinamică, îmbătrânirea fiziologică cu modificări ale homeostaziei organismului sunt luate în considerare în decizia de selectare a medicamentelor pentru vârstnici. Percepția durerii diferă la pacienții geriatrici, deoarece starea clinică este frecvent complicată de alte afecțiuni precum depresia, factorii psihosociali și diferențele culturale. Comorbiditățile, contraindicațiile și posibilele interacțiuni medicament-boală și medicament-medicament sunt luate în considerare pentru alegerea unui analgezic la vârstnici.
Cuvinte cheie: durere, vârstnici, interacțiuni medicamentoase

INTRODUCTION

Pain was originally defined as "a perception of an unpleasant sensory and emotional experience associated with, or described in terms of, potentially actual tissue injury" [1]. Catananti and Gambassi [2] consider pain a complex, subjective and multidimensional experience without objective biological markers.

Pain syndromes have an increased prevalence in elderly patients and they should not be considered a normal consequence of aging, therefore the etiopathogenesis of this syndrome is not easy to establish in the elderly and especially frail people. Identifying the cause of pain is a challenge for the geriatric clinician who requires understanding the complex mechanisms from cellular, molecular to the semiology of its expression and its perception by patients associated with physical, psychological or environmental aggravating factors. The pain is classified as acute or chronic pain and depending on the nociceptors in skin, somatic, visceral pain. Pain control is achieved through various mechanisms to reduce the sensory capacity of the nerve, which can be done at the central or peripheral level.

The pharmacological treatment of pain is based on some drugs that have a specific pharmacodynamics through prevention on:

- Formation of nerve influx, in sensitive endings (local anesthetics, muscle

relaxants, vasodilators, anti-inflam-matory);

- Transmission of nerve influx through sensitive fibers (local anesthetics);
- Pain perception, at the level of integration centers (general anesthetics, antipyretic analgesics, morphinomimetic analgesics).

A common classification of analgesics in substances is:
A. Non-opiod-analgesics
B. Opioid-analgesics
C. Other drugs (antidepressants, entiepileptic)

A. NON-OPIOID MEDICATION
1. Paracetamol (acetaminophen)
It is an effective analgesic for musculoskeletal pain, including osteoarthritis and back pain, and is recommended as the analgesic of first choice in several consensus guidelines [3]. Paracetamol taken in recommended doses is considered safe and is not associated with significant gastrointestinal, renal, cardiovascular or central nervous system adverse effects. It does not provide significant anti-inflammatory or antiplatelet effects as it does not inhibit thromboxane. Given the short withdrawal time, 500 mg every 4 hours is recommended for the desired analgesic effect. Although transient increases in liver transaminases have been reported, these do not translate into liver failure, provided maximum daily doses (4g/24h) are avoided. Several studies report an acute liver failure only in malnourished patients (weight <50 kg) and recommend dose reduction (maximum 2 g/24 h) if paracetamol supplementation is necessary for these patients [3]. Generally, elderly patients also have chronic kidney disease and in this case, doses should be adjusted with increased dosing intervals from 6 to 8 hours when eGFR <10 ml/min/1.73m2.

It can be used for moderate to severe pain in combination with codeine-type opioid, which potentiates the analgesic effect but also has side effects like constipation.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) (Ibuprofen, Ketoprofen, Meloxicam, etc.)
These drugs are the most commonly used in the population but prescribing them should be indicated only for a short period in moderate or acute pain and if there is inadequate pain relief with paracetamol or topical NSAIDs [4]. The lowest dose should be used for the shortest period and therapy should be reviewed regularly.

NSAIDs should be used with great caution in the elderly because of potentially serious side effects. Many NSAIDs are drugs that can be obtained from pharmacies without a prescription, leading to several complications in the elderly and frail. NSAIDs have been involved in up to a quarter (23.5%) of hospital admissions due to adverse reactions in the elderly [5].

Given the different pharmacodynamics of NSAIDs, prescribing should be based on their safety profiles and individual patient risk profiles. According to the Beers criteria made by the American Geriatrics Society, they are part of the class of drugs to be used with caution in the elderly [6].

Among the most common side effects of NSAIDs are gastrointestinal bleeding, peptic ulcer, especially in patients on anticoagulant/antiplatelet therapy. For that reason, it is associated with proton pump inhibitors, which can reduce but not eliminate the risk. Upper gastrointestinal ulcers, severe bleeding or perforation caused by NSAIDs occur in about 1% of patients treated for 3-6 months and in about 2%-4% of patients treated for 1 year [5].

In patients with chronic kidney disease, NSAIDs should not be administered at eGFR <30 ml/min/1.73m2. In patients with heart failure or poorly controlled hypertension, the administration of NSAIDs will cause decompensation of these conditions and should be avoided.

3. Selective COX-2 inhibitors (Celecoxib, Naproxen, etc.)

The European Medicine Agency has made the recommendation that COX-2 selective inhibitors should be contraindicated in patients with ischemic heart disease and/or stroke, should be avoided in patients with risk factors for coronary heart disease and that all patients should be given the lowest effective dose for the shortest time necessary to control symptoms. Although selective Cox-2 inhibitors were initially used enthusiastically because fewer bleeding complications were reported, recent studies have demonstrated renal impairment to the same extent as NSAIDs, with caution when used in patients on chronic diuretics or angiotensin converting inhibitors [7].

4. Steroidal anti-inflammatory drugs (Cortisone, Prednisone, etc.)

This class includes short-acting systemic glucocorticoids with low potency (cortisone, hydrocortisone), intermediate-acting glucocorticoids with medium potency (prednisone, prednisolone, methylprednisolone) and long-acting glucocorticoids with high potency (dexamethasone, betamethasone). They have an anti-inflammatory, anti-allergic and "anti-shock" effect but with a negative effect on carbohydrate metabolism (diabetes mellitus decompensation), protein metabolism, hydroelectrolytic (hydrosaline retention), endocrine (osteoporosis), neurocognitive system (psychosis, depression) and ophthalmic sensory (glaucoma, cataracts). They are usually not used in elderly patients in long-term treatment [6].

B. OPIOID MEDICATION

Opioids are generally safe and provide effective pain relief as part of a comprehensive pain management strategy. The "start low and go slow" approach is essential when administering opioids.

Strong opioids are commonly used in the management of chronic, severe, non-cancer pain in the elderly. A US cohort study from a long-term institution found that the use of extended-release opioids improved functional status and social engagement compared with short-acting opioids [8]. Studies have demonstrated short-term efficacy in persistent musculoskeletal pain, including osteoarthritis and low back pain, and various neuropathic pain, such as post-herpetic neuralgia and diabetic peripheral neuropathy. However, long-term efficacy and safety data are sparse [9].

In the elderly, opioids should be started at 25-50% of the recommended adult dose. Common side effects such as sedation, nausea and vomiting tend to be more severe around opioid initiation or dose increase and usually disappear after 2 or 3 days. On the other hand, constipation does not improve and should be managed with laxative therapy. In the elderly, drowsiness and dizziness occur and are associated with an increased incidence of falls and fractures. Cognitive function is relatively unaffected in patients taking stable doses of opioids, but may be impaired up to 7 days after a dose increase [10].

1. Codeine has no noticeable effect if taken alone and has adverse effects of constipation which requires administration with laxatives.

2. Tramadol is a centrally acting analgesic with two mechanisms of action: weak mu-opioid agonist activity and inhibition of serotonin and norepinephrine reuptake. It should be used with caution in patients taking other serotonergic drugs. May have less effect on respiratory and gastrointestinal function than other opioids, but may cause confusion in the elderly. Tramadol is contraindicated in patients with a history of seizures because it may lower the seizure threshold, especially at doses greater than 300 mg/day.

A prospective, age-controlled study suggests that older people require 20% less Tramadol than younger adults, although

pharmacokinetics remained unaffected by age [11]. Initiation in elderly patients is 25 mg once or twice daily and increased in increments of 25 mg every 2-3 days, up to a maximum of 100 mg/day [6].

3. Morphine-When starting treatment, a low and extended release dose is recommended. In renal dysfunction, a reduced dose should be used or, in case of severe impairment, avoid the use of active metabolites which may accumulate and cause toxicity. Fentanyl patch is frequently used in the elderly [10].

C. OTHER DRUGS
1. Antidepressants (Duloxetine)
Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine**,** have demonstrated efficacy in some neuropathic pain conditions and may have better tolerability than tricyclic antidepressants. RCTs have established the analgesic efficacy of duloxetine in four chronic pain conditions, i.e. diabetic peripheral neuropathy, fibromyalgia, chronic back pain and osteoarthritis, knee pain [12].

Duloxetine is usually started at 30 mg/day and can be increased to 60 mg/day after 2 weeks, if necessary. The most commonly reported side effects include dry mouth, nausea, constipation, diarrhea, fatigue, dizziness, drowsiness and insomnia. The use of duloxetine should be avoided in patients with hepatic impairment or heavy alcohol consumption, as hepatitis and liver failure have been reported [13].

2. Antiepileptic drugs (Gabapentin, Pregabalin)
Antiepileptic drugs, such as gabapentin and pregabalin, have become widely used in neuropathic pain conditions because several studies have demonstrated analgesic efficacy and fewer side effects than older antiepileptic drugs. Efficacy has been demonstrated in diabetic peripheral neuropathy and central pain syndromes [9]. Although the potential for drug-drug

interactions is lower, clearance of gabapentin and pregabalin depends on renal function and dose adjustment is necessary for renal impairment.

Dose titration is required during the initiation of treatment with gabapentin or pregabalin, initiation of therapy with gabapentin 200 mg administered three times daily having similar efficacy and side effects to the lower doses studied. When indicated, treatment should be started at the lowest possible dose and increased very slowly based on response and side effects [5].

General principles for the administration of analgesics to elderly patients
Care is needed in the selection and administration of analgesics to avoid drug–drug or drug–disease interactions at the elderly.

The timing of medication administration is important. Severe, episodic pain requires treatment with fast-acting, short-acting drugs. However, if a patient is experiencing ongoing pain, regular administration of analgesics is most effective, possibly using extended-release preparations [14]. Changes in pharmacodynamics, physiological aging with changes in the body's homeostasis are taken into account in the decision to select drugs for the elderly.

Analgesics administration at the elderly should consider the following aspects:
- Only one drug should be started at a time, using a low dose, and this should be followed by gradual dose titration;
- Allowing sufficiently long intervals between the introduction of medicines to allow assessment of the effect;
- Combination therapy using drugs with different mechanisms of action may have synergistic effects to provide greater pain relief with fewer side effects than higher doses of a single drug;
- Consider using non-pharmacological strategies, such as physiotherapy,

cognitive-behavioral approaches and acupuncture, in combination with medication;

- Treatment should be monitored regularly and adjusted if necessary to improve efficacy and limit adverse events.

CONCLUSIONS
Assessment of pain in elderly patients should be a routine part of medical care by all health professionals, and especially in geriatrics. Pain is highly prevalent in frail elderly with multiple co-morbidities and multiple drugs. The perception of pain differs in geriatric patients because clinical status is frequently complicated by other conditions such as depression, psycho-social factors and cultural differences. Comorbidities, contraindications, and possible drug-disease and drug-drug interactions are considered for choosing an analgesic at the elderly.

Disclosures and conflict of interest statements
There are no potential financial or personal conflicts of interests.

Authors' contributions
Concept and Design: Sorina Capisizu, Ruxandra Mihalache, Andreea Zamfirescu, Justin Aurelian, Sorina Maria Aurelian; *Data Collection:* Ana Prada; *Analy's Literature Research:* Monica Gidei, Costina Gita; *Manuscript Preparation:* Sorina Maria Aurelian, Sorina Capisizu.

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DIAGNOSTIC ISSUES OF DYSPHAGIA IN A FRAIL 72-YEAR OLD PATIENT

Ovidiu-Lucian **Băjenaru**[1,2], Cătălina Raluca **Nuță**[1,2], Gabriel Ioan **Prada**[1,2]

[1]University of Medicine and Pharmacy "Carol Davila" Bucharest
[2]National Institute of Gerontology and Geriatrics "Ana Aslan", Bucharest

Corresponding Author: Băjenaru Ovidiu-Lucian, olucian.b@gmail.com

Abstract. Dysphagia represents the abnormality of swallowing in the upper gastrointestinal tract, including the dysfunction of coordination between the respiratory and nutritional function, which can cause many complications such as dehydration, malnutrition, aspiration pneumonia, suffocation and death especially in a frail patient. Its prevalence is very high and it is even greater when it is related to dementia. We present the case of a 72-year old patient with atrial fibrilation, NYHA class II heart failure with preserved ejection fraction, secondary pulmonary hypertension, chronic obstructive pulmonary disease (COPD), imaging stationary bilateral fibronodular opacities, who manifests mainly with dyspnea at moderate exertion and selective dysphagia for fluids and solids associated with chronic cough with high intensity. The differential diagnosis offers the possibilities of an exacerbation of COPD, a tumor in the mediastinum, a possible esophageal stricture, an eso-bronchial fistula. The positive diagnosis was eso-bronchial fistula after the barium transit examination. To exclude the possibility of neoplasia it was still necessary to continue investigations with chest CT and gastroenterological consultation, recommendations at discharge. Dysphagia is a nonspecific symptom that can be the cause of many diseases in the elderly, fragile patients. Like many other nonspecific symptoms in elderly, we should investigate all the possible causes well, with pluridisciplinarity consults and appropriate investigations.
Key words: dysfagia, frailty, differential diagnostic, elderly patient

Rezumat. Disfagia reprezintă anomalia de deglutiție în tractul gastrointestinal superior, inclusiv disfuncția coordonării dintre funcția respiratorie și cea nutrițională, care poate fi cauza a numeroase complicații precum deshidratare, malnutriție, pneumonie de aspirație, sufocare și deces, în special la un pacient fragil. Prevalența sa este foarte mare și este și mai mare atunci când este legată de demență. Prezentăm cazul unui pacient de 72 de ani cu fibrilație atrială, insuficiență cardiacă clasa II NYHA cu fracție de ejecție conservată, hipertensiune pulmonară secundară, bronhopneumopatie obstructivă cronică (BPOC), imagistică opacități fibronodulare bilaterale staționare, care se manifestă în principal cu dispnee la efort moderat și disfagie selectivă pentru lichide și solide asociate cu tuse cronică de intensitate mare. Diagnosticul diferențial oferă posibilități de exacerbare a BPOC, o tumoră în mediastin, o posibilă strictură esofagiană, o fistulă eso-bronșică. Diagnosticul pozitiv a fost fistula eso-bronșică după examenul de tranzit cu bariu. Pentru a exclude posibilitatea neoplaziei a fost necesară continuarea investigațiilor cu CT toracic și consult gastroenterologic, recomandări la externare. Disfagia este un simptom nespecific care poate fi cauza multor boli la pacienții vârstnici, fragili. Ca multe alte simptome nespecifice la vârstnici, ar trebui să investigăm bine toate cauzele posibile, prin consultații pluridisciplinare și investigații adecvate.
Cuvinte cheie: disfagie, fragilitate, diagnostic diferențial, pacient vârstnic

INTRODUCTION

Dysphagia is a common problem in the elderly, which can be the manifestation of a wide group of diseases, which requires special attention of the clinician in evaluating a patient with such an issue. Dysphagia, according to the etymology of the word, refers to the difficulty of swallowing. Anatomically, it is classified as oropharyngeal dysphagia and esophageal dysphagia. From the point of view of the etiology, it can be either due to a mechanical cause or due to a motor dysfunction. The phenomenon of swallowing involves over 30 nerves and muscles, which implies that although seemingly simple, there are many essential elements in carrying out this process, which gives it fragility, and can be altered in several links. As we know, normal aging involves progressive brain atrophy, which gradually leads to damage to the brain structures responsible for swallowing, as well as a slight atrophy of the muscles [1].

CASE-STUDY ANAMNESIS

We present the case of a 72-year-old patient who came to our clinic for dyspnea at moderate exertion, fatigue, fixation hypomnesia, selective dysphagia for fluids and solids, chronic cough.

From his personal medical history we mention atrial fibrillation with medium heart rate, NYHA class II heart failure with preserved ejection fraction, secondary pulmonary hypertension, COPD, imaging stationary bilateral fibronodular opacities evaluated periodically with CT examination in 2017, 2018 and 2019, diffuse osteoporosis with fracture by objective T5-level compaction at the MRI examination in 2017, without DXA investigation, data provided from a medical letter from 2018, spondylodiscarthrosis (MRI 2017), cerebral atrophy exceeding the age limit (MRI 2017).

From the background medication we mention the treatment with acenocoumarol, metoprolol 100mg/day, furosemide 40m /day, spironolactone 25mg/day, Alpha D3 1mcg/day, atorvastatin 20mg/day, donepezil 10mg/day, memantine 10mg/day.

THOROUGH ASSESSMENT

a) Regarding the **objective examination** we mention dehydration, pale skin, venectasias at the level of the lower limbs, bilateral, cracking during passive mobilization of the large joints, kyphoscoliotic thorax, bilateral basal crackles (left> right), BP = 105 / 70mmHg, HR = 79b/min, irregular, arrhythmic heart sounds, inequidistant, inequipotent, without detectable auscultatory murmurs, Romberg present unsystematized, left eye blindness.

b) **Serum and urinary biochemical parameters**: leukocytosis (10.8 * 103/μL), neutrophilia (7.09 * 103/μL), increased fibrinogen (460mg/dl), increased ESR (33mm/h), slightly low serum potassium (3.4mmol/l -> 3.6mmol/l -> 3.50mmol/l), creatinine 1 mg/dl at admission, then 0.82mg/dl, respectively 0.78mg/dl. In the urine summary there have been present leukocytes 500/ μL, and also proteins present. Urinary sediment showed very fine traces of protein, frequent leukocytes, relatively common microbial flora, frequent flat epithelial cells and very rare round epithelial cells. Since the urine summary and the urinary sediment have been modified, we performed the urine culture where Enterobacter Aerogenes was identified, but because the patient did not present any urinary symptoms, we decided to refrain from initiating the antibiotic treatment.

c) **Abdominal and thyroid ultrasound** showed no significant changes.

d) **DXA examination** confirmed the diagnosis of osteoporosis.

e) The **ophthalmologic examination** found the eye as the only functional and compound myopic astigmatism for which treatment with eye drops with artificial tears, dorzolamide/ timolol solution and bimatoprost was recommended.

f) **Psychological consultation** found moderate mnemonic efficiency, slight deficit of concentration, moderate deficit of abstraction, deficit of integration of elements, moderate capacity for visual organization, deficit of long- and medium-term recall, moderate difficulty of concentration. The MMSE exam was 23/30p, the Clock Drawing Test was 5/10p, and the Geriatric Scale of Depression was 2/15p.

g) The **EKG** showed atrial fibrillation, VR = 84 / min, hypovoltage in the frontal leads, where T waves were flattened diffusely. Cardiological examination with **echocardiography** examination found mild to moderate mitral regurgitation, severe tricuspid regurgitation, probable secondary PAH (pulmonary hypertension), permanent FiA with moderate VR. Because low blood pressure values (TAS below 100mmHg) were found during hospitalization, associated with postural instability and the diagnosis of osteoporosis, the dose of furosemide was reduced from 40mg/day to 20mg twice a

week, blood pressure returning to normal limits, the symptoms improving and reducing the risk of falling and implicitly the occurrence of fractures.

DIFFERENTIAL DIAGNOSIS

Selective dysphagia for solids and fluids associated with chronic cough with high intensity, that isn't probable due to chronic bronchitis in the presence of an exacerbation of chronic obstructive pulmonary disease, has posed the following problems in the differential diagnosis [1]:

- An **exacerbation of COPD**, which is still unlikely, because from a clinical point of view we would have expected an increase in sputum production with colour change, suggestive of a super infection and chest X-ray only enlarged heart in both diameters, fibrous sequel in the bilateral upper lung lobes, linear opacity, probably sequel, right basal, symphysed right costo-diaphragmatic sinus, diminished pulmonary transparency with benign left basal appearance; to re-evaluate this associated pathology, it is recommended to perform a spirometry, but we could not perform it, due to the presence of the COVID pandemic19 [2-4].

- The presence of an **eso-bronchial fistula**, which is the cause for food to enter the respiratory tract, thus triggering cough and dysphagia being justified [5];
- A possible **esophageal stricture**, but they generally occur in patients with gastroesophageal reflux disease, or with another cause of esophageal injury [6];
- A **tumor in the mediastinum**, this can be highlighted at a radiological examination, but in general in this context dysphagia is selective for solids [7-9];
- **Diffuse idiopathic esophageal spasms**, unlikely due to the severity of symptoms;
- **Esophageal achalasia**, the clinical picture being suggestive, although the burning pain that appears in this pathology is missing, due to the regurgitation of gastric juice [10];
- **Scleroderma**, unlikely, although possible, not having many elements from the specific clinical picture of this pathology: Raynaud's phenomenon, telangiectasia, palpitations, gastroesophageal reflux disease [11].

The positive diagnosis was imposed by the barium transit, examination revealed the presence of an eso-bronchial fistula (Fig. 1 and Fig. 2).
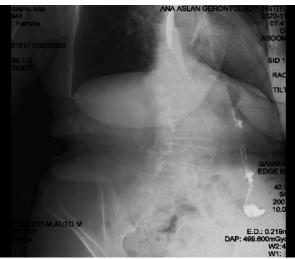

Fig. 1 Eso-bronchial fistula

Fig. 2 Eso-bronchial fistula

The patient was discharged with improved symptoms after hospital treatment, but it is still necessary to continue investigations with chest CT and gastroenterological consultation for a more accurate diagnosis and the establishment of therapeutic conduct, as at present we cannot eliminate the possibility of a neoplasia.

CONCLUSIONS

The peculiarity of this case is to evaluate the possible causes of a nonspecific symptomatology, dysphagia, in an elderly, fragile patient. The more advanced the frailty is and the older the patient is, the more untypical the pathologies manifest, and the clinical reasoning must be as wide as possible, there should be more questions in anamnesis, and it should also be more investigations effectuated.

Conflicts of interest

The authors declare no conflicts of interest.

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THE VARIABILITY OF SLEEP HABITS AND DISORDERS IN ELDERLY POPULATION

*Traian **Purnichi**[1], Maria **Mardirosevici**[1], Marian **Onofreiu**[2]*

[1]*"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest*
[2]*Clinical Hospital of Psychiatry "Prof. Dr. Alexandru Obregia", Bucharest*

Corresponding Author: Traian Purnichi, purnichi.traian@ana-aslan.ro

Abstract. The sleep habits have a very broad spectrum and varies through history with culture and age. Of course, there are a lot of myths about sleep some true but most of them false. Perhaps that the most common myth is that elderly need less sleep than adults. Once we age, we did not require less sleep, but the quality and architecture of sleep changes. The main changes in elderly are: decreasing the amplitude (phase advanced/delayed, internal desynchronization, increasing in variability); cellular/molecular changes (expression of the clock genes, neurobiochemical changes in the SCN and decreased ability of the SCN to drive peripheral oscillators); decreasing the light input (age related losses in photoreception like cataracts, decreased exposure or decreased response). From neurobiological point of view, The orexin levels increases in elderly, and higher value could be fund in elderly with insomnia. This is important because the orexin level is corelated with Alzheimer's disease markers and cognitive decline. Moreover, the growth hormone secretion decreases with age and this may have a serious impact on the person health. The presence of insomnia has a serious consequence on the elderly: increased risk for psychiatric disorders and the risk for cardio-metabolic diseases; it decreased quality of life; may produce cognitive; it increased pain and healthcare utilization and; it induces absenteeism and poor occupational; may increase the risk of falls and hip fractures; may increase the risk of motor vehicle crashes and workplaces accidents and overall increases mortality. In elderly, the presence of sleep disorders may have serious consequences, so they should address the specialist as soon as they notice sleep problems.
Key words: sleep disorders, insomnia, cardiovascular death, cognitive decline, elderly

Rezumat. Somnul şi obiceiurile de a dormi ocupă un spectru foarte larg atât în cadrul istoriei, cât şi în aceeaşi perioadă de timp variind de la cultură la cultură. Sunt foarte multe mituri legate de somn, dar multe sunt false. Probabil cel mai folosit este acela că vârstnici au nevoie de mai puţin somn. O dată cu înaintarea în vârstă se schimbă doar arhitectura somnului, calitatea lui şi nivelul anumitor hormoni. Principalele modificări la vârstnici sunt: scăderea amplitudinii (si modificări de fază avansată/întârziată, desincronizare internă, creşterea variabilităţii); modificări celulare/moleculare (expresia genelor ceasului intern, modificări neurobiochimice în SCN şi scăderea capacităţii SCN de a se sincroniza cu oscilatorii periferici); scăderea aportului de lumină (pierderi legate de vârstă în foto-recepţie, cum ar fi cataracta, scăderea expunerii sau scăderea răspunsului). Din punct de vedere neurobiologic, nivelul de orexină creşte la vârstnici, iar la vârstnicii cu insomnie valorile sunt cu mult mai mari. Acest lucru este important deoarece nivelul de orexină este corelat direct proporţional cu markerii bolii Alzheimer şi cu declinul cognitiv. În plus, secreţia hormonului de creştere scade odată cu vârsta şi acest lucru poate avea un impact grav asupra sănătăţii persoanei. Prezenţa insomniei are consecinţe grave asupra vârstnicilor: creşte riscul de tulburări psihice şi boli cardio-metabolice; scade calitatea vieţii; poate produce deficite cognitive; creşte sensibilitatea la durerea şi utilizarea serviciilor medicale; induce absenteism şi prezenteism; creşte riscul de căderi şi fracturi de şold; poate creşte riscul de accidente auto şi de accidente la locul de muncă şi în general, creşte mortalitatea. La vârstnici, prezenţa tulburărilor de somn poate avea consecinţe grave, aşa că ar trebui să se adreseze specialistului imediat ce observă probleme de somn.
Cuvinte cheie: tulburări de somn, insomnie, mortalitate cardiovasculară, deficit cognitiv, vârstnici

INTRODUCTION

The sleep has been fascinating humans from the beginning of humanity to nowadays. Throughout history, people have attempted to understand it from different perspectives, starting with esoteric terms all the way through to psychiatric ones. Given the high variety of angles applied to the research of sleep, it becomes quite clear that one size does not fit all. The present paper aims to summaries some of these angles in the context of geriatric care. It thus consists of three sections: one is to offer a historical overview of this phenomenon, followed by an attempt to classification and finishing

with a section zooming into the phenomenon of insomnia.

Short overview of the mythology and history of sleep

The ancients were attracted by sleep and dreams, so the Greeks attributed a god to this body function: Hypnos (with the Roman equivalent, Somnus). Hypnos was the son of Nyx (i.e., Night) and Erebus (i.e., Darkness) and he had a brother, Thanatos (i.e., Death). This association took place because in the ancient Greek culture the sleep usually took place in the night and in darkness, while people also noticed the resemblance between a deep sleep and death [1]. Morpheus is one of the sons of Somnus and sent human shapes (Greek morphai) of all kinds to the dreamer, while his brothers Phobetor (or Icelus) and Phantasus sent the forms of animals and inanimate things, respectively. Some similarities can be drawn to the Norse mythology, where the goddess Nótt is the night personified.

Sometime later, during the Middle Ages many superstitions and beliefs revolved around sleep disorders and nightmares explained that these were provoked by all kinds of gods and creatures like: Lamiae and Empusae in the Roman Empire, Lilith/Lilim in the Jewish culture, Old Hag in Anglo-Saxon culture, Bakhtak in Iran and Persia, Noctnisa in Eastern Europe, incubus or succubus in the old Europe and The Flyer in Romania and Bulgaria. Interestingly, the old Teutonic word mar (meaning devil) could be at the base of the German word nachtmar or the English word nightmare, because in that Christian medieval Europe the superstition was that the parasomnias were caused by the evil night visitors. Also, in French, the word for nightmare is cauchermar (caucher – to press + mar-devil), that shows its medieval superstition origin. Interestingly, during the Middle Ages, early scientists started developing the neuropsychiatric approach to sleep disorders. In his book "De Miraculis Occultis Naturae" (1564), the Dutch physician Lemnius Levinus (1505-1568) linked the psychosomatic disease to somnambulism and his theory was supported by other scientists in their books of the epoch [1].

Attemp at a classification

The ways in which people around the world sleep are as heterogenous as the cultures they come from and it can be surprising how much can be learned from the sleep habits of the cultures around the world.

The 'where' of sleep

In Japan for example, people prefer sleeping on tatami mats. A tatami mat is commonly made of rice straw, wood chip boards or polystyrene foam. It is rectangular in shape, its width is always half the size of its length, and it comes in various sizes. These gentle-yet-firm mats were traditionally used as special seating for nobles. In order to sleep on one, a person usually places a thin mattress on top of it, which is called a futon.

In south India, mothers often put their sleeping babies in indoor hammocks made of the light, breathable fabric Sari and mount them so they hang from the ceiling in a bedroom. Also, in areas where malaria is a threat (such as the sub-Saharan African countries, like Ethiopia, Mali, Rwanda, Senegal, Tanzania, and Uganda) beds are often surrounded by nets. Malaria is a serious and sometimes life-threatening disease that is usually transmitted through the bite of an infected mosquito. Because it is a lot harder to fight off mosquitoes during sleep, bed nets, which are often made of strong multi-filament polyester fibers as an attempt to reduce the transmission of the disease by keeping mosquitoes at bay [2].

In South and Central America, for their "siesta" (or nap), people prefer a hammock, which is typically made of cloth, twine, or rope and dips with flexibility as one's body presses into it. There is a practical reason for this choice: since hammocks swing above the ground, they can protect sleepers from ground-based ants, snakes and other critters that are common in tropical

countries. Navy ships also popularized the hammock, because when a sailor sways back and forth in one, he or she is less likely to be tossed to the ground by the lurching boat.

One interesting napping novelty can be observed in Scandinavia: dozens of strollers parked outside. Scandinavian parents often leave strollers with snoozing newborns outside while they finish up their errands inside. This can be, for many peoples from US, a nightmare waiting to happen. For Nordics, it is such a popular belief, that many daycares and preschools in these countries hold nap time outside to expose infants to fresh air more [2].

The 'how' of sleep

In some parts of Asia, getting a few minutes of nap during your lunch break is not only normal, but expected. During lunchtime employees will retire to a dedicated "nap room" to get a few minutes of relaxation. Others will simply lean back in their chair and nod off. Depending on the company and the culture, naps could last anywhere from a few minutes to a full hour. This curious napping habit stems from the fact that many locals living in these countries start their days much earlier than their Western counterparts, with some locals rising as early as 4 am [3].

Some aboriginal communities from Australia, follow age-old customs when it comes to sleep. Rather than sleeping in separate rooms or areas, people sleep in large groups that are designed to keep members of the community safe. Beds are arranged in long rows, with the strongest members of the community sleeping on the perimeter while the younger individuals and the elderly sleep toward the center of the group. This stems from a cultural belief that protection and togetherness is an important ingredient for a restful sleep. This custom can also be seen in some Arabic countries. Many Afghan families will fold up their mattresses and blankets after a night's sleep so that the room can play host to other activities, like meals and entertaining guests. It is also common for entire families to snooze in one room together, rather than retiring to separate bedrooms to sleep.

In Botswana, Zaire and some other African countries, certain traditional hunter-gatherer groups do not follow a set sleep schedule. Instead, they sleep when they feel they need it. Some sleep experts suggest that sleeping in this way could fend off "sleep anxiety", and could even translate to better, more restful sleep [3].

According to a study from the National Sleep Foundation, the UK has the highest percentage of self-proclaimed nocturnal nudists than any other country surveyed. Almost a third of the UK population expresses a preference towards sleeping without any clothes at all. In Spain, children's sleep schedules are the same as the ones of their parents, staying awake until well past 10 pm. This is likely because of two cultural elements: siestas (long midday meals with naps), and much later dinners. Families in Spain often eat dinner as late as 9 pm, so heading off to bed an hour or two following a meal is not out of the ordinary [3].

The biology of sleep

- NREM and REM

Sleep is ubiquitous among mammals and may also be found among lower life forms. As discussed above, the accommodations made to allow and support sleep are different from one environment to another and differ from culture to culture. Sleep is not just the absence of wakefulness but it is rather a complex and multi-dimensional state. Sleep influences all major systems and this relationship is bidirectional, with many of the body's systems also influencing a person's sleep. Sleep problems, including sleep deprivation can have a great deal of influence on one's health, wellness, and longevity [4].

The need for sleep varies between individuals and across the life span. Normally, adults sleep about 7 to 9 hours per night although this can vary considerably; people spend one-quarter to one-third of their lives asleep [3]. The

classical sleep patterns consist of 4 to 5 cycles of paradoxical sleep (rapid eye movement sleep- REM) that are alternating with some deep sleep periods (non-REM sleep) that is further divided into four stages. The sleep-wake cycle is controlled by two separated but interacting processes: the homeostatic (or the recovery) process and the circadian process [5].

It is known that NREM sleep is characterized by some distinctive patterns on the electroencephalography (EEG): "sleep spindles" (12 to 14 Hz in humans) high amplitude and/or slow "delta" waves (circa 0.5 to 1.0 Hz in humans). The NREM sleep constitutes the major portion of the sleep period (about 75 to 80 percent in humans), since the sleep process usually starts with NREM sleep (the main futures of the NREM sleep from the literature [5] are presented in Tab. I) which is then interrupted periodically by episodes of REM sleep (at about 90 min. intervals in humans). The REM sleep is characterized by the occurrence of rapid eye movements, a low voltage-mixed frequency EEG pattern and muscle atonic state. Reports of dreaming can be elicited on awakenings from all stages but are the most vivid and most frequent on awakenings from REM sleep [5].

Tab. I The main cerebral, systemic and endocrine features of NREM sleep

Type of features		
Cerebral	**Systemic**	**Endocrine**
Cerebral temperature decreases	Reductions in motor activity, postural tonus, behavioral responsiveness, metabolic rate, heart rate, respiration rate, ventilatory response to CO2, vasomotor tone, arterial blood pressure, brain, and body temperatures, thermoregulatory setpoint, renal function, decreased intestinal motility.	Reductions in release of cortisol and thyrotropin
Decreased neuronal firing in some areas; increases in others		
Burst pause firing pattern of neurons in several major brain areas		
Drifting, unfocused thought; occasional dreams; occasional reports of no mental activity		Increased secretion of growth hormone, aldosterone, testosterone, prolactin, insulin
Decreased activation of forebrain by reticular system	General parasympathetic dominance	
Hyperpolarization of thalamocortical neurons		
"Sleep-active" neurons in anterior hypothalamus, basal forebrain, amygdala and nucleus of the solitary tract		Increased glucose levels
Reduced cerebral metabolism during slow wave sleep		
Cerebral blood flow varies regionally		

Interestingly the brain does not shut down during sleep. According to one comprehensive study of human sleep, cerebral metabolism is substantially reduced from waking levels only during the high-voltage, slow-wave portion of NREM sleep, which normally constitutes only about 20 percent of total sleep [4]. Therefore, the reductions in energy during sleep are relatively modest. The metabolic savings of sleep over quiet wakefulness have been estimated at around 10 to 15%. Of course, the reductions of activity might be functionally targeted to some specific organ systems. However, the specific organs that require sleep to rest have not been identified.

Moreover, there are complex changes in neuronal firing which vary with the state and with the brain site instead of a massive decrease in neuronal firing. Neurons in thalamic and cortical areas tend to show

modest decreases in rate during NREM sleep followed by increases to the waking level or above during REM sleep. For many of these neurons, the most striking change is the development of a burst-pause firing pattern, which has been interpreted by some as functionally important. The hypothalamic and limbic neurons may show increases or decreases in firing rates in NREM or REM sleep, depending on the specific nuclei recorded by the studies. Brain stem neurons generally show decreased firing rates during NREM sleep, but in REM sleep they may show their highest firing rates in some areas, such as the mesencephalic or pontine reticular formation, or their lowest firing rates in other areas, such as the dorsal raphe or locus coeruleus nuclei [4, 6].

- The sleep/ wake cycle and the importance of their relationship

In the passage from waking to NREM sleep, there is increased firing in neurons of the anterior hypothalamus, nucleus of the solitary tract, and amygdala, which are believed to be involved in sleep generation or behavioral inhibition. Also, some complex changes in patterns of neural activity can occur without changes in average firing rates: for example, in the visual cortex, association cortex, and brain stem of the cat, neurons that fire rapidly during NREM sleep tend to fire even more rapidly during waking, while neurons which fire more slowly during NREM sleep tend to fire even more slowly during waking. Regarding these changes, there is no simple descriptive characteristic of brain activity that points to the sleep functions [4].

From the neurobiological perspective, both sleep and the arousal spectrum are important to be evaluated together because they tend to be a marker for mental health. The arousal spectrum is believed to be linked to 5 major neurotransmitters that form some circuits, in the ascending reticular activating system: histamine, serotonin, dopamine, norepinephrine, and acetylcholine [7]. There is another set of circuits in the hypothalamus, called the sleep/wake switch. The wake center is in the tuberomammillary nucleus (TMN) and the sleep center is in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus. Two sets of neurons are involved: orexin neurons of the lateral hypothalamus that promotes and stabilizes wakefulness (via two peptide neurotransmitters: orexin and hypocretin) and the melatonin sensitive neurons of the suprachiasmatic nucleus (SCN). The SCN is the body internal clock that regulates the circadian activity [7]. Melatonin is secreted by consecutive acetylation and methylation of serotonin in the pineal gland during the night. Its production is turned on by the noradrenergic (NA) neurons of the SNS in the upper spinal cord that passes into the gland through the superior sympathetic ganglions. The NA action on a beta-adrenoreceptor turn on the gene of the enzyme that it requires to produce melatonin. During daytime, melatonin production is suppressed by a SCN output. Also, some beta-blockers prevent melatonin production [8]. This is why for example, agomelatine (and MT1 and $MT2_2$ agonist and 5HT2C antagonist), may improve REM sleep behavior disorder symptoms [9].

The two main neurotransmitters that regulate sleep, from the hypothalamus are GABA (gamma-aminobutyric acid) from the Ventrolateral Preoptic Nucleus (VLPO) and histamine from the tuberomammillary nucleus (TMN). When the wake promoter from the TMN center becomes active and releases histamine to facilitate arousal and in the VLPO to inhibit the sleep promoter. After that, during the day, the homeostatic sleep drive increases and the circadian wake drive diminishes to an eventual tipping point where the sleep promoter from the VLPO is triggered, and GABA is released in the TMN to inhibit wakefulness [7]. So, for example, in treating a disorder with excessive daytime sleepiness, products like modafinil during the day to balance the circadian cycle back to

wakefulness can be recommended. Notably, the exact way that modafinil works is still unclear; some theories hypothesize that by blocking the dopamine transporter (DAT) from the dopamine neurons it increases the dopamine level that promotes the release of histamine from the TMN neurons. For disorders characterized by insomnia, which tend to be more frequent in the geriatric presentation, products that block histamine or that enhance GABA actions can be used. For the homeostatic sleep drive, it is presumed that the sleep is due to fatigue and linked with a neurotransmitter called adenosine which is accumulating during the day and diminishing during the night [7]. Caffeine is the most used antagonist of adenosine, but there are also some endogenous antagonists.

SLEEPING DISORDERS

Examining the sleep patterns of a patient is a basic part of the psychiatric evaluation. The sleep disorders are generally classified in ICD-10 (codes F 51.0, G 47, R and Z) and DSM IV/5, but more fully described in the ICSD (International Classification of the Sleeping Disorders) [10]. In terms of symptomatology, the sleeping disorders can be classified by insomnia (not enough sleep or impossibility to sleep), hypersomnia (excessive daytime sleepiness or drossiness) and parasomnias (unusual events during sleep). A more detailed classification of sleep disorders can be found in Tab. II.

Tab. II Classification of sleep disorders with their corresponding ICD-10 codes

Superordinary type	Disorder name	Code
General sleep disorders	Insomnia (NOS)	G47.00
	Adjustment Insomnia	F51.02
	Other insomnia not due to a substance or known physiological condition	F51.09
	Primary insomnia	F51.01
	Paradoxical insomnia	F51.03
	Sleep Deprivation	Z72.820
	Insomnia Due to Medical Condition	G47.01
	Hypersomnia (NOS)	G47.10
	Hypersomnia Due to Medical Condition	G47.14
	Narcolepsy with Cataplexy	G47.411
	Narcolepsy Without Cataplexy	G47.419
	Recurrent Hypersomnia	G47.13
	Idiopathic Hypersomnia with Long Sleep Time	G47.11
	Idiopathic Hypersomnia Without Long Sleep Time	G47.12
	Primary Hypersomnia	F51.11
	Insufficient sleep syndrome	F51.12
	Other hypersomnia not due to a substance or known physiological condition	F51.19
Sleep related breathing disorders	Obstructive Sleep Apnea	G47.33
	Sleep Related Nonobstructive Alveolar Hypoventilation	G47.34
	Obesity Hypoventilation Syndrome	E66.2
	Sleep Related Hypoventilation/Hypoxemia	G47.36
	Primary Central Sleep Apnea	G47.31
	Cheyne Stokes Breathing Pattern	R06.3
	Central Sleep Apnea/Complex Sleep Apnea	G47.37
	Other Sleep Apnea	G47.39
	Dyspnea, unspecified	R06.00
	Other forms of dyspnea	R06.09
	Periodic breathing	R06.3
	Snoring	R06.83
	Other abnormalities of breathing	R06.89
	Apnea, not elsewhere specified	R06.81
	Unspecified Sleep Apnea	G47.30

	Circadian Rhythm Sleep Disorders (NOS)	G47.20
	Delayed Sleep Phase Type	G47.21
	Advanced Sleep Phase Type	G47.22
	Irregular Sleep-Wake Type	G47.23
	Free-Running Type	G47.24
	Shift Work Type (Shift Work Disorder)	G47.26
Parasomnias	Confusion Arousals	G47.51
	Sleepwalking	F51.3
	Night Terrors	F51.4
	REM Sleep Behavior Disorder	G47.52
	Recurrent Isolated Sleep Paralysis	G47.53
	Nightmare Disorder	F51.5
	Other sleep disorders not due to a substance or known physiological condition	F51.8
	Others parasomnia	G47.59
Sleep Related Movement Disorders	Restless Legs Syndrome RLS	G25.81
	Periodic Limb Movement Disorder	G47.61
Other	Opioid abuse with opioid-induced sleep disorder	F11.182
	Opioid dependence with opioid-induced sleep disorder	F11.282
	Opioid use, unspecified with opioid-induced sleep disorder	F11.982
	Sedative, hypnotic, or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced sleep disorder	F13.182
	Sedative, hypnotic, or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced sleep disorder	F13.282
	Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced sleep disorder	F13.982
	Cocaine abuse with cocaine-induced sleep disorder	F14.182
	Cocaine dependence with cocaine-induced sleep disorder	F14.282
	Cocaine use, unspecified with cocaine-induced sleep disorder	F14.982
	Other stimulant abuse with stimulant-induced sleep disorder	F15.182
	Other stimulant dependence with stimulant-induced sleep disorder	F15.282
	Other stimulant use, unspecified with stimulant-induced sleep disorder	F15.982
	Other psychoactive substance abuse with psychoactive substance-induced sleep disorder	F19.182
	Other psychoactive substance dependence, in remission	F19.21
	Other psychoactive substance dependence with psychoactive substance-induced sleep disorder	F19.282
	Other psychoactive substance use, unspecified with psychoactive substance-induced sleep disorder	F19.982
	Opioid abuse with opioid-induced sleep disorder	F11.182
	Opioid dependence with opioid-induced sleep disorder	F11.282
	Opioid use, unspecified with opioid-induced sleep disorder	F11.982

When evaluating sleep problems, the whole 24 circadian rhythms (sleep journal), the presence of affective disorders and other psychiatric comorbidities (dementia, RLS, PMLS) or somatic comorbidities (asthma, obstructive sleep apnea syndrome, thyroidal afflictions, cardiac problems, etc.) or substance use and habits must be assessed. Additionally, some patient rated questionnaires like the Bristol Sleep Profile, or more research-oriented scales like the Pittsburg Sleep Quality Index, the St. Mary's Sleep Questionnaire, the Leeds Sleep Evaluations Questionnaire or other similar scales can be administered. The most frequent medical investigations required in the cases of sleep problems are: TSH, glycemic value, vitamin D_3 and B_{12} and the ions values, actigraphy (movement assessment), overnight video recording, multiple sleep latency test (helpful for diagnosing narcolepsy or excessive daytime sleepiness) and polysomnography.

Another important aspect of the disorders is characterized by circadian rhythm perturbation that can be perceived as phase delay of phase advance. The disorders with phase delay have the characteristic that the sleep/wake cycle is turned on too late in the 24 hours sequence. In contrast, the phase advance disorder is characterized by the fact that the sleep/wake cycle and the sleep promoter is turned on too early. A clear example is the case of adolescents and the case of the depressed patients who have a phase delay; therefore, their sleep/wake cycle turns on in the mornings when it is time to get out of bed. To reset their cycle, exposure to light in the morning and melatonin intake at night can be recommended. Contrary to this example, the elderly patient is usually phase advanced, therefore recommending them light in the evening and melatonin in the morning can reset their SCN and the sleep/wake cycle should stay off a little bit longer, retuning the patient to a normal rhythm [7].

The authors' perspective is that the psychiatric interview should ask questions about the onset of sleep, as well as about the sleep disturbances after sleep initiation, about early morning wakening, sleep quality, the sensation in the mornings, the frequency of the sleep disorder, about the impact of sleep on daytime activities and about the patient's quality of life. Nap-taking during the day and feeling sleepy may indicate either poor sleeping habits or hypersomnia. The sleep disorders in elderly are usually only the tip of the iceberg; further investigations are needed to seek for the presence of any affective disorders or other comorbidities, including the presence of the periodic leg movement during sleep or the restless leg syndrome. The screening for narcolepsy, obstructive sleep apnea, Sunday night insomnia (i.e., anxiety related to work), Monday morning blues (i.e., tendency towards excessive alcohol consumption during the weekend), the use of caffeine, nicotine and any other drugs, as well as the working shifts and daily schedule should also be considered and assessed [7].

ZOOMING IN ON SLEEP DISORDERS: INSOMNIA AND ITS IMPACT ON THE GERIATRIC POPULATION

Insomnia is a common sleep disorder representing the patient's troubles in falling asleep, staying asleep, or both. As a result, one may get too little and/or poor-quality sleep. An overview of insomnia is presented in Tab. III [10]. As one's sleep changes with age, the quality of sleep is the aspect that suffers the most [11-14]. The main changes of the circadian rhythms with age are: decreases in amplitude (phase advanced/ delayed, internal desynchro-nization, increasing in variability) [11, 12]; cellular/molecular changes (expression of the clock genes, neurobiochemical changes in the SCN and decreased ability of the SCN to drive peripheral oscillators) [13]; decreases in the light input (age related losses in photoreception like cataracts, decreased exposure or decreased response) [14]. All these changes may disrupt the tonic orexin secretion [15]. This means that the sleep and wakefulness phases are out of synchronicity with the environment [16].

Tab. III Overview of insomnia

Insomnia descriptors	Description of characteristics
General characteristics	lying awake for a long time before you fall asleep
	sleeping for only short periods
	being awake for much of the night
	feeling as if you have not slept at all
	waking up too early
Precipitating factors	psychiatric (e.g., anxiety, depression)
	sleep-wake rhythm (e.g., work shifts, jet lag, irregular routine)
	pharmacological (e.g., stimulants, caffeine, alcohol, antidepressants, beta-blockers, etc.)

| physical (e.g., pain, cardiac/urinary/respiratory illnesses, pregnancy) |
| other (e.g., stress/noise/bereavement/worry/arousal/children) |

Importantly, insomnia can have serious impact on the patients' health. Such examples are: increased risk for psychiatric disorders; increased risk for cardio-metabolic diseases; decreased quality of life; cognitive decline; increased pain sensitivity; increased healthcare utilization and costs; absenteeism and poor occupational performances; falls and hip fractures; motor vehicle crashes and workplace accidents; increased mortality [17-20]. A possible explanation for this could be that those with primary chronic insomnia showed significantly higher midnight salivary cortisol concentrations (1.46 vs. 0.76 nmol/l, p=0.02), indicating dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [21]. Also some other studies showed that people with insomnia have a higher peripheric resistance to insulin, but it seems to work both ways, because a recent Japanese study confirmed that diabetes and anxiety are independently and significantly associated with insomnia [22].

Another neurobiological aspect that can explain the consequences of untreated insomnia could be that the orexin levels are elevated with age and much higher in people with insomnia [23]. This aspect is very important because orexin levels are correlated with Alzheimer disease biomarkers. Another study showed a direct correlation between the presence of the chronic insomnia and the cognitive decline [24].

Interestingly, the amount of slow wave sleep decreases with age and along with this phenomenon lower levels of growth hormone secretion are also registered [25]. The consequences of growth hormone (GH) secretion declining with the ageing process, may result in GH deficiency. For the older adults, this could mean a decrease in lean body mass, an increase in body fat, especially in the visceral/abdominal compartment, adverse changes in lipoproteins, and a reduction in aerobic capacity. The increase in central obesity can further inhibit GH secretion.

A controversial and important aspect is linked with the common treatment of insomnia that uses benzodiazepines and the possible risk of fall within the geriatric population as a possible common side effect of hypnotic use. A study that included 34.163 older adults with insomnia (age above 65) that were followed up for 210 days answered this issue. The study concluded that insomnia alone, but not hypnotic use, is associated with a higher risk of fall [26]. So it is beater for the patient to receive treatment, even with hypnotics, with the possible risk of sides' effects, rather than to let the insomnia untreated.

Moreover, a recent prospective study of 10.330 adult participants revealed that people with excessive daytime sleepiness had 2.85-times greater risk (95% CI, 1.33–6.09) of cardiovascular death than those without daytime sleepiness in multivariable analysis corrected for sociodemographic factors, comorbidities and cardiovascular risk factors including depression [27].

In conclusion, the sleep has a broad spectrum and it varies with culture and age. With age, people do not require less sleep, since it is the quality of sleep that changes. The presence of sleep disorders may have serious consequences especially for the geriatric population, therefore they ought to address a specialist as soon as they notice any sleep irregularities.

Conflicts of interest
The authors declare no conflicts of interest.

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SENSE-GARDEN – DESCRIPTION OF A MULTIMODAL PSYCHOSOCIAL INTERVENTION

Ileana **Ciobanu**[1], Rozeta **Drăghici**[2]*, Andreea Georgiana **Marin**[1]*, Mihai-Viorel **Zamfir**[3], Alina **Iliescu**[1], Mihaela **Zamfir**[4], Marius Nicolae **Popescu**[1], Artur J **Serrano**[5], Mihai **Berteanu**[1]

[1] *"Carol Davila" University of Medicine and Pharmacy, Discipline of Rehabilitation Medicine, "Elias" University Hospital, Bucharest, Romania,*
[2] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania,*
[3] *"Carol Davila" University of Medicine and Pharmacy, Physiology Division, Bucharest, Romania,*
[4] *"Ion Mincu" University of Architecture and Urbanism, Department of Synthesis of Architectural Design, MMZ-Individual Architecture Studio, Bucharest, Romania,*
[5] *Norwegian University of Science and Technology-NTNU, Department of Neuromedicine and Movement Science, Trondheim, Norway*

Corresponding Authors: Rozeta Drăghici, rozetadraghici@gmail.com; Andreea Georgiana Marin, andreea.budrica@gmail.com*

Abstract. We are witnessing an accelerated process of population aging and, within this process, the number of older persons living with Major Neurocognitive Disorders is also increasing. Throughout the latest research, there is strong evidence showing the effectiveness of non-pharmacological interventions in the management of cognition and mood disorders, with positive effects on behavioural and psychological symptoms. The aim of the paper is to present the content of an efficient non-pharmacological multimodal psychosocial intervention, designed for improving the quality of life of people with Major Neurocognitive Disorders and recently tested with success. The intervention includes several kinds of experiences based on emotional reminiscence, the 5 senses, cognitive stimulation and training, along with elements of physical activity. Emotions reconnect us with the world around, with the ones we love and with ourselves.
Key words: multimodal psychosocial intervention, Major Neurocognitive Disorders, reminiscence therapy, older persons

Rezumat. Suntem martorii unui proces accelerat de îmbătrânire a populaţiei şi, în acest proces, numărul persoanelor care trăiesc cu tulburări neurocognitive majore este şi el în creştere. Ultimele cercetări arată dovezi serioase ale eficacităţii intervenţiilor non-farmacologice în managementul tulburărilor cognitive şi de dispoziţie, cu efecte positive asupra simptomelor psihologice şi comportamentale. Scopul acestui articol este acela de a prezenta compoziţia unei intervenţii non-farmacologice psihosociale multimodale, create pentru îmbunătăţirea calităţii vieţii persoanelor cu tulburări neurocognitive majore şi testate recent cu succes. Intervenţia include mai multe tipuri de experienţe bazate pe reminiscenţa emoţională, pe cele 5 simţuri, stimulare şi antrenament cognitiv, alături de elemente de activitate fizică. Emoţiile ne reconectează cu lumea din jur, cu cei dragi şi cu noi înşine.
Cuvinte cheie. intervenţie psihosocială multimodală, tulburări neurocognitive majore, terapie prin reminiscenţă, persoane vârstnice

INTRODUCTION

Since pharmacological treatment is the main support for the elderly living with dementia, the global cost of dementia in 2015 was estimated at 818 billion $, representing 1,09% of the global gross domestic product [1]. However, in the long run, the effectiveness of this treatment can be significantly increased by non-pharmacological methods such as psychological interventions, neurocognitive therapies (e.g., cognitive/emotion-oriented interventions, behaviour management techniques, music therapy, animal-assisted therapy [2] or environmental specific features. This is

especially the case in terms of the management of the Behavioural and Psychological Symptoms of Dementia (BPSD). Non-pharmacological intervenetions are effective alternative strategies for BPSD, increasing the quality of life levels of the older persons with neurocognitive disorders, while also facilitating the care process [3]. Caring for people living with neurocognitive disorders requires an interdisciplinary approach so that medication, psychological assistance, occupational therapy, physical activity and space design can synergistically increase the quality of life and well-being.

The latest research has brought strong evidence of the effectiveness of the non-pharmacological interventions in the management of cognition, mood disorders, with positive effects on behavioural and psychological symptoms [4]. These interventions can be divided into four categories outlined by Cammisuli [5]: holistic techniques, brief psychotherapy, cognitive methods, and alternative methods of diet and dietary supplements. These included: physical exercises and physical activities, brain exercises [6], acupuncture [7], aromatherapy [8], physical modalities [9]. Non-pharmacological interventions represent complementary techniques and should be tailored according to the patients' medical condition, resilience, compliance to treatment, Alzheimer's disease (AD) severity, available sanitary and professional resources and caregiver care commitment and support [5]. Even though there are authors emphasizing improve-ments in the patients' quality of life (QoL) after such interventions, studies of higher methodological quality are required to determine the efficacy of non-pharmacolo-gical interventions in people with major neurocognitive disorder. More research is also needed to determine the best practices with regards to non-pharmacological interventions [3].

With regards to space, therapeutic interventions that increase the awareness of the older people with dementia lead to a better reconnection with the surrounding reality [10]. The environment for non-pharmacological interventions plays an important role in enhancing their effectiveness. The symptoms of dementia that are in strong connection with the environment are: spatial disorientation, locomotor disabilities, mood and perception disorders [11, 12]. These can be negatively affected by inappropriate space size, shape, colours or textures, light too bright or, conversely, too dim and by sounds that are difficult to interpret or easy misunderstand [13]. At the same time, a dementia-friendly design can alleviate some of the behavioural and psychological symptoms of dementia such as wandering, spatial and temporal disorientation [14]. The integration of the spatial aspects within the non-pharmacological therapy makes the intervention "multimodal".

A systematic review published in 2020 offers an important conclusion regarding the benefits of multimodal non-pharmacological interventions aiming to improve the cognitive functioning of people with dementia syndromes [15]. The authors identified 26 studies providing results of multimodal therapy programs including two or more different modes of intervention, applied in a personalised manner and measuring a cognitive outcome. Combined cognitive, physical, psychological and psychosocial interventions, nutrition, fasting, gut health, sleep hygiene, stress reduction, detoxification, hormonal health and oxygen therapies/treatments/interventions were reviewed. The findings report a delay of cognitive decline and even cognitive improvements for multimodal intervene-tions. As a result, the non-pharmacological multimodal interventions are a promising approach, able to complement pharmacological methods in order to improve the cognitive functioning of people with dementia [15]. Another systematic review, this time regarding multimodal interventions for patients with

major neurocognitive disorder (MNCD) showed that a combination of physical exercise with cognitive training and activities of daily living, provided for 30 minutes, 3 times per week over at least 8 weeks is recommended for improving global functioning, as well as specific cognitive functions in the patient [16]. The authors also emphasize that cognitive training should focus on memory, executive function, visuospatial function and constructional ability.

Thus, including technology in the intervention can be an effective way to account for all these complex activities and at the same time, be efficient in helping the older adults with MNCD. Multimodal interventions based on information and communication technology (ICT) is an emerging practice in recent years for patients with neurocognitive disorders [10]. A 2020 study concludes that even if people with neurocognitive disorders use ICTs on a daily basis (smartphones and tablets), the use of apps designed to assist memory is limited. Interventions using these technologies are needed to overcome barriers in this population segment that are related to the lack of acceptance of new technologies in people with specific socio-demographic characteristics [17]. A systematic review regarding ICT for reminiscence therapy (RT), published in 2014, concludes that ICT may support RT in many ways, by offering easy access to multimedia RT triggers, new means for communication and participation, with an important reduction of the multiple barriers and limitations of classical RT interventions [18]. Efforts are made to enhance the personalisation of the RT experience offered to people with neurocognitive disorders by means of ICTs [19].

SENSE-GARDEN is such a multimodal intervention program based on an innovative ICT system providing stimuli to the different senses, such as sight, touch, hearing, balance and smell [20]. SENSE-GARDEN aims to meet the needs of the elderly person living with major neurocognitive disorder in terms of emotional communication in a familiar, safe environment, reconnection with reality, stimulation and training of cognitive and physical functions (including proprioception and balance). "The SENSE-GARDEN spaces are self-contained physical rooms equipped with digital technology to create an immersive environment, measuring typically between 25 square meters and are installed inside care facilities." A SENSE-GARDEN integrates digital technologies and individual meaningful media content, which is personalised to create a targeted therapy producing reminiscence effects in the patient [21].

The novelty of the SENSE-GARDEN method consists of the manner in which the intervention is composed and managed in order to create and use emotional memory anchors. These anchors are used to engage the users in the training steps. An ICT based system to offer visual, audio, touch, olfactive and proprioceptive stimuli generating a smooth experience. The intervention is based on reminiscence therapy through meaningful multiple sensory stimulation, focused on emotional reconnection with the self and others, which is used to enable and support reality orientation and improve the participation of the person with major neurocognitive disorder. The intervention combines emotional RT with personalised cognitive and physical training approaches. The 2018 Cochrane systematic review on RT impact on MNCD concludes that there is not enough high-quality methodological research to state that RT can improve QoL for patients with MNCD, but states however that RT is superior to other activities in terms of reconnection and that "RT can now be viewed alongside cognitive stimulation as an eco-psychosocial intervention with a credible evidence-base" [22]. There are many studies showing increases in QoL levels and cognitive measures immediately after

the RT intervention, especially when personalised, no matter the conditions generating the syndrome. Participation outcomes show improvements after RT interventions, too. The intensive character of the intervention program (5 sessions per week) may have influenced the outcomes in a positive manner. The benefits of involvement of the family members in the reminiscence approaches is also emphasized in the Cochrane review [22].

The effectiveness of the SENSE-GARDEN intervention, applied in an intensive manner, for 20 sessions (1 session per day, 5 sessions per week) has been shown in a recently published paper. Study's International registered report identifier is DERR1-10.2196/14096 [23]. The study published in 2022 presents the results if a series of 7 cases. Participants presented with major neurocognitive disorders of vascular and mixed origin. They participated in a SENSE-GARDEN program including personalised and adaptable experiences of Reality Wall, Move to Improve, Memory Lane, Life Road, with scents, old movie clips and music. The program was customised to enable emotional reminiscence and cognitive rehabilitation, along with elements of balance, upper limb (in the butterfly game) and lower limb coordination and aerobic exercise (cycling, in Life Road). The SENSE-GARDEN study protocol is published elsewhere [24]. All parameters assessed during this intensive study showed statistically significant changes after intervention, indicating improvements in all domains of interest: cognitive and physical functioning, activity and participation. The changes were noticed not only in terms of means, but were documented for each participant [23].

THE SENSE-GARDEN EXPERIENCE
The design of the experience
• *Architectural aspects*
The environment in which the multimodal intervention is offered to the user is

important. The space used for intervention delivery in SENSE-GARDEN has been prepared with regards to its interior design and equipment in order to meet the requirements of the delivery of the different experiences, in terms of dementia friendly principles [14] for safe and efficient sensory-motor and visuo-spatial training [25].

The space used for the SENSE-GARDEN needs to enable and support the whole intervention. Thus, an optimal space must be designed in accord with the principles of dementia-friendly architecture and must offer appropriate distances for sensory and motor training as well as for navigation between the media and interactive equipment. Space must provide access and a conducive experience, in a pre-set or ad-hoc established flow. Walls must be neutral in colour (white) and can be plane or curved (in accord with the capabilities of the media projector devices). Natural light providing information in regards of the season, weather and moment of the day should be accompanied with enough artificial light to avoid shadow but allow projected images to keep clarity and colours.

To maintain a state of well-being and therapeutic comfort, the space was designed to include natural plants and natural lighting to maintain a permanent connection with nature. At the same time, natural lighting must be helped by artificial lighting in order for this space to keep its supportive qualities of therapeutic experiences at a constant standard throughout, day and night. Moreover, the facts that natural light fights depression [26] and at the same time, that artificial light helps a good focus on different activities were accounted for. Older persons with neurocognitive disorders need a higher level of lighting [13, 26] but glare and shadows must be avoided. In this aspect, artificial lighting offers additional therapeutic comfort, because it is easier to control. The lighting of the space was, thus, an important aspect within the SENSE-

GARDEN project, enhancing the 6 experiences uniformly or differently depending on the type of training or on the time of day. The architecture was permanently in tandem with the technology, each one potentiating the other.

- *Equipment*

The equipment used to provide the means for the SENSE-GARDEN intervention program included the computer providing an innovative ICT-based technical platform ensuring the integration of the user-technology interfaces, a tablet for the remote control of the therapeutic experiences, a short-throw interactive projector, an All-in-One PC with touchscreen monitor and a four-limb stationary bicycle. The app on the tablet offers the means to create personal profiles and workflows containing personal, thematic, and culturally specific media (personal photographs and videos), as well as general media reminiscence triggers (publicly accessible images, videos, and music). It also offers the therapist the possibility to give real time feedback to the system, through a tablet interface, using emojis to express the emotional status and the emotional reaction of the primary user to the different triggers and activities included in the workflow used during a specific SENSE-GARDEN session.

The equipment is integrated by innovative ICT, to enable smooth workflows and experiences. ICTs are used lately on a positive trend for providing different interventions for PwD and their caregivers [27]. A 2016 systematic review of the literature about ICT applications that have been developed to assist patients with AD and their primary caregivers found out that ICT (information systems and internet) are used for information management as well as for healthcare (assistive technologies, telecare, telemedicine) for people with neurocognitive disorders. The review concludes that the use of ICT equipment should be recommended for the older adults' everyday life, as it has been shown

to improve their QoL as well as their caregivers [28].

The content of the experience
In the SENSE-GARDEN space, the patients were actively involved in a succession of 6 different experiences, as described in Table I. The following sub-sections show samples of tasks that can be given to a SENSE-GARDEN primary user divided by the SENSE-GARDEN activity category.

Initial decompression
Get the user focused on space, time and on activities to be performed during the session (salute, talk about weather, health condition today, remember previous SENSE-GARDEN sessions or explain what it is all about, gain the patient's interest for this).

- *Reality Wall*

Create an atmosphere that engages the patient in reminiscence activities and good feelings (use nonspecific content – movies depicting nature – select the favourite leisure-time geographic spot and features, if possible), attempt to encourage the user to talk about trips of old times they enjoyed, remember space and time markers, as well as the participants and the activities involved. Some new input regarding media content which can be used for future sessions might be obtained. Slow panoramic nature or town videos and relaxing soundscapes are recommended.

- *Memory Lane*

If beneficial, approach the personal memories regarding the patient's family, friends, crafts, profession, hobbies, etc. Use photos from personal events, related music, and allow the user to engage in remembrance activities. If beneficial, enquire about the current status of the family members, of their relationships and of their feelings. Allow the primary user to interact with the photos and help them create correlations and narrative endeavours. Adapt the content features (complexity of image, colours, content,

associated music) to the cognitive and sensory status.

- ***Life Road***

Choose driver-view video recordings with appropriate speed and image quality, preferably recorded in well-known places, to improve reminiscence and space and time orientation. As a supplementary cognitive task, the patient can be involved in samples for train-trip tasks (i.e., keep in mind the number of tunnels, viaducts, train stops; remember geographic highlights, season, flora, activities people are engaged in).

- ***Move to Improve***

Explain the game, each time if necessary. Select the degree of complexity and difficulty of the game in accord with the user's cognitive and sensory limitations. Use a simple static background (the image of a park, mountain pasture, plain field, lake shore or seaside). You may change the background from session to session, to increase curiosity and stimulate exploratory behavior. Then, adapt the tasks to the degree of focusing and engagement you notice. It is important to choose the right soundscape. If the music is too engaging, it may determine the user to dance, and it may also reduce the focus on the cognitive task at hand. Persuade the user to move as much as possible: back and forth to see the image and to act on the butterflies, and with a large range of motion to reach the butterflies from the same position, as many times as possible (i.e., engaging the patient in motor and balance tasks).

Regarding the butterfly game for cognitive, upper limb and balance training, we propose a multi-level approach:

- *level 1*: simple association game: the way it is now, with choices for number and size of flowers, plus the possibility to choose a different background image?

- *level 2*: multiple choice association game. Disturbing elements may appear: butterflies, bees, buzzing wasps and flies, maybe a flying small panda-bear. The user's task is to choose the butterfly, place it on the right flower, then do the same with the bees, but the user has to eliminate the flying panda-bear or other non-identified flying object which is out of context and place it in a recycle bin, or in a mail box.

- *level 3* (or a *level 2bis*): short term memory association game. The user must follow a pattern to train short term memory even more. For example, a color algorithm must be followed. When a lot of differently colored butterflies appear on the screen, along with the same number of colored flowers, the user has to pair them in the order of the colors indicated at the beginning, in a short-lived image. Begin with 2 x 2 pairs and go up to 7 colors and 7 pairs of butterflies and flowers. Please, can you do this? Disturbing elements may appear, to make it more difficult.

- ***Films of My Life***

Choose engaging items, with lyrics and rhythm, such as fragments of old movies (in accord with the personal preferences, rather than the époque). Motivate the user to *engage* in singing or/and remembering the movie plot, song lyrics, characters, gags and stuff.

Final decompression

Remember the content of the session, define the feelings it generated. In a small interview regarding the session, set the space and time coordinates, support the user to take initiative regarding the next activities of the day.

Tab. I Experiences of a SENSE-GARDEN session

The experience	The device used	Media content	Targeted functions
Reality Wall	a short throw interactive projector - reality projection	★videos with nature-depicting images ★personal videos from family vacations	● perception of space ● working memory ● focused attention ● language and communication
Memory Lane	all-in-one PC with touch screen monitor	★personal photos from patient's family album or, when a personal photo album was not available, specific media content in accordance with the personal preferences - music, films, movie stars, profession, books, authors, etc.	● long term memory ● perception of time ● focused attention ● problem-solving ● storytelling - language and communication ● executive function
Life Road	four-limbs stationary bicycle large TV screen or short-throw projector	★real-life routes or ★short movies from family history albums ★working sheets - remembering specific key trigger elements at the end of the training with the stationary bicycle following a virtual bike/train/car trip, by responding to questions	1. physical training ● motor control, coordination ● visual ● proprioceptive 2. cognitive training ● explorative attention ● space attention ● working memory training
Move to Improve	exergame - cognitive training application developed on 3 levels of complexity	★ simple game (easy, moderate or advanced) ★ complexified tasks: ● comparisons and associations ● matching pairs ● digit span backwards	1.cognitive training ● short term memory training ● medium term memory training ● backward memory span ● executive function 2. physical training ● motor control, balance and coordination ● visual ● proprioceptive
Sounds Surround Me	surround system that can be integrated with video projection	★instrumental music, favourite singers, actors, movies and soundscapes, short family videos ★smart lists	● positive affect ● memory ● communication ● engagement
Scent to Memories	intelligent scent release system	★ perfumes with emotional reminiscence effects	● mood ● memory ● engagement

The SENSE-GARDEN Procedure

The therapeutic process is conducted by one clinical psychologist, designated as "case manager", who is responsible for choosing the workflow for each working session and for adapting the complexity

level of the tasks in order to personalise the therapeutic session. One technical manager is also present, as the one responsible for the media content and technical support through all the 6 experiences, in order to provide a smooth and appropriate experience for each participant in the SENSE-GARDEN space. One family caregiver was invited to participate, when available, at the SENSE-GARDEN sessions, in order to catalyse the reminiscence of the past experiences lived by the person with dementia and to enhance the emotional reconnection with the self and with the environment.

The visit to the SENSE-GARDEN room is a personalized intervention of reminiscence therapy and multisensory stimulation. In order to personalise the intervention, the Sensory Profile (adult version) of the participant is created and the ALMA (Art of Life Memory Album) questionnaire [29] is filled in. The Sensory Profile offers insight regarding aspects of sensory processing, sensitivity, sensation seeking or avoidance. The Sensory Profile is considered by professional caregivers for elderly as a valuable tool, offering caregivers a more complete image of the limitations and needs of the person they are caring for [30]. ALMA is a questionnaire focusing on life events, preferences and emotional aspects relating to the participant. It allows the case manager to collect relevant information to set up the SENSE-GARDEN sessions, for example regarding family events, professional activities and hobbies, favourite scents, movies and music preferences, friends, pets, favourite places and tourist destinations, amongst others. The preparation of a session is very time consuming, requiring effort to collect and process the necessary media (e.g., photos may need to be digitalized, videos have to be edited, etc.).

In order to be able to optimally deliver the SENSE-GARDEN experience, the staff is requiremed to have:

- at least 6 months experience in working as a caregiver for people with dementia;
- at least one formal training in these aspects: working with people with dementia, gerontopsychology, reminiscence therapy for elderly, and/or multisensory stimulation for people with dementia;
- knowledge and practical experience regarding physical therapy (exercise) for older people (with and without cognitive challenges) with frailty syndrome;
- high levels of respect and empathy for elderly;
- high levels of creativity as well as clinical reasoning in designing the user profile, the activities, the workflows and the sessions.

The steps for planning a SENSE-GARDEN therapeutic session are:
1. media-content gathering;
2. creating and preparing workflows (media sequences);
3. establishing back-up media-content/ solutions to provide the SENSE-GARDEN session to the user/ patient;
4. preparing the environment, the SENSE-GARDEN room;
5. beginning/ containing and ending the SENSE-GARDEN session - ambient music and fragrance adapted to the personal preferences of the patient and also, to the personalised media-content prepared by the therapist and displayed on the selected devices by the technical manager;
6. obtaining feedback from the user/ patient.

THE SENSE-GARDEN BENEFITS
One of the special outcomes of our study is the improvement of engagement of the participants, as well as the improvement of related parameters, during and after the intervention program. Engagement in social activities is proved as beneficial in preventing or delaying cognitive impairment and assessing engagement and participation provide important insight regarding the effectiveness of an intervention [31]. Engagement is a

multifactorial, global measure and engagement level influences affect, behaviour, and image of self [32]. Social disengagement is a predictor of the risk of cognitive decline and of a lower level of QoL [33]. Mood decline is one of the most potent predictors of decrease of engagement, pushing also the decline of cognitive functioning [34].

An important, but unquantified, effect of the intervention program in SENSE-GARDEN was noticed by the family caregivers in regards to daily life behaviour: improved initiative and increased ability to finalise tasks, to start and sustain communication with family and strangers (even offering voluntary support for different tasks), a better capacity of organising things, a higher level of involvement in family life, and improved space and time orientation. This may be due to the active presence of a therapist during the intervention and to their ability to engage the participants in communication and activities, along with family members, when possible. The active involvement of a younger generation in reminiscence therapy increases the pleasure and engagement of the older person, if common interest is elicited by the items used, and the creation of a library of photos for reminiscence therapy is useful [35].

The positive results of the intervention program are possibly linked to two important factors. On the one hand, the highly personalised nature of the experience, with the use of personal sensory and emotional memory triggers based on each participant's life history. On the other hand, they could be due to the attentive, empathic, and compassionate involvement of a staff member (in the case of our study, a clinical psychologist who acted as case manager for all participants). Nonetheless, the cognitive flow of the whole experience may have benefits on its own, too. Participants were provided with concrete, well-adapted, realistic objectives and simple and intuitive rules. They were engaged in the smooth and well conducted flow of the experience, without distractions and providing important and meaningful stimuli for senses, mind and emotion. These conferred to the SENSE-GARDEN intervention the qualities of a dynamic, personalised and serious game. Tasks' content, intensity and difficulty were adapted to elicit all cognitive functions. The interactivity and the palette of experiences was designed and managed to avoid boredom and disengagement, while optimally stimulating the active participation of the user, which is beneficial, as most previous research shows [23].

The multimodal intervention applied by means of an ICT based intervention is in line with the 2020 recommendations of the Lancet Commission [36] regarding dementia care: (i) the need for holistic post-diagnostic care addressing physical and mental health, social care, and support, and (ii) the use of specific multicomponent interventions as treatments of choice, which represent valuable alternatives to pharmacological interventions for the improvement of the behavioural symptoms. This approach is also in line with the conclusion of the systematic review conducted by Chalfont [37] on multimodal interventions for patients with major neurocognitive disorder: multimodal non-pharmacological interventions can complement singular therapeutic approaches and provide important improvements as they address multiple modifiable risk factors currently understood to influence cognitive decline. Further research is, however, required to offer insight into the mechanisms through which such a multimodal approach provides benefits.

There is a growing number of studies suggesting that physical activity and exercise have positive effects on cognitive function of the elderly [38; 39]. Indeed, greater balance and gait disturbances have been found in people with dementia when compared with older people in general [40;

41] and these have been shown to occur in relatively early stages of the dementia pathway [42]. These declines in balance and motor performance may explain the increased incidence of falls in people with dementia, and have been shown to be a predictive factor for people with dementia needing permanent skilled nursing facility admission [43]. The main reason for the relationship between cognitive function and balance function might be the structural or functional change of the brain. Recently, it was reported that hippocampal volume is associated with maintaining upright posture and balance [44; 45]. Reduced grey matter volume has been found to be related not only to cognitive decline, but also to postural instability [46]. Studies indicate that aerobic exercise and balance training are beneficial for people with dementia, reducing the risk of falling, improving their physical and psycho-cognitive condition, with all subsequent beneficial consequences, including improving the domains "Activities" and "Participation" of the ICF [47; 48; 49]. Importantly, a systematic review [50] showed a positive relation between exercise and improvement in overall cognitive function (operationalised as improvement in MMSE and ADAS-Cog scores). In their review, Mandolesi [51] concluded that physical exercise determines positive biological and psychological effects on the brain and on the cognitive function. Recently, Machado et al suggested that physical exercise is an important neuroprotective modulator, controlling the disease and amplifying significant brain functions. Gallaway et al [52] proposed several potential mechanisms for this, as physical activity can increase blood flow to the brain, improve sleep quality, improve cardiovascular and metabolic status, prevent and treat depression. It has been reported that the combination of aerobic exercise, balance training, cognitive training, the Mediterranean diet and social commitment could reduce the risk of

further cognitive impairment and may improve cognition, mobility, balance and QoL in people with MCI [53]. The parameters of physiotherapy interventions cannot be precisely defined, but it is recognized that aerobic exercise that is intense enough to cause an increase in heart rate and oxygen consumption will be effective if sustained for a period of time (i.e., 20-30 minutes per session and administered repeatedly) [54].

The SENSE-GARDEN technology enables the therapist to create a personal profile of the primary user by uploading processed personal media content, preferred general media content and culture-specific triggers. Based on the triggers, on the Sensory Profile, on the emotional status and reactivity and on the results of the assessment of cognitive functioning, by means of the Clinical Dementia Rating Scale and Mini-Cog assessment tools, as well by clinical interview, personal workflows are created, providing users with activities and experiences adapted to the patient's level of cognitive impairment and disability. This adaptation is regarding the image and sound complexity, task difficulty, the number and features of sensory modalities that are applied simultaneously. A specific workflow is chosen for a specific session by the therapist, by considering the mood and reality orientation of the participant before the session. During the session, workflow activities are conducted and changed by the therapist, while the tasks are adapted in terms of complexity and duration in accordance with the moment's requirements, for a better and more beneficial experience.

The space can contribute to the effectiveness of therapeutic conduct dedicated to people with neurocognitive disorders if it is designed on dementia-friendly principles [55]. In this sense, the dimensions, and proportions of the space and the way in which architectural instruments such as light, shape, colour, sound texture are used are important [13].

A therapeutic space such as the SENSE-GARDEN from Elias Hospital relies on chromatic and design neutrality to enable and to enhance the user experience [20]. Basically, the architectural instruments were combined with the technology in such a way that led to the achievement of a balanced and agreeable proportion between the physical and digital aspects.

A similar approach regarding the design of the intervention to the one in the present study was used in a study published in 2017. Cognitive training, cognitive stimulation, reality orientation, physical therapy, reminiscence therapy and music therapy were applied in what was named Multimodal Cognitive Enhancement Therapy (MCET) in older people with major and mild NCDs. The study, a cross-over (2 periods of 8 weeks separated by 4-week wash-out phase) multicentric double-blind randomised controlled trial, resulted in significant improvement in MMSE score (effect size 0.47), QoL score and behaviour. The MCET was shown to be more efficient than conventional cognitive enhancing activities [56].

In conclusion, after taking part in the SENSE-GARDEN sessions, important improvements were documented in the participants' cognitive and physical functioning, as well as in their emotional condition, behaviour and QoL. However, this is only a starting point in understanding the effectiveness of this intervention, and of the non-pharmacological treatments as a whole. The positive results noticed in the SENSE-GARDEN participants could be explained by some other factors as well, such as the caring nature of the staff or the flow of the experience (regardless of its specificic activity), therefore more evidence is needed to disentangle the effects of the intervention from the effects of any covariates. Another point to consider is that there is no knowldege on whether the observed effects are lasting in the long-term or not. Therefore, in order to be able to draw more precise conclusions on the effectiveness of the intervention, more research is needed. These scientific efforts could lead to ensuring a better life for the older adults living with major neurocognitive disorders.

Conflicts of interest
The authors declare no conflicts of interest.

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DOES SOCIAL SUPPORT MODERATE THE RELATIONSHIP BETWEEN TRAUMA AND THE QUALITY OF LIFE OF OLDER ADULTS?

*Florentina **Nicolescu**[1,2]*, Luxiţa **Băra**[1], Diana-Lucia **Vasile**[1,2], Rozeta **Drăghici**[2,3], Alexandra **Rusu**[3]**

[1]*Institute for the Trauma Study and Treatment, Bucharest*
[2]*University of Bucharest, Faculty of Psychology and Educational Sciences*
[3]*"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest*

Corresponding Authors*: Florentina Nicolescu, florentina_nicolescu@yahoo.com; Alexandra Rusu, alexa0alexandra@gmail.com

Abstract. The issue regarding improving one's wellbeing and quality of life represents a special challenge for the assisted resilience practices targeting the older adult population. Thus, the present study had the main objective of identifying the type of relationship between having gone through traumatic events and one's quality of life when looking at older adults aged 65 and over. A second objective was to investigate to whether or not social support is moderating this relationship. The participants (N=115) were selected from the patients admitted to the "Ana Aslan" National Institute of Gerontology and Geriatrics during the study period and were asked to fill out the Traumatic Experiences Evaluation Inventory, the Quality of Life Scale (WHOQOL-AGE) and the Multidimensional Scale of Perceived Social Support (MSPSS). The regression results showed that one's traumatic experiences are significantly and negatively predicting one's quality of life levels. Social support was not found to be a significant variable, however, the findings have shown that very low and very high levels of social support significantly and negatively influenced the relationship between traumatic experiences and quality of life. As a result, traumatic experiences are a significant predictor of quality of life, and this relationship has a tendency towards worsening at the two extreme levels of perceived social support. Future research will benefit both from testing the mechanisms underlying these results and from investigating what other resilience factors could be responsible for the relationship between traumatic experiences and quality of life.
Key words: quality of life, traumatic experiences, social support, older adults

Rezumat. Problematica creşterii bunăstării şi a calităţii vieţii în contextul populaţiei vârstnice cu istoric traumatic este o provocare specială pentru rezilienţa asistată. Obiectivul acestui studiu a fost acela de a identifica tipul de relaţie existentă între evenimentele traumatice şi calitatea vieţii, la persoanele de peste 65 de ani, cât şi dacă această relaţie este moderată de suportul social. Participanţii (N=115) au fost selectaţi dintre pacienţii internaţi în perioada efectuării studiului la Institutul Naţional de Gerontologie şi Geriatrie „Ana Aslan" şi au fost rugaţi să completeze Inventarul pentru Evaluarea Experienţelor Traumatice, Scala de Calitate a Vieţii (WHOQOL-AGE) şi Scala Multidimensională a Suportului Social Perceput (MSPSS). Rezultatele obţinute din analiza de regresie au arătat că experienţele traumatice prezic în mod semnificativ şi negativ calitatea vieţii. Suportul social nu a moderat semnificativ relaţia dintre parcurgerea experienţelor adverse de pierdere şi calitatea vieţii. Cu toate acestea, rezultatele au arătat faptul că atât la niveluri foarte scăzute, cât şi la niveluri foarte ridicate ale suportului social există un efect moderator semnificativ şi negativ. Drept urmare, experienţele traumatice sunt un predictor semnificativ al calităţii vieţii, iar această relaţie tinde să se înrăutăţească la nivelurile extreme ale suportului social. Studiile viitoare ar beneficia din a testa motivul pentru care aceste rezultate apar, cât şi din a investiga ce alţi factori de rezilienţă ar putea explica relaţia dintre experienţele traumatice şi calitatea vieţii.
Cuvinte cheie: calitatea vieţii, evenimente traumatice, suport social, persoane vârstnice

INTRODUCTION

When talking about the ageing process, all the transformations and progressive losses that occur with growing old are the ones that come to mind. In this process, people start to experience a wide range of negative, uncontrollable and mostly irrevocable changes, such as reductions in functional capacities, in memory, in income, in social relations due to

retirement, as well as the loss of one's professional status, the occurrence of certain age-related diseases that reduce the ability to function normally as well as losing loved ones. In this context, one's resources have to be allocated to managing the losses and to constantly adapting to the new circumstances. The adaptive coping mechanisms must be stimulated and strengthened.

While one's social support and quality of life have benefited from increased attention in the extant literature on the psychological issues of older adults, the results cannot easily be extrapolated to all populations. This is because social relations are highly dependant on the cultural context and structure of a given society [1]. Therefore, the aim of present study is to investigate the relationship between past traumatic experiences and the quality of life of Romanian older adults aged 65 and over, while also testing for the potential moderating effect of social support on this relationship.

Given the theorising of Hobfoll and Ionescu [2], there are two resources that researchers should consider when looking at older adults: a strong feeling of self-efficacy and a high quality social support system. The former refers to the internal resources of having an optimistic attitude towards one's existence and a positive perspective of the future and of the opportunities to grow regardless of one's age. The latter regards the external resources of having both an emotional and material support from others as well as a feeling of belonging to a group. These resources work interdependently and are very useful for an effective adaptation in the face of adversity.

One's social capital with all its components (i.e., trust, feeling of belongingness and social participation) as well as the social support (with its emotional, instrumental and informal dimensions) have a direct effect on one's health [3]. Moreover, these are as important as one's physical health in preventing psychological stress, in disease prevention and health promotion. The loss of the optimal functionality of various organs, and the reduction or loss of certain senses such as vision and hearing lead to social isolation. Therefore, these deficiencies become an added stress factor which decreases the received social support while increasing the older adults' loneliness and psychologicalo stress [4].

As a result, both the lack of social support and the somatic health issues must be approached when promoting mental health among the older adults, because both of these factors are important risk factors of psychological distress. Physical deficiencies contribute to a reduction in social support to a higher extent than one's diagnosis which is why this is an issue pertaining to the societal interest [4]. Social interactions can not only stop the functional decline, but they can also help in recovering some of the lost functions. For example, strong social networks and social support have been shown to be connected to improvements in cognitive function. Moreover, those who reported strong social networks are also evaluated to have a lower mortality and morbidity risk [5]. Thus, when looking at older adults, it is important to ensure a good maintainance of one's levels of physical and psychological activities, of one's functional integrity as well as a consolidation of one's received social support, which is also due to the relationship between one's functional health and one's quality of life.

A favorable exchange with the proximal social environment has positive effects on one's mintal health and wellbeing when this support is high in quality and adapted to one's needs [6]. In older age, a good quality of life and wellebing are defined through the positive perceptions of a good health and functional ability, of the feeling of personal adequacy and utility, of social participation, of good family relations, of the availability of friends and of the received social and economic support. For

example, Zaninotto et al. [as cited in 7], conducted a study on 11.392 older adults aged 65 and over and found that a small number of friends and a lowly perceived social support predicted lower levels of quality of life. The study highlighted the important influence of four factors: health, socio-economical circumstances, psycho-social circumstances and demographic characteristics. The negative predictors were: the limitations imposed by long-term illnesses, the presence of depression, any functional limitations, a lack of mobility and the difficulty in completing daily activities. The socio-economic predictors with a positive influence were: having access to a car, higher income, owning the place they live in, higher educational levels. The positive psychosocial predictors were: the size of one's social network, having trusting relationships with one's family and friends and having a higher number of friends. Thus, an increase in resilience and a decrease in depression could be estimated to have the same levels of success in increasing the quality of life as it would be the case with the reduction of physical disabilities, which makes these variables noteworthy for all medical specialties [7].

An important challenge to increasing the wellbeing and quality of life of older adults is posed by the potential history of traumatic events. In his papers, Dr. Peter A. Levine spoke about trauma over time, about the experiences of people who have been haunted by memories that filled them with fear and horror, with anger, hatred and vengefulness and with the overbearing feeling of having suffered a loss beyond repair [8]. According to DSM-5, trauma and stress related disorders include among others, the reactive attachment disorder, the uninhibited social behaviour disorder, the post-traumatic stress disorder (PTSD), and adaptive disorders [9]. The psychological stress resulting from being exposed to a stressful and/or traumatic event varies from person to person and in some cases, the symptoms can be explained by the context that is eliciting fear or anxiety. These symptoms are the varied expressions of the psychological suffering caused by having gone through catastrophic events [9]. The concept of psychological trauma refers to an event that people cannot make sense of by using their existing psychological capacities, and even normal stress reactions aimed to help in facing adversities become dangerous in the context of a traumatic situation [10].

In conclusion, the quality of life for older adults is characterised by sudden deteriorations, while the individual differences responsible for adapting to the new circumstances are substantial and they are not yet fully understood [11]. Social orientation and involvement can provide further explanations that can go beyond the usual considerations of the health predictors [12]. This is because it has been shown that an active social life during old age is associated with a better wellbeing, with a less steep end-of-life decline and with a delayed onset of terminal decline [11]. For example, older adults that are involved in useful activities (e.g., volunteering, gardening, house chores, social activities) have a higher likelihood to be happy, to function well physically and cognitively, to live longer [13], to show fewer signs of depression [14] and more signs of positive affect [15]. An important role in developing a strong resilience is also played by previous traumatic experiences. The present study will thus attempt to integrate the variables of traumatic experiences, quality of life and social support in a model that might explain the mechanims underlying the previous findings. The first objective is to test whether having gone through any traumatic experiences in the past 5 years can predict older adults' quality of life, while the second objective is to investigate whether social support moderates this relationship. Based on previous research, it can be expected that (i) past traumatic experiences can significantly predict

quality of life (H1) and that (ii) social support is a significant moderator of this relationship (H2).

METHODS
Participants
The study included 115 patients aged between 65 and 94 ($M = 73.87$, $SD = 6.84$; 80 females) admitted to the Central Headquarters of the "Ana Aslan" National Institute of Gerontology and Geriatrics. Based on educational level, participants were distributed as follows: 36% completed 8 years of education, 17% completed 10 years, 27% finished high school and 20% had reported having an upper level education. Those participants who were diagnosed with a severe mental illness or with psychotic elements, with neurocognitive disorders, with severe sensitive deficits or who had a lack of discernment and/or who reported using substances were excluded from the study.
Data collection took place between March and April 2019 through Google Forms. Participants could fill in the questionnaires either on their own or with the help of the researcher. Informed consent was provided before the study commenced. All participants who started the study completed it in full, no particular incidents were reported and no reward was offered for participation. Ethical approval was offered by the Institute's Ethics Committee.
Measures
  * *Quality of life*
In order to measure participants' quality of life the WHOQOL-AGE questionnaire developed by World Health Organisation (WHO) was used. This instrument was adapted for older adults, and it is the shortest questionnaire aut of the QOLs developed by WHO. It consists of 13 positive items, out of which 8 were derived from EUROHIS-QOL and 5 from WHOQOL-OLD [16].
  * *Social support*
The Multidimensional Scale of Perceived Social Support (MSPSS) is a brief research instrument developed to measure

participants' perceived social support from 3 sources: family, friends and other significant people. The scale has 12 items grouped in 3 factors: support received from close ones ("There is a special someone next to me when I need one.", " There is someone I can share my joys and sorrows with."), from one's family ("My family is really trying to help me.", "I receive emotional support and help from my family.") and from one's friends ("My friends are really trying to help me.", "I can count on my friends when things don't work out the way they should."). Each item was scored on a 7-point Likert scale (where 1 = strongly disagree, 7 = strongly agree). The scale showed good levels of reliability with a Cronbach's α of .88 [17].
  * *Traumatic experiences*
The traumatic experiences evaluation inventory was used. This is an experimental questionnaire in process of development and it is part of a larger investigation on the effects of traumatic or stressful events on people. In this investigation, the inventory was administered in combination with other scales. The inventory consists of 18 items, but for the present research only the items pertaining to older adults were used. Examples of traumatic experiences are: losing one's partner, losing any other loved one, accidents, terminal illness, physical and/or psychological abuse, calamities, losing significant possessions, and others.
Procedure
The selected participants were first briefed on the purposes of the study, without giving away the hypotheses. No deception was necessary. Then, they were asked to sign a consent form after which the study started. The questionnaires they filled out were given in the order of traumatic experiences inventory, MSPSS and WHOQOL-AGE. One session lasted approximately 45 minutes.
Design and analysis
The demographic variables of age (i.e., continuous), gender (i.e., categorical) and marital status (i.e., categorical) were

collected in order to be included in the analyses as confounding variables. The outcome variable was the participants' quality of life ratings, which was a continuous variable. The traumatic events (in the 5 years prior to the study) and the social support, both continuous variables, were treated as predictors, with the social support variable being included as a moderator variable as well. A correlational design was used, and regression models were run tot test the hypotheses. The PROCESS 3.0 extension [18] will be used to test for the moderating effect of social support.

RESULTS

Table I depicts both the descriptive statistics for the variables included in the study, and the zero-order correlations between them.

Tab. I Descriptive statistics and zero-order correlations

	M	*SD*	TExp	QoL	Support	SC	Fam	Fr
TExp	1.39	0.79	-					
QoL	50.11	7.85	-.41***	-				
Support	74.87	15.62	.01	.30**	-			
SC	25.85	3.40	-.11	.31**	.47***	-		
Fam	27.92	11.13	.13	.17	.78***	.22*	-	
Fr	21.10	8.26	-.11	.21*	.62***	.19*	.07	-

Notes. *p < .01; **p < .01; ***p < .001
TExp – traumatic experiences, QoL – quality of life, Support – social support, SC – support from close ones, Fam – family support, Fr – friends' support

The regression model including traumatic experiences as a predictor and quality of life as the outcome was staistically significant ($F(3,111) = 7.56$, $p < .001$), explaining 17% of the variance in quality of life. There is a significant and positive relationship between past traumatic experiences and quality of life ($\beta=0.41$, $p < .001$) which supports the first hypothesis of the study.

The model including the moderator showed that both past traumatic experiences ($\beta = -3.96$, t = -3.64, $p < .001$) and social support ($\beta = 0.14$, t = 3.40, $p < .001$) significantly predict quality of life. This means that the more traumatic experiences one's had and the less social support one's received, the poorer one's quality of life will be. Social support was not found to significantly moderate the relationship between the past traumatic experiences and quality of life ($\beta = 0.05$, t = 1.28, $p > .050$). Therefore, the second hypothesis of the study was disconfirmed.

Tab. II Percentage of responses to the MSPSS questionnaire

MSPSS Items	Min.	Max.
There is a special one near me when I need support.	0,8	82,6%
There is a special person that I can share my joys and sorrows with.	0,8	79,1%
My family is really trying to help me.	0	68,6%
I receive the emotional help and support I need from my family.	0	60,8%
In my life there is a special person that is a true source of relief for me.	0,8	71,3%
My friends are really trying to help me.	1,7	18,2%
I can count on my friends when things get rough.	6%	(20 %
I can talk to my family about my problems.	0,8	71,3%
I have friends with whom I can share my joys and sorrows.	4,3%	21,7%
There is a special one in my life who cares about my feelings.	0.8	58,2%
My family is willing to help me make decisions.	0,8	65,2%
I can talk with my friends about my problems.	6,9%	15,6%

Notes. 0% = no response, 0.8% = 1 response, 1.7% = 2 responses, 4.3% = 5 responses, 6% = 7 responses, 6.9% = 8 responses.

Table II depicts the percentage of responses for each MSPSS question, while Table III shows the distribution of traumatic experiences in the sample divided by gender. The maximum values for the participants' level of satisfaction with their quality of life were recorded as follows: 80.8% for the overall evaluation considering the 2-week prior period; 80.8% for the self-evaluation; 76.5% for the evaluation of one's capability to complete daily activities; 84.3% when evaluating personal relationships; 98% for the evaluation of satisfaction with the living conditions; 76.5% for the control over desired things; 70.4% for financial satisfaction; 49% for intimate relations.

Tab. III Number of traumatic experiences per gender

	0	1	2	3	4	Total
Men	3	29	3	0	0	35
Women	4	40	22	12	1	79
Total	7	69	25	12	1	114

The analysis further shows that at very low levels of social support ($\beta = -4.72$, t = -3.67, $p < .001$), as well as at very high levels ($\beta = -3.20$, t = -2.67, $p < .010$), social support significantly influences the relationship between traumatic experiences and quality of life. This shows that social support has deterring effects on the already negative effects of past traumatic experiences and quality of life, indicating that too little, but also too much social support can be maladaptive.

DISCUSSIONS AND CONCLUSIONS
The aim of the present research was to investigate the relationship between the traumatic experiences from the past 5 years and participants' quality of life in a sample of older adults aged 65 years and over. The first hypothesis of the study depicting a significant relationship between traumatic experiences and quality of life was supported by the results. The first regression model showed a positive relatinship between the variables, while the model that included the moderator resulted in a negative relationship between traumatic experiences and quality of life (as expected). It remains unclear why this difference occured. The second hypothesis of the study was not supported by the findings, as social support was not found to significantly moderate the relationship between the key variables of the study.

However, very low and very high levels of social support have been found to negatively influence the relationship between traumatic experiences and quality of life.
The results of the study are raising different issues. First, important factors for resilience other than social support can be investigated in future research, while a special focus can be given to furthering the understanding of the already included variables. Second, a different statistical moderation or even mediation model can be used to understand the mechanisms underlying the found relationships. Moreover, looking at these relationships longitudinally is a worthwhile effort, given the temporal difference between past trauma and present quality of life. Instruments tailored to better identify the factors are needed, given that complex factors, that are specific to one's condition and/or illness significantly impact the post-trauma quality of life [19]. Such factors can be: one's physical and emotional wellbeing, one's functional involvement, the recovery/resilience process, the peri-traumatic experience [19]. One's self-esteem, financial resources, cognitive capacities and so on can be added to the list. Therefore, the resources aiding in obtaining a good level of resilience are numerous and can be individual or

environmental, elementary or composed, distal or proximal [2].

Third, it is interesting that social support overall was not found to moderate the link between past traumatic experiences and quality of life in a statistically significant way, but at its extremes it was found to be an influencing and negative factor. It is true that the majority of the existing studies on the role that social support plays in human resilience processes are correlational and, therefore, there is no possibility for causal inference indicating that social support is either a protective or a risk factor. Furthermore, these findings cannot indicate whether trauma survivors are simply better at developping and maintaining an increased social functioning [20].

However, the results of the present paper can be explained by the scientific literature. Social support does not represent a universal and unequivocal type of support, therefore its effectiveness can vary significantly by the circumstances during which that support is received, as well as its quality. For example, when looking at traumatic stress, the effectiveness of the social support is highly dependant on the links between its source, its kind and the time when it is offered on one hand, and the needs of the individual as well as their or the system's level of development on the other [21]. As a result, offering social support at a time when it is not in line with the needs of the individual will not be effective or perceived as helpful [21]. In fact, social support can be counterproductive and/or maladaptive especially if it is unsolicited, excessive or misaligned to one's needs [22]. Almedom [23] found that cognitive support is perceived as most helpful when the individual is ready to receive it and actually asks for it, but not when it was unsolicited. Thus, designing a study with all these aspects in mind and with instruments better aimed at measuring the objective effectiveness of the received social support can yeild a better understanding of the interesting effects found in the present paper.

This study does not however come without limitations. First, it is unclear why the first statistical model has shown a positive relationship between traumatic experiences and quality of life, relationship that changes in its value sign in the moderating analyses. This can be caused by a methodological flaw that was not found, therefore the results should be interpreted with ease. Second, the study has a correlational design, therefore causation cannot be implied. Third, it is possible that the lack of statistical significance of the moderating effect of social support stems from a lack of power, as the sample size was likely not sufficient for finding an interaction effect.

In conclusion, when considering the psychological health of older adults aged 65 years and over, it is important to investigate the consequences that traumatic life events have on their perceived quality of life. This study has shown a negative relationship between traumatic experiences and quality of life, and a positive one between the received social support and one's quality of life. However, a moderating effect of social support was not found. Interestingly, at very low and at very high levels of social support, a moderating and negative effect was indeed found. This can be explained by the fact that sometimes too much social support can have deterring effects if it is unsolicited or misaligned to the needs of the receiver. It is true that the present study came with limitations, and so, future research can benefit by aiming to replicate the present results and also, by looking at other resilience factors as well. This should be done in the hopes of disentangling the underlying mechanisms that either protect or place at risk the trauma survivor's quality of life.

Conflicts of interest

The authors declare no conflicts of interest.

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THE RISE OF A NEW HOPE: THE EFFECTIVENESS OF VIRTUAL REALITY TECHNOLOGY FOR ELDERLY CARE

*Andrada-Elena **Stan***

Sociology Department, University of Utrecht, Utrecht, The Netherlands

Corresponding Author: Andrada-Elena Stan, research.psycho.logy13@gmail.com

Abstract. With the new advances in technology, there is plenty of room for renewing the therapeutical approaches made available to the public, and, in the case of this paper, to the geriatric population. Previous studies have shown Virtual Reality (VR) technology to be effective in increasing the levels of physical activity, and in improving one's wellbeing and cognitive functions. This is the case for both healthy participants, and for those with cognitive disorders (such as dementia). One aim of the present commentary is to discuss the available literature on how VR aids cognitive functions and wellbeing in the geriatric population. Another aim is to discuss the effectiveness of this technology as a therapeutic approach for complicated grief, a newly introduced disorder with no established treatment. Last, the commentary will bring forth different issues that the implementation of the VR technology may face, as well as different avenues for future research.
Key words: technology, virtual reality, older adults, grief

Rezumat. Avansarea tehnologiei extinde oportunitățile de înnoire a metodelor terapeutice oferite atât publicului larg, cât și, în cazul acestei lucrări, populației geriatrice. Studiile anterioare au arătat că tehnologia de tip Realitate Virtuală (VR) este eficientă în creșterea nivelului de activitate fizică și în îmbunătățirea stării de bine și a funcțiilor cognitive. Acestea sunt valabile atât pentru participanții sănătoși, cât și pentru cei cu disfuncții cognitive (cum este cazul demenței). Unul dintre scopurile acestui comentariu este de a discuta literatura științifică existentă pe tema modului în care tehnologia VR vine în sprijinul populației geriatrice din perspectiva stării de bine și a funcțiilor cognitive. Un alt scop este de a dezbate eficiența acestei tehnologii ca modalitate terapeutică pentru doliul complicat, o patologie nou introdusă care nu are încă un tratament bine stabilit. În final, comentariul va prezenta atât unele dintre potențialele probleme legate de implementarea tehnologiei VR, cât și diferite direcții pentru cercetările viitoare.
Cuvinte cheie: tehnologie, realitate virtuală, vârstnici, doliu

INTRODUCTION

The technological advances brought by the 21st Century have changed the way researchers look at and think about therapeutic practices for all age ranges, but notably for helping the elderly improve their quality of life. With its increase in affordability, Virtual Reality (VR) has been more and more integrated in studies investigating the prevention of the age-related cognitive decline [1, 2, 3] and the treatment of different pathologies such as post-traumatic stress disorder and complicated grief [2, 4]. However, research in this area is still scarce, replications are missing, while the barriers to potential implementation of VR in healthcare systems need to be considered from a policy standpoint. Thus, the aim of the present commentary is to discuss the existing research on the effectiveness of VR in different health areas, while considering the potential obstacles of introducing this technology to the existing healthcare system.

Cognitive training

A first applicability of VR is its use for cognitive training in order to promote healthy ageing in the attempt to prevent (or at least delay) health issues such as dementia [1]. In their review of the benefits of VR for cognitive training, Bauer and Andringa [1] explained that multisensory integration of information is essential for effective learning, especially if accompanied by movement. VR is offering such a possibility for learning due to its immersiveness (through the head-mounted display), while encouraging movement in a safe environment (tracked by the equipment's sensors).

Eisapour et al. [3] looked at three patients with Mild Cognitive Impairment (MCI) and showed that for the elderly, physical exercise is very important in sustaining their wellbeing and cognitive functions. Precisely, exercise was associated with increased fitness, physical functioning, cognitive functioning and positivity in

behaviour [3]. Specifically looking at the cognitive functions, Bauer and Andringa [1] discussed a series of studies investigating learning through VR. Results showed that VR activities/training did increase the amount of learned material. However, the samples used in these studies consisted of university students. The reported studies that also included an elderly participant sample had more mixed results. This leads to two important conclusions: on one hand, more research needs to be done on the learning effectiveness of VR for the elderly and, on the other hand, this should be done consistently.

VR's benefits for improving this vulnerable group's quality of life

From the existing literature on this topic, D'Cunha et al. [2] report an important idea, which is the potential benefit of using VR for elderly with MCI and with dementia (i.e., people living with dementia, PLWD). Since this demographic tends to be socially isolated [5, 6], and since social isolation is positively related to cognitive decline and negatively associated to one's quality of life (QoL) [2]), the characteristics of VR are promising. VR represents an effective way to combat social isolation, by creating the opportunity to socialise with others (real or not) and by engaging patients in cognitive training and in emotionally calming experiences [2, 7]. These latter experiences are of high importance for PLWD who experience a high degree of stress, anxiety and confusion. Moreover, social isolation can be removed even further by adding a touristic feature to the VR experience (i.e. depicting different parts of the world/ museums). This technology can also be utilised to stimulate memory functions [2], which makes it of particular interest for PLWD since through this training, they can regain some level of control over their lives. With this increased level of independence, the elderly's quality of life is also enhanced.

In their study, Guerrero et al. [8] implemented intelligent assistive systems (IASs) in order to help the elderly with their medication intake. This was done in an Augmented Reality (AR), rather than VR environment and it only had a sample of three. The results show that efforts targeting the implementation of this technology are worthwhile, however the

research is in its incipient stage and technical difficulties still pose great obstacles.

There are however, VR projects in place that can help sustain a good quality of life for the elderly which have surpassed these issues (i.e., SENSE-GARDEN) [2, 9]. The benefits of such an equipment is that the patient can communicate, engage in physical activity and in cognitive training, within the comfort of their own homes while supervised by their careers.

VR can also be used as a therapeutic approach in helping people recover from stroke [10, 11], which is possible both by entering patients in a virtual environment, and by asking them to use VR while playing computer games [10]. Living with chronic pain, and even with those types of pain that come with normal ageing is an unpleasant experience, therefore another quality of life benefit from using VR is that it can produce analgesic effects [11]. Therefore, this technology is a tool that can help overcome the burden of different disorders and illnesses, with the possibility to fully recover from them.

A specific example: VR and treating complicated grief

Complicated grief (CG) is a (relatively) newly introduced disorder that exhibits a symptomatology similar to post-traumatic stress and major depressive disorders, without being responsive to the same treatments as these latter ones [12-14]. It occurs when one cannot adapt to the loss of a loved person even after a long period of time has passed since the death event (usually, the time threshold is 6 months after the event, but this limit can change based on the griever's cultural, religious and normative background) [13]. This condition provokes significant impairments to the griever's life on personal, social and work levels, with a significant impact on their physical and mental health [15, 16].

The younger population has been considered at higher risk of developing CG since for them the death event comes more unexpectedly [17]. However, the elderly can also be at high risk of developing it, because they have a higher likelihood of experiencing the deaths of multiple loved ones during their lives [12]. Indeed, this is very much possible: when looking at the

prevalence of CG in adult bereavement, Lundorff et al. [13] have found that the elderly could be placed at higher risk ("could" is being used since their mediation analyses were borderline, therefore not rigorously statistically significant). The authors explain that this could be due to a more precarious health condition on one hand, and due to a loss of social support on the other. Additionally, the Covid-19 pandemic could have also placed the elderly at higher risk of developing CG because of the isolation, health perils imposed on them by the virus, and because of not having a chance of conducting the usual rituals that help them say goodbye [13, 18].

Given the great impact CG is expected to have in these circumstances on the geriatric population, the remaining question is how to effectively treat it. As previous research has shown, CG is not responsive to pharmacological treatment, which would anyway be counter indicated for the geriatric population [13]. Exposure therapy has been shown to be effective in helping patients recover from anxiety and stress related disorders, such as phobias, post-traumatic stress disorder and other trauma related disorders [4, 18]. This is because it helps patients face their fears with an increased intensity in a controlled and monitored environment.

One way of delivering exposure therapy is through VR technology. Pizzoli et al. [18] described a Korean documentary entitled "I Met You", which depicted a mother interacting with the avatar of her lost daughter through VR experience. The mother expressed a sense of relief at the end of the interaction, however the authors warn clinicians about this practice as for some, it can be too sensitive. They recommend the careful development of standardised protocols by trauma experts in using VR exposure therapy of such strength. They also explained that the experience should be of incremental intensity (e.g., by starting with an interaction depicting an environment the deceased had in common with the griever) and should be tailored to each patient's experience, needs and sensitivities.

A first study that did this was conducted by Quero et al. [4]. The researchers screened for patients with adjustment disorders, in which they also included CG symptomatology. They then categorised patients into three groups: waiting list (i.e. control), traditional intervention and VR intervention (i.e., EMMA's World). They also investigated the effects of the intervention at 6 months and 12 months follow-ups. Results showed that both the traditional and VR interventions were beneficial for the patients even at 6 and 12 months after the experiment. Interestingly, at the 12-month follow-up, the VR group showed a higher level of recovery compared to the traditional intervention group. Therefore, a possible conclusion of this study is that both interventions are effective, but in the long-term, the VR one is of superior quality. Moreover, their descriptive statistics showed that more people preferred VR when compared to the traditional intervention.

Although these results are promising, Pizzoli et al.'s [18] worries that not everyone is suitable for or accepting of technological therapies cannot be dissipated just yet [4]. More research is indeed required, and clinicians need to properly design protocols and experiments in the search for an effective therapy. Nevertheless, given that this disorder has a different responsiveness to therapies for comorbid disorders and that it tends to precede more severe ones (like post-traumatic stress) [19], VR exposure therapy is a promising avenue that makes researcher's efforts towards finding a proper treatment worthwhile.

Implementation barriers and subjects for future research

Despite the evident benefits the new technology of VR can bring in the lab, there certainly are some barriers to systematically introducing it in healthcare facilities.

Both the elderly, and the healthcare personnel show signs of digital illiteracy, and it can be challenging to teach them how to use this new tool. New technology can seem scary to use and this could impair one's will to even try to learn. Fortunately, the elderly seem quite intrigued by the equipment and motivated to take part in activities that involve the VR method [1, 7, 20]. However, some patients might find the head-mounted display to be uncomfortable, aspect which should be considered.

Moreover, convincing the healthcare personnel to learn how to use VR can be challenging. They already face a high demanding, stressful job, some of them experiencing burnout [21]; therefore, they might meet the idea of an extra task with resistance. Institutions that would like to adopt this new technology should highlight the benefits of this new method based on the available literature, and explain how this is done in the patients' best interest.

However, a high level of immersiveness and realism is not always good. This is because on one hand, it can cause cybersickness and on the other hand, it can impair the learning of some patients. Cybersickness is represented by the same symptomatology as motion sickness and is evoked by the conflict between the visual input (i.e., seeing on the screen that one is supposed to be moving) and the vestibular input (i.e. the vestibular system telling that one is staying on the spot) [1, 22].

Some patients with dementia might have difficulty learning through a very immersive VR environment, because too much information is being conveyed at the same time [1]. This means that the VR experience needs to be tailored to the needs and characteristics of each individual. It is possible to do this, as the equipment supports the need for personalisation, however this might add weight to the already existing problem of digital illiteracy. Moreover, it makes it more difficult for designing a standardised research protocol required to enable replication across studies.

The need for replication of the existing results showing the effectiveness of VR as a therapeutic approach for the elderly is just one area of interest for future research. Another area is represented by the need to replicate such research that has been done on youth. Bauer and Andringa [1] described studies that found support for VR's alternative in cognitive training, but this research was conducted on university students. In terms of the elderly, the studies they reported in the review showed more mixed results, therefore scientific

efforts should be directed at investigating this age segment in more detail.

Furthermore, replication is not the only promising avenue for future studies, as there are also new areas of interest. One example is the focus on emotional salience. The emotional capabilities seem to be somewhat maintained in the later years and also across health groups (e.g., when looking at dementia versus healthy patients) [1, 23]; since this is a common denominator, it can more easily target the age segment in its entirety. At the same time, this salience is important in aiding learning, therefore it can help interventions aimed at cognitive training [1]. One specific emotion that can be enhanced is hope. As Hsieh [24] has shown, VR can be used to increase children's hope and pleasure levels; if this is replicated in an elderly sample, then specific therapies can be developed to help with cognitive training, but also with protection from psychological illnesses as well (such as complicated grief, depression etc.).

CONCLUSIONS

In conclusion, the now cost-effective VR technology brings up new avenues for therapeutic and research endeavours. It has been found to aid cognition through the multimodal sensory stimulation, effect found for both healthy elderly and for elderly with dementia. Moreover, it shows that it is worthwhile to target efforts at providing the elderly with VR equipment to promote and support active ageing. New possibilities arise, guiding research towards the development of effective VR-based treatments for stress related disorders, and for complicated grief. While it is true that the implementation of VR in a systematic way within the healthcare system can and will face barriers, the existing literature shows that efforts in overcoming these are worthwhile. With time, and with more research, the rise of the new hope represented by VR could become a much needed therapeutic practice, improving the wellbeing of those who came before us: our elderly.

Conflicts of interest
The authors declare no conflicts of interest.

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TITLUL ARTICOLULUI ȘI NUMELE AUTORILOR. Titlul manuscrisului (în limba engleză, precum și versiunea în limba română) trebuie să fie concis și descriptiv (maximum 12 cuvinte), format Times New Roman 12, majuscule, bold. Sub titlu se vor menționa prenumele și numele (bold) autorilor, fără titlu profesional și/sau științific precum și afilierea fiecărui autor, format Times New Roman 12 (italic). Afilierile autorilor vor fi specificate cu numere și nu cu simboluri (de ex. [1]„Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania, [2]„Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania). În situația în care toți autorii au avut contribuții egale la realizarea manuscrisului, ei vor fi menționați într-un subtitlu, în ordine alfabetică împreună cu adresele lor de e-mail. Numele autorului corespondent și adresa de e-mail vor fi menționate imediat după enumerarea afilierilor instituționale ale autorilor.

REZUMAT. După titlu și autori se va insera rezumatul în limba engleză, precum și versiunea în limba română, fiecare cu un număr maxim de 250 de cuvinte, format Times New Roman 12.

CUVINTELE CHEIE. În partea de jos a fiecărei versiuni a rezumatului se vor include 3 până la 5 cuvinte cheie.

SECȚIUNILE. Manuscrisele care prezintă rezultatele unor studii originale trebuie să conțină maximum 2500 de cuvinte și să fie organizate în următoarele secțiuni: Introducere, în care vor fi specificate clar obiectivele și ipotezele studiului; Materiale și Metode; Rezultate; Discuții; Concluzii. In secțiunea „Rezultate" vor fi incluse tabelele și figurile împreună cu titlurile și legendele lor.

FIGURI, TABELE ȘI IMAGINI. Figurile vor fi realizate cu un program statistic, cu titlul scris sub figură, format Times New Roman 10, iar pentru numerotare se vor utiliza cifre arabe. Titlul fiecărui tabel va fi scris deasupra, iar pentru numerotare se vor folosi cifre romane, format Times New Roman 10. Notele explicative vor fi în partea de jos a tabelului. Nu se acceptă repetarea rezultatelor din tabel prin grafice. Dacă sunt incluse imagini ale unor pacienți, este necesar consimțământul scris al pacientului pentru difuzare publică sau pacientul trebuie să fie neidentificabil.

EXPRIMAREA MULȚUMIRILOR. Vor fi menționate înaintea secțiunii „Bibliografie", utilizând maximum 30 de cuvinte. Se pot exprima mulțumiri pentru sprijinul acordat în desfășurarea proiectelor de cercetare.

CONFLICTUL DE INTERESE. Va fi menționat înaintea secțiunii „Bibliografie".

BIBLIOGRAFIA. Referințele trebuie numerotate în ordinea inserării lor în text, între paranteze drepte, folosind cifre arabe (de ex. [1]; [1,3,8]; [9-12]). Bibliografia va cuprinde maximum 30 de titluri reprezentând articole publicate recent (în ultimii 10 ani). Se acceptă articole mai vechi dacă prezintă importanță deosebită în domeniul respectiv. Titlurile bibliografice se vor ordona în funcție de apariția în text. La fiecare lucrare vor fi menționați doar primii trei autori urmați de et al.

Citarea articolelor se face după următorul model:

Pentru articole din revistele științifice: Shapiro A.M.J., Lakey J.R.T., Ryan E.A., et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N. Engl. J. Med., 2000, vol. 343, 4: 230-238.

Pentru articole în format electronic: Niki E. Role of vitaminE as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence, Free Radical Biology and Medicine, 2014, 66: 3–12. http://dx.doi.org/10.1016/j.freeradbiomed. 2013.03.02223557727.

Pentru capitol sau subcapitole din monografii sau tratate: Goadsby P. J. Pathophysiology of headache. In: S. D. Silberstein, R.B. Lipton and D. J. Dalessio (Eds.), Wolff´s headache and other head pain, 7th ed., 2001, Oxford, England: Oxford University Press, pp. 57-72.

Pentru articole prezentate la conferințe: Brown S. & Caste V. Integrated obstacle detection framework. Paper presented at the IEEE Intelligent Vehicles Symposium, May 2004, Detroit, MI.

Pentru articole prezentate la conferințe care apar online: Balakrishnan R. Why aren´t we using 3d user interfaces, and will we ever? Paper presented at the IEEE Symposium on 3D User Interfaces March 25-26, 2006. doi:10.1109/VR.2006.148

ABREVIERILE. La prima utilizare în text, abrevierea (acronimul) trebuie sa fie precedată de expresia integrală.

DENUMIREA MEDICAMENTULUI. Se utilizează numele generic al medicamentului. Atunci când marca de proprietate a fost utilizată în articolul de cercetare, aceasta se scrie în paranteze și apare în secțiunea „Materiale și Metode" a manuscrisului.

UNITĂȚILE DE MĂSURĂ. În manuscris, oriunde se folosesc unități de măsură, acestea vor fi exprimate în sistemul internațional. Temperaturile vor fi specificate în grade Celsius. Presiunea arterială va fi precizată în mm Hg. Rezultatele analizelor laboratorului clinic vor fi exprimate în unitățile de măsură din sistemul internațional SIU.

PERMISIUNILE. Originalitatea conținutului materialelor trimise, respectiv încălcarea dreptului de autor (copyright), cât și respectarea normelor de etică internaționale, sunt doar responsabilitatea autorilor.

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Mai multe informații pot fi obținute la:

Telefon: +4 021 223 71 94

Fax: +4 021 223 14 80

E-mail: rjgerontog@gmail.com și journal@rjgg.ro

Website: www.rjgg.ro, www.srgg.ro sau www.ana-aslan.ro

"Ana Aslan" National Institute of Gerontology and Geriatrics
Otopeni Clinic

"Ana Aslan" National Institute of Gerontology and Geriatrics
Bucharest Clinic